CLINICAL TRIAL PROTOCOL

BNT151-01

Version: 8.0 **Date:** 13 DEC 2023

Sponsor: BioNTech SE

Trial title:	Phase I/IIa, first-in-human, open-label, dose escalation trial with expansion cohorts to evaluate safety, pharmacokinetics, pharmacodynamics, and preliminary efficacy of BNT151 as a monotherapy and in combination with other anti-cancer agents in patients with solid tumors
Brief title:	BNT151 as a monotherapy and in combination with other anti-cancer agents in patients with solid tumors
Trial phase:	I/IIa
Indication:	Solid tumors
Product:	BNT151
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Regulatory identifier(s):	EudraCT number: 2019-003572-39 IND number: 023301
Medical monitor:	See Section 8.12

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Statement of Compliance: This trial will be conducted in according to this protocol, the ethical principles that have their origin in the Declaration of Helsinki, good clinical practice (GCP), and applicable regulatory requirements.

1 PROTOCOL SUMMARY

1.1 Trial synopsis

Trial number: BNT151-01 **Trial phase:** I/IIa

Trial title

Phase I/IIa, first-in-human, open-label, dose escalation trial with expansion cohorts to evaluate safety, pharmacokinetics, pharmacodynamics, and preliminary efficacy of BNT151 as a monotherapy and in combination with other anti-cancer agents in patients with solid tumors

Objectives and endpoints

Objectives	Endpoints
Primary objectives	**Endpoints**
For Part 1: Identify the maximum tolerated dose (MTD) and/or recommended Phase II dose (RP2D) of IMP based on the occurrence of dose limiting toxicities (DLTs) using the following definitions: • MTD defined as the highest tolerated dose where less than 1/3 of the patients experience a DLT. • RP2D based on integrated evaluation of safety, tolerability, clinical benefit, PK, and selected pharmacodynamics (PD) markers, for all dose levels tested.	• Occurrence of DLTs within a patient during the DLT evaluation period.
Assess the safety and tolerability of IMP.	• Occurrence of TEAE within a patient including Grade ≥3, serious, fatal TEAE by relationship. • Occurrence of dose reduction and discontinuation of IMP within a patient due to TEAE.
Secondary objectives	**Endpoints**
Evaluate anti-tumor activity of IMP according to RECIST 1.1.	• The ORR is defined as the proportion of patients in whom a CR or PR (per RECIST 1.1) is observed as best overall response. • The DCR is defined as the proportion of patients in whom a CR or PR or SD (per RECIST 1.1, SD assessed at least 6 weeks after first dose) is observed as best overall response. • The DOR is defined as the time from first objective response (CR or PR per RECIST 1.1) to first occurrence of objective tumor progression (PD per RECIST 1.1) or death from any cause, whichever occurs first.

Exploratory objectives	Endpoints
Evaluate efficacy of IMP in terms of PFS and OS.	• PFS defined as the time from first dose of IMP to first objective tumor progression, or death from any cause, whichever occurs first. • OS defined as the time from first dose of IMP to death from any cause.
Characterize the PK profile of translated IL-2 variant.	• PK parameters (including but not limited to AUC, C_{max}, t_{max}, and $t_{1/2}$).
Identify potentially predictive or other exploratory PD markers.	• Changes in selected cytokines and other soluble innate and adaptive immune system 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 and tumor microenvironment analysis). • Correlate potential predictive biomarkers in tumor and periphery with antitumor response.
Examine potential incidence of immunogenicity by measuring ADAs against translated proteins derived from the IMPs or against PEG lipids.	• Evaluate pre-existing (pre-treatment) and post-treatment ADAs and examine the immunogenicity incidence with treatment.

ADAs = anti-drug antibodies; AUC = area-under-the-concentration-time curve; C_{max} = maximum observed serum concentration; CR = complete response; DCR = disease control rate; DLTs = dose limiting toxicities; DOR = duration of response; IL = interleukin; IMP = investigational medicinal product; MTD = maximal tolerated dose; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PK = pharmacokinetic; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; RP2D = recommended Phase II dose; SD = stable disease; $t_{1/2}$ = half-life; t_{max} = time to C_{max}; TEAE = treatment emergent adverse event.

Trial design

This is an open-label, multicenter Phase I/IIa dose escalation, safety, pharmacokinetic (PK) and PD trial of BNT151 with expansion cohorts in various solid tumor indications.

The monotherapy dose escalation, (Part 1) of this clinical trial will enroll patients with various solid tumors that are metastatic or of advanced unresectable stage for whom there is no available standard therapy likely to confer clinical benefit, or patients who are not candidates for such available therapy. During combination dose escalation (Part 2A), patients with squamous cell carcinoma of head and neck (SCCHN), and hepatocellular carcinoma (HCC) will be enrolled and treated with a combination of BNT151 and pembrolizumab. Once Part 2A of SCCHN and HCC is completed, patients with renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC), and triple negative breast cancer (TNBC) will be enrolled and treated with a combination of BNT151 with the respective standard of care (SoC).

The trial consists of Part 1, Part 2A and Part 2B with adaptive design elements:

- Part 1 will be a monotherapy dose escalation in patients with advanced solid malignancies until the maximum tolerated dose (MTD) and/or recommended Phase II dose (RP2D) of BNT151 as monotherapy are defined. Dose escalation and RP2D regimen may include a pre-conditioning dose, which would be

implemented under the rules defined in Section 4.1.4 Adaptive trial design elements.

The Part 1 of the trial also plans to implement a dedicated biomarker cohort in BNT151 monotherapy:

- The Biomarker Cohort will recruit patients at selected sites in the US only. The objective of the cohort is to observe PD activity and drug-induced changes in the blood and tumor. The gathered data are expected to inform on the drugs mechanism of action and further refine selection of monotherapy dose. This cohort will only enroll patients that are capable and willing to donate serial biopsies. Patients will only be dosed at dose levels at the RP2D level or lower, which have been cleared safe in the monotherapy dose escalation, and where pharmacodynamics activity is expected. Approximately, 20 patients will be enrolled in this cohort.
- Part 2 will start once Part 1 monotherapy dose escalation is completed (exception: Biomarker Cohort in Part 1 can continue enrolling as long as a BNT151 monotherapy dose is established in the dose escalation). It consists of 5 expansion cohorts starting with BNT151 in combination with pembrolizumab in patients with SCCHN (Cohort 1) and HCC (Cohort 2). Safety evaluation of BNT151 in combination with pembrolizumab in Cohorts 1 and 2 will be done at the same time, and data generated in both patient populations will be used to assess safety. Once the safety of the combination is confirmed by the safety review committee (SRC) (for details see the SRC Charter), the 2 cohorts will then enroll independently in expansion and a further 3 cohorts evaluating BNT151 in combination with SoC will be opened for enrollment: RCC (Cohort 3), NSCLC (Cohort 4), and TNBC (Cohort 5). Further cohorts may be opened based on sponsor's decision.

Each Part 2 cohort will consist of 2 sub-parts:

- Part 2A where the dose of BNT151 will be established for each combination using either a safety run-in or abbreviated dose finding based on predefined criteria.

  Part 2B where a predefined number of patients will be treated with the confirmed RP2D of BNT151 in combination with respective SoC. In case the same dosing regimen is used in Parts 2A and 2B (i.e., in case option of safety run-in is adopted), the patients enrolled in Part 2A are eligible for efficacy evaluation in Part 2B. In case a different dosing regimen is used for Part 2A compared to Part 2B (i.e., in case option of abbreviated dose finding is adopted), efficacy generated in Part 2A will be used as supporting data.

In all parts, 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.

Safety will be assessed on a regular basis by means of clinical and laboratory parameters.

Pharmacokinetics (PK) of translated interleukin-2 (IL-2) variant and various PD markers, which may act as indicators of safety and activity of BNT151 monotherapy and in combination with SoC, will be evaluated.

Brief description of the sequence and duration of all trial periods

The Part 1, monotherapy part of the trial will be preceded by an enrollment and screening period of 13 months. Patients are screened at a Screening Visit within 3 weeks prior to the beginning of treatment. During the treatment and dose limiting toxicity (DLT) observation period, patients will be treated with treatment cycles lasting 21 days until progression, or treatment discontinuation of BNT151 due to other factors. Following discontinuation, and a safety follow-up period of 60 days, patients will be followed up for survival every 12 weeks until death.

Part 2, combination therapy expansion will be detailed in a protocol amendment following review of the Part 1 data.

Population

In Part 1, the sample size will be up to 54 DLT-evaluable patients depending on the number of dose limiting toxicities (DLTs) which may occur, with the possible enrollment of up to 10 additional patients if efficacy is seen in a specific tumor type. In addition, approximately 20 patients will be enrolled in the Biomarker Cohort.

The objective for the trial Part 2A and 2B is to further investigate the safety profile and to assess the efficacy of the investigational medicinal product (IMP) in different indications in combination with other approved anti-cancer agents. The design in Part 2A can either be a safety run-in of 6 patients or a short escalation at 2 dose levels according to the 3+3 trial design, therefore the sample size in Part 2A will range from 6 to 12 patients per cohort. The sample size in Part 2B may be based on either Simon two-stage design or one-stage design. The final sample size calculations will be introduced through protocol amendment.

Key inclusion criteria

Patients who meet the following inclusion criteria will be eligible for trial entry:

For all Parts:

1. Histological documentation of the original primary tumor via a pathology report.
2. Measurable disease per response evaluation criteria in solid tumors (RECIST) version 1.1.

For Part 1:

3. Histologically confirmed solid tumor that is metastatic or of advanced unresectable stage and for whom there is no available standard therapy likely to confer clinical benefit, or patient who is not a candidate for such available therapy. If there is no contraindication, patients should have exhausted all SoC therapies before entering the trial.

For Part 2 (including 2A and 2B):

Cohort 1: SCCHN

4. Histologically confirmed, recurrent or metastatic (R/M) SCCHN with disease progression on or after a platinum-based therapy.

Cohort 2: Hepatocellular carcinoma (HCC)

5. Histologically confirmed unresectable or metastatic HCC who have been previously treated with a first-line systemic treatment.

Cohort 3: Renal cell carcinoma (RCC)

6. Histologically confirmed RCC eligible for pembrolizumab in combination with axitinib, for the first-line treatment of patients with advanced RCC.

Cohort 4: Non-small cell lung cancer (NSCLC)

7. Histologically or cytologically confirmed NSCLC eligible for pembrolizumab in combination with pemetrexed and platinum chemotherapy for the first-line treatment of patients with metastatic non-squamous NSCLC, with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations.

Cohort 5: Triple negative breast cancer (TNBC)

8. Histologically confirmed TNBC eligible for atezolizumab in combination with paclitaxel protein-bound for the treatment of unresectable locally advanced or metastatic TNBC whose tumors express programmed death-ligand (PD-L1 stained tumor-infiltrating immune cells of any intensity covering ≥1% of the tumor area), as determined by a Food and Drug Administration (FDA) approved test.

Other inclusion criteria

For all parts:

9. ≥18 years of age.
10. Must sign an informed consent form (ICF) indicating that he or she understands the purpose and procedures required for the trial and are willing to participate in the trial prior to any trial-related assessments or procedures.
11. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1.
12. Adequate coagulation function at screening as determined by:
    - International normalized ratio (INR) or prothrombin time ≤1.5 × upper limit normal (ULN; unless on therapeutic anticoagulants with values within therapeutic window).
    - Activated partial thromboplastin time (aPTT) ≤1.5 × ULN (unless on therapeutic anticoagulants with values within therapeutic window).
13. Adequate hematologic function at screening as determined by:
    - White blood cell (WBC) count ≥3 × 10^9/L.
    - Absolute neutrophil count (ANC) ≥1.5 × 10^9/L (patient may not use granulocyte-colony stimulating factor (G-CSF) or granulocyte-macrophage colony

stimulating factor (GM-CSF) in the past 7 days to achieve these WBC and ANC levels).

- Platelet count ≥100 × 10^9/L.
- Hemoglobin (Hgb) ≥9.0 g/dL.

14. Adequate hepatic function at screening as determined by:
    - Total bilirubin (TBili) ≤1.5 mg/dL (or ≤2.0 mg/dL for patients with known Gilbert's syndrome or liver metastasis).
    - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 × ULN; ≤3 × ULN for patients with liver metastasis.
15. Adequate renal function at screening as determined by:
    - Glomerular filtration rate (GFR) ≥45 mL/min/1.73 m² –

    According to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, expressed as a single equation:

    $GFR = 141 \times \min(Scr/\kappa,1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] × 1.159 [if black]

    Scr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.
    - For creatinine assays using methods traceable to isotope dilution mass spectrometry (IDMS) assigned National Institute of Standards and Technology (NIST) certified reference materials (Levey et al. 2009).
16. Able and willing to attend trial visits as required by the protocol.
17. Women of childbearing potential (WOCBP) must have a negative serum (beta-human chorionic gonadotropin [β-hCG]) test/value at screening. Patients who are postmenopausal or permanently sterilized can be considered as not having reproductive potential.
18. WOCBP must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the entire trial, until 6 months after last BNT151 treatment.
19. A man who is sexually active with a WOCBP 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 BNT151.
20. WOCBP must agree to use highly effective contraception during the trial and for 6 months after receiving the last dose of BNT151. Birth control methods are considered highly effective if they have a failure rate of less than 1% per year, when

used consistently and correctly. Further guidance on contraceptive measures for female patients can be found in Section 10.4.

For the Biomarker Cohort:

21. At selected US sites only: at enrollment patients must agree to have one pre-dose biopsy and lesion that is deemed accessible by the investigator. If possible, at least one on-treatment biopsy should be accessible from same tumor lesion.

Key exclusion criteria

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

Prior and concomitant therapy:

1. Use of any IMP or device within 28 days before administration of first dose of trial treatment.
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. Ongoing participation in the active treatment phase of interventional clinical trial.
4. Receives concurrent systemic (oral or intravenous [IV]) steroid therapy >10 mg prednisone daily or its equivalent for an underlying condition.
5. Has had major surgery within the 4 weeks before the first dose of BNT151.
6. Ongoing or active infection requiring IV treatment with anti-infective therapy that has been administered less than 2 weeks prior to the first dose of BNT151.
7. Has ongoing side effects to any prior therapy or procedures for any medical condition not recovered to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0 Grade ≤1.

   Note: 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 metastases may be eligible if they:
   - had radiotherapy, surgery or stereotactic surgery for the brain metastases;
   - have no neurological symptoms (excluding Grade ≤2 neuropathy);
   - have stable brain metastasis on the computed tomography (CT) or magnetic resonance imaging (MRI) scan within 4 weeks before signing the informed consent; and
   - are not undergoing acute corticosteroid therapy or steroid taper.

Notes: Patients with central nervous system (CNS) symptoms should undergo a CT-scan or MRI of the brain to exclude new or progressive brain metastases. Spinal bone metastases are allowed, unless imminent fracture with cord compression is anticipated.

9. Has a history of a cerebrovascular accident or had transient ischemic attack less than 6 months ago.
10. Effusions (pleural, pericardial, or ascites) requiring drainage.
11. 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 patients with a history of Grave's disease with stable thyroid function. Patients with controlled hyperthyroidism must be negative for thyroglobulin, thyroid peroxidase antibodies, and thyroid stimulating immunoglobulin prior to administration of trial treatment.
12. Known history of seropositivity for human immunodeficiency virus (HIV) with cluster of differentiation 4 positive (CD4+) T-cell (CD4+) counts <350 cells/µL and with a history of acquired immunodeficiency syndrome (AIDS)-defining opportunistic infections.
13. Known history/positive serology for hepatitis B requiring active antiviral 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.
14. Active hepatitis C virus (HCV) infection; patients who have completed curative antiviral treatment with HCV viral load below the limit of quantification are allowed.

