TITLE PAGE

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 chemotherapynaïve extensive-stage small cell lung cancer (ES-SCLC)

Protocol Number:	BNT411-01
Amendment Number:	6.0
Short Title / Acronym:	Safety, pharmacokinetics, pharmacodynamics, and preliminary efficacy trial of BNT411
Trial Phase:	Phase 1/2a
Compound:	BNT411
Sponsor:	BioNTech SE An der Goldgrube 12 55131 Mainz, Germany
Regulatory Agency Identifier Number(s)	IND 144377 EudraCT 2019-003593-17 NCT04101357
Version Number and Date:	Version 6.0, 04 July 2023

STATEMENT OF COMPLIANCE

GCP Compliance

This trial will be conducted in compliance with International Conference on Harmonisation Good Clinical Practice (ICH GCP E6 [R2]), and applicable regulatory requirements.

Confidentiality Statement

The information in this document contains trade secrets and commercial information that are privileged or confidential and may not be disclosed unless such disclosure is required by applicable law or regulations. In any event, persons to whom the information is disclosed must be informed that the information is privileged or confidential and may not be further disclosed by them. These restrictions on disclosure will apply equally to all future information supplied to you that is indicated as privileged or confidential.

Sponsor Signatory:

Dan Zhou, MD **Medical Expert Clinical Trials**	**Date**

Principal Investigator Signatory:

Principal Investigator Signature	**Date**

Name:

Institution:

PROTOCOL UPDATE SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Version 6.0	04 July 2023
Version 5.0_DEU (Germany only)	09 January 2023
Version 5.0	01 July 2022
Version 4.2 (Germany only)	24 June 2021
Version 4.1 (Germany only)	14 May 2021
Version 4.0	13 Nov 2020
Version 3.0	07 May 2020
Version 2.1 (UK only)	11 March 2020
Version 2.0	30 October 2019
Version 1.0	30 September 2019

Overall Rationale for the update to Version 6.0:

In version 6.0, changes were made to global protocol version 5.0 in order to clarify that some endpoints are only applicable to Part 2 of the trial. Other changes were made for clarification/correction. Details are provided in Appendix 11.6.

Overall Rationale for the update to Version 5.0_DEU:

In version 5.0_DEU (Germany-specific protocol), changes were made to global protocol version 5.0 in response to feedback from the German Health Authority (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM). Details are provided in Appendix 11.5.

Overall Rationale for the update to Version 5.0:

In version 5.0, changes were made in response to the COVID-19 pandemic, an inclusion criterion was updated, backfilling of cohorts was introduced, and Germany-specific safety reporting of death events was introduced. Details are provided in Appendix 11.4.

Overall Rationale for the update to Version 4.0:

In Version 4.0, the sponsor changed from BioNTech Small Molecules GmbH to BioNTech SE. SAEs due to disease progression were exempted from the standard expedited reporting process

and some inconsistencies to the previous versions were corrected. Details are provided in Appendix 11.3.

Overall Rationale for the update to Version 3.0:

In Version 3.0, changes for better clarification and consistencies were made as requested by relevant regulatory authorities and ethics committees. Details are provided in Appendix 11.2.

Overall Rationale for the update to Version 2.0:

In Version 2, inconsistencies to the previous versions were corrected. Details have been provided in Appendix 11.1.

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1.1 Synopsis

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<tr><td>Brief Title</td><td>Safety, pharmacokinetics, pharmacodynamics, and preliminary efficacy trial of BNT411</td></tr>
<tr><td>Clinical Phase</td><td>Phase 1/2a</td></tr>
<tr><td>Purpose and Rationale</td><td>This first-in-human (FIH) trial aims to establish a safe dose of BNT411 as a monotherapy and in combination with atezolizumab, carboplatin and etoposide. BNT411 is a toll-like receptor 7 (TLR7) agonist which is expected to mount broad innate and adaptive immune reactions, especially in combination with cytotoxic therapies and immune checkpoint inhibitors.</td></tr>
<tr><td>Objectives and Endpoints</td><td>
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<tr><th>Objectives</th><th>Endpoints</th></tr>
<tr><td>Primary</td><td></td></tr>
<tr><td>•For Parts 1 and 2: Assess safety profile</td><td>• Occurrence of DLTs within a patient during the DLT evaluation period
• Occurrence of 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</td></tr>
<tr><td>•For Part 1: Determine MTD and/or RP2D</td><td>• MTD defined as the highest tolerated dose
• RP2D based on integrated evaluation of safety, tolerability, clinical benefit, PK, and pharmacodynamic data, for all dose levels tested</td></tr>
<tr><td>Secondary</td><td></td></tr>
<tr><td>•For Parts 1 and 2: Establish PK profile</td><td>• PK parameters (AUC, CL and V_D, C_{max}, T_{max}, C_{trough}, and $T_{1/2}$)</td></tr>
<tr><td>•For Part 2: Evaluate anti-tumor activity according to RECIST 1.1</td><td>• ORR defined as the proportion of patients in whom a CR or PR is observed as best overall response.
• DCR defined as the proportion of patients in whom a CR or PR or SD (assessed at least 6 weeks after first</td></tr>
</table>
</td></tr>
</table>

	dose) is observed as best overall 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	• iORR defined as the proportion of patients in whom a iCR or iPR is observed as best overall response. • iDCR defined as the proportion of patients in whom a iCR or iPR or iSD (assessed at least 6 weeks after first dose) is observed as best overall response. • iDOR defined as the time from first objective response (iCR or iPR) to the date of the first occurrence of objective tumor progression (iCPD) or death from any cause, whichever occurs first.
•For Part 2: Evaluate preliminary efficacy	• PFS defined as the time from first dose of BNT411 to first occurrence of objective tumor progression (per RECIST 1.1), or death from any cause, whichever occurs first. • 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 PBMCs)

Key: AUC, area-under-the-concentration-time curve; CL, clearance; Cmax, maximum concentration; (i)CR, (immune) complete response; Ctrough, trough concentration; (i)DCR, (immune) disease control rate; DLTs, dose-limiting toxicities; DOR, duration of response; iCPD, immune confirmed progressive disease; iRECIST, immune RECIST; MTD, maximal tolerated dose; (i)ORR, (immune) objective response rate; OS, overall survival; PBMCs, peripheral blood mononuclear cells; PFS, progression-free survival; PK, pharmacokinetic; (i)PR, (immune) partial response; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended Phase 2 dose; (i)SD,

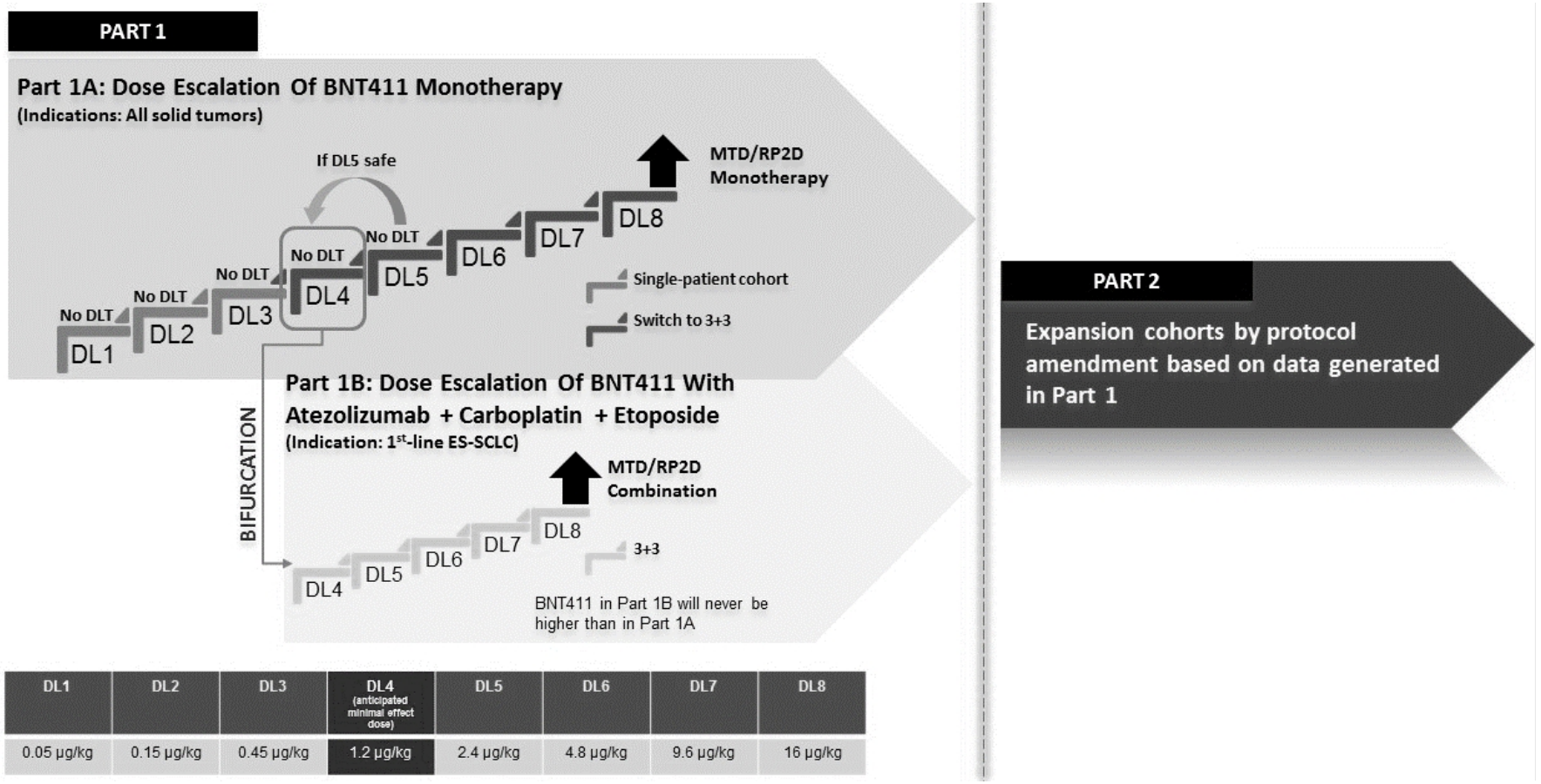
	(immune) stable disease; $T_{1/2}$, terminal half-life; TEAEs, treatment emergent AEs; Tmax, time to Cmax; VD, volume of distribution.
Trial Design	This is an open-label, multicenter, dose -escalation, safety, PK and pharmacodynamic trial of BNT411 with expansion cohorts in a mixed population of patients with solid tumors. The trial consists of three parts: • **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. Part 1B is planned to start before the MTD/RP2D is reached in Part 1A using a bifurcated trial design. The dose level of BNT411 in Part 1B at any given time will always be one dose level below that in Part 1A. In Parts 1A and 1B, patients will receive one infusion of BNT411 every week in a 3-week cycle for the first 4 cycles (on Days 1, 8 and 15 in Part 1A; on Days 2, 8 and 15 in Part 1B). In the following cycles thereafter, BNT411 will be administered every 3 weeks (on Day 1 [Part 1A] or Day 2 [Part 1B] of each 3-week cycle). Treatment will continue until protocol-defined treatment discontinuation criteria are met. The dose escalation in Part 1A starts with an accelerated phase consisting of single patient cohorts followed by larger patient cohorts in Parts 1A and 1B informed by a classical 3+3 design. BNT411 dosing in Part 1A will start at 0.05 µg/kg/administration. To be eligible for DLT assessment, patients should receive all three infusions of BNT411 during the DLT assessment period (Cycle 1). After completion of the DLT period, the Safety Review Committee (SRC) will review the data and propose the dose level for the next cohort of patients. The RP2D will be decided based on integrated evaluation of safety, tolerability, clinical benefit, PK, and pharmacodynamic data, for all dose levels tested. Efficacy will be assessed by on-treatment imaging 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), withdrawal of consent, trial termination by the sponsor, or death, whichever occurs first, regardless of whether patients start a new anti-cancer therapy.
Population	Between 6 to 60 DLT evaluable patients are planned to be enrolled in Part 1A. Between 6 to 30 DLT evaluable patients are planned to be enrolled in Part 1B.

	For the dose escalation (Parts 1A and 1B), approximately 12 sites will be opened in North America and Europe. For possible expansion, approximately 25 to 35 sites will be opened in North America, Europe, and potentially the rest of the World. **Note:** "Enrolled" means a patient's, or their legally acceptable representative's agreement to participate in a clinical trial following completion of the informed consent process. Potential patients who are screened for the purpose of determining eligibility for the trial, but do not participate in the trial, are not considered enrolled, unless otherwise specified by the protocol.
Key Inclusion Criteria	For Part 1A: • Histologically confirmed solid tumor (cytology is allowed for NSCLC, SCLC and pancreatic cancer) that is metastatic or unresectable and for which there is no available standard therapy likely to confer clinical benefit, or patients who are not candidates for such available therapy. For Part 1B: • Histologically or cytologically confirmed ES-SCLC (per the Veterans Administration Lung Study Group [VALG] staging system) who received no prior chemotherapy for extensive stage disease. • Those treated with prior chemo/radiotherapy with curative intent for limited-stage small cell lung cancer (LS-SCLC) should be treatment -free for at least 6 months since last chemo/radiotherapy. • No interstitial lung disease or active, non-infectious pneumonitis. For both Part 1A and Part 1B: • Male and female ≥18 years of age. • Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. • Measurable disease according to RECIST 1.1.
Key Exclusion Criteria	• Has received prior systemic therapy with a TLR7 agonist. • Has been receiving: radiotherapy, chemotherapy, or molecularly-targeted agents or tyrosine kinase inhibitors within 2 weeks or 5 half-lives (whichever is longer) of the start of trial treatment; immunotherapy/monoclonal antibodies within 3 weeks of the start of trial treatment; any live vaccine within 4 weeks of the start of trial treatment; nitrosoureas, antibody-drug conjugates, or radioactive isotopes within 6 weeks of the start of trial treatment. • Receives concurrent systemic (oral or intravenous) steroid therapy >10 mg prednisone daily or its equivalent for an underlying condition. • Receives concurrent strong inhibitors or inducers of major cytochrome P450 enzymes. • Has had major surgery within the 4 weeks before the first dose of BNT411. • Has ongoing or active infection requiring intravenous treatment with anti-infective therapy that has been administered less than two weeks prior to first dose of trial treatment.

	• Has side effects of any prior therapy or procedures for any medical condition not recovered to NCI CTCAE v.5 Grade ≤1. • Has any contraindication to atezolizumab, carboplatin or etoposide as per USPI or SmPC in Part 1B.
Investigational Therapy	In Part 1A, BNT411 will be administered using a 100 mL intravenous infusion on Days 1, 8 and 15 of each 3-week treatment cycle (21 days) of the first 4 cycles. In the following cycles thereafter, BNT411 will be administered every 3 weeks on Day 1 of each 3-week treatment cycle (21 days). In Part 1B, BNT411 will be administered using a 100 mL intravenous infusion on Days 2, 8 and 15 of each 3-week treatment cycle (21 days) of the first 4 cycles. In the following cycles thereafter, BNT411 will be administered every 3 weeks on Day 2 of each 3-week treatment cycle (21 days). Dose reduction or termination will be based on pre-specified dose modification rules or stopping criteria. In Part 1B, 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 Atezolizumab, carboplatin, and etoposide will be used in the commercially available formulation and at the label-recommended doses. For each dosing of BNT411 in Cycle 1, patients will remain in the treatment center and be closely monitored for immediate adverse events (AEs) for at least 6 hours. Hospitalization is required for the first 24 hours after the first BNT411 administration in Cycle 1 for clinical observation and PK sampling. Prolongation of the hospitalization beyond 24 hours may be performed at the investigator's discretion if deemed necessary based on potential risks related to the trial treatment and clinical status of the patient. For each subsequent dose of BNT411 in all cycles, patients will be monitored for at least 6 hours.
Safety Review Committee	An SRC, composed of the investigators and the sponsor's representatives will assess the cumulative safety data (e.g., serious AEs [SAEs], AEs, laboratory data and DLTs where applicable) collected during the trial to help ensure patient's safety. The SRC will make recommendation of the RP2D at the end of both Parts 1A and 1B and will recommend whether to activate the expansion phase (Part 2).
Statistics	No statistical hypotheses are planned to be tested in this trial. Descriptive statistics will be used to analyze continuous and categorical variables. Time-to-event-endpoints (DOR, PFS and OS) will be analyzed using Kaplan-Meier methodology.

1.2 Schema

Figure 1-1: Overall Trial Design



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

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

1.3 Schedule of Activities (SoA)

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

Table 1-1 and Table 1-2, respectively, list all of the assessments to be performed in Parts 1A and 1B (dose escalation phases) of the trial. Table 1-3 (Part 1A) and Table 1-4 (Part 1B) show the timing of the PK and electrocardiogram (ECG) assessments for dose escalation, and Table 1-6 shows the timing for measurement of vital signs in relation to infusions. Table 1-7 (Part 1A) and Table 1-8 (Part 1B) list the biomarker assessments to be performed. All data obtained from these assessments must be reported in the patient's source documentation. With the exception of post-dose blood and urine sampling for PK assessments, all assessments should be performed before trial treatment administration (on the applicable days) or any planned intervention. On the days of tumor imaging, blood sampling can be before or after imaging assessments.

If non-adherence to the SoA will occur related to the COVID-19 pandemic, please review Addendum "Clinical trial protocol addendum related to COVID-19 pandemic Version 3.0 04 Jun 2021".

Information relating to COVID-19 vaccinations including a risk-benefit assessment and guidance for vaccination during this clinical trial is provided in Sections 10.8 and 10.9.

Table 1-1: Schedule of Activities – Part 1A

Treatment Cycle	Screening	Cycle 1-2					Cycle 3-4			Cycle 5–N			Treatment discontinuation [1]	Safety follow-up 1	Safety follow-up 2	Survival follow-up[2]	Unscheduled
Day (D)	**≤21 days prior to Visit C1 (D1)**	**D1**	**D2**	**D3[24]**	**D8**	**D15**	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**-**	**30 days after last dose**	**60 days after last dose**	**Every 12 weeks**	
Visit window		**±D3**	**-**	**+D2 [24]**	**±D1**	**±D1**	**±D3**	**±D1**	**±D1**	**±D 3**	**±D1**	**±D1**	**-**	**+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 Section 8.6.3 and Table 1-3 for details on ECG assessments															
CT/MRI-Scan	X[10]	Refer to Section 8.5.1 of the protocol 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[17]	X	X	X		X[3]
Biochemistry	X[16]	X[17]	X	X	X[17]	X[17]	X[17]	X[17]	X[17]	X[17]	X[17]	X[17]	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[17]	X	X	X		X[3]
Endocrine[18]	X[16]	X[17]					X[17]			X[17]			X				X[3]
Urinalysis	X[16]				X[17]		X[17]		X[17]	X[17]			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 Table 1-3 for details of PK samplings																
Tumor Biopsy, Biomarkers	Refer to Table 1-7 for detailed biomarker assessment schedule																

1 If the patient has to go off treatment per treatment withdrawal criteria (refer 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 protocol 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 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 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 Sections 10.5 and 10.6 of the protocol 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 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 assessments listed under 'unscheduled visit' should be performed and reported in the eCRF. Unscheduled visit assessments should be performed at the investigator's discretion. For information on COVID-19 vaccination during the trial, see Section 10.9.

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 1-2: Schedule of Activities – Part 1B

Treatment Cycle	Screening	Cycle 1-2					Cycle 3- 4					Cycle 5–N				Treatment discon-tinuation[1]	Safety follow-up 1 [27]	Safety follow-up 2 [27]	Survival follow-up[2]	Un-scheduled
Day (D)	**≤21 days prior to Visit C1D1**	**D1**	**D2**	**D3[28]**	**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[28]**	**±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	Please refer to Section 8.6.3 and Table 1-4 for details on ECG assessments																		
CT/MRI-Scan	X[10]	Refer to Section 8.5.1 of the protocol 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[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											
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 treatment administration , 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									X	X	X		X[3]
Serology [19]	X[26]																			
PK Sampling (includes blood and urine)	Refer to Table 1-4 for details of PK samplings																			

Treatment Cycle	Screening	Cycle 1-2					Cycle 3- 4					Cycle 5–N				Treatment discon-tinuation[1]	Safety follow-up 1 [27]	Safety follow-up 2 [27]	Survival follow-up[2]	Un-scheduled
Day (D)	**≤21 days prior to Visit C1D1**	**D1**	**D2**	**D3[28]**	**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[28]**	**±D1**	**±D1**	**±D3**	**-**	**+D2**	**±D1**	**±D1**	**±D3**	**-**	**±D1**	**±D1**	**-**	**+D5**	**±D7**	**±D14**	
Tumor biopsy, biomarkers	Refer to Table 1-8 for detailed biomarker assessment schedule																			

1 If the patient has to go off treatment per treatment withdrawal criteria (refer 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. 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 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 Section 8.6.2 and Table 1-6 of the protocol 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 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 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 Sections 10.5 and 10.6 of the protocol 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 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. For information on COVID-19 vaccination during the trial, see Section 10.9.

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 4 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.

Table 1-3: PK (blood and urine) sampling and ECG assessment in Part 1A

Treatment Cycle	Screening	Cycle 1					Cycle 2			Cycle 3 - N	Treatment Discontinuation	Safety follow-up 1	Safety follow-up 2	UNS
Day	**≤21 days prior to Visit C1D 1**	**D1**	**D2[b]**	**D3 [b]**	**D8**	**D15**	**D1**	**D2[b]**	**D3 [b]**	**D1[c, e]**	**-**	**30 days after last dose**	**60 days after last dose**	**-**
Before BNT411 infusion (on infusion days) or on day of visit	E1	X, E3,U[a]	X, E3,U[a]	X, U[a]	X, E3	X	X, E3,U[a]	X, (E3),U[a]	X	X, E3	X, E1	X, E1	X, E1	X, E1,U[a]
Start of infusion		U[d]												
End of infusion (+5 min)		X, E3			X, E3		X, E3			X,E3				
Start of infusion + 1 hour (±5 min)		X					(X)							
Start of infusion + 2.5 hours (±10 min)		X			X		X			X				
Start of infusion + 4 hours (±15 min)		X			X		X			X				
Start of infusion + 6 hours (±15 min)		X, E3[a,]			X		X, E3[a]			(X)				
Start of infusion + 8 hours (±15 min)		X					(X)							

Note: Time points for blood and urine sampling are to be followed as closely as possible but time deviations no longer than 2 hours will not be reported as protocol deviations as long as the exact times of sampling and dose are known.
E1 – Single ECG assessment.
E3 – Triplicate ECG assessments.
X – Blood sampling.
U – Urine sampling.
UNS – Unscheduled visit.
(X) – Blood sampling will only be performed in potential additional patients enrolled to expand the cohorts for RP2D confirmation.
(E3) – Triplicate ECG assessment will only be performed in potential additional patients enrolled to expand the cohorts for RP2D.

[a] Sampling time and sample volume have to be documented.
[b] Time window for the Day 2 sample in the dose escalation is 24 hours ± 1 hour and for Day 3 sample is 48 hours ± 2 hours after the start of infusion on Day 1.

[c] PK and ECG must be obtained in Cycle 3, Cycle 5, Cycle 7, and every 4 cycles thereafter (i.e., Cycles 3, 5, 7, 11, 15, etc.).
[d] 6-hour urine collection after start of BNT411 infusion and total volume collected should be documented.
[e] After C3D1, PBMCs (for immune phenotyping and TCR profiling) will no longer be collected. Collection of PMBCs at treatment discontinuation and/or unscheduled visits is only required if the patient discontinues trial treatment prior to C3D1.

Table 1-4: PK (blood and urine) sampling and ECG assessment in Part 1B

Treatment Cycle	Screening	Cycle 1					Cycle 2			Cycle 3 - N	Treatment Discontinuation	Safety follow-up 1	Safety follow-up 2	UNS
Day	**≤21 days prior to Visit C1 (D1)**	**D1**	**D2**	**D3[b]**	**D8**	**D15**	**D1**	**D2**	**D3[b]**	**D2[c]**	**-**	**30 days after last dose**	**60 days after last dose**	**-**
Before BNT411 infusion (on infusion days) or on day of visit	E1		X,E3, U[a]	X,E3, U[a]	X,E3	X		X,E3, U[a]	X,(E3) ,U[a]	X,E3	X,E1	X,E1	X,E1	X,E1, U[a]
Start of infusion			U[d]											
End of infusion (+ 5 min)			X,E3		X,E3			X,E3		X,E3				
Start of infusion + 1 hour (± 5 min)			X					(X)						
Start of infusion + 2.5 hours (± 10 min)			X		X			X		X				
Start of infusion + 4 hours (± 15 min)			X		X			X		X				
Start of infusion + 6 hours (± 15 min)			X,E3[a]		X			X,E3[a,]		(X)				
Start of infusion + 8 hours (± 15 min)			X					(X)						

Note: Time points for blood and urine sampling are to be followed as closely as possible but time deviations no longer than 2 hours will not be reported as protocol deviations as long as the exact times of sampling and dose are known.
E1 – Single electrocardiogram (ECG) assessment.
E3 – Triplicate ECG assessments.

X – Blood sampling
U – Urine sampling
UNS – Unscheduled visit
(X) – Blood sampling will only be performed in potential additional patients enrolled to expand the cohorts for RP2D confirmation.
(E3) – Triplicate ECG assessment will only be performed in potential additional patients enrolled to expand the cohorts for RP2D.

[a] Sampling time and sample volume have to be documented.
[b] Time window for the Day 3 sample in the dose escalation is 24 hours ± 1 hour after the start of infusion on Day 2.
[c] PK and ECG must be obtained in Cycle 3, Cycle 5, Cycle 7, and every 4 cycles thereafter (i.e., Cycles 3, 5, 7, 11, 15, etc.)
[d] 6-hour urine collection after start of BNT411 infusion and total volume collected should be documented.
[e] After C3D1, PBMCs (for immune phenotyping and TCR profiling) will no longer be collected. Collection of PMBCs at treatment discontinuation and/or unscheduled visits is only required if the patient discontinues trial treatment prior to C3D1.

Table 1-5: Overview of Safety Reporting in Different Countries

Notes: If not specified otherwise, when AE is mentioned, it should also include SAE.

Country	**Trial Phase**				
	Screening	**Treatment Phase**	**Safety Follow-up Phase**	**Survival Follow-up Phase**	**Beyond Trial Closure** ***(if patient is alive and not lost to follow-up)***
USA	All AEs	All AEs	All AEs	BNT411-related AEs Trial procedure-related AEs	BNT411-related SAEs Trial procedure-related SAEs
UK	All AEs	All AEs	All AEs	BNT411-related AEs Trial procedure-related AEs	BNT411-related SAEs Trial procedure-related SAEs
Spain	All AEs	All AEs	All AEs	BNT411-related AEs Atezolizumab-related AEs Carboplatin-related AEs Etoposide-related AEs Trial procedure-related AEs	BNT411-related SAEs Atezolizumab-related SAEs Carboplatin-related SAEs Etoposide-related SAEs Trial procedure-related SAEs
Germany	All AEs	All AEs	All AEs	All SAEs; if the event is not an SAE, only the following to be reported: BNT411-related AEs Atezolizumab-related AEs Carboplatin-related AEs Etoposide-related AEs Trial procedure-related AEs	All SAEs

Table 1-6: Vital Signs during Parts 1A and 1B

Patients should be monitored for a minimum of 6 hours in the clinic after each administration of BNT411.

Vital signs are measured after BNT411 infusion at the following time points (further assessments can be done at the discretion of the investigator):

BNT411 pre-infusion (up to 30 min before infusion)
15 min after start of infusion (±5 min)*
30 min after end of infusion (±5 min)
60 min after end of infusion (±10 min)
120 min after end of infusion (±15 min)

*If infusion lasts for more than 60 minutes, vital signs should be assessed every 15 minutes (± 5 minutes) for the remaining duration of the infusion.

Table 1-7: Biomarker table – in Part 1A

Treatment Cycle	Screening	Cycle 1-2					Cycle 3-N	Treatment discontinuation	Unscheduled
Day/Week	**≤21 days prior to Visit C1 (D1)**	**D1**	**D2**	**D 3**	**D8**	**D15**	**D1[6]**	**-**	**-**
Visit window		**-**	**1h**	**2h**	**±D1**	**±D1**	**±D3**	**-**	**-**
Tissue compartment									
Tumor FFPE sample	X[1]								
Tumor biopsy	X[2]						X[2]	X[2]	X[2]
Blood compartment									
Cytokines		X[3]						X[3]	X[3]
Immune Phenotyping		X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]
TCR profiling		X[5]					X[5]	X[5]	X[5]

1 A formalin-fixed paraffin-embedded (FFPE) tumor tissue sample (for e.g., immunohistochemistry, tumor mutational burden) must be obtained from each patient from the latest available archival tumor tissue. If such tissue cannot be provided, the sponsor approval of enrollment is needed. Details regarding the preparation of slides and number of slides to be prepared will be described in the lab manual.

2 An optional fresh tumor biopsy (aspirates are not acceptable) which is collected before Cycle 1, Day 1, preferably derived from advanced stage disease. This biopsy needs to contain tumor tissue and is taken after failure/stop of last prior treatment at screening or before first administration of BNT411. Additionally, biopsies should be collected at Week 6 ([+7 days], i.e., after 2 cycles of BNT411) and at disease progression or treatment discontinuation if it is considered feasible without a risk of complications for the patient. If deemed necessary by the investigator, the patient may be called in for an unscheduled visit, optional additional tumor biopsies may be collected if patients have unscheduled biopsies or tumor tissue resection during the course of the trial. Details to the preparation of fresh tumor biopsies will be described in the lab manual.

3 Cytokine samples will be taken at the same time points given for PK sampling with the exception of "end of infusion"– please refer to Table 1-3. Furthermore, cytokine samples will be taken at disease progression or treatment discontinuation. If an adverse event (AE) of cytokine release syndrome (CRS) is suspected, cytokines should be obtained at an unscheduled visit to confirm diagnosis.

4 Immune phenotyping samples are requested at Day 1 (pre-dose), 24 hours / Day 2 (±1 hours) and 48 hours / Day 3 (±2 hours) after start of infusion in Cycles 1 and 2. Furthermore, immune phenotyping samples will be taken pre-dose in Cycles 1 and 2 at Day 8 and Day 15 and pre-dose for every second cycle starting from Cycle 3 (e.g., Cycle 3, 5, 7, etc.) including time of disease progression or treatment discontinuation. Samples can also be taken at an unscheduled visit.

5 T-cell receptor (TCR) profiling (blood) samples are requested at Cycle 1 Day 1 (pre-dose), and at Cycle 3 Day 1 (pre-dose) and at time of disease progression or treatment discontinuation. Samples can also be taken at an unscheduled visit.

6 After C3D1, PBMCs (for immune phenotyping and TCR profiling) will no longer be collected. Collection of PMBCs at treatment discontinuation and/or unscheduled visits is only required if the patient discontinues trial treatment prior to C3D1.

Table 1-8: Biomarker table – in Part 1B

Treatment Cycle	Screening	Cycle 1-2					Cycle 3-N	Treatment discontinuation	Unscheduled
Day/Week	**≤21 days prior to Visit C1 (D1)**	**D1**	**D2**	**D3**	**D8**	**D15**	**D1[6]**	**-**	**-**
Visit window		**-**		**1h**	**±D1**	**±D1**	**±D3**	**-**	**-**
Tissue compartment									
Tumor FFPE sample	X[1]								
Tumor biopsy	X[2]						X[2]	X[2]	X[2]
Blood compartment									
Cytokines			X[3]					X[3]	X[3]
Immune Phenotyping		X[4]		X[4]	X[4]	X[4]	X[4]	X[4]	X[4]
TCR profiling		X[5]					X[5]	X[5]	X[5]

1 A formalin-fixed paraffin-embedded (FFPE) tumor tissue sample (for e.g., immunohistochemistry, tumor mutational burden) must be obtained from each patient from the latest available archival tumor tissue. If such tissue cannot be provided, the sponsor approval of enrollment is needed. Details regarding the preparation of slides and number of slides to be prepared will be described in the lab manual.