    Note: 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.
15. Any contraindication to the combination therapies as per United States prescribing information (USPI) or summary of product characteristics (SmPC) for patients receiving BNT151 in combination with other systemic anticancer agent(s).
16. 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 (including but not limited to adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer, or ductal carcinoma in situ).

    Note: In case of uncertainties it should be discussed with the medical monitor.

Other comorbidities

17. Abnormal electrocardiograms (ECGs) that are clinically significant, such as Fridericia-corrected QT prolongation >480 ms.
18. 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:
    - Ongoing or active infection requiring antibiotic/antiviral/antifungal therapy
    - Concurrent congestive heart failure (New York Heart Association [NYHA] Functional Classification Class III or IV)
    - Concurrent unstable angina
    - Concurrent cardiac arrhythmia requiring treatment (excluding asymptomatic atrial fibrillation)
    - Acute coronary syndrome within the previous 6 months
    - Pulmonary embolism within the previous 3 months
    - Significant pulmonary disease (shortness of breath at rest or on mild exertion) for example due to concurrent severe obstructive pulmonary disease.
19. 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.
20. Is pregnant or breastfeeding.

Trial treatments

The IMP in all parts of the trial is BNT151. The IMP is a preservative-free, sterile ribonucleic acid (RNA)-lipid nanoparticle (LNP) dispersion in an aqueous cryoprotectant buffer for IV administration. For further information on the IMP, refer to the pharmacy manual for BNT151-01.

In Part 1, BNT151 will be administered IV on Day 1 of each 3-week treatment cycle (21 days) after all required procedures and assessments before administration have been completed. Once eligibility is confirmed, administration of BNT151 can be delayed for up to 7 days unless otherwise approved by the sponsor medical monitor.

Patients will be administered BNT151 according to dose levels (0.4 µg/kg starting dose to be escalated to CCI µg/kg). BNT151 will be administered as a body weight-based dosing. A cap of dosing for patients weighing 120 kg and more will be implemented in the proposed clinical trial.

Treatment name	BNT151
Type	Biologic
Designation	Advance Therapy (FDA)/Advance Therapy Medicinal Product (EMA)
Dose formulation	Ampule
Unit dose strength(s)	IMP concentration (0.04 mg/mL). Refer to the Pharmacy Manual for further information
Dosage level(s)	0.4 µg/kg RNA for the first dose, increments up to CCI µg/kg
Route of administration	IV bolus injection/IV infusion (depending on the administered volume)
Use	Experimental (IMP)
Sourcing	Provided centrally by the sponsor
Packaging and labeling	IMP will be provided in a folding box. Each folding box and each vial will be labeled as required per country requirement

IMP = investigational medicinal product; IV = intravenous; RNA = ribonucleic acid.

For Part 2, Cohorts 1 and 2 in combination with SoC treatments, administration schedules and information about the combination treatments will be submitted by amendment.

Statistics

The primary objectives of this trial Part 1 are to assess the safety profile and to identify the MTD and/or RP2D. The Biomarker Cohort examines the exploratory markers for the mechanism of action in the tumor and periphery. Hence, no statistical hypothesis is under test for trial Part 1. For trial Part 2A and 2B hypothesis testing for each expansion cohort may be introduced through protocol amendment.

The sample size for trial Part 1 is driven by accelerated titration design of single-patient cohorts with a switch to the 3+3 trial design. In Part 1, the sample size will be up to 54 DLT-evaluable patients depending on the number of DLTs which may occur (with the possible enrollment of up to 10 additional patients if efficacy is seen in a specific tumor type).

In addition, approximately 20 patients will be enrolled in the Biomarker Cohort with paired biopsies. This sample size is based on the proportion of patients who have achieved at least 50% increase from baseline in lymphocytes (total lymphocytes, CD4+, CD8+, T_{regs}, and NK cells) upon treatment with BNT151. Twenty patients are estimated to have >80% chance to rule out a proportion of 10% if the true proportion is 40% at a 2-sided significance level of 0.05.

The objective for the trial Part 2A and 2B is to further investigate the safety profile and to assess the efficacy of the IMP in different indications in combination with other approved anti-cancer agents. The design in Part 2A can either be a safety run-in of 6 patients or a short escalation at 2 dose levels according to the 3+3 trial design, therefore the sample size in Part 2A will range from 6 to 12 patients per cohort. The sample size in Part 2B may be based on either Simon two-stage design or one-stage design. The final sample size calculations will be introduced through protocol amendment.

The statistical analysis plan (SAP) will be finalized prior to database lock for the main analysis and it will include a more technical and detailed description of the statistical analyses. Any deviations from the planned analyses described in the final SAP will be described and justified in the clinical trial report.

Safety Review Committee (SRC)

A data monitoring committee (DMC) is not planned. 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 recommendations for the adaptive trial design as well as for the recommended dose for pre-conditioning if needed and for Parts 2A and 2B and will recommend whether to activate the Expansion Phase (Part 2).

1.2 Schema (graphical representation of the trial)

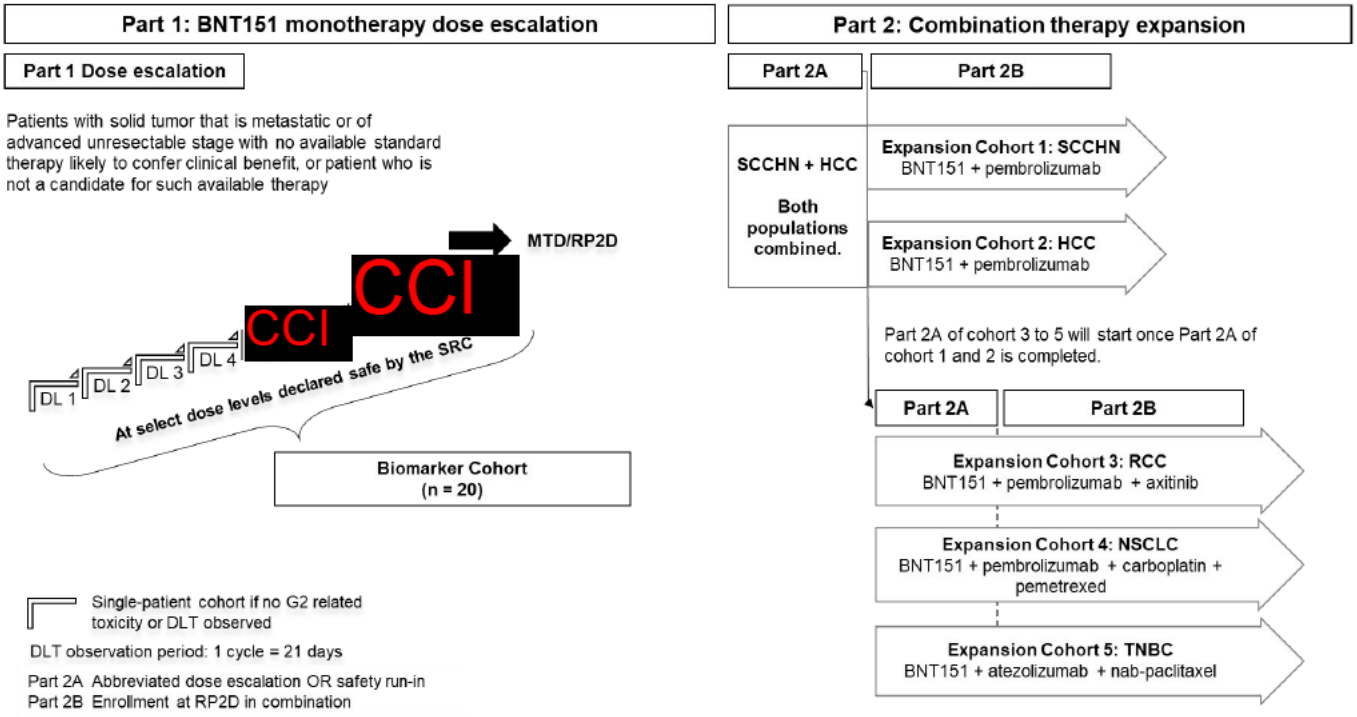

Figure 1: Trial design

The monotherapy dose escalation (Part 1) of this clinical trial will enroll patients with various solid tumors that are metastatic or of advanced unresectable stage and for whom there is no available standard therapy likely to confer clinical benefit, or patient who is not a candidate for such available therapy. During combination dose escalation (Part 2A), patients with SCCHN, and HCC will be enrolled and treated with a combination of BNT151 and pembrolizumab. Once Part 2A of SCCHN and HCC is completed, patients with RCC, TNBC, and NSCLC will be enrolled and treated with a combination of BNT151 with the respective SoC.

DL = dose level; DLT = dose limiting toxicity; G2 = Grade 2; HCC = hepatocellular carcinoma; MTD = maximum tolerated dose; NSCLC = non-small cell lung cancer; RCC = renal cell carcinoma; RP2D = recommended Phase II dose; SCCHN = squamous cell carcinoma of head and neck; SoC = standard of care; SRC = Safety Review Committee; TNBC = triple negative breast cancer.

1.3 Schedule of activities

According to the adaptive trial design of this trial, Part 1 of the trial will start without a pre-conditioning dosing schedule. The schedule of activities (SoA) and procedures for Part 1 with and without a pre-conditioning dosing scheme is shown in Table 1a and Table 1b, with the schedule of PK, exploratory PD, cytokines/chemokines and immunogenicity shown in Table 2a and Table 2b. In case the SRC recommend pre-conditioning, all newly enrolled patients will be treated with the pre-conditioning cycle.

The SoA and procedures for the Biomarker Cohort with and without pre-conditioning is shown in Table 3a and Table 3b, with the schedule of PK, exploratory PD, cytokines/chemokines and immunogenicity shown in Table 4a and Table 4b.

Assessments should be performed before trial treatment administration (on the applicable days) or any planned intervention, with the exception of post-dose blood sampling for exploratory PD, PK, immunogenicity assessments and any samples required for supplementary biomarker assessments. On the days of tumor imaging, blood sampling can be before or after imaging assessments.

In the dosing scheme, one cycle is defined as 21 days. The length of the pre-conditioning cycle is 7 days.

The SoA for the expansion cohorts in Part 2 will be submitted by amendment.

Table 1a: Schedule of activities and procedures – Part 1: Monotherapy with and without pre-conditioning - Screening, treatment cycles, and end of treatment

Treatment cycle (C)	Screening[1]	pC[2]		C1						C2			C3	C4			C5-N		EoT[3]
Day/Week	≤21 d prior to Visit pCD1[2]/C1D1	D1	D2	D1[5]	D2	D3	D5	D8	D15	D1	D2	D8	D1	D1	D2	D8	D1	D2[6]	
Visit window (d)		+3	-	+3	-	-	±1	±1	±1	+3	-	±1	±3	±3	-	±1	±3	-	-
Informed consent	X																		
Demographics	X																		
Eligibility	X																		
Medical history[7]	X																		
Height	X																		
Body weight	X	X		X						X			X	X			X		X
Physical examination[9]	X	X		X						X			X	X			X		X
Vital signs[10]	X	X		X				X	X	X		X	X	X			X		X
ECG[11]	X	X		X						X			X	X			X		X
CT/MRI[12]	X	Refer to Footnote 12																	
ECOG performance status[13]	X	X		X				X	X	X		X	X	X			X		X
ECHO[14]	X																		
Adverse events[15]	X	Continuous																	
Prior/concomitant medication and non-drug therapies[17]	X	Continuous																	
BNT151 administration[19]		X		X						X[20]			X	X			X		
New anti-cancer treatment																			X
Survival follow-up																			

Treatment cycle (C)	Screening[1]	pC[2]		C1						C2			C3	C4			C5-N		EoT[3]
Day/Week	≤21 d prior to Visit pCD1[2]/C1D1	D1	D2	D1[5]	D2	D3	D5	D8	D15	D1	D2	D8	D1	D1	D2	D8	D1	D2[6]	
Visit window (d)		+3	-	+3	-	-	±1	±1	±1	+3	-	±1	±3	±3	-	±1	±3	-	-
LABORATORY ASSESSMENTS (to be performed up to 24 h before administration days, unless indicated otherwise)																			
Hematology[21]	X[22]	X	X	X	X	X	X	X	X	X	X	X	X	X			X		X
Blood chemistry[23]	X[22]	X	X[24]	X	X[24]	X[24]	X[24]	X[24]	X[24]	X	X[24]	X[24]	X	X			X		X
Coagulation factors	X[22]	X		X				X	X	X		X	X	X			X		X
Endocrine[25]	X	X		X						X				X			X[25]		X
Pregnancy test[26]	X	X		X						X			X	X			X		X
Urinalysis[27]	X	X		X						X			X	X			X		X
Serology[28]	X																		
Serum autoantibody sample[29]	X	Perform if a patient experiences a suspected immune-related adverse event																	
Pharmacokinetics		Refer to Table 2a and Table 2b																	
Exploratory pharmacodynamics		Refer to Table 2a and Table 2b																	
Tumor biopsy[30]	X																		X

1 Patients who fail their first screening for trial eligibility may qualify for 2 re-screening opportunities (for a total of 3 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.

2 Applies only to patients with pre-conditioning.

3 If the patient has to go off treatment per treatment withdrawal criteria, the end of treatment (EoT) visit should be performed as soon as possible after permanent discontinuation of BNT151.

4 Survival follow-up may be performed as telephone, e-mail, or clinic visit. Survival follow-up starts 12 weeks after all other trial visits have been completed.

5 Hospitalization is required for the first 24 hours in Cycle 1 Day 1 (C1D1). For each subsequent dose of BNT151, and in pC (if applicable), patients will be monitored for at least 4 hours.

6 Only every 4th cycle starting with Cycle 8 (i.e.: 8th, 12th, 16th …), see Table 2b.

7 Medical history includes cancer and smoking history.

8 Only if clinically indicated.

9 A 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.

10 Temperature, blood pressure, heart rate and respiratory rate as according to Section 8.2.2 on BNT151 administration days. On days when BNT151 is not administered, vital signs only need to be obtained once any time during the visit.

11 12-lead ECG recordings will be obtained during screening, Day 1 of every cycle, EoT, SFU-1, SFU-2, and at ad hoc visit. Patients should be resting in a supine position for at least 10 minutes prior to ECG recording. The interpretation of the ECG recording will be performed locally.

[12] Imaging at screening, on-treatment imaging at Week 6 (+7 d), every 6 weeks (±7 d) for 48 weeks, and every 12 weeks (±7 d) thereafter until disease progression is assessed by the investigator (unless the investigator elects to continue treatment [see below for conditions of continued treatment]), withdrawal of consent, trial termination by the sponsor, or death, whichever occurs first. The RECIST 1.1 criteria will be used for secondary endpoint response evaluation including PFS (Eisenhauer et al. 2009). All images obtained must be submitted to the central imaging vendor. At screening a head and neck imaging is required for patients with SCCHN. Imaging of the pelvis is not required for those patients but is strongly recommended.

[13] During screening ECOG performance status should be assessed no later than 7 days prior to the planned visit C1D1/if applicable planned pCD1.