2 An optional fresh tumor biopsy (aspirates are not acceptable), which is collected before Cycle 1 Day 1, preferably derived from advanced stage disease. This biopsy needs to contain tumor tissue and is taken after failure/stop of last prior treatment at screening or before first administration of BNT411. Additionally, biopsies should be collected at Week 6 ([+7 days], i.e., after 2 cycles of BNT411) and at disease progression or treatment discontinuation if it is considered feasible without a risk of complications for the patient. If deemed necessary by the investigator, the patient may be called in for an unscheduled visit, optional additional tumor biopsies may be collected if patients have unscheduled biopsies or tumor tissue resection during the course of the trial. Details to the preparation of fresh tumor biopsies will be described in the lab manual.

3 Cytokine samples will be taken at the same time points given for PK sampling with the exception of "end of infusion"– please refer to Table 1-4. Furthermore, cytokine samples will be taken at disease progression or treatment discontinuation. If an adverse event (AE) of cytokine release syndrome (CRS) is suspected, cytokines should be obtained at an unscheduled visit to confirm diagnosis.

4 Immune phenotyping samples are requested at D1 (pre-dose) and at D3 i.e. 48 hours (±2 hours) after start of infusion of BNT411 in Cycles 1 and 2. Furthermore, immune phenotyping samples will be taken pre-dose in Cycles 1 and 2 at Day 8 and Day 15 and pre-dose (D1) for every second cycle starting from Cycle 3 (e.g. Cycle 3, 5, 7, etc.) including time of disease progression or treatment discontinuation. Samples can also be taken at an unscheduled visit.

5 T-cell receptor (TCR) profiling (blood) samples are requested at Cycle 1 Day 1 (pre-dose), and at Cycle 3 Day 1 (pre-dose) and at time of disease progression or treatment discontinuation. Samples can also be taken at an unscheduled visit.

6 After C3D1, PBMCs (for immune phenotyping and TCR profiling) will no longer be collected. Collection of PMBCs at treatment discontinuation and/or unscheduled visits is only required if the patient discontinues trial treatment prior to C3D1.

2 Introduction

2.1 Background

2.1.1 Overview of the Disease

Cancer is the second leading cause of death globally and is expected to be responsible for an estimated 9.6 million deaths in 2018 (Center for Disease Control and Prevention 2017; International Agency for Research on Cancer 2017). Refinements in conventional therapies such as chemotherapy, radiotherapy, surgery, and targeted therapies and recent advances in immunotherapies have improved outcomes in patients with advanced cancers. However, many immunotherapy treatments have demonstrated efficacy in only a selected group of cancers (Ventola et al, 2017; Yang et al, 2015). There is an unmet medical need for more effective and less toxic therapies with cures remaining scarce in patients with advanced solid tumors.

Small cell lung cancer (SCLC) accounts for approximately 15% of bronchogenic carcinomas. At the time of diagnosis, approximately 30% of patients with SCLC will have tumors confined to the ipsilateral hemithorax, which can be safely encompassed within a radiation field. These patients are designated as having limited-stage disease (LS-SCLC) (Murray et al, 1993). Patients with tumors beyond the ipsilateral hemithorax, including malignant pleural or pericardial effusion or hematogenous metastases are said to have extensive-stage disease (ES-SCLC).

SCLC is more responsive to chemotherapy and radiation therapy than other cell types of lung cancer; however, a cure is difficult to achieve because SCLC has a greater tendency to be widely disseminated by the time of diagnosis and to recur. ES-SCLC was chosen as the indication to escalate the doses of BNT411 with atezolizumab, carboplatin and etoposide.

2.1.1.1 Incidence and Mortality

The overall incidence of SCLC in the United States and in the United Kingdom has decreased during the past few decades (Govindan et al, 2006; Riaz et al, 2012). The following table shows the estimated number of new cases of lung cancer and deaths from lung cancer (SCLC and non-small cell lung cancer [NSCLC] combined) in the United States in 2018 (American Cancer Society 2019) and in Europe in 2012 (Ferlay et al, 2013).

Lung Cancer	**United States, 2018**	**Europe, 2012**
New Cases	234,030	410,000
Deaths	154,050	353,000

Separate worldwide data for SCLC are not available. The incidence of lung cancer started to decline among men in the early 1980s and has continued to do so over the past 20 years. In contrast, the incidence in women started to increase in the late 1970s and did not begin to decline until the mid-2000s (American Cancer Society 2019; Siegel et al, 2019).

2.1.1.2 Clinical Features

Lung cancer may present with symptoms or be found incidentally on chest imaging. Symptoms and signs may result from the location of the primary local invasion or compression of adjacent thoracic structures, distant metastases or paraneoplastic phenomena. The most common symptoms at presentation are worsening cough, shortness of breath and dyspnea. Symptoms from distant metastases may also be present and include neurological defect or personality change from brain metastases or pain from bone metastases. Infrequently, patients with SCLC may present with symptoms and signs of the paraneoplastic syndromes.

2.1.1.3 Diagnosis

Treatment options for patients are determined by histology, stage, and general health and comorbidities of the patient. Investigations of patients with suspected SCLC focus on confirming the diagnosis and determining the extent of the disease. The procedures used to determine the presence of cancer include the following: history, physical examination, routine laboratory evaluations, chest X-ray, chest computed tomography (CT) scan with infusion of contrast material and biopsy.

Before a patient begins lung cancer treatment, an experienced lung cancer pathologist must review the pathologic material. This is critical because SCLC, which responds well to chemotherapy and is generally not treated surgically, can be confused on microscopic examination with NSCLC (Travis et al, 1999).

2.1.1.4 Prognosis and Survival

Regardless of stage, the current prognosis for patients with SCLC is unsatisfactory despite improvements in diagnosis and therapy made during the past 25 years. Without treatment, SCLC has the most aggressive clinical course of any type of pulmonary tumor, with median survival from diagnosis of only 2 months to 4 months. About 10% of the total population of SCLC patients remain free of disease during the 2 years from the start of therapy, which is the time period during which most relapses occur. Even these patients, however, are at risk of dying from lung cancer (both small and non-small cell types) (Johnson et al, 1990). The overall survival (OS) at 5 years is 5% to 10% (Fry et al, 1996; Johnson et al, 1990; Lassen et al, 1995; Murray et al, 1993).

An important prognostic factor for SCLC is the extent of disease. Patients with LS-SCLC have a better prognosis than patients with ES-SCLC. For patients with LS-SCLC, median survival of 16 months to 24 months and 5-year survival of 14% with current forms of treatment have been reported (Fry et al, 1996; Janne et al, 2002; Murray et al, 1993; Turrisi et al, 1999). In patients with ES-SCLC, median survival of 6 months to 12 months is reported with currently available therapy, but long-term disease-free survival is rare. Prophylactic cranial radiation prevents central nervous system recurrence and can improve survival in patients with good performance status who have had a complete response or a very good partial response to chemoradiation in LS-SCLC or chemotherapy in ES-SCLC (Auperin et al, 1999; Slotman et al, 2007).

2.1.2 Standard Treatment Options for Patients with ES-SCLC

Standard treatment options for patients with ES-SCLC include the following:

1. Combination chemotherapy.
2. Radiation therapy.
3. Immunotherapy.
4. Thoracic radiation therapy for patients who respond to chemotherapy.
5. Prophylactic cranial irradiation (PCI).

2.1.2.1 Combination Chemotherapy

Chemotherapy for patients with ES-SCLC is commonly given as a two-drug combination of platinum and etoposide in doses associated with at least moderate toxic effects (as in LS-SCLC) (Okamoto et al, 2007). Cisplatin is associated with significant toxic effects and requires fluid hydration, which can be problematic in patients with cardiovascular disease. Carboplatin is active in SCLC, is dosed according to renal function, and is associated with less non-hematological toxic effects.

Other regimens appear to produce similar survival outcomes but have been studied less extensively or are in less common use. Doses and schedules used in current programs yield overall response rates of 50% to 80% and complete response rates of 0% to 30% in patients with ES-SCLC (Pujol et al, 2000; Roth et al, 1992). Intracranial metastases from small cell carcinoma may respond to chemotherapy as readily as metastases in other organs (Nugent et al, 1979; Twelves et al, 1990).

2.1.2.2 Combination Chemotherapy and Radiation Therapy

Combination chemotherapy plus chest radiation therapy does not appear to improve survival compared with chemotherapy alone in patients with ES-SCLC.

2.1.2.3 Immunotherapy

Atezolizumab is a humanized, engineered monoclonal antibody against the protein programmed cell death-ligand 1 (PD-L1). On March 18, 2019, the Food and Drug Administration approved atezolizumab in combination with carboplatin and etoposide, for the first-line treatment of adult patients with ES-SCLC. This has marked the first systemic therapy approval for ES-SCLC after almost 30 years.

Approval was based on IMpower133 (NCT02763579), a randomized (1:1), multicenter, double-blind, placebo-controlled trial in 403 patients with ES-SCLC who had received no prior chemotherapy for extensive stage disease and had Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.

Major efficacy outcome measures were OS and progression-free survival (PFS) as assessed by investigator per Response Evaluation Criteria in Solid Tumors (RECIST 1.1) in the intent-to-treat (ITT) population. Median OS was 12.3 months (range: 10.8–15.9 months) for patients receiving atezolizumab with chemotherapy and 10.3 months (range: 9.3–11.3 months) for those receiving placebo with chemotherapy (hazard ratio 0.70; 95% confidence interval [CI]: 0.54, 0.91; p=0.0069). Median PFS was 5.2 months (range: 4.4–5.6 months) compared with 4.3 months (range: 4.2–4.5 months) in the atezolizumab and placebo arms, respectively (HR 0.77; 95% CI: 0.62, 0.96; p=0.0170).

2.1.3 High Unmet Medical Need in ES-SCLC

As stated above, median survival of 6–12 months is reported in ES-SCLC with currently available therapy. There is still a very high unmet medical need to develop new therapies in ES-SCLC, especially an innovative combination therapy to improve outcomes. The combination of immunotherapy and chemotherapy has proven effective, but the outcomes are still unsatisfactory compared to other malignant diseases (i.e., 2-month OS benefit and 0.9-month PFS benefit; IMpower133). Therefore, and in the light of the intended mode of action the development of a combined Toll-like receptor (TLR) 7 agonist with atezolizumab, carboplatin and etoposide to increase efficacy outcomes in ES-SCLC is fully justified.

2.1.4 Introduction to the Investigational Treatment

A promising approach in cancer immunotherapy involves Toll-like receptors (TLR), a group of receptors belonging to the innate immune system. Members of the TLR family are largely expressed by several immune and nonimmune cells, each cell type expressing a different combination of TLRs. Their function is to sense pathogen structures from different origins, such as bacteria, viruses, fungi, or protozoan parasites (Medzhitov et al, 2001; Holldack et al, 2014).

In particular, TLR7 is known to contribute to antitumor responses by affecting immune cells, tumor cells, and the tumor microenvironment (Smits et al., 2008). Recognition by TLR7 activates intracellular pathways that culminate in the induction of type I interferons (IFNs), proinflammatory cytokines, chemokines and in the upregulation of costimulatory molecules. This boost can restore and support the anti-tumoral immunity of the innate and adaptive immune system.

BNT411 is a highly potent and selective small molecule TLR7 agonist of the imidazoquinoline family which comprises other TLR ligands such as imiquimod (CAS-No.99011-02-6), resiquimod (CAS-No. 144875-48-9) and 852A (Cas-No. 532959-63-0).

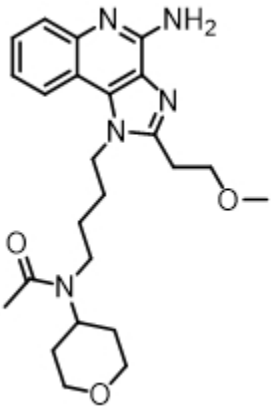
Imiquimod, resiquimod and 852A are being studied as immunotherapy drugs and show strong anti-tumoral activity; however, only imiquimod has been approved for human use so far. Repetitive intravenous administrations of imiquimod at a systemically effective IFNα-inducing dose level is associated with dose-limiting adverse reactions (Holldack et al, 2014; Witt et al, 1993). As a consequence, imiquimod is registered for topical use only in localized diseases such as basal cell carcinoma, genital warts and bladder cancer (Edwards et al, 2000; Spencer et al, 2006; Stanley et al, 2002; Vacchelli et al, 2012). Similarly, repeat-dose intravenous regimens of resiquimod and 852A are not well tolerated, limiting the clinical use of these compounds again to the treatment of localized disease (Lubong Sabado et al, 2015; Rook et al, 2015; Dudek et al, 2007; Dummer et al, 2008; Geller et al, 2010; Spaner et al, 2010; Weigel et al, 2012). This unfavorable safety profile of imiquimod, resiquimod and 852A for intravenous administration may be attributable to the release of a broader array of proinflammatory cytokines (Gorden et al, 2005; Hamm et al, 2009).

BNT411 has been benchmarked in human whole blood preparations and been designed to mediate in this *in vitro* setting at concentrations corresponding to anticipated therapeutic doses primarily IFNα-release, as opposed to a broader array of cytokines to optimize the safety profile (study reports R-19-0027, R-19-0028). Further preclinical studies support this hypothesis and

show a broad safety window in different animal species (see Section 2.1.4.3) in association with an anti-tumoral activity in mouse models (study reports R-19-0011, R-19-0013).

2.1.4.1 Structure

Figure 2-1: Structure of BNT411



Nomenclature	BNT411
Laboratory code	SC100745, SC1.2, Ago1.2
Compound IUPAC Name	*N*-(4-(4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-c]quinolin-1-yl)butyl)-*N*-(tetrahydro-2*H*-pyran-4-yl)acetamide
CAS	2296821-50-4
Molecular weight	439.5579
Exact molecular weight	439.25834
Formula	$C_{24}H_{33}N_5O_3$

2.1.4.2 Mode of action

BNT411 is a selective TLR7 agonist, which activates signaling via the TLR7 pathway. TLR7 is expressed in dendritic cells (DC), primarily plasmacytoid DC, B-cells, and monocytes/macrophages. It is a key sensor for pathogen-associated molecular patterns (PAMPs) expressed on infectious agents (Medzhitov et al, 2001). Signaling through TLR7 initiates a cascade of effects. One is activation of plasmacytoid dendritic cells (pDC) for secretion of interferon alpha (IFNα). IFNα is a critical cytokine, which via pleiotropic mechanisms (direct mediation of tumor cell death; anti-angiogenesis; inhibition of suppressive regulatory T-cells; activation of immune cells, Th1 response), promotes anti-tumoral effects (Smits et al, 2008). TLR7 also activates DCs to efficiently process and present antigens released from dying tumor cells. This results in expansion of cytotoxic T-lymphocytes (CTLs). Expanded and activated T-cells migrate into the tumor tissue, recognize tumor specific antigens and lyse tumor cells

(Vascotto et al, 2019). In addition, TLR7 signaling activates the innate immune system including natural killer (NK) cells and macrophages (Wiedemann et al., 2016; Williams et al, 2016). NK cells are capable of recognizing and lysing tumor cells which have down regulated their human leucocyte antigen (HLA) molecules in order to evade the adaptive immune system.

In aggregate, these effects of TLR7-signaling are strong promoters of an efficient activation of innate and adaptive immunity against cancer cells. Synthetic compounds such as BNT411, which mimic the binding specificity of PAMPs, are considered promising drug candidates, which may overcome cancer-associated immune suppression and promote tumor cell killing. One of the challenges of known TLR7 agonists is the induction of a broader spectrum of pro-inflammatory cytokines beyond INFα, including pyrogenic ones. This effect is hypothesized to be caused by TLR8 cross-signaling and made responsible for dose-limiting side effects upon systemic administration (Gorden et al, 2005; Hamm et al, 2009).

At therapeutic doses in human whole blood assays, BNT411 mediates primarily IFNα-release, whereas release of pyrogenic pro-inflammatory cytokines requires 1-2 orders of magnitude higher doses (study reports R-19-0027, R-19-0028). An *in vitro* benchmarking experiment with other TLR7 agonists has shown that BNT411 induces IFNα at a 10-30-fold lower concentration and causes the secretion of twice the amount of IFNα (C_{max}) than the most active tested comparator compound resiquimod (study report R-19-0028). In line with these observations, proof-of concept studies with BNT411 in mouse and monkey models demonstrated *in vivo* release of high levels of therapeutically relevant IFNα. In addition, at those applied dose ranges anti-tumoral activity was demonstrated in mouse colorectal cancer tumor models (study reports R-19-0011, R-19-0013).

2.1.4.3 Summary of non-clinical studies

Proof of principle for BNT411's mode of action (MoA) has been obtained in animal models and in *in vitro* human whole blood assays. With respect to nonclinical safety, as specified in the ICH S9 guidance, the required non-clinical program was conducted to enable the proposed first-in-human trial. Pivotal toxicology studies followed GLP regulations and were conducted in rats and cynomolgus monkeys.

Note: More details on the non-clinical studies can be found in the investigator's Brochure.

Primary Pharmacodynamics

IFNα as the driver cytokine of the MoA was observed to be the earliest pharmacodynamic marker in human whole blood preparations. Furthermore, upon BNT411 exposure in this *in vitro* setting, IFNα release was more pronounced and occurred at lower concentrations compared with other TLR7 agonist benchmarks. In addition, proinflammatory cytokines like TNFα or IL6 were observed only with significantly higher BNT411 concentrations than needed for a strong IFNα secretion. Due to this primarily release of IFNα at therapeutic doses as opposed to a broader array of cytokines, it is expected that BNT411 can potentially reduce dose-limiting side effects upon systemic administration.

Anti-tumor efficacy of BNT411 in monotherapy could be demonstrated *in vivo* in CT26, a syngeneic colon cancer mouse model. Of note, mice in the treatment group displayed increased frequencies of gp70+ T cells indicating that adaptive immunity contributes to the anti-tumor effect; in line with an elevated IFNα serum level. The combination of BNT411 with oxaliplatin

in the CT26 model resulted in higher reduction of tumor volume as compared to either treatment alone.

Secondary Pharmacodynamics

A receptor screening test evaluated the selectivity and specificity of BNT411 on 55 human receptors, transporters, and ion channels. No inhibition was observed on any of these unrelated targets, demonstrating that BNT411 did not engage with them. Only the human recombinant M1 muscarinic acetylcholine receptor was partly inhibited at concentrations corresponding to non-therapeutic doses.

Safety Pharmacology

In vitro activity of BNT411 on the hERG ion channel was only seen at concentrations approximately 200-fold greater than the anticipated maximally administered dose in humans. Thus, interference with hERG activity is highly unlikely.

Based on the pharmacology of BNT411, a slight but transient increase in body temperature was seen in monkeys shortly after treatment. Further potential cardiovascular effects of BNT411 were monitored in monkeys, as well as effects on the nervous system and on respiratory parameters in rats. However, in the dose range proposed for clinical testing, BNT411 is not anticipated to interfere with the function of these major organ systems.

Pharmacokinetics

Pharmacokinetics of BNT411 was evaluated across different animal species. No accumulation or sex-related differences in exposure were observed with weekly dosing in either rat or monkey. Exposure increases with dose showed a minor non-linearity which was more pronounced in rats than in cynomolgus monkeys.

In vitro plasma protein binding of BNT411 was similar across all tested species and was 64% for human plasma proteins.

In vitro studies on induction/inhibition of drug-metabolizing enzymes did not indicate potential interactions based on the low systemic exposure levels calculated for the proposed clinical dose levels. A study with human liver microsomes and recombinant CYP enzymes revealed that BNT411 was predominantly metabolized by CYP3A4 and CYP3A5.

Toxicology

Toxicological studies included single-dose toxicity in mice, rats, dogs and cynomolgus monkeys; 29-day (once weekly) repeat-dose toxicity studies in rat and cynomolgus; mutagenicity (Ames test); and an *in vitro* phototoxicity test.

Repeat-dose studies in rat and cynomolgus demonstrated effects of BNT411 that are consistent with the pharmacology of the compound. At high toxicological doses observations included changes to the eye in cynomolgus monkeys due to immune cell infiltration and in both species exaggerated pharmacological effects in spleen and lymph nodes. Overall, critical findings were made at toxicological dose levels in vast (200 – 1,000-fold) excess of the highest planned clinical dose.

2.2 Trial Rationale

2.2.1 Rationale for Testing BNT411 in Combination with Chemotherapy and Checkpoint Inhibitors

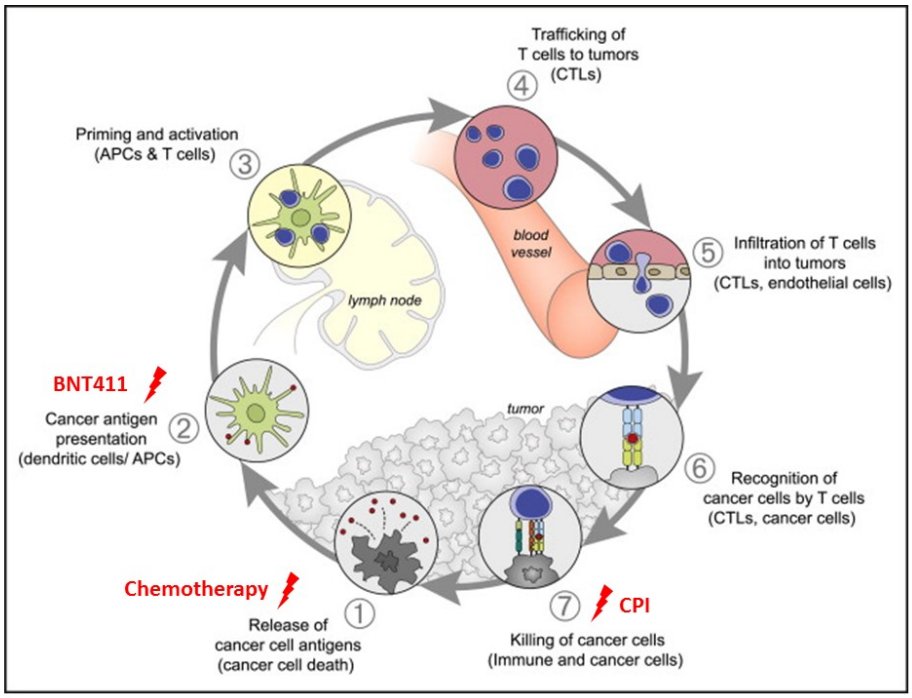
There is a strong unmet medical need to develop new efficacious therapies for patients with advanced malignancies whose disease no longer responds to standard therapy, but also for patients where current standard of care results in only marginal long-term disease-free survival (e.g., ES-SCLC).

It is meanwhile accepted that a dysfunction of the immune system contributes to cancer disease. This paradigm, reflected by the so called “cancer immunity cycle” Figure 2-2 (Chen and Mellman, 2013), stipulates that tumor cell breakdown and release of tumor antigens results in priming of antigen-specific cytotoxic T cells but an efficient immune response to counteract the tumor is prevented by various physiological immune suppressive mechanisms.

The compounds used in the standard of care first-line treatment of ES-SCLC do act in this regard. Chemotherapy (carboplatin, etoposide) induces immunogenic cell death (ICD) (Emens and Middleton, 2015), which is a prerequisite for inducing T cell specificities against a broad diversity of tumor antigens. This involves the release of tumor antigens and the emission of danger-associated molecular patterns (DAMPs) in the tumor microenvironment (TME). The anti-PDL1 antibody atezolizumab counteracts immunosuppressive signals produced by cancer cells or cells in the TME), directed specifically against PD1-positive and thus robustly primed effectors. As SCLC is a high mutational burden cancer, these mechanisms of efficient immune response are further promoted (George et al, 2015; Goodman et al, 2017; Peifer et al, 2012; Rudin et al, 2012). Finally, TLR7 agonists, which have immune effects synergizing with and complementing the ones of chemotherapy and anti-PDL1 blockade, can help to tip the balance towards robust cancer immunity.

In this regard, TLR7 signaling induced by BNT411 is expected to contribute on various levels, e.g. by improving the priming of antigen-specific T cells in the lymph node, and by recruiting additional cellular effectors such as NK cells and by reshaping the TME.

Figure 2-2: Modified Cancer Immunity Cycle from Chen & Mellman, Immunity, 2013.



2.3 Benefit/Risk Assessment

2.3.1 Risk Assessment

As this trial is the first to test BNT411 in humans, all precautions indicated when testing a new systemically active compound in a FIH trial will be taken, including choosing a high medical need patient population. The trial will be conducted at centers experienced in FIH trials, and trial-related procedures will only be performed by qualified physicians and trained nurses. The sponsor also prepares and trains the investigator to closely monitor, dose-delay, dose-reduce or withdraw patients based on adverse events that may occur with BNT411. Furthermore, there will be regular safety data review by the sponsor and the Safety Review Committee (SRC) for identification and evaluation of potential safety concerns. All patients enrolled in this trial will be monitored by qualified health care professionals who will provide care and evaluate the patient's response to the trial drug, in terms of its safety and efficacy.

Beyond that, the sponsor went through a diligent exercise to identify and assess risks specific to BNT411 based on (i) the preclinical data package obtained for BNT411 and its predecessor compound SC1; and (ii) non-clinical and (iii) clinical literature data on other TLR7 agonists. This group of compounds encompasses, for example, 852A, resiquimod, and imiquimod, which are based on the same imidazoquinoline core structure as BNT411. 852A is structurally most closely related to BNT411 and has been extensively tested as an intravenously administered TLR7 agonist in several clinical trials (Astry et al, 2008; Dudek et al, 2007; Dummer et al, 2008; Geller et al, 2010; Harrison et al, 2007; Spaner et al, 2010; Weigel et al, 2012).

One risk, based on preclinical data with BNT411, is ocular toxicity. In one non-clinical, single-dose toxicity study (Study SD_17_001) in monkeys, at doses 200-fold higher than the highest dose to be administered in humans (allometrically scaled to the HED), ocular toxicity occurred

due to infiltration of immune cells into the eyes. For TLR8 agonist motolimod (VTX-2337) ocular inflammation in monkeys has also been described at doses (allometrically scaled to the HED) approximately 170-fold higher than the highest dose applied to humans in a clinical phase 1 study, and ocular AEs were not observed (Northfelt et al. 2015). Taking into account this broad safety window, the risk of BNT411-induced ocular toxicity is considered low.

2.3.1.1 Important identified risks

Cytokine release syndrome

Cytokine release syndrome (CRS) has been recognized as an identified risk for BNT411. It is classified as an important identified risk. CRS is associated with the intended MoA of BNT411 to modulate the immune system via a TLR7-signaling mediated release of a distinct type 1 IFN dominated spectrum of cytokines. The compound has been specifically developed not to activate a broad range of pyrogenic cytokines in the biologically active dose range.

In monkeys (studies SD_18_006 and SD_18_007), slight increase in body temperature was observed at doses (allometrically scaled to the human equivalent dose) corresponding to the two highest dose levels that will be applied in humans. In rats (studies SD_18_003 and SD_18_004), decreased motility and increased respiratory parameters were detected at doses (allometrically scaled to the human equivalent dose) which are 100-fold higher than the highest dose which will be administered in humans.

The sponsor expects elevation of serum levels of indicator cytokines in the majority of patients at biologically active dose levels of BNT411. Systemic effects caused by those cytokines are pharmacodynamic surrogates. Correlating with such laboratory changes, adverse events (AEs) such as mild-to-moderate, transient and manageable flu-like symptoms (e.g. arthralgia, body temperature increased, chills, dehydration, dizziness, fatigue, feeling cold, headache, hot flush, hyperhidrosis, influenza-like illness, myalgia, nausea, pyrexia, tachycardia, and vomiting) are expected to occur. For these clinical manifestations of cytokine elevation, the trial protocol implements management with analgesics or anti-pyretics at recommended commonly used doses.

As BNT411 was developed to release cytokines such as IFNα at an EC50 range lower than the EC50 required for release of cytokines such as TNFα, IL-6, and IL-10, the sponsor gauges the risk of higher grade clinically relevant and unmanageable manifestations of elevated cytokines as low and this protocol addresses the probability of such risks with a risk management plan. Upon stimulation, it has been described for TLR7 agonists that lymphocytes egress to the periphery and return within 24 to 48 hours. This sequestration effect has been attributed to the secretion of IFNα (Perkins et al, 2012) and may present as transient lymphopenia due to redistribution rather than cytotoxicity. Frequent laboratory monitoring is planned to observe this expected effect.

2.3.1.2 Important potential risks

Currently, no important potential risks have been identified for BNT411.

2.3.2 Potential Risks Associated with BNT411 in Combination with Atezolizumab, Carboplatin, and Etoposide

As this is the first trial in humans, the risk of synergistic and/or potentiating toxicities when BNT411 is combined with atezolizumab, carboplatin and etoposide cannot be completely ruled

out. Therefore, the trial seeks to mitigate this risk by implementing a bifurcated trial design to start combination dose escalation. The combination dose escalation will only occur after reasonable data for BNT411 are generated in monotherapy dose escalation. Additionally, the dose level to start the combination dose level and at any given time thereafter will always be one dose level lower than in monotherapy dose escalation. This should mitigate such a potential risk for unknown synergistic and/or potentiating toxicities. Supporting data from preclinical studies of BNT411 in combination with cytotoxic agents also do not suggest any other risks seen in BNT411 monotherapy. The sponsor is also currently performing further preclinical experiments of BNT411 in combination with more chemotherapy agents and anti-PD-L1 antibody.

No indications of organ-specific autoimmunity have been identified for BNT411, or for any other imidazoquinoline compounds. In this trial (Part 1B, Part 2) BNT411 is combined with atezolizumab, which is known in line with its mode of action to be associated with organ-specific autoimmunity and consequently with immune-related adverse events (irAEs). Therefore, irAEs and their management are specifically addressed by this trial protocol, even though the risk of them induced by single agent BNT411 is considered as very low.

In conclusion, the non-clinical and literature data collected so far do not show any potential unacceptable toxicities that cannot be mitigated or managed in the clinical setting. The anticipated benefits of BNT411 in patient populations with high unmet medical needs outweigh the potential risks with the compound.

2.3.3 Benefit Assessment

BNT411 is expected to be beneficial even when used as a monotherapy anticancer agent as shown by preclinical data. The TLR7 agonist could potentially invigorate a systemic immune reaction to confer antitumor immune response. In monotherapy dose escalation, patients have exhausted all available standard-of-care therapies and those patients could potentially benefit from the use of BNT411 monotherapy as the last alternative given the current preclinical pharmacological data generated. There is still a high unmet medical need in patients with advanced or metastatic solid tumors and it is planned to evaluate BNT411 in various suitable tumor indications and settings.

2.3.4 Potential Benefits Associated with BNT411 in Combination with Atezolizumab, Carboplatin and Etoposide

BNT411 is expected to mount tumor-targeted, integrated innate and adaptive immune reactions in combination with cytotoxic therapies and PD1/PDL1 blockade in particular in settings with large tumor load.

The focus of development on ES-SCLC is justified based on its poor prognosis even in the early setting. In IMPower133, atezolizumab in combination with chemotherapy prolonged the median overall survival by 2 months and PFS by 0.9 month, meaning that the medical need is still very high. ES-SCLC is an ideal setting for BNT411 because there is extensive disease and it is highly sensitive to the standard of care, thereby providing an efficient tumor cell death and high -volume release of tumor antigens. As SCLC is a high mutational load tumor type it is expected that it is a rich source for neo-epitopes which would be adjuvanticized by BNT411. Therefore, BNT411 is postulated to enhance the chemo-immunotherapy backbone with atezolizumab, carboplatin and etoposide in ES-SCLC. It could potentially prolong a durable immune response

in a low-tumor-burden environment that should benefit the patients in terms of longer overall survival. Further potential benefits and rationale for the combination are described in Section 2.2.1.