[14] Evaluation of left ventricular function by ECHO scan will be performed during screening, and if clinically indicated at other time points.

[15] Adverse events (AEs) and serious adverse events (SAEs) should be reported from the time of signing the informed consent to 60 days after the patient receives the last dose of BNT151.

[16] Suspected BNT151-related AEs only.

[17] Prior/Concomitant medications and non-drug therapies include all anti-cancer pre-treatments and all previous and on-trial COVID-19 vaccinations.

[18] Only medications and non-drug therapies related to “Suspected BNT151-related AEs” need to be documented.

[19] Patients who experience a delay in the administration of BNT151 should return to the clinic at least every 2 weeks (±3 d) after onset of the delay and assessments listed under ad hoc visit should be performed and reported in the eCRF. Ad hoc visit assessments should be performed at the investigator’s discretion.

[20] Cycle 2 dose should not be given during DLT observation period, which lasts for 21 days.

[21] Hematology includes platelet count, red blood cell (RBC) count, RBC indices, white blood cell count with differential, hemoglobin, hematocrit (for details, see Table 13).

[22] All labs (hematology, blood chemistry, coagulation factors) at the screening visit must be obtained within 7 days prior to the planned C1D1 (if applicable planned pCD1) and again on C1D1 (if applicable pCD1). The following samples will be analyzed locally at the site the patient was enrolled: hematology, blood chemistry, coagulation factors, endocrine, pregnancy test, urinalysis, and serum autoantibody sample (see Table 13). All other laboratory samples will be analyzed centrally.

[23] Blood chemistry panel for the screening and D1 of each cycle sample includes sodium, potassium, magnesium, chloride, bicarbonate or carbon dioxide, glucose, BUN or urea, creatinine, total protein, albumin, pre-albumin, phosphorus, calcium, total bilirubin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, ferritin, and C-reactive protein. For all subsequent sampling, only a reduced panel will be assessed (see Footnote 24).

[24] Reduced blood chemistry panel includes sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, alkaline phosphatase, alanine aminotransferase, and aspartate aminotransferase, lactate dehydrogenase.

[25] TSH, free-T3 and free-T4 will only be measured at screening, pCD1 (if applicable), C1D1, C2D1, on Day 1 of every evenly numbered cycle thereafter (e.g., Cycle 4, 6, 8…), SFU-1, SFU-2, and at EoT.

[26] 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 the local guidelines and regulations.

[27] Includes specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick. Microscopic examination (if blood or protein is abnormal).

[28] 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).

[29] Autoantibody analysis includes anti-nuclear antibody, anti-double-stranded-DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody. For patients who show evidence of immune-mediated toxicity, additional time points may be considered.

[30] If feasible, patients should provide a fresh biopsy (aspirates are not acceptable) performed at screening and treatment discontinuation in the trial. Further serial biopsy during treatment and/or at progression will be performed in the same patients if feasible. The trial site should either provide FFPE (block/slides) or provide fresh formalin fixed tumor biopsy for sponsor processing into FFPE. In case the site and the patients are willing to provide biopsies on-treatment but cannot provide fresh biopsy during screening, archived material is allowed to be used as a screening sample.

AE = adverse event; BUN = blood urea nitrogen; C = cycle; CT = computed tomography; D,d = day; DLT = dose limiting toxicity; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EoT = end of treatment; FFPE = formalin fixed paraffin embedded; FU = Follow-up; MRI = magnetic resonance imaging; pC = pre-conditioning cycle; PFS = progression-free survival; RECIST = Response Evaluation Criteria Solid Tumors; SFU = Safety Follow-up; SCCHN = squamous cell carcinoma of head and neck; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone; wks = weeks.

Table 1b: Schedule of activities and procedures – Part 1: Monotherapy with and without pre-conditioning – Safety follow-up, survival follow-up, and ad hoc visits

Treatment cycle (C)	SFU-1	SFU-2	Survival FU[4]	Ad hoc
Day/Week	30d after last dose	60d after last dose	Every 12 wks	-
Visit window (d)	+5	±7	±14	-
Informed consent				
Demographics				
Eligibility				
Medical history[7]				
Height				
Body weight	X	X		X[8]
Physical examination[9]	X	X		X[8]
Vital signs[10]	X	X		X[8]
ECG[11]	X	X		X[8]
CT/MRI[12]	Refer to Footnote 12			
ECOG performance status[13]	X	X		X[8]
ECHO[14]				X[8]
Adverse events[15]	Continuous		X[16]	X[8]
Prior/concomitant medication and non-drug therapies[17]	Continuous		X[18]	X[8]
BNT151 administration[19]				
New anti-cancer treatment	X	X	X	
Survival follow-up			X[4]	
LABORATORY ASSESSMENTS (to be performed up to 24 h before administration days, unless indicated otherwise)				
Hematology[21]	X	X		X[8]
Blood chemistry[23]	X	X		X[8]
Coagulation factors	X	X		X[8]
Endocrine[25]	X	X		X[8]
Pregnancy test[26]	X	X		X[8]
Urinalysis[27]	X	X		X[8]

Treatment cycle (C)	SFU-1	SFU-2	Survival FU[4]	Ad hoc
Day/Week	**30d after last dose**	**60d after last dose**	**Every 12 wks**	**-**
Visit window (d)	**+5**	**±7**	**±14**	**-**
Serology[28]				
Serum autoantibody sample[29]				X[8]
Pharmacokinetics	Refer to Table 2b			
Exploratory pharmacodynamics	Refer to Table 2b			
Tumor biopsy[30]				X[8]

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4 Survival follow-up may be performed as telephone, e-mail, or clinic visit. Survival follow-up starts 12 weeks after all other trial visits have been completed.

5 Hospitalization is required for the first 24 hours in Cycle 1 Day 1 (C1D1). For each subsequent dose of BNT151, and in pC (if applicable), patients will be monitored for at least 4 hours.

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7 Medical history includes cancer and smoking history.

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9 A 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.

10 Temperature, blood pressure, heart rate and respiratory rate as according to Section 8.2.2 on BNT151 administration days. On days when BNT151 is not administered, vital signs only need to be obtained once any time during the visit.

11 12-lead ECG recordings will be obtained during screening, Day 1 of every cycle, EoT, SFU-1, SFU-2, and at ad hoc visit. Patients should be resting in a supine position for at least 10 minutes prior to ECG recording. The interpretation of the ECG recording will be performed locally.

12 Imaging at screening, on-treatment imaging at Week 6 (+7 d), every 6 weeks (±7 d) for 48 weeks, and every 12 weeks (±7 d) thereafter until disease progression is assessed by the investigator (unless the investigator elects to continue treatment [see below for conditions of continued treatment]), withdrawal of consent, trial termination by the sponsor, or death, whichever occurs first. The RECIST 1.1 criteria will be used for secondary endpoint response evaluation including PFS (Eisenhauer et al. 2009). All images obtained must be submitted to the central imaging vendor. At screening a head and neck imaging is required for patients with SCCHN. Imaging of the pelvis is not required for those patients but is strongly recommended.

13 During screening ECOG performance status should be assessed no later than 7 days prior to the planned visit C1D1/if applicable planned pCD1.

14 Evaluation of left ventricular function by ECHO scan will be performed during screening, and if clinically indicated at other time points.

15 Adverse events (AEs) and serious adverse events (SAEs) should be reported from the time of signing the informed consent to 60 days after the patient receives the last dose of BNT151.

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[25] TSH, free-T3 and free-T4 will only be measured at screening, pCD1 (if applicable), C1D1, C2D1, on Day 1 of every evenly numbered cycle thereafter (e.g., Cycle 4, 6, 8…), SFU-1, SFU-2, and at EoT.

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[29] Autoantibody analysis includes anti-nuclear antibody, anti-double-stranded-DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody. For patients who show evidence of immune-mediated toxicity, additional time points may be considered.

[30] If feasible, patients should provide a fresh biopsy (aspirates are not acceptable) performed at screening and treatment discontinuation in the trial. Further serial biopsy during treatment and/or at progression will be performed in the same patients if feasible. The trial site should either provide FFPE (block/slides) or provide fresh formalin fixed tumor biopsy for sponsor processing into FFPE. In case the site and the patients are willing to provide biopsies on-treatment but cannot provide fresh biopsy during screening, archived material is allowed to be used as a screening sample.

AE = adverse event; BUN = blood urea nitrogen; C = cycle; CT = computed tomography; D,d = day; DLT = dose limiting toxicity; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EoT = end of treatment; FFPE = formalin fixed paraffin embedded; FU = Follow-up; MRI = magnetic resonance imaging; PFS = progression-free survival; RECIST = Response Evaluation Criteria Solid Tumors; SFU = Safety Follow-up; SCCHN = squamous cell carcinoma of head and neck; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone; wks = weeks

Table 2a: Schedule of PK, exploratory PD, cytokines/chemokines and immunogenicity for Part 1: Monotherapy with and without pre-conditioning – Cycle 1 to 4 inclusive

Treatment cycle (C)	pC[1]					C1										C2						C4		
Day (D)	D1				D2	D1					D2	D3	D5	D8	D15	D1				D2	D8	D1	D2	D8
Hours[2]	Pre-dose	1	3	6	24h post dose	Pre-dose	1	3	6	12	24h post dose	-	-	-	-	Pre-dose	1	3	6	24h post dose	-	Pre-dose	24h post dose	-
Time/Visit window	-24h	±5 min	±10 min	±15 min	± 2h	-24h	±5 min	±10 min	±15 min	±2h	±2h	-	±1d	±1d	±1d	-24h	±5 min	±10 min	±15min	±2h	±1d	-24h	±2h	±1d
Pharmacokinetics[3]																								
BNT151 translated IL-2 variant PK (serum)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lipid PK (plasma)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Exploratory Pharmacodynamics[3]																								
Cell phenotype (whole blood)	X		X		X	X		X		X	X		X	X	X	X		X		X	X	X	X	X
sCD25 (serum)	X				X	X					X		X	X	X	X				X	X	X	X	X
Cytokines/chemokines (serum)[4]	X	X		X	X	X	X		X	X	X		X	X		X	X		X	X	X	X	X	X
Immunogenicity[3] (serum for ADAs)																								
Anti-PEG lipid	X					X								X		X					X	X		X
Anti-BNT151 translated IL-2 variant	X					X										X						X		
Extra sample for immunogenicity[5]	X					X								X		X					X	X		X

[1] Applies only to patients with pre-conditioning.

[2] Time points (hours) counted from start of administration of BNT151.

[3] Samples will be analyzed centrally. For details, please see the Laboratory Manual.

[4] Cytokines/chemokines which will be analyzed including but not limited to IFN-α, IP-10, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IFN-γ, TNF-α, IL-12p70, IL-13, and IL-18.

[5] Extra sample for retesting if required.

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

ADAs = anti-drug antibodies; Anti-PEG = Anti-Polyethylene glycol; C = cycle; D,d = day; EoT = end of treatment; IFN = interferon; IL = interleukin; IP = interferon-gamma induced protein; SFU = Safety Follow-up; sCD25 = soluble interleukin-2 receptor; TNF = tumor necrosis factor; pC = pre-conditioning cycle; PD = pharmacodynamics; PK = pharmacokinetics.

Table 2b: Schedule of PK, exploratory PD, cytokines/chemokines and immunogenicity for Part 1: Monotherapy with and without pre-conditioning – Every 4th cycle thereafter, end of treatment, and safety follow-up visits

Treatment cycle (C)	Every 4th cycle thereafter (e.g., C8, C12, …)		EoT	SFU-1	SFU-2
Day (D)	**D1**	**D2**			
Hours[2]	**Pre-dose**	**24h post dose**	**-**	**30d**	**60d**
Time/Visit window	**-24h**	**±2h**	**-**	**±5d**	**±7d**
Pharmacokinetics[3]					
BNT151 translated IL-2 variant PK (serum)	X	X			
Lipid PK (plasma)	X	X			
Exploratory Pharmacodynamics[3]					
Cell phenotype (whole blood)	X	X	X		
sCD25 (serum)	X	X	X		
Cytokines/chemokines (serum)[4]	X	X	X		
Immunogenicity[3] (serum for ADAs)					
Anti-PEG lipid	X		X	X	X
Anti-BNT151 translated IL-2 variant	X		X	X	X
Extra sample for immunogenicity[5]	X		X	X	X

[1] Applies only to patients with pre-conditioning.

[2] Time points (hours) counted from start of administration of BNT151.

[3] Samples will be analyzed centrally. For details, please see the Laboratory Manual.

[4] Cytokines/chemokines which will be analyzed including but not limited to IFN-α, IP-10, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IFN-γ, TNF-α, IL-12p70, IL-13, and IL-18.

[5] Extra sample for retesting if required.

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

ADA = anti-drug antibodies; Anti-PEG = Anti-Polyethylene glycol; C = cycle; D,d = day; EoT = end of treatment; IFN = interferon; IL = interleukin; IP = interferon-gamma induced protein; SFU = Safety Follow-up; sCD25 = soluble interleukin-2 receptor; TNF = tumor necrosis factor; PBMC = peripheral blood mononuclear cells; PD = pharmacodynamics; PK = pharmacokinetics

Table 3a: Schedule of activities and procedures – Part 1: Biomarker Cohort with and without pre-conditioning – Screening, treatment cycles, and end of treatment

Treatment cycle (C)	Screening[1]	pC[2]		C1						C2			C3			C4		C5-N		EoT[3]
Day/Week	≤21 d prior to Visit pCD1[2]/C1D1	D1	D2	D1[5]	D2	D3	D5	D8	D15	D1	D2	D8	D1	D2	D8	D1	D2	D1	D2[6]	
Visit window (d)		+3	-	+3	-	-	±1	±1	±1	+3	-	±1	±3	-	-	±3	-	±3	-	-
Informed consent	X																			
Demographics	X																			
Eligibility	X																			
Medical history[7]	X																			
Height	X																			
Body weight	X	X		X						X			X			X		X		X
Physical examination[9]	X	X		X						X			X			X		X		X
Vital signs[10]	X	X		X				X	X	X		X	X			X		X		X
ECG[11]	X	X		X						X			X			X		X		X
CT/MRI[12]	X	Refer to Footnote 12																		
ECOG performance status[13]	X	X		X				X	X	X		X	X			X		X		X
ECHO[14]	X																			
Adverse events[15]	X	Continuous																		
Prior/concomitant medication and non-drug therapies[17]	X	Continuous																		
BNT151 administration[19]		X		X						X[20]			X			X		X		
New anti-cancer treatment																				X
Survival follow-up																				

Treatment cycle (C)	Screening[1]	pC[2]		C1						C2			C3			C4		C5-N		EoT[3]
Day/Week	≤21 d prior to Visit pCD1[2]/C1D1	D1	D2	D1[5]	D2	D3	D5	D8	D15	D1	D2	D8	D1	D2	D8	D1	D2	D1	D2[6]	
Visit window (d)		+3	-	+3	-	-	±1	±1	±1	+3	-	±1	±3	-	-	±3	-	±3	-	-
LABORATORY ASSESSMENTS (to be performed up to 24 h before administration days, unless indicated otherwise)																				
Hematology[21]	X[22]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X
Blood chemistry[23]	X[22]	X	X[24]	X	X[24]	X[24]	X[24]	X[24]	X[24]	X	X[24]	X[24]	X	X[24]	X[24]	X		X		X
Coagulation factors	X[22]	X		X				X	X	X		X	X		X	X		X		X
Endocrine[25]	X	X		X						X						X		X[25]		X
Pregnancy test[26]	X	X		X						X			X			X		X		X
Urinalysis[27]	X	X		X						X			X			X		X		
Serology[28]	X																			
Serum autoantibody sample[29]	X	Perform if a patient experiences a suspected immune-related adverse event																		
Pharmacokinetics		Refer to Table 4a and Table 4b																		
Exploratory pharmacodynamics		Refer to Table 4a and Table 4b																		
Tumor biopsy[30]	X	Refer to Table 4a and Table 4b																		

[1] Patients who fail their first screening for trial eligibility may qualify for 2 re-screening opportunities (for a total of 3 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.