2.3.5 Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimize risk to patients participating in this trial, the potential risks identified in association with BNT411 are justified by the anticipated benefits that may be afforded to patients with advanced or metastatic solid tumors.

3 Objectives and Endpoints

Objectives and related endpoints are described in Table 3-1 below.

Table 3-1: Objectives and Endpoints

OBJECTIVES	ENDPOINTS
Primary	
• For Parts 1 and 2: Assess safety profile	• Occurrence of DLTs within a patient during the DLT evaluation period • Occurrence of 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	• MTD defined as the highest tolerated dose • RP2D based on integrated evaluation of safety, tolerability, clinical benefit, PK, and pharmacodynamic data, for all dose levels tested
Secondary	
• For Parts 1 and 2: Establish PK profile	• PK parameters (AUC, CL and V_D, C_{max}, T_{max}, C_{trough}, and $T_{1/2}$)
• For Part 2: Evaluate anti-tumor activity according to RECIST 1.1	• ORR defined as the proportion of patients in whom a CR or PR is observed as best overall response. • DCR defined as the proportion of patients in whom a CR or PR or SD (assessed at least 6 weeks after first dose) is observed as best overall 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.

OBJECTIVES	ENDPOINTS
Exploratory	
• For Part 2: Evaluate anti-tumor activity according to iRECIST	• iORR defined as the proportion of patients in whom a iCR or iPR is observed as best overall response. • iDCR defined as the proportion of patients in whom a iCR or iPR or iSD (assessed at least 6 weeks after first dose) is observed as best overall response. • iDOR defined as the time from first objective response (iCR or iPR) to the date of the first occurrence of objective tumor progression (iCPD) or death from any cause, whichever occurs first.
• For Part 2: Evaluate preliminary efficacy	• PFS defined as the time from first dose of BNT411 to first occurrence of objective tumor progression (per RECIST 1.1), or death from any cause, whichever occurs first. • 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 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, immune RECIST; MTD, maximal tolerated dose; (i)ORR, (immune) objective response rate; OS, overall survival; PBMCs, peripheral blood mononuclear cells; PFS, progression-free survival; PK, pharmacokinetic; (i)PR, (immune) partial response; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended Phase 2 dose; (i)SD, (immune) stable disease; $T_{1/2}$, terminal half-life; TEAEs, treatment emergent AEs; T_{max}, time to C_{max}; VD, volume of distribution.

4 Trial Design

4.1 Overall Design

This is an open-label, multicenter Phase 1/2a dose escalation, safety, PK and pharmacodynamic trial of BNT411 with expansion cohorts in a mixed population of patients with solid tumors. The trial consists of three parts:

- **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.

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 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 considered to be the anticipated minimally efficacious dose. Atezolizumab, carboplatin and etoposide will be administered at fixed doses approved for the indication of ES-SCLC.

In case the MTD for monotherapy is identified prior to dose level 5, the bifurcation will start one dose level below the 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, pharmacodynamics and preliminary efficacy data generated.

The dose level of BNT411 in Part 1B at any given time will always be one dose level below that in Part 1A. This approach will allow for rapid and safe triggering of the combination dose escalation. This will lead to the timely optimization of the combination schedule that will be taken to the Phase 2 trial. At the same time, patient safety is safeguarded by generating enough monotherapy data before bifurcation, and clear rules for parallel dose escalations are outlined.

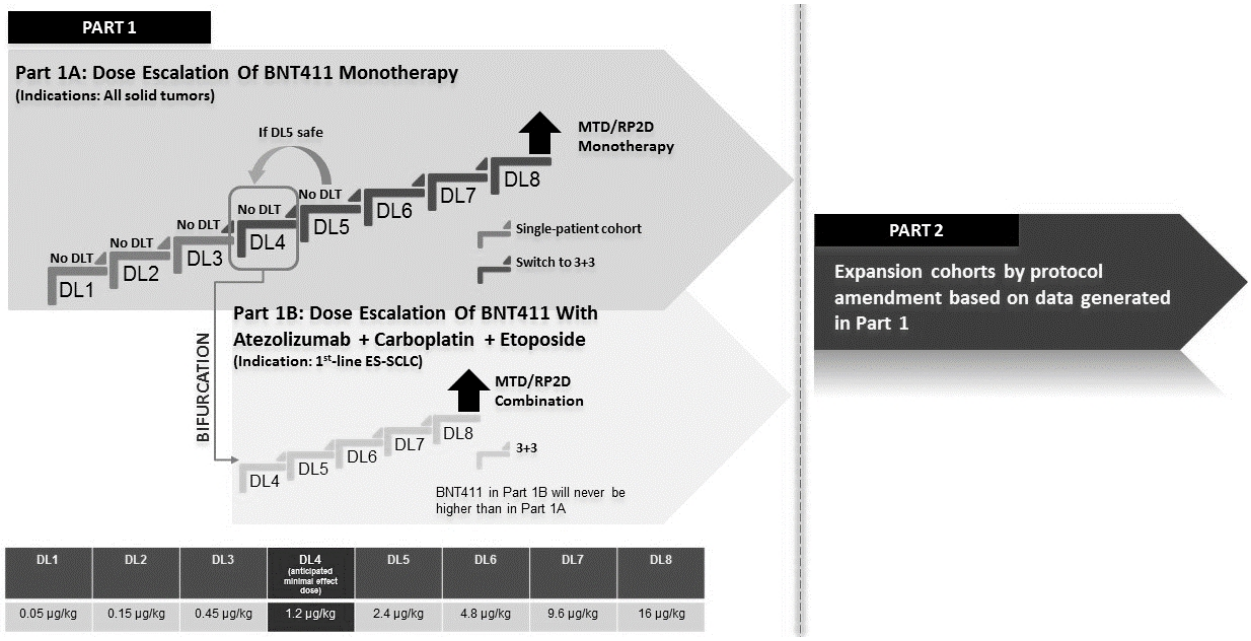
In Part 2, once a dose level is deemed safe and endorsed by the SRC, additional patients can be included at a given dose level of either monotherapy or combination in order to explore, for example, early efficacy in other indications and/or pharmacodynamic signals. Furthermore, different doses and schedules 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 protocol amendment.

In Parts 1A and 1B, patients will receive one infusion of BNT411 every week in a 3-week cycle for the first 4 cycles. In the following cycles thereafter, BNT411 will be administered every 3 weeks. In Part 1B of Cycle 5 onwards, instead of receiving BNT411 on Day 1, patients will receive the BNT411 infusion on Day 2 of each cycle. Treatment will continue until protocol-defined treatment discontinuation criteria are met (refer to Section 7.1).

Efficacy will be assessed by on-treatment imaging 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 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. The RECIST 1.1 criteria will be used for secondary endpoint response evaluation including PFS (Eisenhauer et al, 2009); iRECIST will be used for exploratory endpoint response evaluation (Seymour et al, 2017). All images obtained must be submitted to the central imaging vendor. The design of the trial is shown in Figure 4-1.

Figure 4-1: Overall Trial Design



4.1.1 Dose Escalation (Part 1A and 1B)

4.1.1.1 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 3 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 Section 9.6. The DLT period is defined as one cycle (i.e. 21 days).

During the 3+3 phase, at every dose level to be tested, staggered enrollment will be employed as described below. In each dose level cohort, the 3 patients will be dosed successively with a safety monitoring interval of at least 48 hours between the intravenous administration of BNT411 in the first and the second patient, and between the second and the third patient. The safety monitoring period is reduced to at least 24 hours when expanding a dose level which has already been declared safe.

Hospitalization is required for the first 24 hours after the first BNT411 administration in Cycle 1 for clinical observation and PK sampling. Prolongation of the hospitalization beyond 24 hours may be performed at the investigator's discretion if deemed necessary based on potential risks related to the trial treatment and clinical status of the patient. For the assessments of each cohort, the dose limiting toxicities 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 following dose escalation table (Table 4-1).

Table 4-1: 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 6 evaluable patients or 2 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 Table 4-2.

Table 4-2: 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.

Based on the nonclinical toxicology profile, which does not suggest a steep dose- or exposure-response curve and showed no severe toxicity findings, an initial dose tripling is proposed. Subsequently, standard dose doubling is proposed starting from dose level 4 in line with the FDA Guidance for Industry S9 Nonclinical Evaluation for Anticancer Pharmaceuticals. Based on nonclinical data, dose level 4 is the anticipated minimal efficacious dose. Furthermore, the sponsor proposes seven optional, intermediate dose levels at 0.075, 0.225, 0.9, 1.8, 3.6, 7.2 and 12.8 µg/kg.

To be eligible for DLT assessment, patients should receive all three infusions of BNT411 during Cycle 1 (DLT assessment period). Patients who will not be able to fulfil the criteria for the DLT assessment will be replaced and this only applies to patients who do not experience a DLT. As long as patients do not experience a DLT, patients who have been replaced can continue with BNT411 treatment and follow the same trial procedures until unacceptable toxicity, documented disease progression, and/or the onset of a new anti-cancer therapy (palliative radiotherapy of, for example, painful bone metastases not defined as target lesions will be allowed).

After completion of the DLT period for each cohort, the SRC will review the data from the DLT period – including but not limited to all relevant safety and clinical data – to propose a dose level for the next cohort of patients; PK and pharmacodynamics data, if available, will also be taken into consideration.

The sponsor can backfill a certain dose level cohort to explore and generate more safety, PK, pharmacodynamics, and anti-tumor data up to a total of 14 patients in a given cohort. Staggering would not be implemented as backfilling would occur once the dose level is declared safe by the SRC.

4.1.1.2 MTD and RP2D Definitions

The MTD is defined as the highest tolerated dose.

The RP2D will be determined based on integrated evaluation of safety, tolerability, clinical benefit, PK and pharmacodynamics data, for all dose levels tested. The RP2D will be determined based on aggregate data including, but not limited to, the following rules and considerations:

1. The RP2D will not exceed the MTD.
2. Consideration will be given to toxicities other than DLTs, specifically adverse events (AEs) assessed as related to BNT411 treatment, the nature and frequency of toxicities, and the emergence of any specific category of toxicities.
3. Evidence of clinical activity, as available.
4. Available pharmacodynamics data.

If the RP2D cannot be distinguished using the criteria above, cohort expansion for optimized RP2D determination may take place at up to two dose levels to obtain data for up to six additional patients per dose level. Selection of RP2D will then be based on this larger dataset. If serious related toxicities are observed in later cycles beyond Cycle 1, a reduction of the MTD and/or adjustment of RP2D may be considered. This determination will be made by dose-expansion cohort (DEC) and endorsed by the SRC.

4.1.1.3 Dose Escalation in Part 1B

The rules and details on the bifurcated design are outlined in Section 4.1.

The dose escalation in Part 1B follows the classical 3+3 design as described above in Section 4.1.1.1. However, in the case that any dose level in Part 1B is declared as MTD, dosing in Part 1B should stop. The monotherapy dose escalation in Part 1A can proceed independently of Part 1B until MTD and/or RP2D of BNT411 monotherapy are established. Refer to Section 6.6.5 for safety stopping criteria.

After 4 cycles of treatment, PCI is permitted as per local guidelines and will be reported on the electronic Case Report Form (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. Thoracic radiation with curative intent or the intent to eliminate residual disease is not permitted. Palliative thoracic radiation and other palliative radiotherapies are allowed.

4.1.2 Expansion Phase (Part 2)

As described in Section 4.1, expansion cohorts can be implemented by protocol 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. All decisions for expansion should be endorsed by the SRC.

4.1.3 Adaptive Trial Design Elements

- In order to account for potential interpatient variability with an immunotherapy compound such as a TLR7 agonist, a recommended Phase 2 dose range (RP2DR) instead

of a recommended dose for BNT411 can be implemented based on data generated in dose escalation. The dose range will not exceed the MTD established in the trial and will not exceed more than 3 dose levels.

- Bifurcation is planned to start when Part 1A monotherapy dose level 5 (2.4 µg/kg) evaluation is completed and considered 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 considered to be the anticipated minimally efficacious dose. If minimal pharmacodynamics activity is not reached when monotherapy dose level 5 is completed, bifurcation to Part 1B may happen at a higher dose level. Bifurcation can also start at a lower dose level than dose level 5, if pharmacodynamics activity is seen earlier. However, the following rule always applies: the dose level of BNT411 in Part 1B at any given time will always be one dose level below that in Part 1A. Decision to bifurcate at any given dose level will be discussed and agreed by the SRC.
- Addition or removal of PK time points depending on emerging data on BNT411 can be performed. Samples at various time points post-injection may be added based on emerging data from this trial. If the PK data are uninformative, one or more time points may be removed.
- The sponsor can backfill a certain dose level cohort to explore and generate more safety, PK, pharmacodynamics, and anti-tumor data up to a total of 14 patients in a given cohort. Staggering would not be implemented as backfilling would occur once the dose level is declared safe by the SRC.

4.2 Planned Number of Patients

- Between 6 to 60 DLT evaluable patients are planned to be enrolled in Part 1A.
- Between 6 to 30 DLT evaluable patients are planned to be enrolled in Part 1B.
- For the dose escalation (Parts 1A and 1B), approximately 12 sites will be opened in North America and Europe.
- For possible expansion, approximately 25 to 35 sites will be opened in North America, Europe and potentially the rest of the World.

4.2.1 Replacement of Patients

Patients will be replaced in the following scenarios:

- Patient is not evaluable for DLTs (only applies to patients who do not experience a DLT).
- Patient was enrolled in the trial but did not receive a dose of BNT411.

4.3 Trial Design Rationale

The first part of this trial is a FIH, open-label, dose-escalation trial studying BNT411 monotherapy in patients with different types of malignant solid tumors in order to determine the safety profile of BNT411. The second part aims to determine further the safety profile of BNT411 in combination with atezolizumab, carboplatin and etoposide in patients with ES-SCLC. The third part is the expansion phase to explore BNT411 further as a monotherapy or in combination with atezolizumab, carboplatin and etoposide in select tumor indications. Different treatment schedules and other indications may also be explored in Part 2.

In order to address the trial objectives in this FIH trial, a dose-escalation using an accelerated titration (i.e. single-patient cohort) followed by a 3+3 design was selected. The first three dose levels are assumed to induce no or minimal biological effects in humans and are included to safeguard patient's safety while introducing a novel compound in humans. 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, the single-patient cohorts will be expanded to 3+3-patient cohorts. The single-patient cohorts will accelerate safely to start dosing patients with doses expected to induce minimal biological effects with BNT411. The classical 3+3 design is appropriate for a FIH dose-escalation trial in oncology; however, this trial will consider all data generated to decide on the RP2D.

The safety, PK, pharmacodynamics, and clinical efficacy data combined provide both more flexibility and better accuracy of the estimated RP2D while safeguarding the patient's safety. The MoA of BNT411, a TLR7 agonist stimulating the innate immune system, which further activates the adaptive immune system, allows the trial to be driven by pharmacodynamics. Selected biomarkers, such as type-1 interferons and other cytokines can potentially be used to guide the dose escalation in both Part 1A and Part 1B.

4.3.1 Rationale for Bifurcated Design

One cornerstone of the development rationale is to have a setting with fast and high volume release of tumor antigens from a high-mutational load tumor (see Section 2.1.4.2 and Section 2.2 for details). This is to be achieved by combining with an already efficient but not durable cytotoxic treatment. Therefore, rapid triggering of combination testing is desired. One of the common approaches to integrate the combination assessment in clinical development is by using a bifurcated design, which is pursued in this trial.

In Part 1A, monotherapy dose escalation will be executed through several dose levels and if safety is acceptable and no DLTs are identified, the trial will "bifurcate" to two distinct paths for subsequent escalation. This will allow safety, tolerability, PK and pharmacodynamics of BNT411 in combination with the approved therapy of atezolizumab, carboplatin and etoposide to be assessed and optimized at an early stage. This approach will potentially accelerate further clinical development for early access in areas of high unmet medical need.

4.3.2 Rationale for Body Weight-Based Dosing

Thus far, the development of most of the intravenously applied drugs employs either body-weight-based or body-surface-area-based dosing in the FIH setting. Once clinical PK data are generated, population PK modeling is applied to explore the effect of body weight (BW) and body surface area (BSA) on variability and the dosing is adapted, where applicable. The development of BNT411 follows the same paradigm.

Non-clinical experiments with BNT411 in various animal species (mouse, rat, cynomolgus monkey, dog) have yielded PK data to support BW-based dosing as they have shown similar plasma concentrations and exposure to BNT411 within the respective species. Simulation of human PK parameters based on these non-clinical PK data supports this observation. Therefore, BW-based dosing will be applied in the trial in order to ensure similar plasma concentration (exposure) within dosing cohorts. A cap on dosing for patients weighing 120 kg and more will be implemented in the proposed clinical trial.

4.4 Dose and Schedule Rationale

Administration of TLR7 agonists results in the activation of pDCs followed by their transient depletion. Consequently, the pool of excitable pDCs has to be replenished by expanding and maturing precursor cells from the bone marrow (Markov et al, 2016), a process which takes about 7 days (Bourquin et al, 2011; Tsitoura et al, 2015). It has been described for other TLR7 agonists that this may result in tachyphylaxis, meaning that within this time period, additional administrations will not result in further secretion of IFNα (Bourquin et al, 2011; Tsitoura et al, 2015). To avoid this mechanism and yet ensure frequent stimulation of the immune system, BNT411 will be administered once weekly in the first 4 cycles. These 4 cycles are considered to induce a sufficient immune response. Consequently, BNT411 is applied every 3 weeks as a maintenance therapy after the first 4 cycles instead of every week.

BNT411 will be administered as a 30-minute infusion in the clinic. Preclinical experiments revealed acute adverse effects at lower doses when administered as bolus injection but not as infusion, while pharmacodynamic parameters remained comparable, irrespectively of the duration of compound administration.

The BNT411 starting dose of 0.05 µg/kg is calculated based on a minimally anticipated biologic effect level (MABEL) approach with an additional safety factor of 25:

- Upon BNT411 exposure, IFNα-secretion is the earliest detectable pharmacodynamics marker in human whole blood preparations.
- 4 nM is the minimal effective concentration (MEC) of BNT411 needed to induce IFNα in this *in vitro* setting (Studies R-19-0027 and R-19-0028), which equals approximately a human plasma C_{max} of 2 ng/mL.
- To reach this target plasma concentration, an intravenously applied dose of 1.25 µg/kg is required (based on human pharmacokinetic modeling with animal data; Study BNSM2018002). This dose equals approximately dose level 4 (1.2 µg/kg).
- A safety factor of 25 is applied, resulting in the proposed human starting dose of 0.05 µg/kg.

Based on the nonclinical toxicological profile, which does not indicate a steep dose- or exposure-response curve and does not show any severe toxicity findings, an initial dose tripling for the accelerated titration design in the dose escalation phase Part 1A is suggested. Following this, standard dose doubling is suggested starting from dose level 4 in line with the FDA Guidance for Industry S9 Nonclinical Evaluation for Anticancer Pharmaceuticals. Based on nonclinical data and as described in the MABEL approach, dose level 4 (1.2 µg/kg) is the anticipated minimal efficacious dose.

Information relating to COVID-19 vaccinations including a risk-benefit assessment and guidance for vaccination during this clinical trial is provided in Sections 10.8 and 10.9.

More details on the dose and schedule rationale can be found in the Investigator's Brochure.

4.5 End of Trial Definition

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.

5 Trial Population

5.1 Inclusion Criteria

Each patient who meets all of the following criteria is eligible to enroll in the trial.

For Part 1A:

1. Histologically confirmed solid tumor (cytology is allowed for NSCLC, SCLC and pancreatic cancer) that is metastatic or unresectable and for which there is no available standard therapy likely to confer clinical benefit, or patients who are not candidates for such available therapy.

For Part 1B:

2. Histologically or cytologically confirmed ES-SCLC (per the Veterans Administration Lung Study Group [VALG] staging system) who received no prior chemotherapy for extensive stage disease.
3. Those treated with prior chemo/radiotherapy with curative intent for LS-SCLC should be treatment-free for at least 6 months since last chemo/radiotherapy.
4. No interstitial lung disease or active, non-infectious pneumonitis.

For Both Part 1A and Part 1B

5. Male and female ≥18 years of age.
6. Must sign an informed consent form (ICF) indicating that he or she understands the purpose of and procedures required for the trial and are willing to participate in the trial prior to any trial related assessments or procedures.
7. ECOG performance status of 0 to 1.
8. Measurable disease according to RECIST 1.1.
9. Albumin level at screening ≥30 g/L.
10. Adequate coagulation function at Screening as determined by:
    a. International normalized ratio (INR) or prothrombin time ≤1.5 x upper limit normal (ULN; unless on therapeutic anticoagulants with values within therapeutic window),
    b. Activated partial thromboplastin time (aPTT) ≤1.5 x ULN (unless on therapeutic anticoagulants with values within therapeutic window).
11. Adequate hematologic function at Screening as determined by:
    a. White blood count (WBC) ≥3 x 10^9/L,
    b. Absolute neutrophil count (ANC) ≥1.5 x 10^9/L (patient may not use granulocyte-colony stimulating factor (G-CSF) or granulocyte-macrophage colony stimulating factor (GM-CSF) to achieve these WBC and ANC levels),

c. Platelet count ≥100 x 10^9/L,

d. Hemoglobin (Hgb) ≥9.0 g/dL.

12. Adequate hepatic function at Screening as determined by:

a. Total bilirubin ≤1.5 mg/dL (or ≤2.0 mg/dL for patients with known Gilbert's syndrome),

b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 x ULN; or ≤5 x ULN in patients with metastatic liver disease.

13. Adequate renal function at Screening as determined by:

a. Glomerular filtration rate (GFR) ≥60 mL/min/1.73 m²– e.g. according to the abbreviated Modification of Diet in Renal Disease (MDRD) equation:

$$GFR = 186 \times (SCr^{-1.154}) \times (age^{-0.203})$$

(where SCr, the serum creatinine level, is expressed in mg/dL; multiplied by 0.742 if the patient is female; multiplied by 1.212, if the patient is African-American (Levey et al, 1999).

14. Able to attend trial visits as required by the protocol.

15. Women of childbearing potential (WOCBP) must have a negative serum (beta-human chorionic gonadotropin [beta-hCG]) test/value at Screening. Patients who are postmenopausal or permanently sterilized as defined in Section 10.4 can be considered as not having reproductive potential. Further guidance on contraceptive measures for female patients can be found in Section 10.4.

16. WOCBP must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the entire trial, until 6 months after last BNT411 treatment.

17. A man who is sexually active with a woman of childbearing potential and has not had a vasectomy must agree to use a barrier method of birth control, e.g. either condom with spermicidal foam/gel/film/cream/suppository or partner with occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository, and all men must also not donate sperm during the trial and for 6 months after receiving the last dose of BNT411 (refer Section 10.4 for further recommendations).

18. All patients must provide an FFPE (Formalin Fixed Paraffin Embedded) from the latest available archival tumor tissue. If such tissue cannot be provided, the sponsor's approval of enrollment is needed.

5.2 Exclusion Criteria

A patient who meets any of the following criteria will be excluded from trial participation.

Prior and Concomitant Therapy

1. Has received prior systemic therapy with a TLR7 agonist.
2. Has been receiving: radiotherapy, chemotherapy, or molecularly-targeted agents or tyrosine kinase inhibitors within 2 weeks or 5 half-lives (whichever is longer) of the start of trial treatment; immunotherapy/monoclonal antibodies within 3 weeks of the start of trial

treatment; any live vaccine within 4 weeks of the start of trial treatment; nitrosoureas, antibody-drug conjugates, or radioactive isotopes within 6 weeks of the start of trial treatment.

3. Receives concurrent systemic (oral or intravenous) steroid therapy >10 mg prednisone daily or its equivalent for an underlying condition.
4. Receives concurrent strong inhibitors or inducers of the cytochrome P450 enzymes.
5. Has had major surgery within the 4 weeks before the first dose of BNT411.
6. Has ongoing or active infection requiring intravenous treatment with anti-infective therapy that has been administered less than two weeks prior to first dose of trial treatment.
7. Has side effects of any prior therapy or procedures for any medical condition not recovered to NCI CTCAE v.5 Grade ≤1.

Notes: peripheral neuropathy Grade ≤2 is allowed; alopecia of any grade is allowed.

Medical Conditions

8. Current evidence of new or growing brain or leptomeningeal metastases during screening. Patients with known brain or leptomeningeal metastases may be eligible if they:
   a. had radiotherapy, surgery or stereotactic surgery for the brain or leptomeningeal metastases,
   b. have no neurological symptoms (excluding Grade ≤2 neuropathy),
   c. have stable brain or leptomeningeal disease on the CT or MRI scan within 4 weeks before signing the informed consent,
   d. are not undergoing acute corticosteroid therapy or steroid taper.

   Notes: Subjects with central nervous system symptoms should undergo a CT scan or Magnetic Resonance Imaging (MRI) of the brain to exclude new or progressive brain metastases. Spinal bone metastases are allowed, unless imminent fracture with cord compression is anticipated.
9. Has history of seizures other than isolated febrile seizure in childhood; has a history of a cerebrovascular accident or transient ischemic attack less than 6 months ago.
10. Has effusions (pleural, pericardial, or ascites) requiring drainage.
11. Has eye pathology likely to confound observation of potential ocular AEs (refer to Ophthalmologic Manual).
12. Has a fever ≥38°C within 3 days before signing the ICF.
13. Has a history of autoimmune disease active or past including but not limited to inflammatory bowel disease, systemic lupus erythematosus (SLE), ankylosing spondylitis, scleroderma, or multiple sclerosis. Has any active immunologic disorder requiring immunosuppression with steroids or other immunosuppressive agents (e.g. azathioprine, cyclosporine A) **with the exception** of patients with isolated vitiligo, resolved childhood asthma or atopic dermatitis, controlled hypoadrenalism or hypopituitarism, and euthyroid patients with a history of Grave's disease. Patients with controlled hyperthyroidism must be

negative for thyroglobulin, thyroid peroxidase antibodies, and thyroid-stimulating immunoglobulin prior to trial drug administration.

14. Known history of seropositivity for human immunodeficiency virus (HIV) with CD4+ T-cell (CD4+) counts <350 cells/uL and with a history of acquired immunodeficiency syndrome (AIDS)-defining opportunistic infections.
15. Known history/positive serology for hepatitis B requiring active anti-viral therapy (unless immune due to vaccination or resolved natural infection or unless passive immunization due to immunoglobulin therapy). Patients with positive serology must have Hepatitis B virus (HBV) viral load below the limit of quantification.
16. Active Hepatitis C virus (HCV) infection; patients who have completed curative antiviral treatment with HCV viral load below the limit of quantification are allowed.

Notes: Country specific criteria for Germany - To confirm that a patient would be eligible, an active infection with HIV/Hepatitis B or C should be ruled out by serum blood test at screening (see Section 12.2.1).

17. Has a known hypersensitivity to a component of BNT411 drug product, or another similar compound.
18. Has another primary malignancy that has not been in remission for at least 2 years, with the exception of those with a negligible risk of metastasis or death (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer, or ductal carcinoma in situ).

Note: should be discussed with Medical Monitor in case of uncertainties.

Other Comorbidities

19. Has abnormal electrocardiograms (ECGs) that are clinically significant, such as Framingham-corrected QT interval >480 ms.
20. In the opinion of the treating investigator, has any concurrent conditions that could pose an undue medical hazard or interfere with the interpretation of the trial results; these conditions include, but are not limited to:
    a. ongoing or active infection requiring antibiotic/antiviral/antifungal therapy,
    b. concurrent congestive heart failure (New York Heart Association [NYHA] Functional Classification Class III or IV),
    c. concurrent unstable angina,
    d. concurrent cardiac arrhythmia requiring treatment (excluding asymptomatic atrial fibrillation),
    e. acute coronary syndrome within the previous 6 months,
    f. significant pulmonary disease (shortness of breath at rest or on mild exertion) for example due to concurrent severe obstructive pulmonary disease.
21. Has a cognitive, psychological or psychosocial impediment that would impair the ability of the patient to receive therapy according to the protocol or adversely affect the ability of the

patient to comply with the informed consent process, protocol, or protocol-required visits and procedures.

22. Is pregnant or breastfeeding.

Exclusion criteria added with amended protocol version 3.0 (Prior and Concomitant Therapy)

23. Has any contraindication to atezolizumab, carboplatin or etoposide as per USPI or SmPC in Part 1B.

5.3 Screen Failures

Screen failures are defined as patients who consent to participate in the clinical trial but are not subsequently entered in the trial. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, the reason(s) for screen failures, eligibility criteria, and any serious adverse event (SAE).

Patients who fail their first screening for trial eligibility may qualify for two re-screening opportunities (a total of three screenings per patient) at the investigator's discretion. Patients must re-sign the informed consent form prior to re-screening. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to the treatment may be used; such tests do not need to be repeated for screening or re-screening.

6 Trial Treatment

6.1 Trial Treatment(s) Administered

Trial treatment may refer to the following compounds, either:

1. BNT411, and/or
2. Atezolizumab, and/or
3. Carboplatin, and/or
4. Etoposide.

BNT411 is a highly potent and selective small molecule TLR7 agonist of the imidazoquinoline family being developed by BioNTech and is a new investigational agent to be tested clinically in this trial. In all countries participating in the trial, BNT411 is considered as investigational medicinal product (IMP).

Atezolizumab is a PD-L1 blocking antibody indicated for the treatment of patients with various cancer diagnoses at different stages. Atezolizumab was first approved by FDA on May 18, 2016 to treat urothelial carcinoma, and similar positive opinion by European Medicines Agency (EMA) followed in July 2017. Carboplatin is a platinum coordination compound and etoposide is a topoisomerase inhibitor. They are both cytotoxic agents used in various chemotherapy regimens to treat many cancer indications. On March 18, 2019, the FDA approved atezolizumab in combination with carboplatin and etoposide, for the first-line treatment of adult patients with ES-SCLC. Since then, it has become a standard-of-care treatment in the US. In October 2019, EMA issued similar positive opinion for the combination. 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.

Information relating to COVID-19 vaccinations including a risk-benefit assessment and guidance for vaccination during this clinical trial is provided in Sections 10.8 and 10.9.

6.1.1 BNT411

In Part 1A, BNT411 will be administered using a 100 mL intravenous infusion on Days 1, 8 and 15 of each 3-week treatment cycle (21 days) of the first 4 cycles after all required procedures and assessments have been completed. In the following cycles thereafter, BNT411 will be administered every 3 weeks on Day 1 of each 3-week treatment cycle (21 days) after all required procedures and assessments have been completed.

In Part 1B, BNT411 will be administered using a 100 mL intravenous infusion on Days 2, 8 and 15 of each 3-week treatment cycle (21 days) of the first 4 cycles after all required procedures and assessments have been completed. In the following cycles thereafter, BNT411 will be administered every 3 weeks on Day 2 of each 3-week treatment cycle (21 days) after all required procedures and assessments have been completed.

In both Part 1A and Part 1B, patients will be administered BNT411 according to dose levels outlined in Table 4-2. BNT411 will be administered as a body weight-based dosing. A cap on dosing for patients weighing 120 kg and more will be implemented in the proposed clinical trial.

In Part 1B, 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

For each dosing of BNT411 in Cycle 1, patients will remain in the treatment center and be closely monitored for immediate AEs for at least 6 hours. Hospitalization is required for the first 24 hours after the first BNT411 administration in Cycle 1 for clinical observation and PK sampling. Prolongation of the hospitalization beyond 24 hours may be performed at the investigator's discretion if deemed necessary based on potential risks related to the trial treatment and clinical status of the patient. For each subsequent dose of BNT411 in all cycles, patients will be monitored for at least 6 hours.

6.1.2 Atezolizumab, Carboplatin, and Etoposide

Atezolizumab, carboplatin, and etoposide will be used in the commercially available formulation.

For information on the formulation, packaging, and handling of atezolizumab, carboplatin, and etoposide, see the prescribing information for each drug.

The recommended dosage of atezolizumab is 1200 mg intravenously over 60 minutes every 3 weeks. If the first infusion of atezolizumab is tolerated, all subsequent infusions may be delivered over 30 minutes.

Carboplatin should be administered after completion of atezolizumab by intravenous infusion over 30−60 minutes to achieve an initial target AUC of 5 mg/mL/min (Calvert formula dosing) with standard anti-emetics per local practice guidelines. Because of their immune-suppressive effect, premedication with corticosteroids should be minimized to the extent that is clinically feasible.

On Day 1 of each cycle, etoposide (100 mg/m^2) should be administered intravenously over 60 minutes following carboplatin administration. The dose will be calculated using the Mosteller formula (BSA [m^2] = square root((height [cm] x weight [kg])/3600))

On Day 2 and Day 3 of each cycle, etoposide (100 mg/m^2) should be administered intravenously over 60 minutes. Premedication should be administered according to local standard-of-care. Because of their immune-suppressive effect, premedication with corticosteroids should be minimized to the extent that is clinically feasible.

After the DLT-observation period, if the patient tolerates the combination of atezolizumab+carboplatin+etoposide+BNT411, chemotherapy should continue for a total of 4 cycles; further chemotherapy cycles at the investigator's discretion should be discussed with the Medical Monitor. After completion of chemotherapy, atezolizumab+BNT411 combination should continue until one of the protocol-defined treatment discontinuation criteria is met (Section 7.1).

For the dosing schedule, refer to the Schedule of Activities (SoA), Section 1.3.

6.2 Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all trial treatment received and any discrepancies are reported and resolved before use of the trial treatment.
2. Only patients enrolled in the trial may receive trial treatment and only authorized site staff are allowed to supply or administer trial treatment. All trial treatment must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. Details regarding trial medication preparation are provided in the Pharmacy Manual.
4. The investigator or designee, institution, or the head of the medical institution (where applicable) is responsible for trial treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation, and final disposition records).
5. Further guidance and information for the final disposition of unused trial treatments are provided in the Pharmacy Manual.

6.3 Measures to Minimize Bias: Randomization and Blinding

Not applicable as this is a non-randomized, open-label trial.

6.4 Trial Treatment Compliance

When patients are dosed at the site, they will receive trial treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and the eCRF. The dose of trial treatment and trial patient identification will be confirmed at the time of dosing by a member of the trial site staff other than the person administering the trial treatment.

6.5 Concomitant Therapy and Procedures

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) or procedure that the patient is receiving or undergoing at the time of signing the Informed Consent Form, or receives or undergoes during the trial must be recorded along with, as applicable:

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Concomitant anti-emetics, anti-diarrheal agents, intravenous fluids, or electrolyte replacement based on clinical or laboratory assessments and blood transfusions while on treatment based on individual institutional guidelines will be allowed.

Radiotherapy should be documented in the eCRF including total dose, fractionation and location.

The prohibited medications while on trial treatment are as follows:

- Other anti-cancer therapy not included under trial treatment in a given part of the trial (e.g. Part 1A, Part 1B and Part 2).
- Other prohibited concomitant medications as listed in inclusion and exclusion criteria (Section 5.1 and Section 5.2).
- 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.
- For further guidance on prohibited and restricted medications, please refer to the IB for BNT411, and USPI or SmPCs for atezolizumab, carboplatin and etoposide.

6.5.1 Premedication

As part of its intended mode of action, BNT411 is expected to induce a discrete spectrum of cytokines. These may be associated with flu-like symptoms within the first hours after administration.

Routine premedication with analgesics or anti-pyretics such as acetaminophen/paracetamol, ibuprofen, naproxen, or aspirin at established doses and schedules can be given at the investigator's discretion and patients can be appropriately prehydrated prior to treatment.

Because of their immune-suppressive effect, premedication with corticosteroids should be minimized to the extent that is clinically feasible. The use of corticosteroids as anti-emetics or for any other purposes may be substituted with other drugs from different classes per investigator's discretion. All premedication must be reported on the concomitant medication page in the eCRF.

6.5.2 Rescue Medication

Not applicable.

6.6 Dose Modifications

Dose Limiting Toxicity

In general, a DLT for a drug or other treatment is defined as an adverse event that prevents an increase of the dose level of that treatment (for details on reporting see Section 8.7.8).

For the purpose of dose escalation, the DLT monitoring period will be 21 days. The occurrence of any of the toxicities outlined in this section will be considered a DLT, excluding toxicities clearly related to disease progression or intercurrent illness.

SAEs, non-serious (NS) 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). NCI CTCAE v.5.0 will be used to grade the intensity of AEs.

No indications of organ-specific autoimmunity have been identified for BNT411, or for any other imidazoquinoline compounds. Therefore, the risk of immune-related AEs (irAEs) with BNT411 alone is regarded as low. BNT411 will be combined with atezolizumab in Part 1B of

the dose escalation. Atezolizumab in line with its mode-of-action is associated with organ-specific autoimmunity and consequently with immune-related adverse events.

Therefore, definitions of DLT will be categorized as non-immune-related AEs and immune-related AEs (irAEs).

Other clinically significant toxicities, including a single event or multiple occurrences of the same event, may be considered as DLTs.

AEs occurring after treatment Cycle 1 may be considered DLTs upon discussion between the investigator(s) and the sponsor(s) medical monitor.

Any other toxicity assessed as related to BNT411 treatment, and which in the opinion of the trial investigator(s) and the sponsor(s) medical monitor constitutes a DLT.

Dose-escalation:

Patients experiencing a DLT (an AE fulfilling the DLT criteria within the DLT period of 21 days) should discontinue trial drug immediately. If requested by the investigator, the sponsor may allow a patient with a DLT to continue in the trial and consider a reduced dose. For this decision, a thorough benefit-risk assessment of the individual patient is required and consultation with the SRC needs to be considered.

6.6.1 Dose Limiting Toxicity for Part 1A

Non-immune-related AEs that are considered DLTs:

During the first treatment cycle, any toxicity that is of Grade 3 and that does not resolve to Grade 1 or lower within a week despite the use of medical intervention, or that is of Grade 4, but with exceptions as follows:

- The following events occurring during the DLT period ARE also considered a DLT:
  - Arrhythmia: Grade >2 newly developed arrhythmia of any kind.
  - Absolute leucocyte count $\geq 50 \times 10^9$/L sustained for 14 days.
  - Hypotension of Grade 3 that persists for >4 hours and requires hospitalization.

- The following events occurring during the DLT period ARE **NOT** considered a DLT:
  - Grade ≤3 nausea or vomiting controllable with anti-emetics within 72 hours.
  - Hypotension (systolic pressure <90 mm Hg) of Grade <3 that is of limited duration (less than 72 hours) or can be managed with hydration measures.
  - Hypotension that requires a precautionary admission for observation after Grade 3 hypotension that persists for ≤4 hours.
  - Grade 3 amylase and lipase elevations that are not accompanied by clinical signs/symptoms of pancreatitis.

Immune-related AEs that are considered DLTs:

- Any Grade 4 irAEs regardless of duration.
- Grade 3 colitis that does not downgrade to Grade ≤2 within 3 days after onset of the event despite maximal supportive care including systemic corticosteroids or downgrade to Grade ≤1 or baseline within 14 days.
- Any Grade 3 or Grade 4 non-infectious pneumonitis regardless of duration.

- Any Grade 3 irAE, excluding colitis and pneumonitis, that does not downgrade to Grade ≤2 within 3 days after onset of the event despite maximal supportive care including systemic corticosteroids or downgrade to Grade ≤1 or baseline within 14 days.
- Any Grade 2 pneumonitis that does not resolve to Grade ≤1 within 3 days of the initiation of maximal supportive care.
- Liver transaminase elevation higher than 8×ULN or total bilirubin higher than 3×ULN.
- Any other toxicity that is greater than baseline grade, is clinically significant and/or unacceptable, and is judged to be a DLT by the investigator and the sponsor.
- The definition excludes the following conditions:
  - Grade ≤4 lymphopenia which is not considered clinically significant by the investigator.
  - Grade 3 endocrinopathy that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy and the patient is asymptomatic.
  - Grade 3 inflammatory reaction attributed to a local anti-tumor response (e.g. inflammatory reaction at sites of metastatic disease, lymph nodes) that resolves to Grade ≤1 within 3 weeks.
  - Concurrent vitiligo or alopecia of any AE grade.

6.6.2 Dose Limiting Toxicity for Part 1B

Non-immune-related AEs that are considered DLTs:

During the first treatment cycle, any toxicity that is of Grade 3 and that does not resolve to Grade 1 or lower within a week despite the use of medical intervention, or that is of Grade 4, but with exceptions as follows:

- The following events occurring during the DLT period ARE also considered a DLT:
  - Arrhythmia: Grade >2 newly developed arrhythmia of any kind.
  - Absolute leucocyte count $\geq 50\times10^9$/L sustained for 14 days.
  - Hypotension of Grade 3 that persists for >4 hours and requires hospitalization.

- The following events occurring during the DLT period ARE **NOT** considered a DLT:
  - Any Grade 3 or 4 neutropenia, leucopenia, anemia and thrombocytopenia that can be solely attributed to chemotherapy compounds.
  - Grade ≤3 nausea or vomiting controllable with anti-emetics within 72 hours.
  - Hypotension (systolic pressure <90 mm Hg) of Grade <3 that is of limited duration (less than 72 hours) or can be managed with hydration measures.
  - Hypotension that requires a precautionary admission for observation after Grade 3 hypotension that persists for ≤4 hours.
  - Grade 3 amylase and lipase elevations that are not accompanied by clinical signs/symptoms of pancreatitis.

Immune-related AEs that are considered DLTs:

- Any Grade 4 irAEs regardless of duration.
- Grade 3 colitis that does not downgrade to Grade ≤2 within 3 days after onset of the event despite maximal supportive care including systemic corticosteroids or downgrade to Grade ≤1 or baseline within 14 days.
- Any Grade 3 or Grade 4 non-infectious pneumonitis regardless of duration.

- Any Grade 3 irAEs, excluding colitis and pneumonitis, that does not downgrade to Grade ≤2 within 3 days after onset of the event despite maximal supportive care including systemic corticosteroids or downgrade to Grade ≤1 or baseline within 14 days.
- Any Grade 2 pneumonitis that does not resolve to Grade ≤1 within 3 days of the initiation of maximal supportive care.
- Liver transaminase elevation higher than 8×ULN or total bilirubin higher than 3×ULN.
- Any other toxicity that is greater than baseline grade, is clinically significant and/or unacceptable, and is judged to be a DLT by the investigator and the sponsor.
- The definition excludes the following conditions:
  - Grade ≤4 lymphopenia which is not considered clinically significant by the investigator.
  - Grade 3 endocrinopathy that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy and the patient is asymptomatic.
  - Grade 3 inflammatory reaction attributed to a local anti-tumor response (e.g. inflammatory reaction at sites of metastatic disease, lymph nodes) that resolves to Grade ≤1 within 3 weeks.
  - Concurrent vitiligo or alopecia of any AE grade.

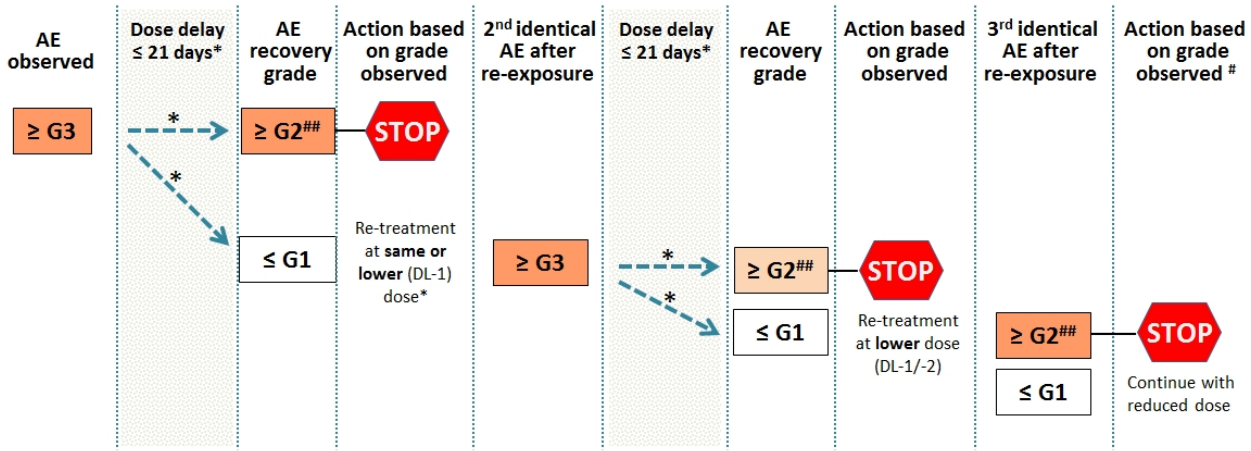
6.6.3 Dose Modification Guidance

6.6.3.1 Handling of Adverse Events Fulfilling the DLT Criteria after the DLT Period has ended in Part 1A

AEs that fulfill the DLT criteria after the DLT period has ended in the dose-escalation phase of Part 1A of the trial (i.e. from Cycle 2 Day 1 and beyond) or during the expansion phase (i.e. from Cycle 1 Day 1 and beyond) should be handled as shown in Figure 6-1.

Please Note: Patients must complete the DLT monitoring period prior to implementing the dose modification criteria outlined in this section.

Figure 6-1: Handling of adverse events fulfilling the DLT criteria after the DLT-observation period has ended – Part 1A



DL, dose level
*Dose delay: Next dose of BNT411 can maximally be delayed 21 days unless approved otherwise by the sponsor medical monitor.

No delay for recovery from Grade ≥2 allowed
Unless grade at baseline was Grade ≥2 and AE has resolved to baseline grade.

Note: Grade 4 AEs fulfilling DLT criteria will always lead to BNT411 discontinuation.

First occurrence of AE fulfilling DLT criteria Grade 3:

- As a first measure, administration of BNT411 needs to be withheld.
- Investigator must contact sponsor for thorough discussion in order to decide whether the patient should be withdrawn from BNT411 treatment or next dosing should be delayed.
- Administration of BNT411 can be delayed for up to 21 days (i.e. one cycle) unless otherwise approved by the sponsor's medical monitor. If the intensity resolves to Grade ≤1 or baseline within this period, re-treatment may be considered under the following circumstances:
    - Sponsor and investigator will discuss any safety concerns in order to decide whether the next dose of BNT411 should be administered at the same dose level or one dose level lower (DL-1). Intermediate dose levels defined in the protocol may also be considered. The sponsor may also consult the SRC.

Second occurrence of an identical AE Grade 3 after re-exposure to BNT411:

- As a first measure, administration of BNT411 needs to be withheld.
- If re-treatment leads to an identical AE with the same intensity, the next administration of BNT411 can be delayed for up to 21 days unless otherwise approved by the sponsor's medical monitor. If the intensity of the AE resolves to Grade ≤1 or baseline within this period, re-treatment may be considered under the following conditions:
    - The next dose of BNT411 should be administered at one dose level lower (DL-1 or DL-2) than the dose level causing the recurrence of the AE. Intermediate dose levels defined in the protocol may be considered.

Third occurrence of an identical AE Grade ≥2 after re-exposure to BNT411:

- As a first measure, administration of BNT411 needs to be withheld.
- If re-treatment at a lower dose leads to a third identical AE with intensity Grade ≥2, the patient must permanently discontinue trial drug. No dose delay is allowed. However, if the AE is Grade ≤1 or baseline, re-treatment may be considered under the following condition:
    - The next dose of BNT411 should be administered at the same reduced dose level (DL-1 or DL-2).

Please note:

- Re-escalation of BNT411 dose is not allowed for patients who previously have been dose-reduced.

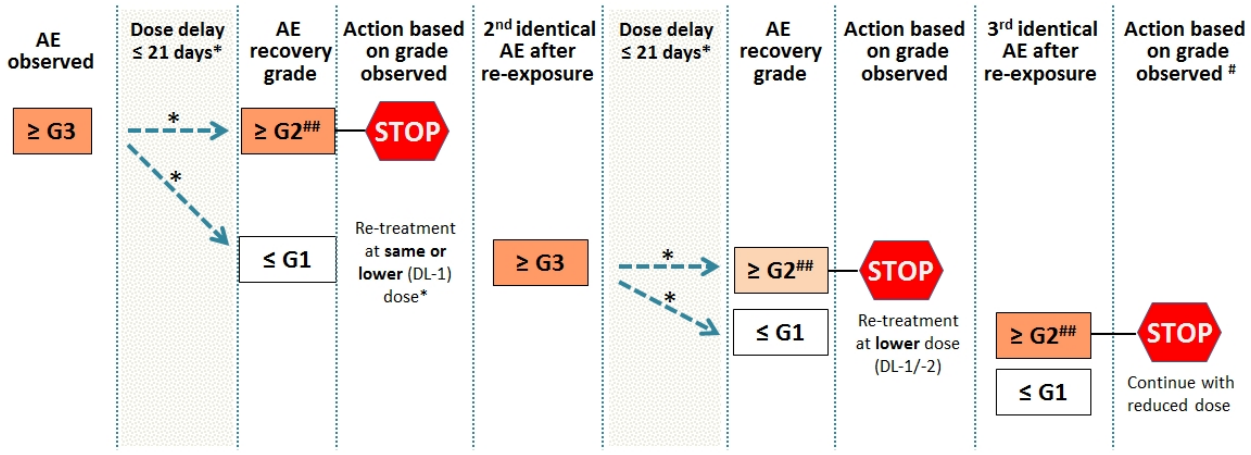
- BNT411 must be permanently discontinued if the patient experiences an AE fulfilling the DLT criteria (after the DLT period has ended for the dose escalation or during the expansion) that fails to resolve to Grade ≤1 within 21 days after the planned dosing date unless otherwise approved by the sponsor's medical monitor.
- BNT411 must be permanently discontinued if more than 2 dose reductions are required.
- BNT411 must be permanently discontinued in the case of a dose delay of more than 21 days due to toxicity possibly related to BNT411 unless otherwise approved by the sponsor's medical monitor.
- The investigators are encouraged to contact the sponsor in the case of any safety concerns that need thorough discussion and evaluation.

6.6.3.2 Handling of Adverse Events Fulfilling the DLT Criteria after the DLT Period has ended in Part 1B

AEs that fulfill the DLT criteria after the DLT period has ended in the dose-escalation phase of Part 1B of the trial (i.e. from Cycle 2 Day 1 and beyond) or during the expansion (i.e. from Cycle 1 Day 1 and beyond) should be handled as shown in Figure 6-2.

Please Note: Patients must complete the DLT monitoring period prior to implementing the dose modification criteria outlined in this section.

Figure 6-2: Handling of adverse events fulfilling the DLT criteria after the DLT-observation period has ended – Part 1B



DL, dose level
*Dose delay: Next dose of BNT411 can maximally be delayed 21 days unless approved otherwise by the sponsor medical monitor.
No delay for recovery from Grade ≥2 allowed
Unless grade at baseline was Grade ≥2 and AE has resolved to baseline grade.

Note: Grade 4 AEs fulfilling DLT criteria will always lead to BNT411 discontinuation.

First occurrence of AE fulfilling DLT criteria Grade 3:

- As a first measure, administration of BNT411 needs to be withheld.
- Investigator must contact sponsor for thorough discussion in order to decide whether the patient should be withdrawn from BNT411 treatment or next dosing should be delayed.
- Administration of BNT411 can be delayed for up to 21 days (i.e. one cycle) unless otherwise approved by the sponsor's medical monitor. If the intensity resolves to Grade ≤1 or baseline within this period, re-treatment may be considered under the following circumstances:
    - Sponsor and investigator will discuss any safety concerns in order to decide whether the next dose of BNT411 should be administered at the same dose level or one dose level lower (DL-1). Intermediate dose levels defined in the protocol may also be considered. The sponsor may also consult the SRC.

Second occurrence of an identical AE Grade 3 after re-exposure to BNT411:

- As a first measure, administration of BNT411 needs to be withheld.
- If re-treatment leads to an identical AE with the same intensity, the next administration of BNT411 can be delayed for up to 21 days unless otherwise approved by the sponsor's medical monitor. If the intensity of the AE resolves to Grade ≤1 or baseline within this period, re-treatment may be considered under the following conditions:
    - The next dose of BNT411 should be administered at one dose level lower (DL-1 or DL-2) than the dose level causing the recurrence of the AE. Intermediate dose levels defined in the protocol may be considered.

Third occurrence of an identical AE Grade ≥2 after re-exposure to BNT411:

- As a first measure, administration of BNT411 needs to be withheld.
- If re-treatment at a lower dose leads to a third identical AE with intensity Grade ≥2, the patient must permanently discontinue trial drug. No dose delay is allowed. However, if the AE is Grade ≤1 or baseline, re-treatment may be considered under the following condition:
    - Next dose of BNT411 should be administered at the same reduced dose level (DL-1 or DL-2).

Please note:

- Re-escalation of BNT411 dose is not allowed for patients who previously have been dose-reduced.
- BNT411 must be permanently discontinued if the patient experiences an AE fulfilling the DLT criteria (after the DLT period has ended for the dose escalation

or during the expansion) that fails to resolve to Grade ≤1 within 21 days after the planned dosing date unless otherwise approved by the sponsor medical monitor.

- BNT411 must be permanently discontinued if more than 2 dose reductions are required.
- BNT411 must be permanently discontinued in the case of a dose delay of more than 21 days due to toxicity possibly related to BNT411 unless otherwise approved by the sponsor's medical monitor.
- The investigators are encouraged to contact the sponsor in the case of any safety concerns that need thorough discussion and evaluation.
- If the causal relationship of AE cannot be attributed to either BNT411, atezolizumab, carboplatin and etoposide, BNT411 should be discontinued; atezolizumab, carboplatin and etoposide should be dose modified as per the US Prescribing Information or the Summary of Product Characteristics.

6.6.4 Dose Modification for Specific Adverse Events

6.6.4.1 Immune-related Adverse Events (irAEs) – For Part 1B Only

Guidance for BNT411 dose modification and management of irAEs is provided in the Table 6-1 below. For Grade 1 irAEs, trial treatment should be continued with close monitoring. Corticosteroids taper should be initiated over the course of at least 4 to 6 weeks when the irAE improves to Grade ≤1. Permanent discontinuation of trial treatment is recommended with Grade 4 toxicities with the exception of endocrinopathies that have been controlled by hormone replacement. Trial treatment should also be permanently discontinued for any Grade 3 irAE that recurs and for any life-threatening irAE. For additional guidance on the recommended management of irAEs, please refer to the *Management of Immune-Related Adverse Events in Patients Treated with Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Practice Guideline* (Brahmer et al, 2018). Furthermore, guidelines for the monitoring and management of potential cytokine release syndrome (CRS) can be found in Attachment 12.1.

Table 6-1: BNT411 Dose Modification and Management of irAEs

Immune-related AEs	Toxicity Grade (CTCAE v5.0)	Dose Modification	Guidance for Management of irAEs
Pneumonitis	Grade 1-2	1st occurrence If there is radiographic evidence of pneumonitis progression, hold treatment until there is evidence of improvement/ resolution to Grade 1 or less[1] 2nd occurrence: Permanently discontinue	Monitor for signs and symptoms of pneumonitis Evaluate for pneumonitis with radiographic imaging For Grade ≥2: Consider initiation of corticosteroid treatment (initial dose of 1-2 mg/kg prednisone or equivalent followed by taper). Corticosteroid taper should be initiated when the irAE improves to Grade ≤1
	Grade 3 or 4	Permanently discontinue	
Colitis	Grade 2	Hold treatment until resolved to baseline[1]	Monitor for signs and symptoms of colitis. Consider gastroenterology consultation and confirm diagnosis of colitis Consider administration of corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper Corticosteroid taper should be initiated when the irAE improves to Grade ≤1
	Grade 3	Refer to Sections 6.6.3.1 and 6.6.3.2	
	Grade 4	Permanently discontinue	
T1DM or Hyperglycemia	Newly diagnosed T1DM or Grade 3-4 hyperglycemia	Refer to Sections 6.6.3.1 and 6.6.3.2	Monitor for hyperglycemia or other signs and symptoms of diabetes Consider endocrinology consultation Consider administration of insulin for type 1 diabetes Consider administration of anti-hyperglycemic medication in patients with hyperglycemia
Hypophysitis	Grade 2	Continue treatment at the discretion of the investigator	Monitor for signs and symptoms of hypophysitis. Consider endocrinology consultation Consider administration of corticosteroids and initiate hormonal replacements as clinically indicated. Corticosteroid taper should be initiated upon irAE improving to Grade ≤1
	Grade 3 or 4	Refer to Sections 6.6.3.1 and 6.6.3.2	
Hyperthyroidism	Grade 2	Continue treatment at the discretion of the investigator	Monitor for signs and symptoms of thyroid disorders Consider management with thionamides and beta-blockers as appropriate
	Grade 3-4	Refer to Sections 6.6.3.1 and 6.6.3.2	
Hypothyroidism	Grade 2	Continue treatment at the discretion of the investigator	Monitor for signs and symptoms of thyroid disorders. Consider endocrinology consultation Consider initiation of thyroid replacement hormones per standard of care
	Grade 3-4	Refer to Sections 6.6.3.1 and 6.6.3.2	

Immune-related AEs	Toxicity Grade (CTCAE v5.0)	Dose Modification	Guidance for Management of irAEs
Nephritis and Renal Dysfunction	Grade 1	Consider temporary hold pending consideration of baseline renal function and to confirm etiology[1]	Monitor for changes in creatinine levels For Grade ≥2: – If worsening or no improvement, consider administration of corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper – Corticosteroid taper should be initiated upon irAE improving to Grade ≤1
	Grade 2	Hold treatment until resolved to baseline[1]	
	Grade 3-4	Permanently discontinue	
Skin Adverse Reactions	Grade 1-2	Continue treatment at the discretion of the investigator	Based on the severity of the adverse reaction, consider administration of corticosteroids. Corticosteroid taper should be initiated upon irAE improving to Grade ≤1 For signs or symptoms of SJS or TEN, withhold and refer the patients for specialized care. If SJS or TEN is confirmed, permanently discontinue
	Grade 3	Refer to Sections 6.6.3.1 and 6.6.3.2	
	Grade 4	Permanently discontinue	
All other immune-related AEs	Grade 2	Continue treatment at the discretion of the investigator	Based on type and severity of AE, consider administration of corticosteroids. Permanently discontinue for any Grade 3 irAE that recurs and for any life-threatening irAEs
	Grade 3	Refer to Sections 6.6.3.1 and 6.6.3.2 and or discontinue based on the type of event.	
	Grade 4	Permanently discontinue	

[1] The next dose of BNT411 can maximally be delayed for 21 days unless approved otherwise by the sponsor's medical monitor. If irAE resolves within 21 days to baseline, restart treatment at the same dose level after consultation with the sponsor's medical monitor.
AE, adverse event; irAEs, immune-related AEs; CTCAE, Common Terminology Criteria for Adverse Events; T1DM, type 1 diabetes mellitus; SJS, Steven Johnsons Syndrome; TEN, toxic epidermal necrolysis

6.6.4.2 Infusion-Related Reactions (IRRs)

IRR is a general risk to be considered for any new compound administered intravenously irrelevant of its MoA. IRR is typically of immediate onset after the compound's administration. We cannot exclude the risk of IRR with BNT411 due to the given limited experience with BNT411.

The following treatment guidelines are provided below for patients who experience an IRR associated with administration of BNT411 treatment.

- Grade 1- If an IRR Grade 1 occurs, the infusion does not need to be interrupted and can be continued at the investigator's discretion at half the infusion rate under close medical supervision.
- Grade 2-3- If an IRR Grade 2 or Grade 3 occurs, the infusion should be interrupted and appropriate medical management instituted. The infusion may be re-started at the investigator's discretion at half the infusion rate under close medical supervision if symptoms have resolved to Grade ≤1 within an hour.
    - Patients who have experienced prior infusion related Grade 2 or Grade 3 reactions in the trial should be premedicated. Premedication to prevent IRR in subsequent infusions may be administered at the investigator's discretion according to local guidelines but preferably includes an antihistamine (e.g., diphenhydramine 50 mg orally twice daily [po] or equivalent antihistamine), acetaminophen/paracetamol (e.g. acetaminophen 500-1000 mg po or equivalent), and if considered necessary, patients should receive corticosteroids at a suggested maximum dose of 100 mg prednisone or equivalent.
    - If the patient has a second Grade 3 IRR despite premedication, the infusion should be stopped and the patient should be withdrawn from treatment.
- Grade 4- If anaphylaxis or Grade 4 IRR occurs, administration of BNT411 should be discontinued immediately and permanently, and appropriate medical therapy should be administered.

Please note:

- At all times during BNT411 infusion, immediate emergency treatment of an anaphylactic reaction according to institutional standards must be assured. In order to treat possible anaphylactic reactions, for instance, dexamethasone 10 mg and epinephrine in a 1:1000 dilution or equivalents should always be available along with equipment for assisted ventilation.
- All premedication must be reported on the concomitant medication page in the eCRF.

6.6.5 Safety Stopping Criteria

Across all patients in both Part 1A and Part 1B, the following rules apply:

1. The trial will be paused for:
    a. Any death possibly related to BNT411
    b. Two Grade 4 AEs that are considered possibly, probably, or definitely related to BNT411

If a suspected DLT occurs, a SRC meeting will be held as rapidly as possible. In the meantime, dosing of the ongoing patients in that cohort will continue unless there is reason to suspect there is an unacceptable safety risk based on the nature and/or severity of the observed DLT.

The SRC will decide whether and when the trial can be restarted after approval of a substantial amendment by the regulatory authorities and EC; or with the sponsor's concurrence, whether the trial should be stopped. Further information on the SRC is described in Section 9.6 and in the SRC Charter.

In individual patients, treatment with BNT411 should be discontinued due to safety concerns under the following conditions:

1. If the patient experiences an AE fulfilling the DLT criteria.
2. If the patient experiences an AE that fulfils the DLT criteria after the DLT period has ended in the dose-escalation or during the expansion phase, but that fails to resolve to Grade ≤1 within 21 days after the planned dosing date or any other dose delay of more than 21 days due to toxicity possibly related to BNT411, unless otherwise approved by the sponsor's medical monitor.
3. In case of a drug-related or life-threatening Grade 4 AE that does not fulfill the DLT criteria (excluding asymptomatic Grade 4 elevations in non-hematological laboratory values that resolve to Grade ≤2 within 14 days [± medical intervention]) unless otherwise approved by the sponsor's medical monitor.
4. If more than two dose reductions are required.
5. Patients with any eye disorders Grade ≥3, especially the occurrence of retinal detachment and marked decrease in visual acuity.
6. In case of cytokine release syndrome (CRS) Grade 4, the patient should be discontinued from treatment.
7. Second occurrence of an IRR of Grade ≥3 despite premedication prior to second infusion.
8. First occurrence of anaphylaxis or Grade 4 IRR.

Please note:

Patients should, whenever possible, irrespective of the reason for discontinuation, be examined as soon as possible.

6.6.6 Safety Alert Communication Plan

Safety data such as DLTs, SAEs, SUSARs, or safety-relevant protocol deviations which may impact all patients in the trial will be communicated by the medical monitor through "Safety Alert Email" to the investigators and site staff to inform them about abovementioned safety issues. If recruitment has to be suspended, or dosing to be withheld in all patients, this countermeasure will be detailed in the safety alert email. If necessary, the email will also give guidance to the Investigators to promptly contact the patients and inform about any safety issue which may require patients to come for unplanned visit or any other measures as appropriate. If the email is not acknowledged, the site will be telephoned until contact is made with appropriate site staff. Furthermore, a SRC meeting will be held as rapidly as possible. Investigators and site

staff who do not attend SRC meetings will be provided with an email update of all SRC decisions within 24 hours of each meeting.

6.6.7 Atezolizumab Dose Modification and Management of Specific Adverse Events

Dose modifications for atezolizumab are permitted according to the atezolizumab Prescribing Information valid in a given country and local standard-of-care. Management of specific adverse events should be done according to the atezolizumab Prescribing Information and local standard of care.