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[5] Hospitalization is required for the first 24 hours in Cycle 1 Day 1 (C1D1). For each subsequent dose of BNT151, and in pC (if applicable), patients will be monitored for at least 4 hours.

[6] Only every 4th cycle starting with Cycle 8 (i.e.: 8th, 12th, 16th …), see Table 4b.

[7] Medical history includes cancer and smoking history.

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[9] A 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.

[10] Temperature, blood pressure, heart rate and respiratory rate as according to Section 8.2.2 on BNT151 administration days. On days when BNT151 is not administered, vital signs only need to be obtained once any time during the visit.

[11] 12-lead ECG recordings will be obtained during screening, Day 1 of every cycle, EoT, SFU-1, SFU-2, and at ad hoc visit. Patients should be resting in a supine position for at least 10 minutes prior to ECG recording. The interpretation of the ECG recording will be performed locally.

[12] Imaging at screening, on-treatment imaging at Week 6 (+7 d), every 6 weeks (±7 d) for 48 weeks, and every 12 weeks (±7 d) thereafter until disease progression is assessed by the investigator (unless the investigator elects to continue treatment [see below for conditions of continued treatment]), withdrawal of consent, trial termination by the sponsor, or death, whichever occurs first. The

RECIST 1.1 criteria will be used for secondary endpoint response evaluation including PFS (Eisenhauer et al. 2009). All images obtained must be submitted to the central imaging vendor. At screening a head and neck imaging is required for patients with SCCHN. Imaging of the pelvis is not required for those patients but is strongly recommended.

[13] During screening ECOG performance status should be assessed no later than 7 days prior to the planned visit C1D1/if applicable planned pCD1.

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[18] Only medications and non-drug therapies related to “Suspected BNT151-related AEs” need to be documented.

[19] Patients who experience a delay in the administration of BNT151 should return to the clinic at least every 2 weeks (±3 d) after onset of the delay and assessments listed under ‘ad hoc visit’ should be performed and reported in the eCRF. Ad hoc visit assessments should be performed at the investigator’s discretion.

[20] Cycle 2 dose should not be given during DLT observation period, which lasts for 21 days.

[21] Hematology includes platelet count, red blood cell (RBC) count, RBC indices, white blood cell count with differential, hemoglobin, hematocrit (for details, see Table 13).

[22] All labs (hematology, blood chemistry, coagulation factors) at the screening visit must be obtained within 7 days prior to the planned C1D1 (if applicable planned pCD1) and again on C1D1 (if applicable pCD1). The following samples will be analyzed locally at the site the patient was enrolled: hematology, blood chemistry, coagulation factors, endocrine, pregnancy test, urinalysis, and serum autoantibody sample (see Table 13). All other laboratory samples will be analyzed centrally.

[23] Blood chemistry panel for the screening and D1 of each cycle sample includes sodium, potassium, magnesium, chloride, bicarbonate or carbon dioxide, glucose, BUN or urea, creatinine, total protein, albumin, pre-albumin, phosphorus, calcium, total bilirubin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, ferritin, and C-reactive protein. For all subsequent sampling, only a reduced panel will be assessed (see Footnote 24).

[24] Reduced blood chemistry panel includes sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, alkaline phosphatase, alanine aminotransferase, and aspartate aminotransferase, lactate dehydrogenase.

[25] TSH, free-T3 and free-T4 will only be measured at screening, pCD1 (if applicable), C1D1, C2D1, on Day 1 of every evenly numbered cycle thereafter (e.g., Cycle 4, 6, 8…), SFU-1, SFU-2, and at EoT.

[26] 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 the local guidelines and regulations.

[27] Includes specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick. Microscopic examination (if blood or protein is abnormal).

[28] 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).

[29] Autoantibody analysis includes anti-nuclear antibody, anti-double-stranded-DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody. For patients who show evidence of immune-mediated toxicity, additional time points may be considered.

[30] The mandatory fresh pre-treatment biopsy must be between signature of informed consent and before the first dose, the on-treatment biopsy should be taken post-dose, preferred on C2D5-12, and an optional biopsy can be taken at disease progression or EoT.

AE = adverse event; BUN = blood urea nitrogen; C = cycle; CT = computed tomography; D,d = day; DLT = dose limiting toxicity; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EoT = end of treatment; FFPE = formalin fixed paraffin embedded; FU = Follow-up; MRI = magnetic resonance imaging; pC = pre-conditioning cycle; PFS = progression-free survival; RECIST = Response Evaluation Criteria Solid Tumors; SFU = Safety Follow-up; SCCHN = squamous cell carcinoma of head and neck; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone; wks = weeks.

Table 3b: Schedule of activities and procedures – Part 1: Biomarker Cohort with and without pre-conditioning – Safety follow-up visits, survival follow-up, and ad hoc visits

Treatment cycle (C)	**SFU-1**	**SFU-2**	**Survival FU[4]**	**Ad hoc**
Day/Week	**30d after last dose**	**60d after last dose**	**Every 12 wks**	**-**
Visit window (d)	**+5**	**±7**	**±14**	**-**
Informed consent				
Demographics				
Eligibility				
Medical history[7]				
Height				
Body weight	X	X		X[8]
Physical examination[9]	X	X		X[8]
Vital signs[10]	X	X		X[8]
ECG[11]	X	X		X[8]
CT/MRI[12]	Refer to Footnote 12			
ECOG performance status[13]	X	X		X[8]
ECHO[14]				X[8]
Adverse events[15]	Continuous		X[16]	X[8]
Prior/concomitant medication and non-drug therapies[17]	Continuous		X[18]	X[8]
BNT151 administration[19]				
New anti-cancer treatment	X	X	X	
Survival follow-up			X[4]	
LABORATORY ASSESSMENTS (to be performed up to 24 h before administration days, unless indicated otherwise)				
Hematology[21]	X	X		X[8]
Blood chemistry[23]	X	X		X[8]
Coagulation factors	X	X		X[8]
Endocrine[25]	X	X		X[8]
Pregnancy test[26]	X	X		X[8]
Urinalysis[27]	X	X		X[8]

Treatment cycle (C)	SFU-1	SFU-2	Survival FU[4]	Ad hoc
Day/Week	**30d after last dose**	**60d after last dose**	**Every 12 wks**	**-**
Visit window (d)	**+5**	**±7**	**±14**	**-**
Serology[28]				
Serum autoantibody sample[29]				X[8]
Pharmacokinetics	Refer to Table 4b			
Exploratory pharmacodynamics	Refer to Table 4b			
Tumor biopsy[30]	Refer to Table 4b			

[1] Patients who fail their first screening for trial eligibility may qualify for 2 re-screening opportunities (for a total of 3 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.

[2] Applies only to patients with pre-conditioning.

[3] If the patient has to go off treatment per treatment withdrawal criteria, the end of treatment (EoT) visit should be performed as soon as possible after permanent discontinuation of BNT151.

[4] Survival follow-up may be performed as telephone, e-mail, or clinic visit. Survival follow-up starts 12 weeks after all other trial visits have been completed.

[5] Hospitalization is required for the first 24 hours in Cycle 1 Day 1 (C1D1). For each subsequent dose of BNT151, and in pC (if applicable), patients will be monitored for at least 4 hours.

[6] Only every 4th cycle starting with Cycle 8 (i.e.: 8th, 12th, 16th ...), see Table 4b.

[7] Medical history includes cancer and smoking history.

[8] Only if clinically indicated.

[9] A 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.

[10] Temperature, blood pressure, heart rate and respiratory rate as according to Section 8.2.2 on BNT151 administration days. On days when BNT151 is not administered, vital signs only need to be obtained once any time during the visit.

[11] 12-lead ECG recordings will be obtained during screening, Day 1 of every cycle, EoT, SFU-1, SFU-2, and at ad hoc visit. Patients should be resting in a supine position for at least 10 minutes prior to ECG recording. The interpretation of the ECG recording will be performed locally.

[12] Imaging at screening, on-treatment imaging at Week 6 (+7 d), every 6 weeks (±7 d) for 48 weeks, and every 12 weeks (±7 d) thereafter until disease progression is assessed by the investigator (unless the investigator elects to continue treatment [see below for conditions of continued treatment]), withdrawal of consent, trial termination by the sponsor, or death, whichever occurs first. The RECIST 1.1 criteria will be used for secondary endpoint response evaluation including PFS (Eisenhauer et al. 2009). All images obtained must be submitted to the central imaging vendor. At screening a head and neck imaging is required for patients with SCCHN. Imaging of the pelvis is not required for those patients but is strongly recommended.

[13] During screening ECOG performance status should be assessed no later than 7 days prior to the planned visit C1D1/if applicable planned pCD1.

[14] Evaluation of left ventricular function by ECHO scan will be performed during screening, and if clinically indicated at other time points.

[15] Adverse events (AEs) and serious adverse events (SAEs) should be reported from the time of signing the informed consent to 60 days after the patient receives the last dose of BNT151.

[16] Suspected BNT151-related AEs only.

[17] Prior/Concomitant medications and non-drug therapies include all anti-cancer pre-treatments and all previous and on-trial COVID-19 vaccinations .

[18] Only medications and non-drug therapies related to "Suspected BNT151-related AEs" need to be documented.

[19] Patients who experience a delay in the administration of BNT151 should return to the clinic at least every 2 weeks (±3 d) after onset of the delay and assessments listed under 'ad hoc visit' should be performed and reported in the eCRF. Ad hoc visit assessments should be performed at the investigator's discretion.

[20] Cycle 2 dose should not be given during DLT observation period, which lasts for 21 days.

[21] Hematology includes platelet count, red blood cell (RBC) count, RBC indices, white blood cell count with differential, hemoglobin, hematocrit (for details, see Table 13).

[22] All labs (hematology, blood chemistry, coagulation factors) at the screening visit must be obtained within 7 days prior to the planned C1D1 (if applicable planned pCD1) and again on C1D1 (if applicable pCD1). The following samples will be analyzed locally at the site the patient was enrolled: hematology, blood chemistry, coagulation factors, endocrine, pregnancy test, urinalysis, and serum autoantibody sample (see Table 13). All other laboratory samples will be analyzed centrally.

[23] Blood chemistry panel for the screening and D1 of each cycle sample includes sodium, potassium, magnesium, chloride, bicarbonate or carbon dioxide, glucose, BUN or urea, creatinine, total protein, albumin, pre-albumin, phosphorus, calcium, total bilirubin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, ferritin, and C-reactive protein. For all subsequent sampling, only a reduced panel will be assessed (see Footnote 24).

[24] Reduced blood chemistry panel includes sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, alkaline phosphatase, alanine aminotransferase, and aspartate aminotransferase, lactate dehydrogenase.

[25] TSH, free-T3 and free-T4 will only be measured at screening, pC1D1 (if applicable), C1D1, C2D1, on Day 1 of every evenly numbered cycle thereafter (e.g., Cycle 4, 6, 8…), SFU-1, SFU-2, and at EoT

[26] 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 the local guidelines and regulations.

[27] Includes specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick. Microscopic examination (if blood or protein is abnormal).

[28] 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).

[29] Autoantibody analysis includes anti-nuclear antibody, anti-double-stranded-DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody. For patients who show evidence of immune-mediated toxicity, additional time points may be considered.

[30] The mandatory fresh pre-treatment biopsy must be between signature of informed consent and before the first dose, the on-treatment biopsy should be taken post-dose, preferred on C2D5-12, and an optional biopsy can be taken at disease progression or EoT.

AE = adverse event; BUN = blood urea nitrogen; C = cycle; CT = computed tomography; D,d = day; DLT = dose limiting toxicity; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EoT = end of treatment; FFPE = formalin fixed paraffin embedded; FU = Follow-up; MRI = magnetic resonance imaging; PFS = progression-free survival; RECIST = Response Evaluation Criteria Solid Tumors; SFU = Safety Follow-up; SCCHN = squamous cell carcinoma of head and neck; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone; wks = weeks

Table 4a: Schedule of PK, exploratory PD, cytokines/chemokines and immunogenicity and biopsies for the Biomarker Cohort with and without pre-conditioning in selected US sites only – Screening, treatment cycles 1 to 2 inclusive

Treatment Cycle (C)	Screening	pC[1]					C1										C2					
Day (D)		D1				D2	D1					D2	D3	D5	D8	D15	D1				D2	D8
Hours[2]		Pre-dose	1	3	6	24h post dose	Pre-dose	1	3	6	12	24h post dose	-	-	-	-	Pre-dose	1	3	6	24h post dose	-
Time/Visit window	≤21 d prior to Visit pCD1[2]/C1D1	-24h	±5 min	±10 min	±15 min	±2h	-24h	±5 min	±10 min	±15 min	±2h	±2h	-	±1d	±1d	±1d	-24h	±5 min	±10 min	±15 min	±2h	±1d
Pharmacokinetics[3]																						
BNT151 translated IL-2 variant PK (serum)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lipid PK (plasma)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Exploratory pharmacodynamics[3]																						
Cell phenotype (whole blood)		X		X		X	X		X		X	X		X	X	X	X		X		X	X
sCD25 (serum)		X				X	X					X		X	X	X	X				X	X
Cytokines/ chemokines (serum)[4]		X	X		X	X	X	X		X	X	X		X	X		X	X		X	X	X
Immunophenotyping of peripheral immune cells		X					X							X	X		X					X
Next generation sequencing																						
Cell pellet[5]							X															
Immunogenicity[3] (serum for ADAs)																						
Anti-PEG lipid		X					X								X		X					X
Anti-BNT151 translated IL-2 variant		X					X										X					
Extra sample for immunogenicity[6]		X					X								X		X					X
Tissue assessment																						
Tumor biopsy	X[7]	X[7] (one on-treatment biopsy if feasible, within first 2 cycles, preferred on C2D5-12)																				

[1] Applies only to patients with pre-conditioning.
[2] Time points (hours) counted from start of administration of BNT151.
[3] Samples will be analyzed centrally. For details, please see the Laboratory Manual.

[4] Cytokines/chemokines which will be analyzed including but not limited to IFN-α, IP-10, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IFN-γ, TNF-α, IL-12p70, IL-13, and IL-18.

[5] Cell pellet to support the genetic analysis by next generation sequencing should be generated from the spin down of whole blood for lipid PK plasma.

[6] Extra sample for retesting if required.

[7] The mandatory fresh pre-treatment biopsy must be between signature of informed consent and before the first dose, and the on-treatment biopsy should be taken post-dose, preferred on C2D5-12, and an optional biopsy can be taken at disease progression or EoT.

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

ADAs = anti-drug antibodies; Anti-PEG = Anti-Polyethylene glycol; C = cycle; D,d = day; EoT = end of treatment; IFN = interferon; IL = interleukin; IP = interferon-gamma induced protein; SFU = Safety Follow-up; sCD25 = soluble interleukin-2 receptor; TNF = tumor necrosis factor; pC = pre-conditioning cycle; PK = pharmacokinetics.