6.6.8 Carboplatin Dose Modification and Management of Specific Adverse Events

Dose modifications for carboplatin are permitted according to the carboplatin Prescribing Information valid in a given country and local standard-of-care. Management of specific adverse events should be done according to the carboplatin Prescribing Information and local standard of care.

6.6.9 Etoposide Dose Modification and Management of Specific Adverse Events

Dose modifications for etoposide are permitted according to the etoposide Prescribing Information valid in a given country and local standard-of-care. Management of specific adverse events should be done according to the etoposide Prescribing Information and local standard of care.

6.7 Treatment after the End of the Trial

Patients who show some level of clinical benefit during the trial may be permitted to receive further cycles of treatment if discussed with the sponsor.

7 Discontinuation of Trial Treatment and Patient Discontinuation/Withdrawal

7.1 Discontinuation of Trial Treatment

Patients will receive BNT411 treatment until one of the predefined discontinuation of treatment criteria has been met:

- Radiographic disease progression per RECIST 1.1 (Section 8.5.1) or confirmed radiographic disease progression by iRECIST (if applicable),
- Death,
- Unacceptable AEs requiring BNT411 discontinuation (refer to Safety Stopping Criteria – Section 6.6.5),
- Investigator believes that it is in the best interest of the patient to stop BNT411 treatment,
- Withdrawal of consent,
- Pregnancy
- Lost to follow-up

If BNT411 treatment is permanently discontinued for other reasons than radiographic disease progression, every effort should be made to continue tumor assessments.

Further information on discontinuation of atezolizumab, carboplatin and etoposide should be referred to the respective SmPC or USPI.

Patients should, whenever possible, irrespective of the reason for discontinuation, be examined as soon as possible and the treatment discontinuation visit should be performed (Section 8.3).

7.1.1 Temporary Discontinuation

See Section 6.6.5.

7.1.2 Rechallenge

For instructions/considerations regarding re-treatment of patients who have experienced a DLT see Sections 6.6.3.1 (Part 1A) and 6.6.3.2 (Part 1B), and for those who have experienced an IRR, see Section 6.6.4.2.

7.2 Withdrawal from the Trial

Patients will be withdrawn from the trial (dose escalation or expansion) for the following reasons:

- A patient may withdraw from the trial at any time at his or her own request,
- At the discretion of the investigator for safety, behavioral, compliance, or administrative reasons,
- Lost to follow-up,
- Patient died,
- Trial closure.

If the patient withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a patient withdraws from the trial, he or she may request destruction of any samples taken and not tested, and the investigator must document this in the site trial records.

The sponsor will make any effort to ensure patients are followed up for completion of safety assessment in the trial. See Table 1-1 and Table 1-2 for data to be collected at the time of trial discontinuation and follow-up and for any further evaluations that need to be completed.

When a patient withdraws consent, the reason for withdrawal is to be documented in the eCRF and in the source document. Trial drug assigned to the withdrawn patient may not be assigned to another patient.

7.2.1 Withdrawal from the Use of Research Samples

The patient may withdraw their consent for future use of research samples at any time. To initiate the sample destruction process, the investigator must notify the sponsor of withdrawal of consent for the research samples and to request sample destruction. The sponsor will then initiate the process for sample destruction. If requested, the investigator will receive written confirmation from the sponsor that the samples have been destroyed. If the patient withdraws consent for research samples, the sponsor may retain and continue to use any data from samples already analyzed before such a withdrawal of consent. Samples will be destroyed after they are no longer needed for the clinical trial.

7.2.2 Safety Follow-up Evaluations

Patients discontinuing from treatment for any reason will have safety follow-up visits 30 days (+5 days) and 60 days (±7 days) after the patient receives the last dose of BNT411. Separate safety follow-up visits should also be done after discontinuation of atezolizumab, carboplatin and etoposide, if it occurs ≥21 days later than BNT411. If the patient initiates new anti-cancer treatment within 60 days of the last dose of trial treatment, the safety follow-up visit should be performed prior to starting new anti-cancer treatment. Once new anti-cancer treatment is initiated, the patient will move into survival follow-up.

7.3 Lost to Follow up

For patients whose status is unclear because they fail to appear for trial visits without stating an intention to withdraw consent, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent form and by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be considered lost to follow-up until due diligence has been completed (where possible, three telephone calls and, if necessary, a certified letter to the patient’s last known mailing address or local equivalent methods). Patients lost to follow-up should be recorded as such on the appropriate disposition eCRF.

8 Trial Assessments and Procedures

- Trial procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue trial treatment.
- Adherence to the trial design requirements, including those specified in the SoA, is essential and required for trial conduct.
- All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the patient's routine clinical management (e.g. blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- In case the COVID-19 pandemic creates challenges that may interfere with the conduct of this clinical trial, the addendum "Clinical trial protocol addendum related to COVID-19 pandemic Version 3.0 04 Jun 2021" gives guidance and outlines assistance on protocol procedures, patient enrollment and requirements within the established protocol.
- Information relating to COVID-19 vaccinations including a risk-benefit assessment and guidance for vaccination during this clinical trial is provided in Sections 10.8 and 10.9.

The schedule of assessments to be performed in Parts 1A and 1B of the trial are summarized in Table 1-1 to Table 1-8 in Section 1.3.1. With the exception of post-dose blood and urine sampling for PK assessments, all assessments should be performed before trial treatment administration (on the applicable days) or any planned intervention. On the days of tumor imaging, blood sampling can be before or after imaging assessments.

8.1 Screening Procedures

Informed consent must be obtained within 21 days before Day 1 of Cycle 1 of Part 1 (A or B). Patients must provide written informed consent before any other screening-specific assessments are performed. Trial sites must maintain a log of all consenting patients which will include date and time of consent.

Consenting patients who meet eligibility criteria will be enrolled in the trial and will be assigned a patient number.

Screening assessments will be performed as summarized in Table 1-1 and Table 1-2. Screening will be initiated and completed within 21 days before Day 1 of Cycle 1 for Parts A and B.

Women of child-bearing potential must have a negative serum pregnancy test conducted at screening.

Vital signs and ECG will be performed as described in Sections 8.6.2 and 8.6.3.

Laboratory safety tests (hematology, biochemistry, coagulation, endocrine [thyroid stimulating hormone (TSH), triiodothyronine (T3) and thyroxine (T4) and urinalysis) will be assessed as described in Section 8.6.4.

All patients will have a CT-scan with contrast or MRI of thorax, abdomen, and pelvis during screening. Evaluation of left ventricular function, either by echocardiogram (ECHO) or multigated acquisition (MUGA) scan, will be performed at Screening (or within 21 days of screening) and as clinically indicated at other time points.[1] 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 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 before the Cycle 1 Day 1 visit. Scans that exceed the 21-day window may be used for trial enrollment with sponsor approval.

Note: country specific information for Germany.[2]

8.2 Procedures During Treatment Visits for Cycles 1-N

The assessments to be performed are shown in Table 1-1 and Table 1-2.

Details about these assessments are provided in Sections 8.5 to 8.12.

8.3 Treatment Discontinuation

The evaluations to be performed are detailed in Table 1-1 and Table 1-2**.** If the treatment discontinuation visit coincides with a regularly scheduled cycle visit, the treatment discontinuation evaluations will supersede those of the regularly scheduled cycle visit.

8.4 Other Visits

8.4.1 Safety Follow-up

The evaluations to be performed are detailed in Table 1-1 and Table 1-2.

8.4.2 Survival Follow-up

The evaluations to be performed are detailed in Table 1-1 and Table 1-2.

[1] Note: country specific information for Germany: left ventricular function should only be assessed by an ECHO scan (see Section 12.2.1).
[2] Country specific information 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 (see Section 12.2.1).

8.4.3 Unscheduled Visits

The evaluations that may be performed are detailed in Table 1-1 and Table 1-2.

8.5 Efficacy Assessments

8.5.1 Anti-tumor Activity Assessment – CT/MRI Imaging

Anti-tumor activity will be evaluated according to RECIST 1.1 (Eisenhauer et al, 2009) and iRECIST criteria (Seymour et al, 2017) (see Sections 10.5 and 10.6). Efficacy will be assessed by on-treatment imaging 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 below]), withdrawal of consent, trial termination by the sponsor, or death, whichever occurs first, regardless of whether patients start a new anti-cancer therapy.

In all parts of the trial, treatment should be discontinued in all patients who exhibit evidence of progressive disease by RECIST 1.1. However, to better accommodate standard clinical practice which is guided by the fact that these patients have, in general, limited treatment options and such options have limited efficacy and significant toxicity, patients may be considered for treatment beyond progression at the discretion of the investigator and after appropriate discussion with the patient and obtaining informed consent, only if all of the following criteria are met:

- Absence of clinical symptoms or signs indicating clinically significant disease progression
- No decline in performance status
- Absence of rapid disease progression or threat to vital organs or critical anatomical sites [e.g. central nervous system (CNS) metastasis, respiratory failure due to tumor compression, spinal cord compression] requiring urgent alternative medical intervention
- No significant, unacceptable or irreversible toxicities related to trial treatment
- Patients must provide written consent to acknowledge deferring alternative treatment options including other clinical trials in favor of continuing trial treatment at the time of initial progression.

Patients who continue treatment beyond radiographic disease progression per RECIST 1.1 should be closely monitored clinically and with a follow-up scan in 6 weeks or sooner if symptomatic deterioration occurs. Treatment should be discontinued if clinical deterioration due to disease progression occurs at any time, or if persistent disease growth is confirmed in a follow-up scan. In addition, patients should be discontinued for unacceptable toxicity or for any other signs or symptoms of deterioration attributed to disease progression as determined by the investigator after an integrated assessment of radiographic data and clinical status.

Patients who discontinue treatment for reasons other than radiographic disease progression (e.g. toxicity) will continue scheduled tumor assessments at the same frequency as would have been followed if the patient had remained on trial treatment.
Patients whose treatment schedule has been changed (e.g., delay due to toxicity) still should follow the original tumor assessment schedule (every 6 weeks [±7 days] for 48 weeks, and every 12 weeks [±7 days] thereafter).

8.6 Safety Assessments

Safety assessments are described in Sections 8.6.1 to 8.6.8, with the exception of AEs, which are described in Section 8.7. Planned time points for all safety assessments are provided in the SoA. More frequent assessments may be performed at the investigator's discretion, if medically indicated.

8.6.1 Physical Examination

Physical examinations will be performed (by inspection, palpation, and auscultation) by a physician at the trial site according to the SoA (Table 1-1 and Table 1-2).

A complete physical examination will be performed at screening, up to 21 days prior to first administration of IMP. The complete physical examination includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Abnormalities (clinical significant findings) observed at screening will be recorded on the general Medical History/Concomitant Diseases page of the eCRF, if started before signing the ICF. New or worsened clinically significant abnormalities after signing the ICF have to be recorded on the AE page of the eCRF.

A limited, system-directed physical examination will be performed at the other times noted in the SoA and as clinically indicated at other time points. New or worsened clinically significant abnormalities will be recorded on the AE page of the eCRF.

Height and weight will be assessed at screening. Weight will be assessed at additional time points as indicated in the SoA. Assessment of weight should be repeated at any time if there are apparent weight changes.

8.6.2 Vital Signs

Vital signs will be assessed by the appropriate trial personnel at the time points listed in the SoA (Table 1-1 and Table 1-2).

During dose escalation, body temperature, pulse rate, respiratory rate, and blood pressure will be assessed as summarized in Table 1-6 on BNT411 administration days. On days when BNT411 is not administered, vital signs only need to be obtained once, at any time during the visit.

Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the patient in a quiet setting without distractions (e.g. television, cell phones).
- Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded on the eCRF.

8.6.3 Electrocardiograms

Triplicate (during trial treatment) or single (at other time points) 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3, Table 1-3 and Table 1-4) using an ECG machine that

automatically calculates the pulse rate and measures PR, QRS, QT, and corrected QT (QTc) intervals. For the assessment the subjects will be in the supine position, lying still and quietly until the assessment has been done.

In general, increases in QT/QTc to >500 ms or of >60 ms over baseline are commonly used as thresholds for potentially discontinuing trial treatment; consultation with a cardiologist should be considered for any such increases to determine whether they are clinically significant.

At each time point at which triplicate ECGs are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 5 minutes.

8.6.4 Clinical Safety Laboratory Assessments

The following laboratory assessments will be performed as summarized in the SoA: hematology, biochemistry, endocrine parameters (TSH, T3 and T4), coagulation profile, and urinalysis (see Section 10.2 for details).

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the trial in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the trial or within 60 days after the last dose of trial treatment should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.

All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA.

If laboratory values from non-protocol specified laboratory assessments performed at the institution’s local laboratory require a change in patient management or are considered clinically significant by the investigator (e.g. SAE or AE or dose modification), then the results must be recorded in the eCRF.

8.6.5 Eye Examination

Eye examinations are to be performed by an ophthalmologist and should include at least visual acuity testing and slit-lamp exam 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. 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.).

The investigator should perform an unscheduled eye examination with a direct ophthalmoscope if there is suspicion of worsening of the eyesight. Patients should be referred to an

ophthalmologist at the investigator's discretion even before the performance of indirect ophthalmoscopy, and at any time point of the trial.

8.6.6 ECOG Performance Status

ECOG performance status will be assessed at the time points indicated in Table 1-1 and Table 1-2 using the following scale:

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

8.6.7 Pregnancy Testing

In this trial, patients are considered to have reproductive potential, unless they are postmenopausal or permanently sterile. Details and definitions are provided in Section 10.4. See Table 1-1 and Table 1-2 for the time points when pregnancy tests should be performed for women of childbearing potential. A serum pregnancy test is performed at screening. Thereafter, urine pregnancy test is sufficient unless indicated otherwise. A serum pregnancy test is warranted to confirm a positive urine pregnancy test.

See Section 8.7.5 for details of reporting pregnancies.

8.6.8 Echocardiogram or multigated acquisition scan

Evaluation of left ventricular function, either by echocardiogram (ECHO) or multigated acquisition (MUGA) scan, will be performed at Screening (or within 21 days of screening) and as clinically indicated at other time points.[1]

8.7 Adverse Events and Serious Adverse Events

The definitions of AEs and SAEs can be found in Section 10.3.

[1] Note: country specific information for Germany: left ventricular function should only be assessed by an ECHO scan (see Section 12.2.1).

AEs will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the trial treatment or trial procedures, or that caused the patient to discontinue the trial or trial treatment (see Section 7).

8.7.1 Time Period and Frequency for Collecting AE and SAE Information

All SAEs and AEs will be collected from the signing of the ICF until the safety follow-up visit at the time points specified in the SoA (Section 1.3, Table 1-5).

All SAEs will be recorded and reported by the investigator to the sponsor or designee immediately and no later **than 24 hours after becoming aware of the event**, as indicated in Section 10.3.

Investigators are not obligated to actively seek AE or SAE information after conclusion of the trial participation. However, if the investigator learns of any SAE, including a death, at any time after a patient has been discharged from the trial, and he/she considers the event to be reasonably related to the trial treatment or trial participation, the investigator must promptly notify the sponsor.

Safety-related information / paper-based SAE reports (initial and follow-up reports) are to be sent to the safety contact details outlined in Section 10.3.4.

8.7.2 Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

8.7.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each patient at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.

8.7.4 Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a trial treatment under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a trial treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC),

and investigators. The execution of expedited reporting to the different entities may be delegated as detailed in the trial-specific Safety Management Plan. Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary. An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g. summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.7.5 Pregnancy

Any female participant who becomes pregnant while participating in the trial will discontinue the IMP. Details of all pregnancies in female patients and, if indicated, female partners of male patients will be collected (procedures described in Section 10.4.1).

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.4.1.

Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs (details defined in Section 10.4.1).

8.7.6 Death Events

AEs leading to death will be recorded and analyzed (for details see Section 10.3.3). Deaths will also be followed up during survival follow-up. After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including but not limited to targeted therapy and immunotherapy) will be collected via phone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent for survival follow-up or the sponsor terminates the trial). If a patient requests to be withdrawn from survival follow-up, this request must be documented in the source documents and signed by the investigator.

Deaths clearly related to the progression of the disease will not be documented and reported as AEs or SAEs. These deaths must be collected on the death page of the eCRF.

In Germany only: Any death, irrespective whether causally related to disease progression or not, will be documented as AE and reported as SAE.

8.7.7 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

The progression of underlying disease (e.g., new metastases) during trial participation is not considered as an AE.

Because disease progression is common for patients with cancer, it will not be reported according to the standard process for expedited reporting of an SAE even though the event may meet the definition of a SAE. These events will be recorded on the corresponding page in the patient's eCRF.

NOTE: symptoms resulting from the progression and clearly stated as related to the progressive disease (PD) and fatal cases clearly related to the progression will not be documented and reported as AEs and SAEs. However, specific symptoms at time of progression that are considered to be caused by other reason, and fatal cases where other reason rather than the PD may not be discarded, will have to be documented as AEs and reported as SAEs if applicable.

In Germany only: deaths related to disease progression will be reported as AEs or SAEs.

8.7.8 Dose Limiting Toxicity

See Sections 6.6.1 and 6.6.2 for the definition of DLTs in this trial.

A DLT has to be documented on an SAE report form and forwarded to the safety contacts as described later in this document. DLT reporting needs to be carried out in the same way as SAE reporting (i.e., no more than 24 hours after learning of the event) as described in Section 10.3.4.

8.8 Treatment of Overdose

For this trial, an overdose is defined as a patient receiving a dose of BNT411 15% in excess of the intended dose specified in this protocol. Guidance on overdose for atezolizumab, carboplatin and etoposide should be referred to SmPC and USPI.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the patient.

Medication errors include infusion rate errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product.

All events of overdose and/or medication errors with BNT411 must be reported from the investigational site to the sponsor within 24 hours of awareness whether associated with an AE or not.

In addition, overdose and/or medication errors with BNT411 must also be recorded in the AE page of the eCRF when associated with signs, symptoms or clinical sequelae (see Section 10.3.1).

Overdose, medication errors, misuse and abuse do not automatically make an AE serious, but if the consequences are serious, for example death or hospitalizations, the event is serious and must be reported as an SAE.

Rescue medication to reverse the action of BNT411 is not available. In case of overdose, medication errors, misuse, and/or abuse of trial drug, patients should receive supportive care according to local guidelines and potential side effects of BNT411 should be treated symptomatically.

In the event of an overdose, the investigator should:

i. Contact the Medical Monitor immediately.

ii. Closely monitor the patient for any AE/SAE and laboratory abnormalities until BNT411 can no longer be detected systemically.

iii. Obtain a plasma sample for PK analysis if requested by the Medical Monitor (determined on a case-by-case basis).

iv. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

8.9 Pharmacokinetics

Plasma and urine samples will be collected for measuring concentrations of BNT411 and its major metabolites. Table 1-3 and Table 1-4 describe the timing of collection of samples for PK assessments during dose escalation. For urine sampling, the exact time of sampling and the volume (mL) excreted at each time point before infusion of BNT411 must be documented. Total amount of urine has to be collected within the first 6 hours following start of the infusion and total volume excreted should be documented on C1D1. 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, except for the 6-hour urine collection.

The following PK parameters will be determined when appropriate (including but not limited to): 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}], pre-dose trough concentrations [C_{trough}], terminal half-life [$T_{1/2}$], and accumulation ratio [R_A].

Further details are provided in the laboratory manual.

8.10 Pharmacodynamic Biomarkers

The trial will include pharmacodynamic assessments based on changes in selected cytokines and other activation markers. Cytokine samples will be taken at the same time points as for PK sampling – see Table 1-3 and Table 1-4.

Furthermore, cytokine samples will be taken at disease progression or treatment discontinuation. If an adverse event of CRS is suspected, cytokines should be obtained at an unscheduled visit to support the diagnosis.

Table 1-7 (Part 1A) and Table 1-8 (Part 1B) provide details of biomarker assessments to be performed during dose escalation. Samples will be collected from all patients. Biomarker assessments will include tumor biopsy, blood sampling for cytokine analysis, and further analysis, that may include immune phenotyping, tumor mutational burden and TCR profiling. Further details regarding sample types, volumes etc. are provided in the laboratory manual.

Samples may be analyzed to monitor pharmacodynamics by evaluating changes in systemic and intratumoral immune response (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]) in blood and tumor tissue compared to baseline. Additionally, targeted sequencing may be performed for profiling of T-cell receptors (TCR profiling) in order to identify potential markers that may predict clinical response (see Section 8.11).

Samples for biomarker analysis can be used up to 5 years after the end of the trial. Biomarker analyses may be deferred or not performed, if during or at the end of the trial, it becomes clear that the analysis will not have sufficient scientific value for biomarker evaluation, or if there is

not enough sample to allow adequate evaluation. In the event that the trial is terminated early or shows poor clinical efficacy, completion of biomarker assessments is based on justification and intended utility of the data.

8.11 Genetics

Where required by local or country specific regulations, each patient must sign a separate informed consent form if he or she agrees to genetic testing (DNA and RNA) of the collected samples.

These analyses may include the following:

i. Identification of tumor specific mutations on a DNA level to evaluate tumor mutational burden (TMB) as a potential predictive marker
ii. Identification of mRNA expression pattern of immune-relevant genes in the tumor as a potential predictive marker
iii. Profiling of T-cell receptors (TCRs) in the periphery and tumor as a potential predictive marker as well as a surrogate for pharmacodynamics

If a patient refuses to consent to DNA and RNA research in these specific regions, the patient is still eligible to participate in the trial.

8.12 Immunogenicity Assessments

Immunogenicity is not being evaluated in this trial.

8.13 24/7 Coverage for Urgent Protocol-related Medical Questions

In a trial-related health emergency, when the assigned Medical Monitor for the trial cannot be reached by a caller, for discussion of urgent protocol Medical-related questions an on-call physician can be reached 24 hours per day, 7 days per week via an ICON Call-Centre:

To reach the ICON HelpDesk for 24/7 Coverage of Urgent Protocol-related Medical Questions, dial the local number found here: https://icophone.iconplc.com/24-7-Medical.pdf

9 Statistics

9.1 Statistical Hypotheses

No statistical hypotheses are planned to be tested in this trial.

9.2 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 to 60 DLT evaluable patients are planned to be enrolled in the Part 1A, and between 6 to 30 DLT evaluable patients are planned to be enrolled in the Part 1B.

9.3 Analysis Sets

Modified Intent to Treat Set

The modified ITT (mITT) set is defined as all patients who are assigned to BNT411 and have a baseline and at least one on-treatment/post-treatment tumor response assessment.

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 and meet the minimum exposure criterion 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. A patient is considered to have met the minimum exposure criterion if the relative dose intensity (RDI) of BNT411 in Cycle 1 is 100%.

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

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, while the mITT set will be used for efficacy analyses (Part 2 only).

9.4 Statistical Analyses

Statistical analyses will be performed by the BioNTech or a designated CRO. All statistical analyses will be carried out using SAS®, Version 9.4 or higher, and/or other statistical software as required.

The statistical analysis plan will be finalized prior to database snapshot for the main statistical analysis, it will include a more technical, and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1 General Considerations

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

Categorical variables will be summarized by cohort presenting absolute and relative frequencies (n and %) of patients in each category.

Time-to-event-endpoints (DOR, PFS and OS) will be analyzed using Kaplan-Meier methodology by cohort and censored in accordance with the FDA Guidance: "Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics" and the EMA guidance "Guideline on the evaluation of anti-cancer medicinal products in man". Censoring rules will be defined in the SAP.

The median survival time (including 95% confidence limits according to Brookmeyer and Crowley) and the first and third quartile will be presented. Survival rates (including 95% confidence interval based on Greenwood's formula) as well as the number and percentage of patients with events, censored and under risk will be displayed for selected time points (e.g. at 3, 6, 12 months). The time-to-event analysis will be illustrated using Kaplan-Meier plots.

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

9.4.2 Primary Endpoint(s)

The primary objective of the trial is to assess the safety profile of the regimen based on the following endpoints:

- Occurrence of dose limiting toxicities (DLTs) within a patient during the DLT evaluation period
- Occurrence of treatment-emergent adverse events (TEAE) within a patient including grade ≥3, serious, fatal TEAE by relationship
- Occurrence of dose reduction and discontinuation of BNT411 within a patient due to treatment-emergent adverse events (TEAE)

And to determine the MTD and/or RP2D defined as follows:

- MTD – the highest tolerated dose
- RP2D based on integrated evaluation of safety, tolerability, clinical benefit, PK, and pharmacodynamics data, for all dose levels tested.

A treatment emergent AE is defined as any AE with an onset date on or after the first administration of trial treatment (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 by the investigator. Treatment-emergent AEs will be summarized overall and by treatment arm. The trial treatment includes BNT411, atezolizumab, carboplatin, and etoposide.

AEs will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA®) coding system to get a System Organ Class (SOC) and Preferred Term (PT) for each AE and graded for severity using NCI CTCAE v5.0.

The number and percentage of patients reporting at least one AE will be summarized by PT nested within SOC for each of the following AE types:

- any AE
- related AE
- Grade ≥3 AE
- related Grade ≥3 AE
- any SAE
- related SAE
- SAE leading to death
- AE leading to dose reduction
- AE leading to permanent discontinuation of treatment
- DLT.

Moreover, the number and percentage of patients with any AE will be summarized by worst NCI CTCAE grade by PT nested within SOC.

DLTs will be presented in terms of listings presenting the reported term and MedDRA PT and SOC term, its time of onset, duration, and outcome, relationship, NCI CTCAE grade, and seriousness including dose exposure data.

9.4.3 Secondary Endpoint(s)

For Parts 1 and 2:

- Establish the PK profile, including estimating the following parameters: AUC, CL and V_D, C_{max}, T_{max}, C_{trough}, and $T_{1/2}$

For Part 2:

- Evaluate anti-tumor activity according to RECIST 1.1 (Eisenhauer et al, 2009), including the following:
  - ORR defined as the proportion of patients in whom a CR or PR is observed as best overall response.
  - DCR defined as the proportion of patients in whom a CR or PR or SD (assessed at least 6 weeks after first dose) is observed as best overall response.
  - DOR defined as the time from first objective response (CR or PR) to the first occurrence of objective tumor progression (PD) or death from any cause, whichever occurs first.

The ORR and DCR will be summarized with absolute and relative frequencies along with two-sided 95% Clopper-Pearson confidence intervals by cohort. Patients not meeting the criteria for CR or PR for ORR (CR or PR or SD for DCR), including those without any post-baseline tumor assessments, will be considered as non-responders.

DOR will be analyzed using Kaplan-Meier methodology as described in Section 9.4.1.

9.4.4 Exploratory Endpoint(s)

For Part 2:

Exploratory endpoints include evaluation of anti-tumor activity according to iRECIST:

- iORR defined as the proportion of patients in whom a iCR or iPR is observed as best overall response.
- iDCR defined as the proportion of patients in whom a iCR or iPR or iSD (assessed at least 6 weeks after first dose) is observed as best overall response.
- iDOR defined as the time from first objective response (iCR or iPR) to the first occurrence of objective tumor progression (iCPD) or death from any cause, whichever occurs first.

The iORR and iDCR will be summarized with absolute and relative frequencies along with two-sided 95% Clopper-Pearson confidence intervals by cohort. Patients not meeting the criteria for iCR or iPR for iORR (iCR or iPR or iSD for iDCR), including those without any post-baseline tumor assessments, will be considered as non-responders.

iDOR will be analyzed using Kaplan-Meier methodology as described in Section 9.4.1.

If too few responders are observed, this exploratory analysis may be omitted.

A preliminary assessment of efficacy will also be included based on evaluation of:

- PFS defined as the time from first dose of BNT411 to first occurrence of objective tumor progression, or death from any cause, whichever occurs first.
- OS defined as the time from first dose of BNT411 to death from any cause.

PFS and OS will be analyzed using Kaplan-Meier methodology as described in Section 9.4.1.

For Parts 1 and 2:

A preliminary assessment of biomarkers that might act as pharmacodynamics, anti-tumor, and safety indicators will also be included:

- assess the pharmacodynamics based on immune system activation as shown by changes in select cytokines and other activation markers.

9.4.5 Other Safety Analyses

Other safety analyses will be detailed in the statistical analysis plan (SAP).

9.4.6 Other Analyses

Other analyses will be detailed in the SAP.

9.5 Interim Analyses

No formal interim analysis is planned. However, data will be reviewed by the SRC after each cohort. The main statistical analysis will be performed once all patients have completed treatment and safety follow-up.

9.6 Safety Review Committee (SRC)

A Safety Review Committee (SRC), composed of the investigators and the sponsor's representatives will assess the cumulative safety data (e.g. SAEs, AEs, laboratory data and DLTs where applicable) collected during the trial to help ensure patient's safety.

The SRC will make recommendations for the RP2D at the end of both Parts 1A and 1B and will recommend whether to activate the expansion phase (Part 2).

Meetings with the SRC will take place at the time points outlined in the latest version of the signed SRC charter.

If a toxic dose is reached, the Medical Monitor will email the investigators and site staff to inform them that recruitment has been suspended pending review by the SRC. If the email is not acknowledged, the site will be telephoned until contact with the appropriate site staff is made. Investigators and site staff who do not attend SRC meetings will be provided with an email update of all SRC decisions within 24 hours of each meeting.

10 Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical, and Trial Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

- This trial will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g. advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the trial is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate hazard to trial patients.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the trial to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the trial at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the trial and for 1 year after completion of the trial.

10.1.3 Informed Consent Process

- The investigator or his/her representative will explain the nature of the trial to the patient or his/her legally authorized representative and answer all questions regarding the trial.
- Patients must be informed that their participation is voluntary. Patients or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health

Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or trial center.

- The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the trial and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Patients must be re-consented to the most current version of the ICF(s) during their participation in the trial.
- A copy of the ICF(s) must be provided to the patient or the patient's legally authorized representative.
- Patients who are rescreened are required to sign a new ICF.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each patient the objectives of the exploratory research. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a patient's agreement to allow any remaining specimens to be used for exploratory research. Patients who decline to participate in this optional research will not provide this separate signature.

10.1.4 Data Protection

- Patients will be assigned a unique identifier by the sponsor. Any patient records or datasets that are transferred to the sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.
- The patient must be informed that his/her personal trial-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient who will be required to give consent for their data to be used as described in the informed consent
- The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5 Data Quality Assurance

- All patient data relating to the trial will be recorded on electronic CRF (eCRF) unless transmitted to the sponsor or designee electronically (e.g. laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit trial-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

- Monitoring details describing strategy (e.g. risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this trial including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other patients (e.g. Contract Research Organizations).
- Trial monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the trial is being conducted in accordance with the currently approved protocol and any other trial agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this trial must be retained by the investigator for 25 years after trial completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.6 Source Documents

- Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the trial. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the ICH Guideline for Good Clinical Practice.

10.1.7 Trial and Site Start and Closure

The trial start date is the date on which the clinical trial will be open for recruitment of patients.

The first act of recruitment is the signing of the ICF by the first patient and will be the trial start date.

The sponsor designee reserves the right to close the trial site or terminate the trial at any time for any reason at the sole discretion of the sponsor. Trial sites will be closed upon trial completion. A trial site is considered closed when all required documents and trial supplies have been collected and a trial-site closure visit has been performed.

The investigator may initiate trial-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a trial site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of patients by the investigator
- Discontinuation of further trial treatment development

If the trial is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the trial of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the patient and should assure appropriate patient therapy and/or follow-up.

10.1.8 Publication Policy

- The results of this trial may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of trial results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.
- The overall publication policy for the trial data is addressed in the clinical agreement for each investigator site.

10.1.9 Dissemination of Clinical Trial Data

A final ICH E3 conform report integrating all trial results will be prepared by the sponsor.
In all cases, trial results will be reported in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the trial or the country in which the trial was conducted.
Clinical trial data and documentation will be disseminated as required per applicable laws and regulations, e.g., the European Union (EU) Regulation No 536/2014, EU Regulation 1049/2001, and the US Final Rule, which implements Section 801 of the Food and Drug Administration Amendments Act (FDAAA 801). Clinical documents under such laws includes protocols and protocol amendments, SAPs, ICH E3 clinical study reports.
This trial will be registered, and trial results be publicly posted, on publicly accessible trial registries (e.g., ClinicalTrials.gov, EU Clinical Trials Register, etc.) as required per applicable laws and regulations.

If this clinical trial is used to support marketing authorization packages/submissions, the sponsor will comply with the EU Policy 0070, the proactive publication of clinical data on the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, ICH E3 clinical study reports, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. under Phase 2 of this policy, “clinical data” includes the publishing of individual patient data.
Even if not required by applicable laws and regulations, this trial will be registered, and trial results be publicly posted on ClinicalTrials.gov.
The results for all primary and secondary outcome measures, irrespective of outcome, will be submitted for publication in academic journals (for further details, see Section 10.1.8).

10.2 Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 10-1 will be performed by either local or central laboratories as detailed in the relevant footnotes to Table 1-1 and Table 1-2.

- If a sample is required for local and central assessment/ analysis, it is important that the sample for central analysis is obtained at the same time as the local sample. Additionally, if the local laboratory results are used to make either a trial treatment decision or response evaluation, the results must be entered into the eCRF.
- Protocol-specific requirements for inclusion of patients, including pregnancy testing, are detailed in Section 5.1 of the protocol.
- Additional tests may be performed at any time during the trial as determined necessary by the investigator or required by local regulations.

Table 10-1: Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count	RBC Indices: Mean corpuscular volume (MCV) Mean corpuscular hemoglobin (MCH)	White blood cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
	Red blood cell (RBC) Count			
	Hemoglobin			
	Hematocrit			
Biochemistry	Blood urea nitrogen (BUN)	Potassium, Magnesium Chloride, Phosphate (inorg.) Lactate dehydrogenase (LDH), Amylase	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose (non-fasting)	Calcium	Alkaline phosphatase	Albumin
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilirubinogen, nitrite and leukocyte esterase • Microscopic examination (if blood or protein is abnormal)			
Coagulation Factors	• Prothrombin time • Activated partial thromboplastin time (aPTT) • International normalized ratio (INR)			
Endocrine Tests	• TSH, free T3 and free T4			
Pharmacodynamics and biomarkers	• Blood sampling for cytokine analysis, immune phenotyping			
Serology	• Country specific procedure for Germany: To confirm trial eligibility, 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).			
Other Screening Tests	• Highly sensitive serum human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)			

Investigators must document their review of each laboratory safety report.
The results of each test must be entered into the eCRF.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical trial patient, temporally associated with the use of trial treatment, whether or not considered related to the trial treatment. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of trial treatment. • A **treatment-emergent AE** (**TEAE**) is defined as any AE with an onset date on or after the first administration of trial treatment (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 occurring after the period of observation (60 days after last treatment dose) will be considered as treatment-emergent only if assessed as related to the trial treatment by the investigator.

Events Meeting the AE Definition
• New conditions or worsening of pre-existing conditions detected or diagnosed after signing patient informed consent • Any abnormal laboratory test results (hematology, biochemistry, endocrine parameters, coagulation profile or urinalysis) or other safety assessments (e.g. ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, considered **clinically significant** in the medical and scientific judgment of the investigator (i.e. medical conditions that have medical consequences for the subject) or laboratory value or other clinical test that is associated with symptoms or leads to a change in trial treatment or concomitant treatment or discontinuation from trial treatment. • Any exacerbation of pre-existing medical condition (a worsening in the character, frequency, or severity of a known medical condition). This includes any condition resulting from concomitant illnesses, reactions to concomitant medications, or progression of concomitant disease states. • Recurrence of a previous medical condition not present at baseline or exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

Events Meeting the AE Definition
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either trial treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • Trial procedure related AEs (caused by a protocol-mandated intervention, including those that occur prior to assignment of trial treatment, such as tumor biopsies). • Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than anticipated for the patient's condition. The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient's condition. However, specific symptoms at time of progression that are considered to be caused by other reason, and fatal cases where other reason rather than the PD may not be discarded and will have to be documented as AEs and reported as SAEs if applicable. *In Germany only: Deaths related to disease progression will be documented as AEs and reported as SAEs.* • Any abnormal laboratory findings which are evaluated and documented in the source data as not clinically significant (e.g., an abnormal laboratory value without any clinical manifestation, such as transient lymphopenia after infusion of BNT411 due to redistribution), should not be documented as an AE. • The disease/disorder being studied, or anticipated progression, signs, or symptoms of the disease/disorder being studied, unless more severe than anticipated for the patient's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the trial that do not worsen.

10.3.2 Definition of SAE

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Is considered medically important: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical treatment to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

The terms “severe” and “serious” are not synonymous. Severity refers to the intensity of an AE (e.g. rated as mild, moderate, or severe); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

SAE exemptions are defined in Section 10.3.3 of this appendix.

A **suspected unexpected serious adverse reaction (SUSAR)** is an adverse event that is considered to have a positive causal relationship to the IMP and is classified as unexpected by the sponsor. A related adverse event is classified as unexpected when the nature or severity (= intensity) is not consistent with the applicable product information (reference safety information, i.e. the Investigator’s Brochure (IB) for an unauthorized IMP or summary of product characteristics for an authorized product). **SUSARs are subject to expedited reporting by the sponsor to the appropriate regulatory authorities, ethics committees and participating investigators**.

10.3.3 Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the eCRF, i.e.
  - intensity according to NCI CTCAE v5.0,
  - seriousness,
  - action taken (with trial treatment and other actions),
  - outcome, and
  - causal relationship/causality.
- All assessments as well as the AE term (diagnosis/description), start date and time of onset, and end date and time must be documented in the source data and the eCRF. To avoid colloquial expressions, the AE should be documented in standard medical terminology. The AE should be evaluated and documented as a diagnosis rather than individual signs or symptoms. If a definite diagnosis is not possible, the individual signs and symptoms should be documented (each as a single AE).
- Data pertaining to AEs will be collected during each trial visit. Based on the subject's spontaneous description, or the investigator's inquiry or examination during each visit,

AE and SAE Recording

the clinical significance of any sign or symptom will be evaluated by the investigator.

- The definition of clinical significance includes medical conditions that have medical consequences for the subject. Examples of medical consequences are as follows (list is not exhaustive):
    - Ongoing treatment or (re)start of a treatment (includes drug and non-drug therapies)
    - Further investigations within a narrow time-frame (e.g. ultrasound testing, gastroscopy, coloscopy)
    - Impact on upcoming trial treatment (e.g., treatment with a reduced dose, delay of treatment start, cancellation of treatment)
- Clinically significant findings must be documented as AEs in the source data and eCRF. Findings that are evaluated and documented in the source data as not clinically significant (e.g., an abnormal laboratory value without any clinical manifestation) should not be documented as an AE. All clinically significant symptoms, diseases, and syndromes present at the baseline visit should not be documented as an AE but as medical history/concomitant disease
- It is not acceptable for the investigator to send photocopies of the patient's medical records to the sponsor or any involved clinical research organization in lieu of completion of the AE/SAE eCRF page.
- Whenever copies of medical records for certain cases are requested by the sponsor, all patient identifiers, with the exception of the patient number, need to be redacted on the copies of the medical records before submission to the sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Period of observation:

- The period of observation starts after informed consent has been obtained. After informed consent, all AEs and SAEs should be reported until 60 days after the last dose of trial treatment.
- AEs occurring later than 60 days after the last trial treatment must only be documented if a relationship to trial treatment or trial procedure is suspected.

AE and SAE Recording

- SAEs will continue to be reported until 60 days after the last dose of IMP. All SAEs for which the investigator suspects a relationship to IMP or trial procedure have to be reported to the safety contact (given in Section 10.3.4), even if they occur after the end of the period of observation. In Germany, all SAEs, regardless of relatedness, that occur in a patient throughout his or her lifetime should be reported (Section 12.2.1).
- Investigators will seek information on AEs at each subject contact. All AEs, whether reported by the subject or noted by trial personnel, will be recorded in the subject's medical record and on the AE eCRF.
- The investigator should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the subject is lost to follow-up, or the subject withdraws consent. Every effort should be made to follow all SAEs considered to be related to trial treatment or trial-related procedures until a final outcome can be reported.

SAE exemptions:

- Hospitalizations for respite care or solely for coordination of care (including hospice arrangements) will not be considered as reportable SAEs.
- Visits to a hospital by ambulance or to the emergency room without admission will not be regarded as hospitalization unless the event fulfills any other of the seriousness criteria.
- Hospitalizations that were necessary solely because of subject requirement for outpatient care outside of normal outpatient clinic operating hours will not be considered as reportable SAEs.
- Planned hospitalizations required by the protocol (e.g., for trial treatment administration or insertion of access device for trial treatment administration) will not be considered as reportable SAEs.
- Hospitalizations for procedures or interventions of a pre-existing condition of the subject (elective surgery = planned, non-emergency surgical procedure) will not be considered as reportable SAEs:
    - if it was planned and documented in the subject record before the trial-specific subject informed consent was signed, or
    - if it was scheduled during the trial when elective surgery became necessary and the subject has not experienced an AE.

AE and SAE Recording

NOTE: Hospitalization of this type should be avoided during trial treatment.

- Routine treatment or monitoring of the underlying disease not associated with any deterioration in the subject's condition.
- Hospitalization of a subject for monitoring and symptomatic treatment for up to 24 hours due to a transient inflammatory reaction of Grade 1 or 2 will not be considered an SAE (but needs to be documented as an AE).
- Deaths clearly related to the progression of the disease will not be documented and reported as AEs or SAEs. These deaths must be collected on the death page of the eCRF.

  In Germany only: Deaths related to disease progression will be documented as AE and reported as SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the trial and assign it to 1 of the intensity categories according to NCI CTCAE v.5.0.

AEs that are not listed in NCI CTCAE v5.0 should be classified according to the investigator's discretion as close as possible to NCI CTCAE v5.0, based on the comparison with the most severe case encountered in past training and clinical experience.

Each AE must be classified in one of the following 5 categories:

- Grade 1 - Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 - Moderate: Minimal, local, or non-invasive intervention indicated; limiting age appropriate instrumental Activities of Daily Living (ADL)*.
- Grade 3 - Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
- Grade 4 - Life-threatening consequences: urgent intervention indicated.
- Grade 5 - Death related to AE.

* Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money etc.

** Self-care ADL refers to bathing, dressing and undressing, feeding oneself, using the toilet, taking medications, and not bedridden.

With regards to the intensity of an AE, the following must be documented in the source data and eCRF:

Assessment of Intensity

- Initial intensity of the AE
- Maximum intensity of the AE
- For each change of intensity***
    - new grade of intensity
    - date of change (= start of new grade of intensity)

***A change of intensity only needs to be documented if there is a clearly definable change in grading of the AE (e.g. a laboratory result changes from severe to moderate according to NCI CTCAE criteria).

NOTE: The NCI CTCAE grading does not automatically correspond to the seriousness criteria, i.e. the term 'severe' describes the intensity of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as 'serious', which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning.

Assessment of Causality

- The investigator is obligated to assess the relationship between trial treatment and each occurrence of each AE/SAE.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to trial treatment administration will be considered and investigated.
- The following table can be taken as guidance:

Causality Assessment:

Causality Term	Assessment Criteria	Assessed as
Certain	- Event or laboratory test abnormality, with plausible time relationship to drug intake - Cannot be explained by disease or other drugs - Response to withdrawal plausible (pharmacologically, pathologically) - Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon) - Rechallenge satisfactory, if necessary	Related
Probable/ Likely	- Event or laboratory test abnormality, with reasonable time relationship to drug intake - Unlikely to be attributed to disease or other drugs - Response to withdrawal clinically reasonable - Rechallenge not required	Related

Assessment of Causality

Possible	- Event or laboratory test abnormality, with reasonable time relationship to drug intake - Could also be explained by disease or other drugs - Information on drug withdrawal may be lacking or unclear	Related
Unlikely	- Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) - Disease or other drugs provide plausible explanations	not related

Nevertheless, it is sufficient to document the causality in the source data and eCRF as

- related,
- not related

For an event considered "related to trial treatment" there is a **reasonable possibility** of a causal relationship (there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out).

For an event considered "not related to trial treatment" there is **no reasonable possibility** of a causal relationship.

- The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- Events caused by the procedure of trial treatment administration should be differentiated from events caused by the trial treatment itself. Only events suspected to be caused by the trial treatment itself should be documented as related to trial treatment, but not events caused by the procedure of trial treatment administration (e.g. reactions at the injection site of trial treatment likely to be caused by the procedure of trial treatment administration, discomfort after blood drawing). Such AEs need to be documented as "related to trial procedure" with the causing procedure specified.

Action taken by the investigator to trial treatment

Action(s) taken by the investigator as a result of an AE must be documented.

Action(s) taken with trial treatment by the investigator can be:

- Dose not changed (= continuation of trial treatment administration according to the trial protocol)
- Dose reduced
- Trial treatment withdrawn temporarily (= interruption and resumption):
  - Delayed start of the next vaccination
  - Cancellation of administration at a given visit
  - Interruption of trial treatment administration during a given visit
- Trial treatment permanently withdrawn (= discontinuation)
- Unknown (e.g., in case the subject is lost to follow-up)
- Not applicable (e.g., in case treatment with trial treatment has not yet started or event starts after last trial treatment administration)

Other action(s) that may be taken by the investigator include:

- None
- Initiation of a concomitant drug therapy for the treatment of the AE
- Termination of a concomitant drug therapy (please specify; e.g. if this might be the cause of the AE)
- Change of the dose of a concomitant medication
- Hospitalization or prolongation of hospitalization (please complete SAE-Form)
- Initiation/termination of a non-drug therapy
- Other (please specify)

Outcome of events

The investigator has to assess the outcome of an AE (and not the subject's outcome) at the time of documentation based on the following categories:

- **Recovered/Resolved** (= complete resolution of the AE)
- **Recovered/Resolved with sequelae** (= subject recuperated but retained pathological conditions resulting from the AE; the sequelae should be indicated)
- **Recovering/Resolving** (= AEs which are improving but not yet resolved completely)
- **Not recovered/Not resolved** (= AEs which are ongoing without improving or still present when the subject dies due to another AE)

Outcome of events

- **Fatal** (= death due to the AE)*
- **Unknown** (e.g., in case the subject is lost to follow-up).

* In case of a fatal event, the event term should not be "death" but the underlying event which led to death (death = outcome). If there is more than one AE in a fatal case, only the AE leading to death will be attributed with the outcome "fatal". A copy of an autopsy report should be submitted if available.

All ongoing AEs will be followed until resolution, considered by the investigator to be stable or chronic (resolved with sequelae), the subject is lost to follow-up, the subject withdraws consent, or it has been determined that trial treatment or participation is not the cause of the AE and a plausible explanation for the cause of the event has been found. If no final status is reached at the end of the subject's trial participation, the investigator must confirm the unavailability of a final status. For AEs not related to the trial treatment, the investigator must confirm the unavailability of a final status at the end of the safety period for the respective subject.

Every effort should be made to follow all SAEs considered to be related to trial treatment or trial-related procedures until a final outcome can be reported.

Documentation of particular situations

- AEs that are secondary to other events:

  In general, AEs that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary AE that is separated in time from the initiating event should be documented as an independent AE in the source data and eCRF (e.g., if vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be documented as an AE; If vomiting results in severe dehydration, both events should be documented as AEs separately).

- Recurrent Adverse Events

  A recurrent AE is one that resolves between subject evaluation time points (i.e., visits) and subsequently recurs. Each recurrence of an AE should be documented as a separate AE in the source data and eCRF.

Documentation of particular situations

- Abnormal Laboratory Results and Vital Signs Values

  Not every laboratory or vital signs abnormality needs to be documented as an AE. For laboratory/vital signs abnormalities, the following definitions and documentation rules apply:

  A laboratory/vital signs abnormality is clinically significant if it:

  - is a sign of a disease or syndrome. In this case, only the diagnosis of the causing disease or syndrome needs to be documented as an AE.
  - results in specific symptom(s) but no diagnosis of a disease or syndrome can be made. In this case, only the symptom(s) need to be documented as AE(s).
  - is not a sign of a disease or syndrome and does not result in specific symptoms but leads to a change in trial treatment or in a medical intervention. In this case, the laboratory/vital signs abnormality must be documented as an AE.

  Any laboratory/vital signs abnormality for which none of the above-mentioned criteria are applicable are not clinically significant and should therefore not be documented as an AE.

- Increased Body Temperature and Fever

  The normal range for the body temperature is defined as >35°C to <38°C. For results within this range no source data entry for clinical significance is required, and no AE needs to be documented. If an investigator rates a body temperature result within this range as clinically significant, the clinical significance needs to be documented in the source data and an AE (e.g. with the term “body temperature increased”) needs to be documented. For results out of this range, a source data entry for clinical significance is required and an AE needs to be documented. The AE should be described (verbatim) and rated (intensity) according to NCI CTCAE criteria v5.0:

  - Fever Grade 1: 38°C - 39°C
  - Fever Grade 2: >39°C - 40°C
  - Fever Grade 3: >40°C for ≤24h
  - Fever Grade 4: >40°C for >24h
  - Fever Grade 5: death due to fever

  Since fever is an anticipated reaction to BNT411 and the sponsor is very interested in details of body temperature changes, an increase of body temperature ≥38 °C should be rated as clinically significant and documented as an AE. Conversely, there should be very good reasons if an increase of body temperature ≥38 °C is rated as not clinically significant and is not documented as an AE.

Documentation of particular situations
In order to reflect the body temperature results adequately in the verbatim term of the AEs, the following should be considered: • A clinically significant increase in body temperature <38 °C should be documented as an AE with the verbatim "body temperature increased". • A clinically significant increase in body temperature ≥38 °C should be documented as an AE with the verbatim "fever" or "pyrexia". • Deaths All deaths that occur during the period of observation must be recorded on the AE eCRF and immediately reported as an SAE to the sponsor, regardless of relationship to trial treatment. In addition to reporting as an SAE, the applicable eCRF must be completed. Exemptions to the SAE definition, as defined in Section 10.3.3, also apply for fatal cases. Death should be considered an outcome ("fatal") and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical event on the AE eCRF. If there is more than one AE in a fatal case, the outcome "fatal" should be selected only for the AE leading to death. If the cause of death is unknown and cannot be ascertained at the time of reporting, "unexplained death" should be recorded on the AE eCRF. If the cause of death becomes available later (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term "sudden death" should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death"). Deaths that occur after the AE reporting period should be recorded on the applicable eCRF, regardless of cause. *In Germany only:* Any death, irrespective if causally related to disease progression or not, will be documented as AE and reported as SAE. • Adverse Events Associated with an Overdose or Error in Drug Administration An overdose is the accidental or intentional use of a drug in an amount (per administration or cumulatively) higher than the dose being studied (for BNT411) or higher than the maximum recommended dose according to the authorized product information (for approved concomitant medications). An overdose or incorrect administration of a drug is not itself an AE, but it may result in an AE. Intentional overdoses taken with possible suicidal/self-harming intent should be reported regardless of sequelae. All AEs associated with an overdose or incorrect administration should be documented as an AE in the source data and eCRF and reported as SAE if applicable.

Follow-up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a patient dies during participation in the trial or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any post-mortem findings (including histopathology) if an autopsy or any other testing has been performed. • New or updated information will be recorded in the originally completed eCRF. • The investigator will submit any updated SAE data to the contacts given in Section 10.3.4 within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE Reporting to Sponsor
Safety-related information / Paper-based SAE reports (initial and follow-up reports) have to be sent to the following fax number or email address: **Safety Report Fax No.:** PPD **Safety Report Email Address:** In the case where an investigator or any other trial team member has questions with regards to **safety reporting**, these can be addressed to: **Email:** PPD *Please note **that for medical questions** the medical monitor for this trial should be contacted* (for contact information see Section 8.13). • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE eCRF pages within the designated reporting time frames.

SAE Reporting to Sponsor

- Information for final description and evaluation of a case report may not be available within the required time frames for reporting. Nevertheless, for regulatory purposes, initial reports should be submitted if the following minimal information is available:
    - An identifiable subject (number, initials)
    - A suspected medicinal product
    - An identifiable reporting source (investigator/trial site identification)
    - An event or outcome that can be identified as serious

- After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. If additional information regarding a previously submitted SAE is obtained, a follow-up SAE report should be sent to the sponsor (indicating that this is a "follow-up" report) without delay and accompanied by appropriate anonymous supporting documentation (e.g., hospital reports), until a final outcome and date are available.

- Completed reporting forms need to be signed by an investigator before faxing/mailing them to the safety contact provided above. Blank reporting forms are provided to the investigator during the site initiation visit and are filed in the Investigator Site File (ISF).

- If any medical records (for example hospital discharge reports) are considered as relevant case information by the investigator, it is recommended that the investigator directly provides the medical report to the contact details described above. In the case of an SAE including a hospital stay for the subject, the respective discharge letter needs to be provided by the site as soon as it is available, at a minimum. To ensure clear allocation of the record to a specific subject and SAE, the investigator should additionally complete and sign a paper follow-up form (titled: Additional Information and Follow-Up Form) and provide the follow up form together with the pseudonymized medical record.

- Original, completed reporting forms have to be filed in the ISF, with copies in the Trial Master File. All events initially reported on a paper-based reporting form also have to be documented in the eCRF.

- If explicitly required according to national legislation, the investigator must submit copies of the SAEs to the ethics committee (EC) or authority and retain documentation of these submissions in the Site Trial File.

10.4 Appendix 4: Definition of Reproductive Potential and Contraception

Definition of reproductive potential and measures of contraception for BNT411 are detailed below. Further guidance for other trial treatment agents should be according to the authorized product information (for approved concomitant medications).

Female Patients

In this trial, patients are considered to have reproductive potential, UNLESS they are post-menopausal or permanently sterile:

- A postmenopausal state is defined as no menses, in patients >45 years of age, for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in patients not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

All female patients must agree not to donate eggs (ova, oocytes) for the purpose of assisted reproduction during the trial and for 6 months after receiving the last dose of BNT411.

Female patients of reproductive potential must agree to use adequate contraception during and for 6 months after the last BNT411 administration. Adequate contraception is defined as highly effective methods of contraception (Table 10-2). Birth control methods are considered highly effective if they have a failure rate of less than 1% per year, when used consistently and correctly.

Table 10-2: Highly Effective Methods of Contraception

• Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[1] (oral, intravaginal, or transdermal) in combination with a barrier method or/and an intrauterine device • Progestogen-only hormonal contraception associated with inhibition of ovulation[1] (oral, injectable, or implantable) in combination with a barrier method or/and an intrauterine device • Intrauterine device[2] • Intrauterine hormone-releasing system[2] • Bilateral tubal occlusion[2] • Vasectomized partner[2, 3] • Sexual abstinence[4]
1 Hormonal contraception may be susceptible to interaction with BNT411, which may reduce the efficacy of the contraception method. Therefore, hormonal contraception method alone is not considered as a highly effective method of contraception. **Hormonal contraception should be combined with a barrier method or/and an intrauterine device to be a highly effective method of contraception.**
2 Contraception methods that in the context of this guidance are considered to have low user dependency.
3 Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the woman of child-bearing potential (trial patient) and that the vasectomized partner has received medical assessment of the surgical success.
4 In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

Table adapted from 'Recommendations related to contraception and pregnancy testing in clinical trials. Advisory non-binding guidance represented at the CTFG-meeting in Rome 2014' (MHRA 2014).

Male Patients

1. Recommendations for male patients with pregnant partner:

Male contraception (condom) is recommended in order to avoid exposure of an existing embryo/fetus. Contraception should be continued for 6 months after receiving the last dose of BNT411.

2. Recommendations for male patients with non-pregnant WOCBP partner:

The male patient should use condom during treatment and for 6 months after receiving the last dose of BNT411. For a non-pregnant WOCBP partner, contraception recommendations should also be considered.

All men must also not donate sperm during the trial and for 6 months after receiving the last dose of BNT411.

10.4.1 Collection of Pregnancy Information

Details will be collected of all pregnancies in female participants that occurred after the start of trial intervention and until 90 days after the last dose of BNT411. These details will be collected

after obtaining the necessary signed informed consent from pregnant participants (and if applicable their partners).

After obtaining the necessary signed informed consent from pregnant female partners directly, details will be collected of all pregnancies in female partners of male participants that occurred after the start of trial intervention and until 28 days after the last dose of BNT411. This applies only to male participants who receive BNT411.

The initial and follow-up information must be documented on the paper-based Pregnancy Reporting Form and **submitted to the sponsor within 24 hours** of learning of a participant's pregnancy/partner's pregnancy. The completed form needs to be sent to the Safety Report Fax number or Email detailed in Section 10.3.4. Completed pregnancy forms need to be signed by an investigator before faxing/mailing them to the sponsor. Blank reporting forms are provided to the investigator during the site initiation visit and are filed in the ISF.

The investigator will collect follow-up information on the subject/subject's partner and the neonate and the information will be forwarded to the sponsor. Pregnancy follow-up should describe the outcome of the pregnancy, including any voluntary or spontaneous termination, details of the birth, the presence or absence of any congenital abnormalities, birth defects, maternal or newborn complications and their presumed relation to the BNT411. Generally, the follow-up will be of a duration determined in consultation with the pediatrician.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-trial pregnancy related SAE considered reasonably related to the trial intervention by the investigator will be reported to the sponsor. While the investigator is not obligated to actively seek this information in former trial subjects, he or she may learn of an SAE through spontaneous reporting.

10.5 Appendix 5: Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)

Evaluation of Target Lesions

- **Complete Response** - Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (the sum may not be "0" if there are target nodes).
- **Partial Response** - At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive Disease** - At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on trial (this includes the baseline sum if that is the smallest on trial). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression.)
- **Stable Disease** - Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum of diameters while on trial.

Evaluation of Non-Target Lesions

- **Complete Response** - Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
- **Non-complete response/Non-progressive disease** - Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- **Progressive Disease** - Unequivocal progression of existing non-target lesions will be defined as the overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy (see Section 5.1). In the absence of measurable disease, change in non-measurable disease comparable in magnitude to the increase that would be required to declare progressive disease for measurable disease. Examples include an increase in a pleural effusion from 'trace' to 'large,' an increase in lymphangitic disease from localized to widespread.

Appearance of New Lesions

The appearance of new lesions is considered progressive disease according to RECIST v1.1. Considering the unique response kinetics that have been observed with immunotherapy, new lesions may not represent true disease progression. In the absence of rapid clinical deterioration,

patients may continue to receive trial treatment if investigators consider that patients continue to benefit from treatment.

Evaluation of Overall Response

For the overall response based on RECIST v1.1, confirmation of CR and PR is required by a repeat, consecutive assessment no less than 4 weeks from the date of first documentation. A confirmatory scan will also be required after an initial assessment of progressive disease for the purpose of managing treatment and in order to conduct the exploratory iRECIST analysis. If a patient discontinues the trial due to progressive disease and begins another treatment, a confirmatory scan is not required. If the next protocol-scheduled scan is due within 2 weeks after the confirmatory scan was obtained, the protocol-scheduled scan does not need to be done. Treatment of patients may continue between the initial assessment of progressive disease and confirmation of progressive disease (which is not required by RECIST v1.1). These patients may continue to receive trial therapy beyond confirmed progressive disease if investigators consider that patients continue to receive benefit from treatment. In the absence of clinical deterioration, such modifications to the RECIST may discourage the early discontinuation of treatment and provide a more complete evaluation of trial therapy anti-tumor activity than would be seen with conventional response criteria.

Table 10-3 provides overall responses for all possible combinations of tumor responses in target and non-target lesions with or without the appearance of new lesions.

Table 10-3: Evaluation of Overall Response

Target Lesions	Non-target Lesions	New Lesions	Overall Response
Complete response	Complete response (or no non-target lesion)	No	Complete response
No target lesion[a]	Complete response	No	Complete response
Complete response	Not evaluable[b]	No	Partial response
Complete response	Non-complete response/ non-progressive disease	No	Partial response
Partial response	Non-progressive disease and not evaluable (or no non-target lesion)[b]	No	Partial response
Stable disease	Non-progressive disease and not evaluable (or no non-target lesion)[b]	No	Stable disease
Not all evaluated	Non-progressive disease	No	Not evaluable
No target lesion[a]	Not all evaluated	No	Not evaluable
No target lesion[a]	Non-complete response/ non-progressive disease	No	Non-complete response/ non-progressive disease
Progressive disease	Any	Yes/No	Progressive disease
Any	Progressive disease	Yes/No	Progressive disease
Any	Any	Yes	Progressive disease
No target lesion[a]	Unequivocal progressive disease	Yes/No	Progressive disease
No target lesion[a]	Any	Yes	Progressive disease

[a] Defined as no target lesion at baseline.

[b] Not evaluable is defined as when either no or only a subset of lesion measurements are made at an assessment.

10.6 Appendix 6: iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics

Assessment at Screening and Prior to RECIST 1.1 Progression

Until radiographic disease progression based on RECIST 1.1, there is no distinct iRECIST assessment.

Assessment and Decision at RECIST 1.1 Progression (Section 8.5.1)

For patients who show evidence of radiological PD by RECIST 1.1 as determined by the investigator, the investigator will decide whether to continue a patient on trial intervention until repeat imaging is obtained 4 to 8 weeks later (using iRECIST for patient management). This decision by the investigator should be based on the patient's overall clinical condition.

Any patient deemed clinically unstable should be discontinued from trial intervention at site-assessed first radiologic evidence of PD, and is not required to have repeat tumor imaging for confirmation of PD by iRECIST.

If the investigator decides to continue treatment, the patient may continue to receive trial intervention and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per investigator assessment. Images should continue to be sent into the central imaging vendor for potential retrospective Blinded Independent Central Review (BICR).

Tumor flare may manifest as any factor causing radiographic progression per RECIST 1.1, including:

- Increase in the sum of diameters of target lesion(s) identified at baseline to ≥20% and ≥5 mm from nadir

Note: The iRECIST publication uses the terminology "sum of measurements," but "sum of diameters" will be used in this protocol.

- Unequivocal progression of nontarget lesion(s) identified at baseline
- Development of new lesion(s)

iRECIST defines new response categories, including immune unconfirmed progressive disease (iUPD) and immune confirmed progressive disease (iCPD). For purposes of iRECIST assessment, the first visit showing progression according to RECIST 1.1 will be assigned a visit (overall) response of iUPD, regardless of which factors caused the progression.

At this visit, target and nontarget lesions identified at baseline by RECIST 1.1 will be assessed as usual.

New lesions will be classified as measurable or non-measurable, using the same size thresholds and rules as for baseline lesion assessment in RECIST 1.1. From measurable new lesions, up to 5 lesions total (up to 2 per organ), may be selected as New Lesions – Target.

The sum of diameters of these lesions will be calculated and kept distinct from the sum of diameters for target lesions at baseline. All other new lesions will be followed qualitatively as New Lesions – Non-target.

Assessment at the Confirmatory Imaging

On the confirmatory imaging, the patient will be classified as progression confirmed (with an overall response of iCPD), or as showing persistent unconfirmed progression (with an overall response of iUPD), or as showing disease stability or response (iSD/iPR/iCR).

Confirmation of Progression

Progression is considered confirmed, and the overall response will be iCPD, if ANY of the following occurs:

- Any of the factors that were the basis for the iUPD at the previous visit show worsening
    - For target lesions, worsening is a further increase in the sum of diameters of ≥5 mm, compared to any prior iUPD time point
    - For nontarget lesions, worsening is any significant growth in lesions overall, compared to a prior iUPD time point; this does not have to meet the "unequivocal" standard of RECIST 1.1
    - For new lesions, worsening is any of these:
        - An increase in the new lesion sum of diameters by ≥5 mm from a prior iUPD time point
        - Visible growth of new nontarget lesions
        - The appearance of additional new lesions
- Any new factor appears that would have triggered PD by RECIST 1.1

Persistent iUPD

Progression is considered not confirmed, and the overall response remains iUPD, if:

- None of the progression-confirming factors identified above occurs AND
- The target lesion sum of diameters (initial target lesions) remains above the initial PD threshold (by RECIST 1.1)

Additional imaging for confirmation should be scheduled 4 to 8 weeks from the imaging on which iUPD is seen. The assessment of the subsequent confirmation imaging proceeds in an identical manner, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR.