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Table 4b: Schedule of PK, exploratory PD, cytokines/chemokines and immunogenicity and biopsies for the Biomarker Cohort with and without pre-conditioning in selected US sites only – Cycles 3- 4, Every 4th cycle thereafter, end of treatment, and safety follow-up visits

Treatment Cycle (C)	C3			C4		Every 4th cycle thereafter (e.g., C8, C12, …)		EoT	SFU-1	SFU-2
Day (D)	D1	D2	D8	D1	D2	D1	D2			
Hours[2]	Pre-dose	24h post dose	-	Pre-dose	24h post dose	Pre-dose	24h post dose		30d	60d
Time/Visit window	-24h	±2h	±1d	-24h	±2h	-24h	±2h	-	±5d	±7d
Pharmacokinetics[3]										
BNT151 translated IL-2 variant PK (serum)	X	X	X	X	X	X	X			
Lipid PK (plasma)	X	X	X	X	X	X	X			
Exploratory pharmacodynamics[3]										
Cell phenotype (whole blood)	X	X	X	X	X	X	X	X		
sCD25 (serum)	X	X	X	X	X	X	X	X		
Cytokines/ chemokines (serum)[4]	X	X	X	X	X	X	X	X		
Immunophenotyping of peripheral immune cells	X		X	X		X		X		
Next generation sequencing										
Cell pellet[5]										
Immunogenicity[3] (serum for ADAs)										
Anti-PEG lipid	X		X	X		X		X	X	X
Anti-BNT151 translated IL-2 variant	X			X		X		X	X	X
Extra sample for immunogenicity[6]	X		X	X		X		X	X	X
Tissue assessment										
Tumor biopsy								X[7]		

[1] Applies only to patients with pre-conditioning.
[2] Time points (hours) counted from start of administration of BNT151.
[3] Samples will be analyzed centrally. For details, please see the Laboratory Manual.
[4] Cytokines/chemokines which will be analyzed including but not limited to IFN-α, IP-10, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IFN-γ, TNF-α, IL-12p70, IL-13, and IL-18.
[5] Cell pellet to support the genetic analysis by next generation sequencing should be generated from the spin down of whole blood for lipid PK plasma.
[6] Extra sample for retesting if required.

[7] The mandatory fresh pre-treatment biopsy must be between signature of informed consent and before the first dose, and the on-treatment biopsy should be taken post-dose, preferred on C2D5-12, and an optional biopsy can be taken at disease progression or EoT.

Investigators must adhere to the given time points. However, due to possible time deviations that may occur in clinical practice, those will not be reported as protocol deviations.
ADAs = anti-drug antibodies; Anti-PEG = Anti-Polyethylene glycol; C = cycle; D,d = day; EoT = end of treatment; IFN = interferon; IL = interleukin; IP = interferon-gamma induced protein; SFU = Safety Follow-up; sCD25 = soluble interleukin-2 receptor; TNF = tumor necrosis factor; PK = pharmacokinetics.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

TRIAL-SPECIFIC ABBREVIATIONS

Abbreviation	Explanation
ADAs	Anti-drug antibodies
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AR	Adverse reaction
AST	Aspartate aminotransferase
AUC	Area under the curve
BC	Breast cancer
CD4+; CD8+	Cluster of differentiation 4 positive; Cluster of differentiation 8 positive
CLS	Capillary leak syndrome
C_{max}	Maximum observed serum concentration
CNS	Central nervous system
CPI	Checkpoint inhibitors
CPS	Combined positive score
CR	Complete response
CRS	Cytokine release syndrome
CT	Computed tomography
D	Day
DCR	Disease control rate
DILI	Drug induced liver injury
DL	Dose level
DLp	Pre-conditioning dose
DLT	Dose limiting toxicity
DNA	Desoxyribonucleic acid
DOR	Duration of response
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
(e)CRF	(Electronic) case report form
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
FDA	Food and Drug Administration
FFPE	(Fresh) formalin fixed paraffin embedded
FIH	First-in-human
G2	Grade 2
GFR	Glomerular filtration rate
GLP	Good laboratory practice
hAlb-hIL2var	Human albumin-IL2 variant

Abbreviation	Explanation
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
HR	Hazard ratio
ICB	Immune checkpoint blockade
IDMS	Isotope dilution mass spectrometry
IFN	Interferon
IL	Interleukin
IL-2R(ß)	Interleukin 2 receptor (ß)
INR	International normalized ratio
IRR	Injection/Infusion-related reactions
IV	Intravenous
LNPs	Lipid nanoparticles
MABEL	Minimum anticipated biological effect level
mNSCLC	Mutant NSCLC
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NIST	National Institute of Standards and Technology
NK	Natural killer
NSCLC	Non-small cell lung cancer
ORR	Objective response rates
OS	Overall survival
PBMC	Peripheral blood mononuclear cells
PD	Progressive disease or pharmacodynamics (depending on context)
PD-1	Programmed death receptor 1
PD-L	Programmed death-ligand
PEG	Polyethylene glycol
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PR	Partial response
R/M	Recurrent or metastatic
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RP2D	Recommended Phase II dose

Abbreviation	Explanation
SAP	Statistical analysis plan
SCCHN	Squamous cell carcinoma of head and neck
sCD25	Soluble interleukin-2 receptor
SD	Stable disease
SmPC	Summary of Product Characteristics
SoC	Standard of care
SOC	System Organ Class
STAT5	Signal transducer and activator of transcription 5
$t_{1/2}$	Half life
TBili	Total bilirubin
TMB	Tumor mutational burden
TNBC	Triple negative breast cancer
TS	Thymidylate synthase
ULN	Upper limit of normal
USPI	United States Prescribing Information
VEGF	Vascular endothelial growth factor receptors
WBC	White blood cells
WOCBP	Women of childbearing potential

For standard abbreviations, see Section 10.9.

2 INTRODUCTION

2.1 Trial rationale

Outcomes remain poor for patients with relapsed or refractory advanced solid tumors. Treatment options include further palliative chemotherapy, which might be less well tolerated after previous repeated exposure to cytotoxic compounds, or best supportive care, and trial treatments without proven benefit. Therapy in this population is not curative, with an expected overall survival (OS) of a few months. Immunotherapy has emerged as an effective treatment option in some cancers with high, unmet medical needs. Specifically, immune checkpoint inhibitors (CPIs) are approved across various cancer indications and act by invigorating pre-existent anti-tumor-specific T cells. Even though CPIs are providing clear clinical benefit, the medical need is still high for various cancer types and CCI [redacted].

Recombinant IL-2, aldesleukin, was the first approved cancer immunotherapy and has been used for decades in the treatment of late stage malignant melanoma and renal cell cancer (Atkins et al. 1999, Rosenberg 2007, Klapper et al. 2008). The therapeutic effect of IL-2 primarily depends on its potential to activate and expand tumor specific cluster of differentiation 8 positive (CD8+) effector T cells. Recombinant IL-2 has a very short half-life in the range of min and therefore requires high and frequent dosing, which in turn potentiates its side effects (Lotze et al. 1986). A particular challenge of IL-2 for cancer treatment is the preferential stimulation of regulatory T cells (T_{reg}) which dampen anti-tumor immune responses already at low IL-2 doses. Activation of CD8+ effector T cells on the other hand requires higher IL-2 amounts due to the expression of an IL-2 receptor of lower affinity. The candidate treatment BNT151 encodes an IL-2 variant, which was designed to facilitate sustained delivery of the encoded IL-2 variant with prolonged half-life and to display markedly reduced T_{reg} activation. By increasing activation of effector T cells as well as decreasing activation of counteracting T_{reg}, BNT151 administration is believed to yield higher efficacy as compared to recombinant IL-2 while ameliorating peak dose mediated toxicities. Furthermore, due to its beneficial pharmacokinetic properties, BNT151 should require less frequent dosing, compared to aldesleukin with short half-life, which requires frequent dosing which then increases the risks of toxicities.

As BNT151 provides an essential T-cell growth and survival factor, CCI [redacted] Tumor cell break down by such agents results in release of tumor antigens in conjunction with immune modulation (immunogenic cell death) promoting activation of T cells recognizing such antigens. CCI [redacted]

The main purpose of the trial is to determine safety, exploratory PD, PK, and preliminary efficacy of BNT151 as a monotherapy and in combination with other anti-cancer agents. This will be achieved by running a Phase I dose escalation in both monotherapy and in combination with other anti-cancer agents.

mRNA underlies an innovative and sophisticated drug platform to deliver a protein-based therapy but, ongoing data do potentially suggest an occurrence of interpatient variability especially in translation that can affect correct determination of effective dose, as well as establishing a confident safety profile of the product. Therefore, the implementation of the Biomarker Cohort to further elucidate the differences and understand the variabilities is justified. Dose levels that have been cleared by the SRC in the dose escalation will be investigated in the monotherapy Biomarker Cohort, in order to further investigate the mode of action of BNT151, to allow optimization of future combinations with other anti-cancer agents, and to assess the interpatient variability. The RP2D of BNT151 monotherapy and in combination with other anti-cancer agents will then be tested further in the Expansion Phase to seek a preliminary signal of efficacy/anti-tumor activity. Establishing a safe and efficacious dose is crucial for successful development of new anti-cancer therapy, which will ultimately benefit the patients.

The IL-2 variant-encoding BNT151 provides an innovative new approach for the treatment of solid tumors, especially in combination with existing SoC.

2.2 Background

2.2.1 Overview of the disease(s)

Cancer is the second leading cause of death globally and is expected to be responsible for an estimated 9.6 million deaths in 2018 (Bray et al. 2018). In general, metastasis of a solid tumor is associated with a poor prognosis.

2.2.1.1 Treatment of advanced and metastatic solid tumors

Refinements in conventional therapies such as chemotherapy, radiotherapy, surgery, and targeted therapies and recent advances in immunotherapies have improved outcomes in patients with advanced solid tumors. In the last few years, the FDA and European Medicines Agency (EMA) have approved 6 CPIs: one monoclonal antibody targeting the cytotoxic T-lymphocyte antigen 4 (CTLA-4) pathway, ipilimumab, and 6 antibodies targeting PD-L/PD-L1, including atezolizumab, avelumab, durvalumab, nivolumab, cemiplimab and pembrolizumab, in various cancer indications, mainly solid tumors (Gentzler et al. 2016, Ribas and Wolchok 2018). While these approvals have dramatically changed the landscape of cancer treatment, the majority of cancer patients, including those with tumors considered CPI-‘sensitive’ (e.g., melanoma, NSCLC, urothelial carcinoma, kidney cancer) either do not respond or become resistant to these agents (Arora et al. 2019). In addition, some of the most prevalent tumors, colorectal, breast cancer (BC) and prostate cancer, are largely refractory to checkpoint inhibition (Borcherding et al. 2018).

Many immunotherapies have demonstrated efficacy in only a selected subgroup of cancers, such as those expressing PD-L1 (Tecentriq® US Prescribing Information), with microsatellite instability (MSI)/mismatch repair (MMR) deficiency or high tumor mutational burden (TMB) (Luchini et al. 2019), and even novel targeted agents only address very small sub-populations across tumor types (Vitrakvi® US Prescribing Information). Indeed, despite considerable early success and relatively fewer side effects compared to other

systemic therapies, the majority of cancer patients do not respond to CPIs or novel targeted therapies (Arora et al. 2019).

With cures remaining scarce in patients with advanced solid tumors, there is an unmet medical need for more effective and less toxic therapies, in particular those that have synergistic mechanisms of action with the CPIs.

2.2.1.2 Squamous cell carcinoma of the head and neck

Globally, over 600,000 patients are diagnosed with SCCHN annually (Bray et al. 2018), with approximately 65,000 patients diagnosed and approximately 14,000 deaths occurring annually in the US secondary to SCCHN (Siegel et al. 2019). Infection with human papillomavirus (HPV), specifically HPV-16 and 18, are risk factors for developing SCCHN, particularly oropharyngeal cancers involving the tonsils or the base of the tongue (Chaturvedi et al. 2011). Approximately 25,000 SCCHN patients per year in the US develop locally R/M disease. Once patients reach this advanced state, SCCHN remains essentially incurable and 5-year survival is less than 50% (American Cancer Society 2019a).

2.2.1.2.1 Treatment of advanced/metastatic SCCHN

Treatments with anti-PD-1 antibody have recently demonstrated substantial anti-tumor activity in patients with advanced SCCHN. Pembrolizumab received accelerated approval in the US based on response rate (18%) and modest durability of response in patients with R/M SCCHN whose disease had progressed after platinum-containing chemotherapy (second-line therapy), irrespective of HPV status (Chow et al. 2016).

Pembrolizumab also recently demonstrated substantial anti-tumor activity in a Phase III trial relative to SoC (EXTREME: cetuximab + cisplatin or carboplatin + fluorouracil), first-line in patients with R/M SCCHN (Burtness et al. 2019, Rischin et al. 2019). Patients with a high (≥20) or any level (≥1) of combined positive score (CPS) (Burtness et al. 2019) who received pembrolizumab had a statistically significant improvement in OS vs. EXTREME alone: Hazard ratio (HR) 0.61 (0.45-0.83); P = 0.0007 and HR 0.78 (0.64-0.96); P = 0.0086, respectively. The overall response rates (ORRs) with pembrolizumab in the CPS ≥20 and ≥1 groups were 31% and 49%, respectively, though response rates with EXTREME were higher in the respective cohorts. Pembrolizumab has recently been approved by the FDA for monotherapy or combination use in the first-line setting based on improvements in OS and is likely to become the global standard (Keytruda® US Prescribing Information, Taberna et al. 2019).

Taken together, these data demonstrate that strong anti-tumor activity against SCCHN can be achieved by stimulating T cells targeting tumor antigens. In fact, with pembrolizumab moving into first-line SCCHN treatment, the role of chemo-based regimens such as EXTREME is in flux, as such therapies have not been evaluated after failure with anti-PD-(L)1 therapy.

Although the recent advances in therapy for advanced SCCHN have increased OS, the disease remains incurable, and pembrolizumab did not increase the response rate over EXTREME, only the duration of response (DOR). Furthermore, less than half of all SCCHN patients have a CPS score ≥20, implying that the majority of these patients will

not obtain benefits from pembrolizumab therapy. Treatments that not only enhance activity among high PD-L1 expressing SCCHN patients but also those that have low expression are needed to improve outcomes for this unmet patient population. The mechanism of action of BNT151 and strong anti-tumor activity of therapies that enhance T-cell activity make SCCHN a highly suitable candidate to target with this novel immunotherapy combined with CPI.

2.2.1.3 Hepatocellular carcinoma (HCC)

HCC results in up to 1 million deaths annually worldwide, making it the second leading cause of cancer-related death in the world (Kim and El-Serag 2019); it is diagnosed in just over 40,000 patients in the US per year, resulting in approximately 30,000 deaths. Five-year survival is very poor, at 18% overall and 2% for metastatic disease (American Cancer Society 2019c). The incidence of liver cancer in the US has more than doubled in the last two decades (Bray et al. 2018, White et al. 2017). Most patients are diagnosed with incurable disease. Besides stage at diagnosis, hepatic reserve per Child-Pugh classification is a major determinant of treatment.

2.2.1.3.1 Treatment of unresectable HCC

Select patients with advanced, unresectable HCC may benefit from liver-directed non-surgical therapies. For most other patients, systemic therapy is considered, but cytotoxic chemotherapy has modest efficacy, with no clear impact on OS (NCCN Guidelines® Hepatobiliary Cancers 2020). In patients with Child-Pugh A/B7, the multi-kinase inhibitor sorafenib represents the current SoC in first-line, improving OS compared to placebo (10.7 vs. 7.9 months), with an ORR of 2% (Llovet et al. 2008). Lenvatinib has been shown to be non-inferior to sorafenib in Child-Pugh A disease only, with a longer time to treatment failure (7.4 vs. 3.7 months) and an increased ORR of 24% (Cheng et al. 2017). Regorafenib was superior to placebo after progression on first-line therapy with sorafenib, with an improvement in median OS (10.6 vs. 7.8 months) (Bruix et al. 2017). Other kinase inhibitors have shown similar results (NCCN Guidelines® Hepatobiliary Cancers 2020).

The role of sorafenib as SoC in first-line will be challenged by the recent FDA decision to grant approval to atezolizumab in combination with bevacizumab for patients with unresectable or metastatic HCC who have not received prior systemic therapy, due to superiority in OS (median OS not reached vs 13.2 months) and progression-free survival (PFS) (6.8 vs 4.3 months) in the IMbrave150 trial (Cheng et al. 2019).

A Phase I/II trial of nivolumab in patients with Child-Pugh A or B demonstrated a median OS of 15 months, with ORR of 23% in the sorafenib-naïve cohort and 19% in the sorafenib-experienced cohort (El-Khoueiry et al. 2017). These results led to accelerated approval by the FDA for nivolumab as second-line therapy for patients who have been previously treated with sorafenib. Nivolumab was safe in patients with underlying HBV and HCV. More recently, pembrolizumab reported an ORR of 17%, including one complete response (CR) in Child-Pugh A, sorafenib pre-treated patients. Pembrolizumab was approved by the FDA for a second-line indication in late 2018.

The Phase III studies of both pembrolizumab vs. placebo in second-line therapy and nivolumab vs. sorafenib in first-line therapy recently reported no significant improvement in

OS, putting into question the role of these agents in HCC (Finn et al. 2020, Yau et al. 2019). While the approval of atezolizumab in combination with bevacizumab in first-line represents progress, HCC remains an indication of high medical need. Agents that could improve upon the rather low response rates and impact long term outcomes are desperately needed in first and later lines of therapy.

2.2.1.4 Renal cell carcinoma (RCC)

Renal cell carcinoma (RCC) denotes cancer originating from kidney epithelium and accounts for >90% of cancers in the kidney. The disease encompasses >10 histological and molecular subtypes, of which clear cell RCC is the most common, accounting for most cancer-related deaths (Hsieh et al. 2017). RCC is diagnosed in over 70,000 people annually in the US, and just under 15,000 die of their disease (around 300,000 cases and 134,000 deaths worldwide) (Hsieh et al. 2017). Despite recent advances in systemic treatment, the 5-year survival rate for patients with distant metastases is only 12% and median OS remains around 2.5 years in studies where maximum systemic treatment is given (Hsieh et al. 2017, American Cancer Society 2019e). The incidence of RCC has been rising in the last few years, most likely due to increased incidental findings of early stage tumors with the increased use of CT and MRI scanning (American Cancer Society 2019e).

2.2.1.4.1 Treatment of metastatic RCC

Resection of the primary tumor in patients with RCC is recommended since it appears to confer a survival advantage, although recent data is challenging that paradigm (Méjean et al. 2018). Prior standard systemic therapies, cytokines (interferon) interferon alpha (IFN-α) and IL-2, are now only used in selected patients, based on incremental improvements with other agents in terms of response, PFS and OS (NCCN Guidelines® Kidney Cancer 2020).

Vascular endothelial growth factor receptors (VEGF)-targeted kinase inhibitors dominate the SoC for metastatic disease in both first and second-line. Overall, sorafenib has a broad label, sunitinib, pazopanib and the combination of bevacizumab and IFN-α are approved as first-line options whereas axitinib and cabozantinib are approved in the second-line (Hsieh et al. 2017). Indeed, arguably, the landmark trial of first-line systemic therapy of metastatic RCC was the Phase III trial of sunitinib versus IFN-α reported in 2007 in which the superiority of sunitinib in terms of response rate, PFS and OS was reported (Motzer et al. 2007). This trial established sunitinib as the SoC, and the drug remains the comparator for Phase III studies of new drugs. The mammalian/mechanistic target of rapamycin (mTOR) inhibitors everolimus and temsirolimus are approved as single agents in the second-line setting and in the first-line in patients with poor-risk status (Motzer et al. 2008, Hudes et al. 2007).

More recent is the data with CPIs, with nivolumab monotherapy in second-line and the nivolumab-ipilimumab combination in first-line. The first-line trial in more than 1,000 patients showed worse outcomes for the combination in favorable-risk patients and significantly improved results for the intermediate and poor-risk patients. ORR and CR rates were 42% vs. 27% and 9% vs. 1%, both $p<0.001$, respectively, with the CPI combination vs. sunitinib. Although OS was significantly improved in the intermediate and poor-risk patients (HR 0.63; $p<0.001$), the median PFS was essentially identical in both

arms (NCCN Guidelines® Kidney Cancer 2020, Motzer et al. 2019). Given the substantial toxicity of this combination, and because the survival benefit appears to be restricted to poor/intermediate risk patients, especially among those who express PD-L1 (about 26% of patient population), it is not clear that combination CPIs will become a first-line standard therapy in practice, despite the recent FDA and EMA approvals (Yervoy® US Prescribing Information and EU Summary of Product Characteristics).

After immune CPIs and antiangiogenic targeted therapies were found to improve outcomes, the combination of these 2 approaches has been studied in clinical trials and shown to result in longer OS when compared with monotherapy. An open-label, Phase III randomized controlled trial comparing sunitinib with the combination of pembrolizumab and axitinib enrolled 861 patients who had received no previous systemic therapy for metastatic disease. With 12.8 months median follow-up, 1-year OS was 90% in the pembrolizumab plus axitinib arm compared with 78% in the sunitinib arm (HR 0.53; 95% confidence interval (CI), 0.38-0.74; P <0.0001) (Rini et al. 2019). This has led to recent FDA approval for the combination of pembrolizumab and axitinib in first-line setting of RCC.

In the second-line setting, after VEGF-targeted therapy, nivolumab showed a significant improvement in OS versus everolimus (25 vs. 19.6 months at the median, HR 0.73, P = 0.0018) with a substantial improvement in both response rate and DOR (21.5 vs. 3.9% with a median duration of 23 vs. 13.7 months) (Opdivo® US Prescribing Information and Summary of Product Characteristics). Nivolumab monotherapy is, therefore, now a recommended option in second-line therapy (NCCN Guidelines® Kidney Cancer 2020, Motzer et al. 2019).

Despite these advances, it is clear that the majority of patients still do not benefit from systemic checkpoint therapy. The medical need remains in this non-responder majority and also in those who do initially respond but then progress on CPI.

2.2.1.5 Triple negative breast cancer

There is still a substantial unfulfilled medical need in advanced and metastatic BC and TNBC, in particular. Of the over one-quarter of a million cases of BC diagnosed annually in the US, over 40,000 die of their disease. The 5-year survival rate for women with BC is 27% (American Cancer Society 2019b) and median survival (OS) remains around 2.5 years in studies where maximum systemic treatment is given (Zielinski et al. 2016). Median OS varies by type of disease, with bone-only metastatic disease survival topping 7 years for some subgroups, while metastatic TNBC, which represents 10-20% of cases, has the worst prognosis and a median OS of less than 1 year (Parkes et al. 2018, Dent et al. 2007).

2.2.1.5.1 Treatment of advanced/metastatic TNBC

Hormone-receptor positive BC has proven largely refractory to PD-1 and PD-L1 inhibition (Gentzler et al. 2016), and clinical trials of checkpoint inhibition have focused on TNBC, where response rates appear to be between 5-20% in a selected PD-L1-positive patient population (Nanda et al. 2016, Lyons et al. 2019) or around 60% in first-line combination with nab-paclitaxel (Schmid et al. 2018). The first Phase III trial to report in this setting

showed that atezolizumab significantly improves PFS in both the overall and PD-L1-selected population (with approx. 2 months improvement), but only improves OS in PD-L1-positive disease (from 15.5 to 25 months) (Schmid et al. 2018). Atezolizumab has obtained approval in the US and approval in the EU, but only in the <20% of patients whose tumors overexpress PD-L1 >1% (European Medicines Agency Tecentriq (atezolizumab), Summary of opinion, Mittendorf et al. 2014, Sun et al. 2016, Tecentriq® US Prescribing Information). The advent of atezolizumab in first-line also leaves an open question as to an appropriate second-line treatment for these patients. Thus, despite recent advances, metastatic TNBC remains an area of high medical need in three specific patient populations:

- The 40% of PD-L1 positive patients whose tumors do not respond to the atezolizumab combination.
- The PD--L1-non-expressing tumors, which do not respond to CPIs at all and progress rapidly, irrespective of treatment.
- Patients who may have originally responded to first-line treatment, but whose disease has progressed on atezolizumab.

2.2.1.6 Non-small cell lung cancer (NSCLC)

In the US in 2019, it is estimated that approximately 228,000 patients were diagnosed with lung cancer and 80 to 85% of these cases were of NSCLC histology (American Cancer Society 2019d). In 2019, lung cancer accounted for approximately 24% of all cancer-related deaths in the US, remaining the leading cause of cancer deaths worldwide (Bray et al. 2018).

The etiologic association of NSCLC with exposure to tobacco carcinogens is of particular relevance for cancer immunotherapy, as current approaches targeting immune checkpoints exhibit increased responses in tumors with a high number of somatic mutations, as is the case in smoking induced NSCLC. Conversely, immune checkpoint blockade (ICB) has been significantly less successful in never-smokers, including a majority of ALK-rearranged or EGFR-mutated NSCLC (Garassino et al. 2018).

2.2.1.6.1 Treatment of metastatic NSCLC

Most patients with NSCLC present at an advanced stage of the disease and are symptomatic at the time of diagnosis, with a related poor prognosis and no curative options. In Stage IV, systemic palliative treatment is recommended, including cytotoxic chemotherapy, immune CPIs, and a series of targeted agents in selected molecularly-defined subsets of NSCLC patients.

The approved anti-PD-(L)1 inhibitors nivolumab, pembrolizumab, durvalumab and atezolizumab have demonstrated substantial anti-tumor activity, and are changing the treatment paradigm in driver mutation-negative NSCLC. Anti-PD-(L)1 therapies are now approved as monotherapy or combination therapy with chemotherapy in first-line, and as monotherapy in second-line (Imfinzi® US Prescribing Information, Keytruda® US Prescribing Information, Opdivo® US Prescribing Information and Summary of Product Characteristics, Tecentriq® US Prescribing Information).

Pembrolizumab has demonstrated an OS benefit over cisplatin-based doublet chemotherapy in NSCLC patients with high PD-L1 (>50% on tumor cell [TC]) expression in the front-line setting (Reck et al. 2016). Furthermore, consolidation therapy with durvalumab delays tumor progression or death after chemoradiation of locally advanced NSCLC (Antonia et al. 2017). Studies of adjuvant therapy of early disease with CPIs are ongoing.

Clearly, CPIs have improved survival in many of these NSCLC patient populations, but few patients are obtaining long term cures. Patients progressing on or after CPIs have few therapeutic options. Although salvage cytotoxic chemotherapy, docetaxel monotherapy in particular, is commonly used in this setting, outcomes remain poor. Median OS in the second-line setting ranges from 7.5 months with docetaxel monotherapy to 10.5 months with docetaxel and ramucirumab (Garon et al. 2014). There is sparse clinical data on the efficacy of cytotoxic chemotherapy after failure of ICB; cohort studies suggest an improved ORR in patients pre-treated with ICB compared to ICB-naïve patients, but this has yet to be described in a prospective study.

ICB is rapidly becoming the SoC in all patients with NSCLC in the front-line, either as monotherapy, or in combination with chemotherapy. All these patients will relapse with few effective therapies available to them. Thus, NSCLC patients previously treated with CPI represents a population of unmet medical need for whom novel approaches are needed.

Unlike SCCHN, EGFR mutations play a significant role in driving tumor development and progression in approximately 20% of NSCLC adenocarcinomas (mutant NSCLC: mNSCLC). Unlike driver mutation-negative NSCLC, mNSCLC does not respond well to checkpoint inhibition after anti-EGFR therapy, for unclear reasons. One explanation for the lack of anti-PD-L1 efficacy in this large subgroup is that mNSCLC does not carry as high a mutational load as driver mutation-negative NSCLC, making these tumors less amenable to native adaptive immune attack by T cells (Miura et al. 2018). There is, thus, also a need to explore novel agents in combination with CPIs in EGFR-positive tumors, to find out whether they can be rendered immune responsive.

Despite the significant advances in NSCLC treatment with anti-PD-L1 therapy, advanced disease remains largely incurable. NSCLC is a very good candidate for evaluation of novel approaches, with a demonstrated susceptibility to immune modulation with monotherapy CPIs and sub-populations of less sensitive tumors.

2.2.2 Introduction to the investigational treatment

The IMP under evaluation in this trial is BNT151. Further information on combination therapies in Part 2 will be done by protocol amendment.

2.2.2.1 Investigational medicinal product (IMP)

2.2.2.1.1 BNT151

The active pharmaceutical ingredient of BNT151 is a single stranded, pharmacologically optimized, 5′-capped messenger RNA coding for an IL-2/serum albumin fusion construct. The RNA is formulated as LNPs for IV administration and for selective delivery of the RNA to the liver. Upon entering liver cells, the RNA is translated into the encoded

cytokine/albumin fusion construct, which is then secreted and becomes systemically available to act on T cells in the tumor, in lymphoid compartments and in the periphery to potentiate their anti-tumor efficacy.

IL-2 is a key cytokine in T-cell homeostasis and pivotal for the differentiation, proliferation, survival and effector functions of T cells (Bamford et al. 1994, Blattman et al. 2003, Gillis and Smith 1977, Kamimura and Bevan 2007). The RNA in BNT151 encodes an IL-2 variant that is modified such that it (1) stimulates effector T cells and natural killer (NK) cells with higher potency than its wild type counterpart and (2) displays markedly reduced stimulation of T regulatory (T_{reg}) cells, hence limiting their counter-regulatory immune suppressive function.

Fusion of the IL-2 variant to the human serum albumin sequence in the encoding RNA contributes to a favorable PK in 2 ways. First, the molecular size of the fusion protein is well above the threshold for renal clearance. Second, albumin fusion proteins are taken up via micropinocytosis into cells, but instead of undergoing lysosomal degradation are salvaged by the membrane-bound neonatal Fc receptor (FcRn), and are reshuttled back into the circulation. Both mechanisms are expected to significantly prolong the plasma half-life (Kontermann 2011).

2.2.2.2 Potential combination therapies in Part 2

2.2.2.2.1 Pembrolizumab (Keytruda®)

Pembrolizumab, a PD-1-blocking antibody, is an approved marketed product both in Europe and the US for various solid tumors. Pembrolizumab is a humanized monoclonal immunoglobulin G4 (IgG4) kappa antibody. Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response.

Please refer to United States Prescribing Information (USPI) or Summary of Product Characteristics (SmPC) for further information on pembrolizumab.