Resolution of iUPD

Progression is considered not confirmed, and the overall response becomes iSD/iPR/iCR, if:

- None of the progression-confirming factors identified above occurs, AND
- The target lesion sum of diameters (initial target lesions) is not above the initial PD threshold

The response is classified as iSD or iPR (depending on the sum of diameters of the target lesions), or iCR if all lesions resolve.

In this case, the initial iUPD is considered to be pseudo-progression, and the level of suspicion for progression is "reset." This means that the next visit that shows radiographic progression, whenever it occurs, is again classified as iUPD by iRECIST, and the confirmation process is repeated before a response of iCPD can be assigned.

Management Following the Confirmatory Imaging

If repeat imaging does not confirm PD per iRECIST, and the patient continues to be clinically stable, trial treatment may continue and follow the regular imaging schedule. If PD is confirmed, patients will be discontinued from trial treatment.

Detection of Progression at Visits After Pseudo-progression Resolves

After resolution of pseudo-progression (i.e. achievement of iSD/iPR/iCR), iUPD is indicated by any of the following events:

- Target lesions
  - Sum of diameters reaches the PD threshold (≥20% and ≥5 mm increase from nadir) either for the first time, or after resolution of previous pseudo-progression. The nadir is always the smallest sum of diameters seen during the entire trial, either before or after an instance of pseudo-progression.
- Nontarget lesions
  - If nontarget lesions have never shown unequivocal progression, their doing so for the first time results in iUPD.
  - If nontarget lesions have shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of non-target lesions, taken as a whole.
- New lesions

- New lesions appear for the first time

- Additional new lesions appear
- Previously identified new target lesions show an increase of ≥5 mm in the new lesion sum of diameters, from the nadir value of that sum

- Previously identified non-target lesions show any significant growth

If any of the events above occur, the overall response for that visit is iUPD, and the iUPD evaluation process (see Assessment at the Confirmatory Imaging above) is repeated. Progression must be confirmed before iCPD can occur.

10.7 Appendix 7: Veterans Administration Lung Study Group (VALG) Staging System for SCLC

Stage	Characteristics
Limited SCLC	Disease confined to the ipsilateral hemithorax which can be safely encompassed within a radiation field
Extensive SCLC	Disease beyond the ipsilateral hemithorax, including malignant pleural or pericardial effusion or hematogenous metastases

SCLC = small cell lung cancer.

10.8 Appendix 8: Risk-benefit assessment of COVID-19 vaccination in BNT411-01 trial

BNT411 is a highly potent and selective small molecule TLR7 agonist of the imidazoquinoline family which comprises other TLR ligands such as imiquimod (CAS-No. 99011-02-6), resiquimod (CAS-No. 144875-48-9) and 852A (CAS-No. 532959-63-0).

Clinically, due to its mechanism of action, chills, fever, malaise and all other flu-like symptoms may be the first and most commonly seen adverse reactions in patients treated with BNT411.

At this time, there are three COVID-19 vaccines authorized and recommended in the US: the Pfizer-BioNTech COVID-19 vaccine (COMIRNATY), Moderna COVID-19 vaccine (Spikevax), and Johnson & Johnson/Janssen COVID-19 vaccine. These vaccines are described on the US Centers for Disease Control and Prevention (CDC)'s vaccine page. In the EU and the UK, the same vaccines are authorized and recommended with the addition of the Oxford/AstraZeneca COVID-19 vaccine. The Pfizer-BioNTech COVID-19 vaccine (COMIRNATY) and the Moderna COVID-19 vaccine (Spikevax) are mRNA vaccines, whereas both the Johnson & Johnson/Janssen and Oxford/AstraZeneca COVID-19 vaccines are viral vector vaccines. None of the vaccines are a live virus vaccine mentioned by the protocol as per exclusion criterion 2 (i.e., received any live vaccine within 4 weeks of the start of trial treatment).

The COVID-19 pandemic is an ongoing pandemic with different stages and impacts at any one time across the whole world. The governments of the countries involved in this trial have started a nationwide vaccination program including vaccination for oncology patients. All prominent regulatory, government and professional bodies have recommended COVID-19 vaccination even in oncology patients under active treatment. To date, there is no clear or specific guidance for patients enrolled in interventional oncology clinical trials and decisions should be taken on a case-by-case basis.

Recently results for the short-term safety of the Pfizer-BioNTech mRNA COVID-19 vaccine in oncology patients treated with immune checkpoint inhibitors were published (Waissengrin et al. 2021). Considering the high mortality rates due to COVID-19 in cancer patients undergoing treatment, the data supports current guidelines and calls for vaccination of patients being treated with immune checkpoint inhibitors, especially during pandemic surges.

The interaction of BNT411 with all the vaccines approved in the US, EU, and UK is not known. It is unlikely that there will be any data of TLR7 in combination with any of the COVID-19 vaccines. However, the sponsor assesses the risk of significant side effects of BNT411 in combination with COVID-19 vaccine to be low. The National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO) recommend for the COVID-19 vaccine to be administered on the same day as oncology therapy, including immunotherapy. However, since BNT411 is still under development in a Phase 1 trial and no comprehensive clinical data is available yet, the sponsor would recommend at least a 7-day interval between COVID-19 vaccination and administration of BNT411 as a precaution. The Pfizer/ BioNTech COVID-19 vaccine COMIRNATY results in high antigen expression for around 72 h which then decreases to low levels after approximately one week (EMA assessment report 2020). If administered within the timeframe of high COVID-19 antigen expression, BNT411 is anticipated to strongly boost COVID-19 vaccine induced T-cell responses. On one hand this could result in an improved efficacy of the vaccine however, on the other hand it could also lead to an increased

reactogenicity as well as to reduced expansion of tumor antigen specific T cells due to T cell competition. For this reason, the sponsor would recommend at least a 7-day interval between BNT411 treatment and COVID-19 vaccination.

A longer interval may be necessary during the DLT-observation period, before the dose of BNT411 has been declared safe as per the trial design. The oncologist should always assess the situation on an individual basis and discuss with the sponsor. Considering the high morbidity and mortality from COVID-19 in patients with cancer, the benefits of vaccination are likely to far outweigh the risks of vaccine-related AEs in patients enrolled in clinical trials (Desai et al. 2021).

10.9 Appendix 9: COVID-19 vaccination in BNT411-01 trial during the pandemic

BioNTech as the sponsor of the BNT411-01 trial recommends that patients and their physicians discuss on an individual basis the risks and benefits of COVID-19 vaccination in the context of the BioNTech oncology trials, considering also guidelines from the FDA, EMA, US Centers for Disease Control and Prevention (CDC), American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO) and local agencies. Taking this into account, COVID-19 vaccination may be performed with the following recommendations:

- Patients with prior COVID-19 vaccination may be allowed to enter the trial with a wash-out period of at least 7 days since the last COVID-19 vaccine dose.
- For patients already enrolled in the clinical trial and still receiving trial treatment, COVID-19 vaccination may be allowed if an interval of at least 7 days is ensured between the COVID-19 vaccination and the trial treatment.
- COVID-19 vaccination during the DLT evaluation period in the dose escalation parts of the trial should be avoided to prevent any confounding effect of the vaccination on the DLT evaluation. However, as the data in dose escalation are accumulating, the decision to vaccinate should be made by the treating oncologist, and any decision should be discussed with the sponsor's Medical Monitor.
- Administration of COVID-19 vaccine during participation in the BNT411-01 trial should be documented as a concomitant medication.
- Previous administration of COVID-19 vaccine or past confirmed infection of COVID-19 by reverse transcription polymerase chain reaction (RT-PCR) before enrolment in the BNT411-01 trial should be documented in the prior/concomitant medication form and medical history, respectively.

10.10 Appendix 10: Abbreviations

ADL	Activities of Daily Living
AEs	adverse events
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APCs	antigen presenting cells
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area-under-the-concentration-time curve
Beta hCG	beta-human chorionic gonadotropin
BSA	body surface area
BW	body weight
CI	confidence interval
CL	clearance
C_{max}	maximum concentration
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CR	complete response
CRS	cytokine release syndrome
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLs	cytotoxic T-lymphocytes
C_{trough}	trough concentration
CYPs	cytochrome P450 enzymes
DAMPs	danger-associated molecular patterns
DC	dendritic cells
DCR	disease control rate
DEC	dose-expansion cohort
DLTs	dose-limiting toxicities
DOR	duration of response
ECG	electrocardiogram

ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
ES-SCLC	extensive stage small cell lung cancer
FFPE	formalin fixed paraffin embedded
FIH	first-in-human
FSH	follicle stimulating hormone
GFR	glomerular filtration rate
GLP	Good Laboratory Practice
GM-CSF	granulocyte-macrophage colony stimulating factor
G-CSF	granulocyte-colony stimulating factor
HBV	hepatitis B virus
HCV	hepatitis C virus
Hgb	hemoglobin
HIV	human immunodeficiency virus
HLA	human leucocyte antigen
ICD	immunogenic cell death
ICF	informed consent form
iCPD	immune confirmed progressive disease
iCR	immune complete response
iDCR	immune disease control rate
IEC	Independent Ethics Committees
IFNα	interferon alpha
IMP	Investigational Medicinal Product
INR	International normalized ratio
iORR	immune objective response rate
iPR	immune partial response
irAEs	immune-related AEs
IRB	Institutional Review Board
iRECIST	immune RECIST
IRR	infusion-related reaction
ISF	Investigator Site File

iSD	immune stable disease
ITT	intent to treat
iUPD	immune unconfirmed progressive disease
LS-SCLC	limited-stage small cell lung cancer
MABEL	minimum anticipated biological effect level
mAbs	monoclonal antibodies
MDRD	modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MoA	mode of action
MRI	magnetic resonance imaging
MTD	maximal tolerated dose
MUGA	multigated acquisition
NCI	National Cancer Institute
NIMPs	Non-Investigational Medicinal Products
NOAEL	no-observed-adverse-effect level
NK	natural killer
NS	non-serious
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
PAMP	pathogen associated molecular patterns
PBMCs	peripheral blood mononuclear cells
PCI	prophylactic cranial irradiation
PD	progressive disease
pDCs	plasmacytoid dendritic cells
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PT	Preferred Term
QTc	corrected QT interval

RDI	relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended phase 2 dose
RP2DR	RP2D range
SAE	serious adverse event
SAP	statistical analysis plan
SCCHN	squamous cell carcinoma of the head and neck
SCLC	small cell lung cancer
SCr	serum creatinine
SD	stable disease
SJS	Steven Johnsons Syndrome
SLE	systemic lupus erythematosus
SmPC	summary of product characteristics (EMA)
SoA	Schedule of Activities
SOC	System Organ Class
SRC	Safety Review Committee
SUSAR	suspected unexpected serious adverse reaction
$T_{1/2}$	terminal half-life
T3	triiodothyronine
T4	thyroxine
TAAs	tumor-associated antigens
TCR	T-cell receptor
TEAEs	treatment-emergent adverse events
TLR7	toll-like receptor 7
T_{max}	time to Cmax
TMB	tumor mutational burden
TME	tumor microenvironment
TSH	thyroid stimulating hormone
ULN	upper limit normal
USPI	US prescribing information (FDA)
VALG	Veterans Administration Lung Study
VD	volume of distribution

WBC	white blood count
WOCBP	women of childbearing potential

10.11 Appendix 11: Protocol Version/Amendment History

10.11.1 Version 2: 30 October 2019

Overall Rationale for the update to Version 2

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	~~Data Monitoring~~ Safety Review Committee	Data Monitoring Committee replaced by Safety Review Committee to ensure consistency throughout the protocol
Tables 1-1 and 1-2 Schedule of Activities	Safety follow-up 1, visit window +5 days aligned with section 7.2.2 (replaced +/- with +5 days).	Typo corrected
	Coagulation factors and endocrine: X under Unscheduled visit.	Correction of activity in the Table
	Footnotes 19 (Medical History): Medical history includes cancer history and 20 (Prior/Concomitant Medications and Non-Drug Therapies): Prior/Concomitant Medications and Non-Drug Therapies include all anti-cancer pre-treatments added to Table 1-1 and footnotes 22 and 23 added to table 1-2, respectively.	Footnotes added to better explain what will be collected under Medical history and Prior/Concomitant Medications and Non-Drug Therapies.
	Added: Informed Consent for genetic testing to both Table 1-1 and 1-2	Activity of taking informed consent for genetic testing was missing in Version 1
	Table 1-1: Cycle 1-2, D3, vital signs: X added	Correction of vital signs activity in the table 1-1, aligning with table 1-2

	Table 1-2, footnote 17: After 4 cycles, prophylactic cranial irradiation (PCI) is permitted as per local guidelines and will be reported on the ~~Prophylactic Cranial Irradiation~~ Cancer Radiotherapy eCRF. Table 1-2 Survival Follow-up: every 12 weeks after last dose Added X under survival follow-up with footnote 21 (Table 1-1) and 24 (Table 1-2): Prior/Concomitant Medication and Non-Drug therapies only for BNT related AEs	Correction of the eCRF form to report PCI Alignment of Table 1-2 with Table 1-1 Added to align with Section 10.3.3
4.1.1.1 Dose Escalation in Part 1A	After completion of the DLT period for each cohort, the SRC will review the data from the DLT period – including but not limited to all relevant safety and clinical data – to propose a dose level for the next cohort of patients; PK and pharmacodynamics data, if available, will also be taken into consideration.	Rephrased to make it clearer that PK and pharmacodynamics data are not mandatory for dose decision making, but will be considered if available.
4.5 End of Trial Definition	However, maximal trial duration is 3 years after the last patient's first treatment. Thereafter, the Sponsor will ensure treatment for ongoing patients with a potential treatment benefit.	Rephrased to further clarify, deleting the words "post-trial treatment" that might be confusing
6.1.2 Non Investigational Medicinal Products	Etoposide: The dose will be calculated using the Mosteller formula (BSA [m2] = square root((height [cm] x weight [kg])/3600))	Explained how to calculate the etoposide dose, which was not mentioned in Version 1.

6.5 Concomitant Therapy and Procedures	Replaced “enrollment” by “signing of the Informed Consent Form: Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) or procedure that the patient is receiving or undergoing at the time of signing the informed consent or receives or undergoes during the trial must be recorded Added “treatment”: The prohibited medications while on trial treatment are as follows	Rephrased to clarify the starting point of recording concomitant therapy Rephrasing for clarification’s sake
7.1 Discontinuation of Trial Treatment	Added: Lost to follow-up	Missing in Version 1
8.1 Screening procedures	Added: Evaluation of left ventricular function, either by echocardiogram (ECHO) or multigated acquisition (MUGA) scan, will be performed at Screening and as clinically indicated at other time points. See new section 8.6.8	ECHO or MUGA mentioned in the SoAs, were not listed under the screening procedures
8.6.1 Physical Examination	Replaced “baseline” with “screening” and change of wording: Abnormalities (clinical significant findings) observed at screening will be recorded on the general Medical History/Concomitant Diseases page of the eCRF, if started before signing the ICF. New or worsened clinically significant abnormalities after signing	Rephrased for further clarification and to better align sections 8.6.1 and 10.3.1 Definition of AE

	the ICF have to be recorded on the AE page of the eCRF.	
8.6.3 Electrocardiograms	Added: For the assessment the subjects will be in the supine position, lying still and quietly until the assessment has been done.	The subject's position was not mentioned in Version 1.
8.7.6 Death Events	~~If the patient withdraws completely from the trial, the trial staff may use a public information source to obtain information about survival status only, if not applicable by local law.~~	Removed because not applicable for a phase1/safety trial.
8.8 Treatment of Overdose	In addition, overdose and/or medication errors with BNT411 must also be recorded in the AE page of the eCRF ~~whether~~ when associated with an AE ~~or not~~.	Rephrased to align with section 10.3.3
8.11 Genetics	Where required by local or country specific regulations, each patient must sign a separate informed consent form if he or she agrees to ~~provide samples for genomic biomarker analysis~~ genetic testing (DNA and RNA) of the collected samples.	Rephrased to avoid confusion about genetic testing.
8.12 Biomarkers	Additionally, ~~genomic analyses~~ targeted sequencing will be performed for TCR profiling in order to identify potential markers that may predict clinical response (see Section 8.11).	Rephrased to avoid confusion about genetic testing
Table 10-1 Protocol-required Safety Laboratory Assessments	Albumin assessment added under Biochemistry	Albumin assessments were not listed under the screening procedures, whereas an Albumin level is mentioned under inclusion criteria:

		Albumin level at screening ≥3 mg/dL
10.3.1 Definition of AE	Rephrased: New conditions or worsening of pre-existing conditions detected or diagnosed after signing patient informed consent ~~even though it may have been present before the start of the trial~~.	Rephrased to align sections 8.6.1 and section 10.3.1
8.5.1 Anti-tumor Activity assessment – CT/MRI Imaging	Anti-tumor activity will be evaluated according to RECIST 1.1 (Eisenhauer et al., 2009) and iRECIST criteria (Seymour et al., 2017) ~~and include estimation of ORR, DCR and DOR, and iORR, iDCR and iDOR~~ (see ~~Section 3,~~ Sections 10.5 and 10.6).	Endpoints deleted, will be statistically estimated
Synopsis, Table 1-1 and 1-2 footnote 11, 4.1 Overall Design, 8.5.1 Anti Tumor Activity Assessment CT-MRI Imaging	Efficacy will be assessed by on-treatment imaging at Week 6 (+7 days), every 6 weeks (±7 days) for ~~50~~ 48 weeks, and every 12 weeks (±7 days) thereafter until disease progression is assessed by the investigator (unless the investigator elects to continue treatment), withdrawal of consent, trial termination by the Sponsor, or death, whichever occurs first, regardless of whether patients start a new anti-cancer therapy.	Changed 50 weeks to 48 weeks, to avoid confusion about when to take images – 48 weeks is a multiplier of 6 weeks

10.11.2 Version 3.0: 07 May 2020

Rationale for the update to version 3.0:

Minor editorial changes, such as the correction of typing errors, are not specifically listed.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	IMP changed to BNT411 under Primary Endpoints and Exploratory Endpoints.	Rephrased for consistency.
	Trial design, Part 2 shortened for clarity: Deleted: "A "backfilling" approach will be implemented where more patients will be enrolled in selected dose levels in both Part 1A and Part 1B to explore further safety and anti-tumor activity."	Rephrased for clarity.
	Added to Key Exclusion Criteria: "any live vaccine received within 4 weeks of the start of trial treatment"	Added for consistency.
	Added to Key Exclusion Criteria: "Any contraindications to atezolizumab, carboplatin or etoposide as per USPI or SmPC in Part 1B"	Added for consistency.
Schedule of Activities Part 1A (Table 1-1)	Serology added to the table as country specific testing in Germany for HIV and Hepatitis B/C at screening visit. Including new footnote 22.	Requested by EC Cologne, Germany.
	Footnote 9: ECHO or MUGA scan: Country specific information added for Germany, only ECHO scan permitted.	Requested by EC Cologne Germany.
	Pregnancy Test in Cycle 3-4 and Cycle 5-N: "As indicated clinically per investigator's assessment and per local guidelines and regulations." Footnote 18: 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.	Rephrased for clarity.

Section # and Name	Description of Change	Brief Rationale
Schedule of Activities Part 1B (Table 1-2)	Serology added to the table as country specific testing in Germany for HIV and Hepatitis B/C at screening visit. Including new footnote 25.	Requested by EC Cologne, Germany.
Schedule of Activities Part 1B (Table 1-2)	Footnote 1: Added: "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)."	Rephrased for consistency.
	Footnote 9: ECHO or MUGA scan: Country specific information added for Germany, only ECHO scan permitted.	Requested by EC Cologne, Germany.
	Footnote 12: Added "or atezolizumab, or carboplatin, or etoposide, whichever occurs later"	Rephrased for consistency.
	Footnote 13: Country-specific information added: "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 Section 12.2.1 for further details."	Rephrased for consistency.
	Pregnancy Test in Cycle 3-4 and Cycle 5-N: "As indicated clinically per investigator's assessment and per local guidelines and regulations." Footnote 21: 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.	Rephrased for clarity.

Section # and Name	Description of Change	Brief Rationale
	New footnote 26 added: "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)."	Rephrased for consistency.
Schedule of Activities (Table 1-3, and 1-4)	Triplicate ECG assessments added to Day 1 Visit of Cycle 3-N, before and at the end of BNT411 infusion in Phase 1A. Urine sampling added for any unscheduled visits in Part 1A and Part 1B.	Correction of inconsistency between table and footnote.
Schedule of Activities New Table 1-5	Added: Table 1 5 Overview of Safety Reporting in Different Countries	Added due to country specific amendments introduced with this protocol version.
Schedule of Activities (prev. Table 1-6, now 1-7)	Timing of immune phenotyping samples specified to "D1 (pre-dose), 24 hours / D2 (±1 hours) and 48 hours / D3 (±2 hours) after start of infusion in Cycles 1 and 2."	Time point of biomarker sampling further specified.
Schedule of Activities (prev. Table 1-7, now 1-8)	D2 replaced by D1 Timing of immune phenotyping samples specified to: "D1 (pre-dose) and at D3 i.e. 24 hours (±1 hours) after start of infusion of BNT411 in Cycles 1 and 2."	Time point of biomarker sampling further specified.
2.3.2 Potential Risks Associated with BNT411 in Combination with Atezolizumab, Carboplatin, and Etoposide	New section added. Further information given on the risk mitigation strategy of BNT411 given in combination with atezolizumab, carboplatin, and etoposide in Part 1b.	Requested by EC Cologne, Germany.
2.3.3 Benefit Assessment	New text added explaining benefits of BNT411 as a monotherapy anticancer agent.	Requested by EC Cologne, Germany.
2.3.4 Potential Benefits Associated with BNT411 in	New section added.	Requested by EC Cologne, Germany.

Section # and Name	Description of Change	Brief Rationale
combination with Atezolizumab, Carboplatin, and Etoposide	The text in this section covers potential benefits associated with combination therapy and previously belonged to section 2.3.3	
4.1.1.1 Dose Escalation in Part 1A	Added: “Once a single-patient cohort has been expanded, all future cohorts will follow the 3+3 design.”	Rephrased for clarity.
	Added: “Prolongation of the hospitalization beyond 24 hours may be performed at the investigator’s discretion if deemed necessary based on potential risks related to the trial treatment and clinical status of the patient.”	Additional information added for clarification.
	Added/rephrased: “As long as patients do not experience a DLT, patients who have been replaced can continue with BNT411 treatment and follow the same trial procedures until unacceptable toxicity, documented disease progression, and/or the onset of a new anti-cancer therapy (palliative radiotherapy of, for example, painful bone metastases not defined as target lesions will be allowed).”	Rephrased for clarity.
4.1 Overall Design (and Synopsis)	Trial design, Part 2 shortened for clarity: Deleted: “A “backfilling” approach will be implemented where more patients will be enrolled in selected dose levels in both Part 1A and Part 1B to explore further safety and anti-tumor activity.”	Rephrased for clarity.
4.1.3 Adaptive Trial Design Elements	Added: “The backfilling will be performed once the RP2Ds for both Part 1A and Part 1B are defined up to a total of 12 patients per cohort. This will be implemented through protocol amendment for Part 2.”	Rephrased for clarity.
5.1 Inclusion Criteria	9. Albumin level at screening ~~≥3 mg/dL~~ ≥30 g/L	Correction
	Added to 15.: “Further guidance on contraceptive measures for female patients can be found in Section 10.4.”	Added for clarification.

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria (and Synopsis)	Added to 2.: "any live vaccine within 4 weeks of the start of trial treatment"	Added for consistency.
	Added: "23. Any contraindications to atezolizumab, carboplatin or etoposide as per USPI or SmPC in Part 1B"	Added for consistency.
	Added note to exclusion criteria 16: "Country specific criteria for Germany: To confirm that a patient would be eligible, an active infection with HIV/Hepatitis B or C should be ruled out by serum blood test (see Section 12.2.1)."	Requested by EC Cologne, Germany.
6.1 Trial Treatment(s) Administered	Text added specifying that BNT411 is considered IMP in all countries participating in this trial. Additionally, in Germany and Spain only, atezolizumab, carboplatin, and etoposide will also be considered IMPs.	Added for clarification.
6.1.1 BNT411 (and Synopsis)	Previous headline: "Investigational Medicinal Product (IMP)" was replaced by "BNT411". Deleted first line: "The IMP in both Part 1A and Part 1B is BNT411."	Changed due to country specific amendments introduced with this protocol version.
6.1.2 Atezolizumab, Carboplatin, and Etoposide (and Synopsis)	Previous headline: Non-Investigational Medicinal Products (NIMP) was replaced by "Atezolizumab, Carboplatin, and Etoposide". Deleted first line: "Atezolizumab, carboplatin, and etoposide are background treatments and are considered NIMPs."	Changed due to country specific amendments introduced with this protocol version.
6.5 Concomitant Therapy and Procedures	Added: "For further guidance on prohibited and restricted medications, please refer to the IB for BNT411, and USPI or SmPCs for atezolizumab, carboplatin and etoposide."	Added for clarification.
6.6.6 Safety Alert Communication Plan	Section added	Added for clarification.

Section # and Name	Description of Change	Brief Rationale
6.7.4.1 Immune-related Adverse Events (irAEs) – For Part 1B Only (Attachment 12.1 added as new section)	Added: "Furthermore, guidelines for the monitoring and management of potential cytokine release syndrome (CRS) can be found in Attachment 12.1."	Added for clarification.
6.7.5 Safety Stopping Criteria	Added (in italics)/rephrased: "The SRC will decide whether and when the trial can be restarted *after approval of a substantial amendment by the regulatory authorities and EC*; or with the sponsor's concurrence, whether the trial should be stopped."	Added for clarification.
7.2.2 Safety Follow-up Evaluations	Added: "Separate treatment discontinuation visits should also be done after discontinuation of atezolizumab, carboplatin and etoposide, if it occurs ≥21 days later than BNT411."	Added for clarity.
8.1 Screening Procedures	Added footnote: "Note: country specific information for Germany: left ventricular function should only be assessed by an ECHO scan (see Section 12.2.1)."	Requested by EC Cologne, Germany.
	Added footnote: "Country specific information 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 (see Section 12.2.1)."	Requested by EC Cologne, Germany.
8.6.7 Pregnancy Testing	Added: "A serum pregnancy test is performed at screening. Thereafter, urine pregnancy test is sufficient unless indicated otherwise. A serum pregnancy test is warranted to confirm a positive urine pregnancy test."	Added for clarification.

Section # and Name	Description of Change	Brief Rationale
8.6.8 Echocardiogram or multigated acquisition scan	Added footnote: "Note: country specific information for Germany: left ventricular function should only be assessed by an ECHO scan (see Section 12.2.1)."	Requested by EC Cologne, Germany.
8.8 Treatment of Overdose	Added: "Guidance on overdose for atezolizumab, carboplatin and etoposide should be referred to SmPC and USPI."	Additional information added for clarification.
8.12 Biomarkers	Added: "Biomarker analyses may be deferred or not performed, if during or at the end of the trial, it becomes clear that the analysis will not have sufficient scientific value for biomarker evaluation, or if there is not enough sample to allow adequate evaluation. In the event that the trial is terminated early or shows poor clinical efficacy, completion of biomarker assessments is based on justification and intended utility of the data."	Added to clarify that biomarker analysis is not obligatory.
9.3 Analysis Sets	IMP changed to BNT411 for the modified ITT and the safety set.	Rephrased due to country specific amendments introduced with this protocol version.
9.4 Statistical Analysis	9.4.1: IMP changed to "trial treatment (i.e. BNT411, or atezolizumab, carboplatin, and etoposide)." 9.4.2: IMP changed to BNT411 under Primary Endpoint(s) IMP changed to "trial treatment" in the paragraph defining AEs.	Rephrased due to country specific amendments introduced with this protocol version.
9.4 Statistical Analysis	Moved pharmacodynamics assessment of biomarkers from 9.3 Secondary Endpoint(s) to 9.4. Exploratory endpoint(s).	Correction of inconsistency between chapter 3 and chapter 9.
10.2 Appendix 2: Clinical Laboratory Tests	Endocrine tests: "free T3 and free T4" rather than "T3 and T4"	Correction of inconsistency between SoAs and Table 10.1.

Section # and Name	Description of Change	Brief Rationale
	Country-specific serology testing added for Germany.	
10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	IMP exchanged with "trial treatment" to align with the statistical section. Except in the section specifying reporting of SAEs after last dose of IMP. Added to "Period of observation": "In Germany, all SAEs, regardless of relatedness, that occur in a patient throughout his or her lifetime should be reported (Section 12.2.1)" Deleted from "SAE exemptions": "SAEs occurring after the period of observation or after initiation of another anti-cancer therapy will not be considered an SAE."	Rephrased due to country specific amendments introduced with this protocol version.
10.4 Appendix 4	Added to Table 10-2: "Therefore, hormonal contraception method alone is not considered as a highly effective method of contraception. Hormonal contraception should be combined with a barrier method or/and an intrauterine device to be a highly effective method of contraception." Added contraception recommendations for male patients.	Requested by BfArM, Germany.
10.4.1 Collection of Pregnancy Information	"IMP" exchanged with "BNT411"	Rephrased due to country specific amendments introduced with this protocol version.
10.8 Appendix 8: Abbreviations	Two missing abbreviations were added.	Correction
11 References	Three references were added from new Section 12.1.	Update
12.1 Management Recommendations in Case of a Potential Cytokine	New section added	Added for better guidance and clarification to the investigators.

Section # and Name	Description of Change	Brief Rationale
Release Syndrome (CRS)		
12.2 Country Specific Information	New section added	Overview of all country specific information is provided in this new section

10.11.3 Version 4.0: 13 November 2020

Minor editorial changes, such as the correction of typing errors, are not specifically listed.