2.2.2.2.2 Atezolizumab (Tecentriq®)

Atezolizumab is a monoclonal antibody that binds to PD-L1 and is an approved marketed product both in Europe and in the US for various solid tumors. It blocks PD-L1 interactions with both PD-1 and B7.1 receptors. This releases the PD-L1/PD-1 mediated inhibition of the immune response, including activation of the anti-tumor immune response without inducing antibody dependent cellular cytotoxicity.

Please refer to USPI or SmPC for further information on atezolizumab.

2.2.2.2.3 Axitinib (Inlyta®)

Axitinib inhibits receptor tyrosine kinases including vascular endothelial growth factor receptors VEGFR-1, VEGFR-2, and VEGFR-3 at therapeutic plasma concentrations. These receptors are implicated in pathologic angiogenesis, tumor growth, and cancer progression. VEGF-mediated endothelial cell proliferation and survival were inhibited by

axitinib *in vitro* and in mouse models. Axitinib was shown to inhibit tumor growth and phosphorylation of VEGFR-2 in tumor xenograft mouse models.

Please refer to USPI or SmPC for further information on axitinib.

2.2.2.2.4 Nab-paclitaxel (Abraxane®)

Nab-paclitaxel is an albumin-bound form of paclitaxel with a mean particle size of approximately 130 nanometers. It is a microtubule inhibitor that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. Paclitaxel induces abnormal arrays or 'bundles' of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

Please refer to USPI or SmPC for further information on nab-paclitaxel.

2.2.2.2.5 Carboplatin

Carboplatin is a platinum coordination compound. Carboplatin, like cisplatin, produces predominantly interstrand desoxyribonucleic acid (DNA) cross-links rather than DNA-protein cross-links. This effect is apparently cell cycle nonspecific. The aquation of carboplatin, which is thought to produce the active species, occurs at a slower rate than in the case of cisplatin. Despite this difference, it appears that both carboplatin and cisplatin induce equal numbers of drug-DNA cross-links, causing equivalent lesions and biological effects. The differences in potencies for carboplatin and cisplatin appear to be directly related to the difference in aquation rates.

Please refer to USPI or SmPC for further information on carboplatin.

2.2.2.2.6 Pemetrexed

Pemetrexed is a folate analog metabolic inhibitor that exerts its action by disrupting folate-dependent metabolic processes essential for cell replication. *In vitro* studies have shown that pemetrexed inhibits thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT), which are folate-dependent enzymes involved in the de novo biosynthesis of thymidine and purine nucleotides. Pemetrexed is taken into cells by membrane carriers, such as the reduced folate carrier and membrane folate binding protein transport systems. Once in the cell, pemetrexed is converted to polyglutamate forms by the enzyme folylpolyglutamate synthetase. The polyglutamate forms are retained in cells and are inhibitors of TS and GARFT. Polyglutamation is a time- and concentration-dependent process that occurs in tumor cells and is thought to occur (to a lesser extent) in normal tissues. Polyglutamated metabolites are thought to have an increased intracellular half-life resulting in prolonged drug action in malignant cells.

Please refer to USPI or SmPC for further information on pemetrexed.

2.3 Benefit/risk assessment

More detailed information about the known and expected benefits and risks, and reasonably expected adverse event (AE) for this trial are given in the investigator's brochure (IB).

2.3.1 Risk assessment as a monotherapy (for Part 1)

As this trial is the first to test BNT151 in humans, all precautions indicated when testing a new systemically active compound in a first-in-human (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 AEs that may occur with BNT151.

Furthermore, there will be regular safety data review by the sponsor and the 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 an exercise to identify and assess risks specific to BNT151 related to either the translated protein, i.e., an IL-2 variant, or to the formulation of the RNA drug substance with LNPs. In particular, the following data sources were used: (i) the preclinical data package obtained for BNT151 monotherapy and in combination with several other agents in development (e.g., RNA-encoded cancer vaccine, anti-PD-1/PD-L1); and (ii) nonclinical and (iii) clinical literature data published on other IL-2-based therapies either still in development or approved. This group of compounds encompasses, for example, recombinant IL-2 (aldesleukin) approved for the treatment of adults with metastatic RCC and metastatic melanoma; bempegaldesleukin (NKTR-214; Nektar Therapeutics) in clinical trials across a few cancer indications; anti-fibroblast activation protein (FAP)/IL-2 fusion protein RO6874281/ RG-7461 (Roche); an engineered fusion protein comprised of a circularly permuted IL-2 and IL-2 Receptor (IL-2R) α, ALKS-4230 (Alkermes); a variant of recombinant human IL-2 that is PEGylated at one specific site, THOR-707 (Synthorx); an enhanced version of IL-2 that preferentially binds to IL-2Rβ, MDNA-109 (Medicinna); and a recombinant fusion protein comprised of cergutuzumab, a genetically engineered human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody directed against carcinoembryonic antigen linked to amunaleukin, an engineered, mutated variant form of interleukin-2 (IL-2v), RG-7813 (Roche).

One identified risk with high-dose IL-2 therapy (aldesleukin) is capillary leak syndrome (CLS). CLS begins immediately after aldesleukin treatment starts and is marked by increased capillary permeability to protein and fluids and reduced vascular tone. In most patients, this results in a concomitant drop in mean arterial blood pressure within 2 to 12 hours after the start of treatment. With continued therapy, clinically significant hypotension (defined as systolic blood pressure below 90 mm Hg or a 20 mm Hg drop from baseline systolic pressure) and hypoperfusion will occur. In addition, extravasation of protein and fluids into the extravascular space will lead to the formation of edema and creation of new effusions. The exact cause of CLS is only partially understood. It is

believed that pro-inflammatory cytokines from IL-2 activated NK cells play an essential role. The sponsor assesses this risk associated with BNT151 to be low to medium: due to the need of translation of the active protein from RNA, serum levels of human albumin-IL2 variant (hAlb-hIL2var) rise slowly over several hours, and remain elevated for a prolonged period of time. These characteristics enable treatment with a reduced number of doses as well as with a lower dose, mitigating the risk associated with repeated high-dose IL-2 administration as required for aldesleukin.

The above mentioned side effects of high-dose IL-2 therapy are also risks of a therapy with BNT151. As BNT151 is a potent variant of the key T-cell homeostatic cytokine IL-2 that mediates the differentiation, proliferation, survival and effector functions of T cells, exaggerated pharmacology and over-activation of the immune system is an identified potential risk. Overall, BNT151 therapy was well tolerated in nonclinical toxicology and PD studies in mice and cynomolgus monkeys at doses ranging from CCI µg/kg after repeated administration and no clear signs of a CLS syndrome were apparent. Hematology data did show a transient decrease of white blood cells (WBCs), mainly lymphocytes, which might be related to the homing to lymphoid organs, extravasation or increased adherence to vessel walls with a subsequent lymphoproliferation. An immediate and transient induction of interferon gamma-induced protein 10 (IP-10), IFN-γ and to a lesser extent IL-6 was observed. A slight increase in liver enzymes was observed as described in the literature for IL-2 (Nakagawa et al. 1996). Histopathology data from a good laboratory practice (GLP) toxicity study in mice did only reveal slight changes in liver (Kupffer cell hypertrophy/hyperplasia) and spleen (lymphoid hyperplasia of the periarteriolar lymphoid sheath). Nevertheless, frequent laboratory monitoring is planned to observe the biochemical and hematological effect. For the clinical manifestations of cytokine elevation, the trial protocol implements management with analgesics or antipyretics at recommended commonly used doses.

As summarized, data from the toxicology study in mice did not indicate strong effects from BNT151 treatment. On the other hand, PD data including a dedicated non-GLP study in mice point towards a strong activation of NK cells after BNT151 treatment, especially in combination with an additional activation by type I IFN release (i.e., by the RNA lipoplex [RNA-LPX] vaccine). It is hypothesized that the expansion and activation of NK cells by BNT151 can lead to adverse effects by release of pro-inflammatory cytokines such as IFN-γ. The detrimental effects were ameliorated by dose reduction, which correlates to lower doses to be administered in the clinical trial. Furthermore, the sponsor showed that an initial treatment with a lower dose of BNT151 leaves the NK cells in a refractory state that abolishes the BNT151-mediated adverse effects for consecutive higher doses in mice. The planned FIH addresses this potential phenomenon by a possibility to perform dose escalation with a lower lead-in dose. In addition, a non-GLP study in mice combining BNT151 with an anti-PD-1 treatment did not result in enhanced safety-related findings.

Furthermore, patients in the clinical trial should have normal cardiac, pulmonary, hepatic, and CNS function at the start of therapy. Careful monitoring of the patient's fluid and organ perfusion status is planned by frequent determination of blood pressure and heart rate, and by monitoring organ function, which includes assessment of mental status and urine output.

Another risk identified with aldesleukin is mental status change and other CNS-related changes. Safety pharmacology data from mice with BNT151 do not indicate effects on neurological safety. However, as these effects are not easily detected in animals, all patients should have thorough evaluation and treatment of CNS metastases, and have a scan to show disease control in the brain prior to receiving BNT151.

Aldesleukin is also shown to exacerbate pre-existing or initial presentation of autoimmune disease and inflammatory disorders. The sponsor mitigates this risk by exclusion of patients with prior autoimmune or inflammatory disorders.

Furthermore, the potential risk of IL-2-based therapies and other pro-inflammatory cytokines to induce cardiac toxicity such as acute coronary syndrome and heart arrhythmias is addressed in the clinical trial by exclusion of high-risk patients. ECG and echocardiogram (ECHO) are to be performed at screening and ECG also on Day 1 of each cycle. Patients are also closely monitored for such events in the clinic. It is worth mentioning that no indications of such potential risks were noted in animals tested with BNT151.

Other AEs most commonly seen with IL-2-based therapies such as mild-to-moderate, transient and manageable flu-like symptoms (e.g., arthralgia, body temperature increase, chills, dehydration, dizziness, fatigue, feeling cold, headache, hot flush, hyperhidrosis, myalgia, nausea, pyrexia, tachycardia, and vomiting) may occur. The systemic effects could be PD surrogates caused by cytokine elevation. The trial protocol implements management with supportive care drugs, such as analgesics, antipyretics, antiemetics and antidiarrheals at recommended commonly used doses.

A potential risk is the liver-targeting LNP formulation, which contains four synthetic lipids. Two of them are used in approved drug products (e.g., Doxil® and Onpattro®). The two other lipids are used in products in currently running clinical trials (e.g., NCT03639714 at clinical trials.gov). Formulation-related toxicities were assessed in nonclinical studies in mice and cynomolgus monkeys. The animals were treated with the LNP formulation without RNA payload (empty LNPs). Overall, no findings including histopathology assessment were reported compared to the control group treated with saline in the different studies. Frequent laboratory monitoring including liver parameters is planned.

In conclusion, the nonclinical 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 BNT151 in patient populations with high, unmet medical needs outweigh the potential risks with the compound.

2.3.2 Potential risks associated with BNT151 in combination with pembrolizumab, axitinib, carboplatin, pemetrexed, atezolizumab, and nab-paclitaxel

This part of the clinical trial protocol (CTP) will be updated by amendment when the profile of BNT151 is better understood from Part 1. The decision to expand is based on the totality of data generated in Part 1. All decisions for expansion should be endorsed by the SRC.

Once the monotherapy RP2D is established the trial will proceed with the Part 2 Expansion, where BNT151 will be used in combination therapy in various Cohorts.

As this is the first trial in humans, the risk of synergistic and/or potentiating toxicities when BNT151 is combined with pembrolizumab, axitinib, carboplatin, pemetrexed, atezolizumab, and nab-paclitaxel cannot be completely ruled out. Therefore, the trial seeks to mitigate this risk by implementing a safety run in trial if no potential overlapping toxicities between BNT151 and SoC are anticipated based on the BNT151 monotherapy safety profile. If overlapping toxicity is expected based on the data in the monotherapy part, an abbreviated dose escalation of BNT151 in combination with SoC will be performed.

The combination dose escalation will only occur after reasonable data for BNT151 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 the monotherapy MTD and/or RP2D. If safe, the BNT151 dose will be escalated to monotherapy MTD and/or RP2D. If the starting dose is declared too toxic, dose levels with PK/PD activity below the starting dose can be explored in the combination. This should mitigate such a potential risk for unknown synergistic and/or potentiating toxicities.

Supporting data from preclinical studies of BNT151 in combination with PD-1 blockade also do not suggest any additional toxicity beyond that of BNT151 alone. For this reason, we will start the combination part with two cohorts treated with BNT151 and pembrolizumab to generate sufficient safety data before BNT151 is combined with cancer therapies other than pembrolizumab.

This section will be expanded by amendment to better address potential risks associated with BNT151 in combination treatments (providing a risk assessment for each combination treatment in turn) once the BNT151 monotherapy safety profile is better understood from Part 1, and the risk of synergistic and/or potentiating toxicities when BNT151 is used in combination therapies in Part 2 can be better predicted.

2.3.3 Benefit assessment as a monotherapy (for Part 1)

Preclinical studies demonstrated that monotherapy of tumor-bearing mice with BNT151 resulted in potent anti-tumor activity with increased rejection rates and significantly prolonged survival, which was further augmented by administration of anti-PD-1/PD-L1 ICB or RNA-based tumor antigen vaccination in several mouse tumor models.

Based on preclinical antitumoral activity and mechanistic data, BNT151 is expected to mount tumor-targeted, integrated innate and adaptive immune reactions as a monotherapy, as well as in combination with other background therapies such as cytotoxic therapies, targeted therapies and other cancer immunotherapies in particular in settings with large tumor load. There is still a high unmet medical need in patients with advanced or metastatic solid tumors and it is planned to evaluate BNT151 in various suitable tumor indications and settings.

For monotherapy, IL-2-based treatments have long been recognized to have moderate single-agent activity in the classically “immune-sensitive” tumors such as melanoma and RCC (DeVita et al. 2018). However, the literature also shows anecdotal evidence of patients having tumor shrinkage and durable disease control in other tumor types such as

sarcomas, lymphomas, NSCLC, ovarian, colorectal, endometrial cancers and HCC (Bentebibel et al. 2019, Benyunes et al. 1993, Bukowski et al. 1990, Sznol et al. 1993).

2.3.4 Benefit assessment in combination with SoC (for Part 2)

This part of the CTP will be updated by amendment when the profile of BNT151 is better understood from Part 1. The decision to expand is based on the totality of data generated in Part 1. All decisions for expansion should be endorsed by the SRC.

BNT151 is expected to mount tumor-targeted, integrated innate and adaptive immune reactions in combination with cytotoxic therapies and PD-1 blockade in particular in settings with large tumor load.

Combination therapy of BNT151 with pembrolizumab is an appropriate combination to test, as we have shown synergistic effects of this combination in preclinical studies. We have chosen three other tumors (RCC, NSCLC and TNBC) in this trial based on the sensitivity of these tumors for IL-2 and/or anti-PD-1 blockade.

2.3.5 Overall benefit/risk conclusion

Taking into account the measures taken to minimize the risk for patients participating in this trial, the potential risks identified in association with BNT151 are justified by the anticipated benefits that may be provided to patients with advanced or metastatic solid tumors.

3 OBJECTIVES AND ENDPOINTS

Objectives and related endpoints are described in Table 5 below.

The objectives and endpoints are for BNT151 monotherapy and in combination with SoC, unless otherwise specified.