Section # and Name	Description of Change	Brief Rationale
Front page and headers throughout	Change of sponsor from BioNTech Small Molecules GmbH to BioNTech SE	Change of sponsor
Schedule of Activities Part 1A and 1B (Table 1-1 and Table 1-2)	21-day time window prior to Screening added for ECHO/MUGA	Correction to match time window for CT/MRI-scan
	Survival follow-up to start after all other protocol required visits have been completed rather than 12 weeks after last dose.	Correction
	24-hour time window for laboratory assessments corrected to 3 days.	Correction
PK sampling and ECG assessment in Part 1A and 1B (Table 1-3 and 1-4 and Section 8.9)	Added: "Six-hour urine collection after start of BNT411 infusion and total volume collected should be documented." Removed: Urine sampling later than 6 hours after start of BNT411 infusion.	Specification of urine sampling
	Footnotes X and E3 rewritten for clarification: Blood sampling/ECG only to be performed in potential additional patients enrolled to expand the cohorts for RP2D confirmation.	Clarification
Overview of Safety Reporting in Different Countries (Table 1-5)	Added for all countries to the survival follow-up phase: "Trial procedure related AEs" Added for USA, UK, and Spain beyond trial closure: "Trial procedure-related SAEs"	Corrected for consistency with the rest of the protocol
Section 4.1.3 Adaptive Trial Design Elements	Added: "Bifurcation is planned to start when Part 1A monotherapy dose level 5 (2.4 µg/kg) evaluation is completed and considered safe. At this point,	Bifurcation further specified

Section # and Name	Description of Change	Brief Rationale
	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 considered to be the anticipated minimally efficacious dose. If minimal pharmacodynamics activity is not reached when monotherapy dose level 5 is completed, bifurcation to Part 1B may happen at a higher dose level. Bifurcation can also start at a lower dose level than dose level 5, if pharmacodynamics activity is seen earlier. However, the following rule always applies: the dose level of BNT411 in Part 1B at any given time will always be one dose level below that in Part 1A. Decision to bifurcate at any given dose level will be discussed and agreed by the SRC."	
6.6 Dose Modifications And 2.3.2 Potential Risks Associated with BNT411 in Combination with Atezolizumab, Carboplatin, and Etoposide	~~Neither for other imidazoquinoline compounds nor for BNT411 indications for organ-specific autoimmunity have been identified.~~ No indications of organ-specific autoimmunity have been identified for BNT411, or for any other imidazoquinoline compounds.	Rephrased for clarity
8.7.6 Death Events	Added: "Deaths clearly related to the progression of the disease will not be documented and reported as AEs and SAEs. These deaths must be collected on the death page of the eCRF."	SAEs due to disease progression were exempted from the standard expedited reporting process
8.7.7 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs	Added: statement that SAEs due to disease progression will be exempted from the standard expedited reporting process. Deleted: "~~However, specific symptoms resulting from the progression and fatal cases due to the progression have to be documented as AEs and reported as SAEs if applicable.~~"	SAEs due to disease progression were exempted from the standard expedited reporting process

Section # and Name	Description of Change	Brief Rationale
8.9 Pharmacokinetics	Removed: "Serum samples" Adapted urine sampling as in Tables 1-3 and 1-4 (see above)	Specification of urine sampling
	Accumulation ratio [R_A] added to PK parameters	Specification of PK measurements
8.14 24/7 Coverage for Urgent Protocol-related Medical Questions	Updated with new ICON contact details.	Update
10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Added to "Events NOT Meeting the AE Definition": • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient's condition. However, specific symptoms at time of progression that are considered that may be caused by other reason, and fatal cases where other reason rather than the PD may not be discarded and will have to be documented as AEs and reported as SAEs if applicable. Deleted: • ~~The progression of underlying disease (e.g. new metastases) during trial participation is not considered an AE. However, specific symptoms resulting from the progression and fatal cases due to the progression have to be documented as AEs and reported as SAEs if applicable.~~	Updated to match criteria for SAE reporting
10.3.3 Recording and Follow-Up of AE and/or SAE	~~The period of observation starts after informed consent has been obtained. After informed consent, but prior to initiation of trial treatment, all AEs (but only SAEs caused by a protocol-mandated~~	Updated to match criteria for SAE reporting

Section # and Name	Description of Change	Brief Rationale
	~~intervention) should be reported until 60 days after the last dose of trial treatment.~~ The period of observation starts after informed consent has been obtained. After informed consent, but prior to initiation of trial treatment, all AEs and SAEs should be reported until 60 days after the last dose of trial treatment.	

10.11.4 Version 5.0: 01 July 2022

Minor editorial changes, such as the correction of typing errors, are not specifically listed.

Section # and Name	Description of Change	Brief Rationale
Sponsor signature page	Change of sponsor signatory from: PPD MD (Chief Medical Officer) to: PPD MD (Senior Director Clinical Development)	Update
Section 1.3.1 Dose Escalation Phases (Parts 1A and 1B) And Section 4.4 Dose and Schedule Rationale And Section 6.1 Trial Treatment(s) Administered And Section 8 Trial Assessments and Procedures	Added reference to COVID-19 addendum V3.0 and reference to Sections 10.8 and 10.9 with information about COVID-19 vaccinations during the trial.	Changes made due to the COVID-19 pandemic.
Section 1.3 Schedule of Activities (SoA) Table 1-1 Schedule of Activities – Part 1A and Table 1-2 Schedule of Activities – Part 1B	Footnote added (#24 in Table 1-1 and #28 in Table 1-2, same text): "The visit window of +2d on Day 3 should only be used if absolutely necessary due to immune phenotyping."	Time windows specified.
Section 1.3 Schedule of Activities (SoA) Table 1-1 Schedule of Activities – Part	Added to footnote #4: "Physical examination should be performed before drug administration." New footnote #12: "ECOG status should be assessed before drug administration."	Clarification of trial procedures.

Section # and Name	Description of Change	Brief Rationale
1A and Table 1-2 Schedule of Activities – Part 1B		
Section 1.3 Schedule of Activities (SoA) Table 1-7 Biomarker table – in Part 1A and Table 1-8 Biomarker table – in Part 1B	Footnote #5 moved from the first column "TCR profiling [5]" to each of the "X"s to clarify that no TCR profiling required at C2D1.	Clarification of trial procedures.
Section 4.1.1.1 Dose Escalation in Part 1A	Added: "The safety monitoring period is reduced to at least 24 hours when expanding a dose level which has already been declared safe."	Clarification of trial procedures.
	Added: "The sponsor can backfill a certain dose level cohort to explore and generate more safety, PK, pharmacodynamics, and anti-tumor data up to a total of 14 patients in a given cohort. Staggering would not be implemented as backfilling would occur once the dose level is declared safe by the SRC."	Backfilling of cohorts introduced.
Section 4.1.3 Adaptive Trial Design Elements	Added: "• The sponsor can backfill a certain dose level cohort to explore and generate more safety, PK, pharmacodynamics, and anti-tumor data up to a total of 14 patients in a given cohort. Staggering would not be implemented as backfilling would occur once the dose level is declared safe by the SRC."	Backfilling of cohorts introduced.
Section 1.1 Synopsis and Section 4.2	Number of trial sites adjusted from 6 to 12 in North America and Europe.	Update.

Section # and Name	Description of Change	Brief Rationale
Planned Number of Patients	For possible expansion, location increased from North America and Europe to "potentially the rest of the World."	
Section 5.1 Inclusion Criteria	11. d: Deleted: "may not transfuse or use erythropoietin to obtain this Hgb level"	Many cancer patients will only reach ≥9.0 g/dL Hgb following transfusion or erythropoietin. Removal of this wording allows inclusion of these patients who do not have any other treatment options and may benefit from participating in this clinical trial.
Section 6.6.1 Dose Limiting Toxicity for Part 1A and 6.6.2 Dose Limiting Toxicity for Part 1B	Added to immune-related AEs that are NOT considered DLTs: "o Grade ≤4 lymphopenia which is not considered clinically significant by the investigator."	It has been described for TLR7 agonists that upon stimulation, lymphocytes egress to the periphery and return within 24 to 48 hours and that this may present as transient lymphopenia (see Section 2.3.1 for further detail). Frequent laboratory monitoring is planned to observe this expected effect.
Section 8.13 24/7 Coverage for Urgent Protocol-related Medical Questions	ICON Helpdesk contact information updated	Update.
Section 8.5.1 Anti-tumor Activity Assessment – CT/MRI Imaging	Added: "Patients whose treatment schedule has been changed (e.g., delay due to toxicity) still should follow the original tumor assessment schedule (every 6 weeks (±7 days) for 48 weeks, and every 12 weeks (±7 days) thereafter)."	Clarification of trial procedures.
Section 8.6.3 Electrocardiograms	The full set of triplicates should be completed in less than 5 minutes.	Update.

Section # and Name	Description of Change	Brief Rationale
	(before: 4 minutes)	
Section 8.7.6 Death Events	Added: "In Germany only: Any death, irrespective whether causally related to disease progression or not, will be documented as AE and reported as SAE."	Update of trial procedures in Germany only.
Section 8.7.7 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs	Added: "*In Germany only: deaths related to disease progression will be reported as AEs or SAEs.*"	Update of trial procedures in Germany only.
8.10 Pharmacodynamic Biomarkers	Combined text from previous "Section 8.10 Pharmacodynamics" and "Section 8.11 Biomarkers" into one section.	Update of document.
Section 10.1.9 Dissemination of clinical trial data	Added new section.	Update.
Section 10.2 Appendix 2: Clinical Laboratory Tests Table 10-1 Protocol-required Safety Laboratory Assessments	Added Magnesium under Biochemistry assessments	Update of lab assessments to be made.
Section 10.3.3 Recording and Follow-Up of AE and/or SAE	Added to "AE and SAE Recording": "*In Germany only: Deaths related to disease progression will be documented as AE and reported as SAE.*"	Update of trial procedures in Germany only.
	Added to "Documentation of particular situations":	

Section # and Name	Description of Change	Brief Rationale
	"*In Germany only: Any death, irrespective if causally related to disease progression or not will be documented as AE and reported as SAE.*"	
Section 10.8 Appendix 8: Risk-benefit assessment of COVID-19 vaccination in BNT411-01 trial	Added new section.	Changes made due to COVID-19 pandemic.
Section 10.9 Appendix 9: COVID-19 vaccination in BNT411-01 trial during the pandemic	Added new section.	Changes made due to COVID-19 pandemic.

10.11.5 Version 5.0_DEU: 09 January 2023

Minor editorial changes, such as the correction of typing errors, are not specifically listed.

Section # and Name	Description of Change	Brief Rationale
Section 4.1.3	Rewording of the backfilling approach.	For clarity.
Section 10.11.4	Detailed rationale provided on the change to inclusion criterion 11d.	Rationale not previously provided.

10.11.6 Version 6.0: 04 July 2023

Minor editorial changes, such as the correction of typing errors, are not specifically listed.

Section # and Name	Description of Change	Brief Rationale
Section 1.1, Section 3, Section 9.3, Section 9.4.3, Section 9.4.4	Specifying that the efficacy secondary endpoint (*Evaluate anti-tumor activity according to RECIST 1.1*) and exploratory endpoints (*Evaluate anti-tumor activity according to iRECIST* and *Evaluate preliminary efficacy*) are only applicable for Part 2 of the trial	Owing to the heterogeneity of cancer types and limited number of patients in Part 1A and B, it is not meaningful to assess efficacy

Section # and Name	Description of Change	Brief Rationale
Section 1.1, Section 4.2, Section 9.2	Population: Number of patients in Part 1A increased to 6 to 60 DLT evaluable patients (previously 6 to 33 DLT evaluable patients)	Owing to the high levels of recruitment for Part 1A of the trial
Section 1.3	Table 1:1: Footnote number changed for Endocrine assessments	Correction of error
Section 1.3	Tables 1.3, 1.4, 1.7, and 1.8: Footnote added to specify that PBMC collection will no longer be required after C3D1	Change due to ethical considerations – samples taken after C3D1 may not be used for analysis
Section 4.5	End of trial definition altered: Patients are no longer required to be followed-up for survival for at least 1 year. Patients will continue to follow the SoA defined by the protocol unless the medical monitor gives approval not to do so	For dose escalation cohorts (Part 1), OS data is not required – this is to align with the aforementioned change in efficacy endpoints (applicable for Part 2 only)
Section 2.3.1	Risk assessment adapted: Cytokine release syndrome now listed as an ‘Important identified risk’ for BNT411. Addition of a sentence to state that there are no important potential risks for BNT411	To align with the updated version of the investigator’s brochure
Section 10.3.4	SAE reporting contact details updated	To reflect updated reporting information

11 References

American Cancer Society 2019 Cancer Facts & Figures. Available at: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2019/cancer-facts-and-figures-2019.pdf. Acc: March 20, 2019.

Astry, C., Birmachu, W., Harrison, L.I., and Meng, T.C. (2008). Cutaneous pharmacodynamics of a toll-like receptor 7 agonist, 852A, in humans. J Clin Pharmacol *48*, 755-762.

Auperin, A., Arriagada, R., Pignon, J.P., Le Pechoux, C., Gregor, A., Stephens, R.J., Kristjansen, P.E., Johnson, B.E., Ueoka, H., Wagner, H.*, et al.* (1999). Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. N Engl J Med *341*, 476-484.

Bourquin, C., Hotz, C., Noerenberg, D., Voelkl, A., Heidegger, S., Roetzer, L.C., Storch, B., Sandholzer, N., Wurzenberger, C., Anz, D.*, et al.* (2011). Systemic cancer therapy with a small molecule agonist of toll-like receptor 7 can be improved by circumventing TLR tolerance. Cancer Res *71*, 5123-5133.

Brahmer, J.R., Lacchetti, C., Schneider, B.J., Atkins, M.B., Brassil, K.J., Caterino, J.M., Chau, I., Ernstoff, M.S., Gardner, J.M., Ginex, P.*, et al.* (2018). Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol *36*, 1714-1768.

Center for Disease Control and Prevention 2017 Leading causes of death. Available at: https://www.cdc.gov/nchs/fastats/leading-causes-of-death.htm.

Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 Available at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf. Accessed July 20, 2018.

Chen, D.S., and Mellman, I. (2013). Oncology meets immunology: the cancer-immunity cycle. Immunity *39*, 1-10.

Desai, A., Gainor, J.F., Hegde, A., Schram, A.M., Curigliano, G., Pal, S., Liu, S.V., Halmos, B., Groisberg, R., Grande, E., *et al*. (2021). COVID-19 vaccine guidance for patients with cancer participating in oncology clinical trials. Nat Rev Clin Oncol.*18*, 313-319.

Dudek, A.Z., Yunis, C., Harrison, L.I., Kumar, S., Hawkinson, R., Cooley, S., Vasilakos, J.P., Gorski, K.S., and Miller, J.S. (2007). First in human phase I trial of 852A, a novel systemic toll-like receptor 7 agonist, to activate innate immune responses in patients with advanced cancer. Clin Cancer Res *13*, 7119-7125.

Dummer, R., Hauschild, A., Becker, J.C., Grob, J.J., Schadendorf, D., Tebbs, V., Skalsky, J., Kaehler, K.C., Moosbauer, S., Clark, R.*, et al.* (2008). An exploratory study of systemic administration of the toll-like receptor-7 agonist 852A in patients with refractory metastatic melanoma. Clin Cancer Res *14*, 856-864.

Edwards, L. (2000). Imiquimod in clinical practice. J Am Acad Dermatol *43*, S12-17.

Eisenhauer, E.A., Therasse, P., Bogaerts, J., Schwartz, L.H., Sargent, D., Ford, R., Dancey, J., Arbuck, S., Gwyther, S., Mooney, M.*, et al.* (2009). New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer *45*, 228-247.

Emens, L.A., and Middleton, G. (2015). The interplay of immunotherapy and chemotherapy: harnessing potential synergies. Cancer Immunol Res *3*, 436-443.

European Medicines Agency Assessment report: EMA/707383/2020 2021.

FDA Guidance for Industry S9 Nonclinical Evaluation for Anticancer Pharmaceuticals 2011.

Ferlay, J., Steliarova-Foucher, E., Lortet-Tieulent, J., Rosso, S., Coebergh, J.W., Comber, H., Forman, D., and Bray, F. (2013). Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer *49*, 1374-1403.

Fry, W.A., Menck, H.R., and Winchester, D.P. (1996). The national cancer data base report on lung cancer. Cancer *77*, 1947-1955.

Geller, M.A., Cooley, S., Argenta, P.A., Downs, L.S., Carson, L.F., Judson, P.L., Ghebre, R., Weigel, B., Panoskaltsis-Mortari, A., Curtsinger, J.*, et al.* (2010). Toll-like receptor-7 agonist administered subcutaneously in a prolonged dosing schedule in heavily pretreated recurrent breast, ovarian, and cervix cancers. Cancer Immunol Immunother *59*, 1877-1884.

George, J., Lim, J.S., Jang, S.J., Cun, Y., Ozretic, L., Kong, G., Leenders, F., Lu, X., Fernandez-Cuesta, L., Bosco, G.*, et al.* (2015). Comprehensive genomic profiles of small cell lung cancer. Nature *524*, 47-53.

Goodman, A.M., Kato, S., Bazhenova, L., Patel, S.P., Frampton, G.M., Miller, V., Stephens, P.J., Daniels, G.A., and Kurzrock, R. (2017). Tumor Mutational Burden as an Independent Predictor of Response to Immunotherapy in Diverse Cancers. Molecular cancer therapeutics *16*, 2598-2608.

Gorden, K.B., Gorski, K.S., Gibson, S.J., Kedl, R.M., Kieper, W.C., Qiu, X., Tomai, M.A., Alkan, S.S., and Vasilakos, J.P. (2005). Synthetic TLR agonists reveal functional differences between human TLR7 and TLR8. Journal of immunology (Baltimore, Md: 1950) *174*, 1259-1268.

Govindan, R., Page, N., Morgensztern, D., Read, W., Tierney, R., Vlahiotis, A., Spitznagel, E.L., and Piccirillo, J. (2006). Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: analysis of the surveillance, epidemiologic, and end results database. J Clin Oncol *24*, 4539-4544.

Hamm, S., Rath, S., Michel, S., and Baumgartner, R. (2009). Cancer immunotherapeutic potential of novel small molecule TLR7 and TLR8 agonists. J Immunotoxicol *6*, 257-265.

Harrison, L.I., Astry, C., Kumar, S., and Yunis, C. (2007). Pharmacokinetics of 852A, an imidazoquinoline Toll-like receptor 7-specific agonist, following intravenous, subcutaneous, and oral administrations in humans. J Clin Pharmacol *47*, 962-969.

Holldack, J. (2014). Toll-like receptors as therapeutic targets for cancer. Drug discovery today *19*, 379-382.

International Agency for Research on Cancer 2017 Cancer fact sheets. Available at: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx.

Janne, P.A., Freidlin, B., Saxman, S., Johnson, D.H., Livingston, R.B., Shepherd, F.A., and Johnson, B.E. (2002). Twenty-five years of clinical research for patients with limited-stage small cell lung carcinoma in North America. Cancer *95*, 1528-1538.

Johnson, B.E., Grayson, J., Makuch, R.W., Linnoila, R.I., Anderson, M.J., Cohen, M.H., Glatstein, E., Minna, J.D., and Ihde, D.C. (1990). Ten-year survival of patients with small-cell lung cancer treated with combination chemotherapy with or without irradiation. J Clin Oncol *8*, 396-401.

Lassen, U., Osterlind, K., Hansen, M., Dombernowsky, P., Bergman, B., and Hansen, H.H. (1995). Long-term survival in small-cell lung cancer: posttreatment characteristics in patients surviving 5 to 18+ years--an analysis of 1,714 consecutive patients. J Clin Oncol *13*, 1215-1220.

Lee, DW, Santomasso BD, Locke FL, Ghobadi A, Turtle CJ, Brudno JN, et al. (2019). ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant. Apr;25(4):625-638

Levey, A.S., Bosch, J.P., Lewis, J.B., Greene, T., Rogers, N., and Roth, D. (1999). A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med *130*, 461-470.

Lubong Sabado, R., Pavlick, A., Gnjatic, S., Cruz, C.M., Vengco, I., Hasan, F., Spadaccia, M., Darvishian, F., Chiriboga, L., Holman, R.M*., et al.* (2015). Resiquimod as an Immunologic Adjuvant for NY-ESO-1 Protein Vaccination in Patients with High Risk Melanoma. Cancer Immunology Research, canimm.0202.2014.

Markov, O., Mironova, N., Vlasov, V., and Zenkova, M. (2016). Molecular and Cellular Mechanisms of Antitumor Immune Response Activation by Dendritic Cells. Acta Naturae *8*, 17-30.

Medzhitov, R. (2001). Toll-like receptors and innate immunity. Nature reviews Immunology *1*, 135-145.

MHRA 2014 Clinical Trial Facilitation Group (CTFG) Recommendations related to contraception and pregnancy testing in clinical trials. Available at: https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf Accessed September 26, 2019.

Murray, N., Coy, P., Pater, J.L., Hodson, I., Arnold, A., Zee, B.C., Payne, D., Kostashuk, E.C., Evans, W.K., Dixon, P*., et al.* (1993). Importance of timing for thoracic irradiation in the combined modality treatment of limited-stage small-cell lung cancer. The National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol *11*, 336-344.

Neelapu SS. (2019). Managing the toxicities of CAR T-cell therapy. Hematol Oncol. 2019 Jun;37 Suppl 1:48-52.

Northfelt, D.W., Ramanathan, R.K., Cohen, P.A., Von Hoff, D.D., Weiss, G.J., Dietsch, G.N., Manjarrez, K.L., Randall, T.D., and Hershberg, R.M. (2014). A Phase I Dose-Finding Study of the Novel Toll-like Receptor 8 Agonist VTX-2337 in Adult Subjects with Advanced Solid Tumors or Lymphoma. Clinical Cancer Research *20*, 3683.

Nugent, J.L., Bunn, P.A., Jr., Matthews, M.J., Ihde, D.C., Cohen, M.H., Gazdar, A., and Minna, J.D. (1979). CNS metastases in small cell bronchogenic carcinoma: increasing frequency and changing pattern with lengthening survival. Cancer *44*, 1885-1893.

Okamoto, H., Watanabe, K., Kunikane, H., Yokoyama, A., Kudoh, S., Asakawa, T., Shibata, T., Kunitoh, H., Tamura, T., and Saijo, N. (2007). Randomised phase III trial of carboplatin plus etoposide vs split doses of cisplatin plus etoposide in elderly or poor-risk patients with extensive disease small-cell lung cancer: JCOG 9702. Br J Cancer *97*, 162-169.

Peifer, M., Fernandez-Cuesta, L., Sos, M.L., George, J., Seidel, D., Kasper, L.H., Plenker, D., Leenders, F., Sun, R., Zander, T.*, et al.* (2012). Integrative genome analyses identify key somatic driver mutations of small-cell lung cancer. Nat Genet *44*, 1104-1110.

Perkins, H., Khodai, T., Mechiche, H., Colman, P., Burden, F., Laxton, C., Horscroft, N., Corey, T., Rodrigues, D., Rawal, J.*, et al.* (2012). Therapy with TLR7 agonists induces lymphopenia: correlating pharmacology to mechanism in a mouse model. Journal of clinical immunology *32*, 1082-1092.

Pujol, J.L., Carestia, L., and Daures, J.P. (2000). Is there a case for cisplatin in the treatment of small-cell lung cancer? A meta-analysis of randomized trials of a cisplatin-containing regimen versus a regimen without this alkylating agent. Br J Cancer *83*, 8-15.

Riaz, S.P., Lüchtenborg, M., Coupland, V.H., Spicer, J., Peake, M.D., and Møller, H. (2012). Trends in incidence of small cell lung cancer and all lung cancer. Lung Cancer *75*, 280-284.

Rook, A.H., Gelfand, J.M., Wysocka, M., Troxel, A.B., Benoit, B., Surber, C., Elenitsas, R., Buchanan, M.A., Leahy, D.S., Watanabe, R.*, et al.* (2015). Topical resiquimod can induce disease regression and enhance T-cell effector functions in cutaneous T-cell lymphoma. Blood *126*, 1452-1461.

Roth, B.J., Johnson, D.H., Einhorn, L.H., Schacter, L.P., Cherng, N.C., Cohen, H.J., Crawford, J., Randolph, J.A., Goodlow, J.L., Broun, G.O.*, et al.* (1992). Randomized study of cyclophosphamide, doxorubicin, and vincristine versus etoposide and cisplatin versus alternation of these two regimens in extensive small-cell lung cancer: a phase III trial of the Southeastern Cancer Study Group. J Clin Oncol *10*, 282-291.

Rudin, C.M., Durinck, S., Stawiski, E.W., Poirier, J.T., Modrusan, Z., Shames, D.S., Bergbower, E.A., Guan, Y., Shin, J., Guillory, J.*, et al.* (2012). Comprehensive genomic analysis identifies SOX2 as a frequently amplified gene in small-cell lung cancer. Nat Genet *44*, 1111-1116.

Seymour, L., Bogaerts, J., Perrone, A., Ford, R., Schwartz, L.H., Mandrekar, S., Lin, N.U., Litiere, S., Dancey, J., Chen, A.*, et al.* (2017). iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol *18*, e143-e152.

Siegel, R.L., Miller, K.D., and Jemal, A. (2019). Cancer statistics, 2019. CA Cancer J Clin *69*, 7-34.

Slotman, B., Faivre-Finn, C., Kramer, G., Rankin, E., Snee, M., Hatton, M., Postmus, P., Collette, L., Musat, E., and Senan, S. (2007). Prophylactic cranial irradiation in extensive small-cell lung cancer. N Engl J Med *357*, 664-672.

Smits, E.L., Ponsaerts, P., Berneman, Z.N., and Van Tendeloo, V.F. (2008). The use of TLR7 and TLR8 ligands for the enhancement of cancer immunotherapy. The oncologist *13*, 859-875.

Spaner, D.E., Shi, Y., White, D., Shaha, S., He, L., Masellis, A., Wong, K., and Gorczynski, R. (2010). A phase I/II trial of TLR-7 agonist immunotherapy in chronic lymphocytic leukemia. Leukemia *24*, 222-226.

Spencer, J.M. (2006). Pilot study of imiquimod 5% cream as adjunctive therapy to curettage and electrodesiccation for nodular basal cell carcinoma. Dermatol Surg *32*, 63-69.

Stanley, M.A. (2002). Imiquimod and the imidazoquinolones: mechanism of action and therapeutic potential. Clin Exp Dermatol *27*, 571-577.

Travis, W.D., Colby, T.V., Corrin, B., Shimosato, Y., and Brambilla, E. (1999). Histological typing of lung and pleural tumours. Springer-Verlag.

Tsitoura, D., Ambery, C., Price, M., Powley, W., Garthside, S., Biggadike, K., and Quint, D. (2015). Early clinical evaluation of the intranasal TLR7 agonist GSK2245035: Use of translational biomarkers to guide dosing and confirm target engagement. Clin Pharmacol Ther *98*, 369-380.

Turrisi, A.T., 3rd, Kim, K., Blum, R., Sause, W.T., Livingston, R.B., Komaki, R., Wagner, H., Aisner, S., and Johnson, D.H. (1999). Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. N Engl J Med *340*, 265-271.

Twelves, C.J., Souhami, R.L., Harper, P.G., Ash, C.M., Spiro, S.G., Earl, H.M., Tobias, J.S., Quinn, H., and Geddes, D.M. (1990). The response of cerebral metastases in small cell lung cancer to systemic chemotherapy. Br J Cancer *61*, 147-150.

Vacchelli, E., Galluzzi, L., Eggermont, A., Fridman, W.H., Galon, J., Sautes-Fridman, C., Tartour, E., Zitvogel, L., and Kroemer, G. (2012). Trial watch: FDA-approved Toll-like receptor agonists for cancer therapy. Oncoimmunology *1*, 894-907.

Vascotto, F., Petschenka, J., Walzer, K.C., Vormehr, M., Brkic, M., Strobl, S., Rösemann, R., Diken, M., Kreiter, S., Türeci, O.*, et al.* (2019). Intravenous delivery of the toll-like receptor 7 agonist SC1 confers tumor control by inducing a CD8+ T cell response. Oncoimmunology.

Ventola, C.L. (2017). Cancer Immunotherapy, Part 3: Challenges and Future Trends. P T *42*, 514-521.

Waissengrin, B., Agbarya, A., Safadi, E., Padova, H., Wolf, I. (2021). Short-term safety of the BNT162b2 mRNA COVID-19 vaccine in patients with cancer treated with immune checkpoint inhibitors. Lancet Oncol. *5*, 581-583.

Weigel, B.J., Cooley, S., DeFor, T., Weisdorf, D.J., Panoskaltsis-Mortari, A., Chen, W., Blazar, B.R., and Miller, J.S. (2012). Prolonged subcutaneous administration of 852A, a novel systemic toll-like receptor 7 agonist, to activate innate immune responses in patients with advanced hematologic malignancies. Am J Hematol *87*, 953-956.

Wiedemann, G.M., Jacobi, S.J., Chaloupka, M., Krachan, A., Hamm, S., Strobl, S., Baumgartner, R., Rothenfusser, S., Duewell, P., Endres, S.*, et al.* (2016). A novel TLR7 agonist reverses NK cell anergy and cures RMA-S lymphoma-bearing mice. Oncoimmunology *5*, e1189051.

Williams, C.B., Yeh, E.S., and Soloff, A.C. (2016). Tumor-associated macrophages: unwitting accomplices in breast cancer malignancy. npj Breast Cancer *2*, 15025.

Witt, P.L., Ritch, P.S., Reding, D., McAuliffe, T.L., Westrick, L., Grossberg, S.E., and Borden, E.C. (1993). Phase I trial of an oral immunomodulator and interferon inducer in cancer patients. Cancer Res *53*, 5176-5180.

Yang, Y. (2015). Cancer immunotherapy: harnessing the immune system to battle cancer. J Clin Invest *125*, 3335-3337.

12 Attachments

12.1 Management Recommendations in Case of a Cytokine Release Syndrome (CRS)

The following guidelines should serve as recommendations to trial physicians to monitor and manage a potential case of CRS. The guidelines should not replace any clinical decisions made by the physicians based on their sound clinical judgment depending on individual patient's situation. In any given situation, all measures must be taken by the trial physicians to ensure the optimal clinical management is delivered to the patients based on the diagnosis.

For assessment, reporting and analysis of CRS in connection with this trial, all events will be graded according to CTCAE version 5.0 as shown in Table 12-1.

Table 12-1: CRS grading per CTCAE version 5.0

Grading system	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
CTCAE version 5.0	Fever, with or without constitutional symptoms	Hypotension responding to fluids. Hypoxia responding to <40% FiO2	Hypotension managed with one pressor. Hypoxia requiring ≥40% FiO2	Life-threatening consequences; urgent intervention needed	Death
CRS Definition: A disorder characterized by fever, tachypnea, headache, tachycardia, hypotension, rash, and/or hypoxia caused by the release of cytokines.					

For treatment recommendations for the management of CRS, the following guidelines are adapted based on the American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. The CRS consensus grading of ASTCT (previously known as American Society for Bone Marrow Transplant) is given in Table 12-2 (Lee et al, 2019).

Table 12-2: American Society for Transplantation and Cellular Therapy CRS consensus grading

CRS parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever[1]	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
with				
Hypotension	None	Not requiring vasopressors	Requiring vasopressor with or without vasopressin	Requiring vasopressors (excluding vasopressin)
and/or[2]				
Hypoxia	None	Requiring low-flow nasal cannula[3] or blow-by	Requiring high-flow nasal cannula, facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)

Abbreviations: BiPAP, Bilevel positive airway pressure; CPAP, Continuous positive airway pressure; CRS, Cytokine release syndrome; CTCAE, Common terminology criteria for adverse events.

1) Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who have CRS then receive antipyretic or anti-cytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.
2) CRS grade is determined by the more severe event: Hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring one vasopressor, and hypoxia requiring low-flow nasal cannula is classified as Grade 3 CRS.
3) Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/minute. Low-flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading

For the management of CRS, the following guidelines should apply (Table 12-3):

Table 12-3: Guidelines for management of cytokine release syndrome

ASTCT CRS Grade	Management
Grade 1	• Antipyretics and i.v. hydration • Diagnostic work-up to rule out infection • Consider growth factors and antibiotics if neutropenic
Grade 2	• Supportive care as in Grade 1 • i.v. fluid boluses and/or supplemental oxygen • Tocilizumab +/- dexamethasone or its equivalent of methylprednisolone
Grade 3	• Supportive care as in Grade 1 • Consider monitoring in ICU • Vasopressor support and/or supplemental oxygen • Tocilizumab + dexamethasone 10-20 mg i.v. q6h or its equivalent of methylprednisolone

ASTCT CRS Grade	Management
Grade 4	• Supportive care as in Grade 1 • Monitoring in ICU • Vasopressor support and/or supplemental oxygen via positive pressure ventilation • Tocilizumab + methylprednisolone 1000 mg/d

Abbreviations: ASTCT: American Society for Transplantation and Cellular Therapy (previously known as: ASBMT, American Society for Bone Marrow Transplant); BiPAP, Bilevel positive airway pressure; CPAP, Continuous positive airway pressure; CRS, Cytokine release syndrome; ICU, Intensive care unit; i.v., Intravenous.
Source: Neelapu 2019.

12.2 Country Specific Information

12.2.1 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).

For evaluation of left ventricular function, only an ECHO scan will be performed.

Atezolizumab, carboplatin, and etoposide in Part 1B and Part 2 are considered as IMPs along with BNT411.

All SAEs that occur in the patient throughout his or her lifetime should be reported.

12.2.2 Spain

Atezolizumab, carboplatin, and etoposide in Part 1B and Part 2 are considered as IMPs along with BNT411.