Table 5: Objectives and endpoints

Objectives and endpoints

Objectives	Endpoints
Primary objectives	**Endpoints**
For Part 1: Identify the maximum tolerated dose (MTD) and/or recommended Phase II dose (RP2D) of IMP based on the occurrence of dose limiting toxicities (DLTs) using the following definitions: • MTD defined as the highest tolerated dose where less than 1/3 of the patients experience a DLT. • RP2D based on integrated evaluation of safety, tolerability, clinical benefit, PK, and selected PD markers, for all dose levels tested.	• Occurrence of DLTs within a patient during the DLT evaluation period.

Objectives	Endpoints
Assess the safety and tolerability of IMP.	• Occurrence of TEAE within a patient including Grade ≥3, serious, fatal TEAE by relationship. • Occurrence of dose reduction and discontinuation of IMP within a patient due to TEAE.
Secondary objectives	**Endpoints**
Evaluate anti-tumor activity of IMP according to RECIST 1.1.	• The ORR is defined as the proportion of patients in whom a CR or PR (per RECIST 1.1) is observed as best overall response. • The DCR is defined as the proportion of patients in whom a CR or PR or SD (per RECIST 1.1, SD assessed at least 6 weeks after first dose) is observed as best overall response. • The DOR is defined as the time from first objective response (CR or PR per RECIST 1.1) to first occurrence of objective tumor progression (PD per RECIST 1.1) or death from any cause, whichever occurs first.
Exploratory objectives	**Endpoints**
Evaluate efficacy of IMP in terms of PFS and OS.	• PFS defined as the time from first dose of IMP to first objective tumor progression, or death from any cause, whichever occurs first. • OS defined as the time from first dose of IMP to death from any cause.
Characterize the PK profile of translated IL-2 variant.	• PK parameters (including but not limited to AUC, C_{max}, t_{max}, and $t_{1/2}$).
Identify potentially predictive or other exploratory PD markers.	• Changes in selected cytokines and other soluble innate and adaptive immune system 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 and tumor microenvironment analysis). • Correlate potential predictive biomarkers in tumor and periphery with antitumor response.
Examine potential incidence of immunogenicity by measuring ADAs against translated proteins derived from the IMPs or against PEG lipids.	• Evaluate pre-existing (pre-treatment) and post-treatment ADAs and examine the immunogenicity incidence with treatment.

ADAs = anti-drug antibodies; AUC = area-under-the-concentration-time curve; CL = clearance; C_{max} = maximum observed serum concentration; CR = complete response; DCR = disease control rate; DLTs = dose limiting toxicities; DOR = duration of response; IL = interleukin; IMP = investigational medicinal product; MTD = maximal tolerated dose; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PK = pharmacokinetic; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; RP2D = recommended Phase II dose; SD = stable disease; $t_{1/2}$ = half-life; t_{max} = time to C_{max}; TEAE = treatment emergent adverse event.

4 TRIAL DESIGN

4.1 Overall design

This is an open-label, multicenter Phase I/IIa dose escalation, safety, PK and PD trial of BNT151 with expansion cohorts in various solid tumor indications.

The monotherapy dose escalation (Part 1) of this clinical trial will enroll patients with various solid tumors that are metastatic or of advanced unresectable stage for whom there is no available standard therapy likely to confer clinical benefit, or patients who are not candidates for such available therapy. During combination dose escalation (Part 2A), patients with SCCHN, and HCC will be enrolled and treated with a combination of BNT151 and pembrolizumab. Once Part 2A of SCCHN and HCC is completed, patients with RCC, TNBC, and NSCLC will be enrolled and treated with a combination of BNT151 with the respective SoC.

The trial consists of Part 1, Part 2A and Part 2B with adaptive design elements:

- **Part 1** will be a monotherapy dose escalation in patients with advanced solid malignancies until the MTD and/or RP2D of BNT151 as monotherapy are defined. Dose escalation and RP2D regimen may include a pre-conditioning dose, which would be implemented under the rules defined in Section 4.1.4 Adaptive trial design elements.

The Part 1 of the trial also plans to implement a dedicated biomarker cohort in BNT151 monotherapy:

- The Biomarker Cohort will recruit patients at selected sites in the US only. The objective of the cohort is to observe PD activity and drug-induced changes in the blood and tumor. The gathered data are expected to inform on the drugs mechanism of action and further refine selection of monotherapy dose. This cohort will only enroll patients that are capable and willing to donate serial biopsies. Patients will only be dosed at dose levels at the RP2D level or lower, which have been cleared safe in the monotherapy dose escalation, and where pharmacodynamics activity is expected. Approximately, 20 patients will be enrolled in this cohort.
- **Part 2** will start once Part 1 monotherapy dose escalation is completed (exception: Biomarker Cohort in Part 1 can continue enrolling as long as a BNT151 monotherapy dose is established in the dose escalation). It consists of 5 expansion cohorts starting with BNT151 in combination with pembrolizumab in patients with SCCHN (Cohort 1) and HCC (Cohort 2). Safety evaluation of BNT151 in combination with pembrolizumab in Cohorts 1 and 2 will be done at the same time, and data generated in both patient populations will be used to assess safety. Once the safety of the combination is confirmed by the SRC (for details see the SRC Charter), the 2 cohorts will then enroll independently in expansion and a further 3 cohorts evaluating BNT151 in combination with SoC will be opened for enrollment: RCC (Cohort 3), NSCLC (Cohort 4) and TNBC (Cohort 5). Further cohorts may be opened based on sponsor's decision.

Each Part 2 cohort will consist of 2 sub-parts:

- **Part 2A** where the dose of BNT151 will be established for each combination using either a safety run-in or abbreviated dose finding based on predefined criteria described in Section 4.1.4 Adaptive trial design elements.
- **Part 2B** where a predefined number of patients will be treated with the confirmed RP2D of BNT151 in combination with respective SoC. In case the same dosing regimen is used in Parts 2A and 2B (i.e., in case option of safety run-in is adopted), the patients enrolled in Part 2A are eligible for efficacy evaluation in Part 2B. In case a different dosing regimen is used for Part 2A compared to Part 2B (i.e., in case option of abbreviated dose finding is adopted), efficacy generated in Part 2A will be used as supporting data.

In all parts, 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 for conditions of continued treatment]), withdrawal of consent, trial termination by the sponsor, or death, whichever occurs first.

Further information on efficacy assessment can be found in Section 8.1.1.

Safety will be assessed on a regular basis by means of clinical and laboratory parameters, as defined in the schedule of activities (SoA, Section 1.3).

PK of translated IL-2 variant and various markers, which may act as indicators of safety and activity of BNT151 monotherapy and in combination with SoC, will be evaluated, as defined in SoA.

The overall trial design is shown in Figure 1.

4.1.1 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 PD data, for all dose levels tested. The RP2D will be determined according to the following guidelines:

- The RP2D will not exceed the MTD.
- Toxicities other than DLTs will be considered, including: treatment emergent adverse events (TEAEs) assessed as related to BNT151 treatment but not considered dose limiting, the nature and frequency of toxicities, and the emergence of any specific category of toxicities.
- Evidence of clinical activity, as available.
- Available PK and PD data.

If the RP2D cannot be distinguished using the criteria above, cohort expansion for optimized RP2D determination may take place at up to 2 dose levels to obtain data for up to 6 additional patients per dose level. 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 the SRC.

4.1.2 Dose escalation Part 1 - Monotherapy dose escalation

The monotherapy dose escalation starts with an accelerated phase consisting of single-patient cohorts followed by larger patient cohorts informed by a classical 3+3 design (i.e., accelerated titration design). The single-patient cohorts will be expanded to 3+3-patient cohorts in case one of the following occurs:

- Grade ≥2 related toxicity.
- DLT.

The SRC will review safety data and all available preliminary efficacy and PK/PD data and recommend to switch to 3+3. Once a single-patient cohort has been expanded, all future cohorts will follow the 3+3 design.

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. 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 IV administration of BNT151 in the first and the second patient, and between the second and the third patient. The 48 hour safety monitoring interval does not apply to patients enrolled into the Biomarker Cohort, as this cohort only opens dose levels that have already been deemed safe by the SRC.

Hospitalization is required for the first 24 hours in Cycle 1 Day 1. For the assessments of each cohort, the DLTs will be collected for the first treatment cycle, i.e., a DLT evaluation period of 21 days. For hospitalization and DLT evaluation period during the adaptive trial design, please see Section 4.1.4.

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 6).

Table 6: 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 one dose level below. The sponsor will decide, based on SRC recommendation, 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 SRC recommendation

DLT = dose limiting toxicity; MTD = maximal tolerated dose; SRC = Safety Review Committee.

The dose escalation will potentially (dependent on data collected during the trial) evaluate BNT151 at [redacted] main dose levels as shown in Table 7. In the case that patients show Grade 2 (G2) AE(s) deemed to be related to BNT151 at a particular dose, the dose increment may follow either the predefined intermediate dose levels or lower intermediate dose levels, at the discretion of the SRC.

For dose levels used for the Adaptive trial design, please see Section 4.1.4.

Table 7: BNT151 dose increments

DL	Dose[1]	Dose increment
1	0.4 µg/kg	Starting dose
2	2.0 µg/kg	400% (5×)
3	4.0 µg/kg	100% (2×)
4	8.0 µg/kg	100% (2×)
CCI [redacted]		

[1] 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.
Dose increment is shown as % increase over previous dose/fold change of previous dose.
DL = dose level.

For BNT151 to provide the pharmacologically active IL-2 variant a sequence of events has to occur, including (i) selective delivery of the RNA to the liver, (ii) liver cell transfection, (iii) translation of RNA to protein and (iv) secretion (refer to Section 2.2.2.1.1). This complex process justifies a rather conservative FIH dose of 0.4 µg/kg BNT151, which encompasses the minimum anticipated biological effect level (MABEL) dose and a safety

factor of 50. 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 5-time dose increment is proposed. Subsequently, standard dose increment is proposed starting from dose level 2 in line with the FDA Guidance for Industry "S9 Nonclinical Evaluation for Anticancer Pharmaceuticals". CCI [redacted]

Any patient who experiences a DLT after receiving BNT151 should be counted, regardless of the amount of BNT151 exposure.

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, clinical, PK and PD data – to propose a dose level for the next cohort of patients.

4.1.2.1 Biomarker Cohort

For the Biomarker Cohort at selected US sites only: at enrollment patients must agree to have one pre-dose biopsy and lesion that is deemed accessible by the investigator. If possible, at least one on-treatment biopsy (preferred C2D5-12) should be accessible from same tumor lesion. Patients will be screened within 3 weeks prior to the beginning of treatment. Patients will be treated with treatment cycles lasting 21 days until progression, or treatment discontinuation of BNT151 due to other factors. Following discontinuation, and a safety follow-up period of 60 days, patients will be followed up for survival every 12 weeks until death.

4.1.3 Expansion Part 2 - Expansion Phase

This part of the CTP will be updated by amendment when the profile of BNT151 is better understood from Part 1. The decision to expand is based on the totality of data generated in Part 1. All decisions for expansion should be endorsed by the SRC.

Once the monotherapy RP2D is established the trial will proceed with the Part 2 Expansion Phase. The Expansion Phase will be conducted in 5 cohorts as follows:

- Cohort 1: SCCHN – BNT151 + pembrolizumab
- Cohort 2: HCC – BNT151 + pembrolizumab

The following cohorts will only be initiated once Part 2A for Cohorts 1 and 2 is completed:

- Cohort 3: RCC – BNT151 + pembrolizumab + axitinib
- Cohort 4: NSCLC – BNT151 + pembrolizumab + carboplatin + pemetrexed
- Cohort 5: TNBC – BNT151 + atezolizumab + nab-paclitaxel

The Expansion Phase may be amended based on data generated in Part 1. The Expansion Phase will follow either Simon two-stage or Khan one-stage design (Khan et al. 2012) with details specified in a substantial amendment based on Part 1 trial results. The purpose of the Expansion Phase is to confirm the dose and schedule of BNT151 in combination with SoC. Cohorts 3 to 5 will only start after sufficient data are generated in Cohorts 1 and 2 since BNT151 is combined with anti-cancer therapies other than

pembrolizumab. Further details on the Expansion Phase will be implemented by protocol amendment after completion of Part 1.

4.1.4 Adaptive trial design elements

The following adaptive design elements define conditions under which changes to the trial design may be implemented based on the SRC recommendation. Further changes not specified here would be introduced via an amendment to this protocol.

4.1.4.1 Monotherapy dose escalation with pre-conditioning dose in Part 1

In preclinical studies, it was shown that mice tolerated a higher dose of BNT151 after exposure to a lower dose in the previous cycle. This effect is most likely based on dose dependent stimulation of NK cells by the translated IL-2 variant. The IL-2 variant mediates a transient activation and expansion of NK cells, which release cytokines such as IFN-γ as part of their innate immune function. These cytokines in turn may mediate AEs, such as temporary weight loss and lethargy observed in mice. NK cell numbers normalize within 14 days after BNT151 exposure. Re-challenges with BNT151, one to 3 weeks after the first treatment do not result in further NK cell stimulation or associated adverse effects such as weight loss in mice. NK cell expansion is BNT151 dose dependent and a low starting dose of BNT151 is better tolerated, yet is still capable of inducing refractory NK cells. An initial low dose can therefore increase the tolerability of a subsequent high-dose.

To address the potential occurrence of a first dose effect observed in patients that was observed in mice, an adaptive design element is implemented in this trial. The sponsor hypothesizes that an initial lower lead-in dose that shows minimal NK-related activity could act as a pre-conditioning and may be a suitable measure in order to mitigate potential toxicity of subsequently increased BNT151 doses.

The protocol may open a monotherapy dose escalation with pre-conditioning if there are indications for a first dose effect. For assessment of whether there is such an effect, not only AE profile data shall be taken in account, but also include PK, pharmcodynamics and other biomarker data, including exploratory biomarkers. SRC approval is required to initiate the pre-conditioning dose escalation.

The pre-conditioning dose escalation will be conducted at the following potential dose levels as shown in Table 8 (the final dose levels will be determined based on the data generated).

Table 8: Dose escalation in monotherapy with pre-conditioning

Dose level	pCD1	C1D1	C2D1….CXD1
1	DLp	DLp+1	DLp+1
2	DLp	DLp+2	DLp+2
3	DLp	DLp+3	DLp+3
4	DLp	DLp+4	DLp+4
…	DLp	DLp+…	DLp+…
…	DLp	DLp+…	DLp+…
n	DLp	DLp+n	DLp+n

Dose levels defined in the text below.
DLT observation period: C1 (21 d).
C = cycle; D = day; DLT = dose limiting toxicity; DLp = pre-conditioning dose (equals either maximum tolerated dose [MTD] for monotherapy without pre-conditioning or the recommended pre-conditioning dose); n = the maximum dose level in Table 7 and Section 4.1.1; pC = pre-conditioning cycle.

The doses will be applied as follows:

- The monotherapy MTD will be assigned as a pre-conditioning dose (DLp). In case the MTD in monotherapy is not established, the SRC may also recommend a DLp based on the clinical data.
- DLp will always stay the same.
- Each patient will start with DLp in pre-conditioning Cycle (cycle length 7 days).
- In Cycle 1, the dose will be increased following the classical 3+3 design up to DLp+n until the MTD/RP2D are defined.
- The intended dose in C1D1 may follow either the CCI main dose levels as shown in Table 7 CCI [redacted] at the discretion of the SRC.
- Patients will be observed for DLT starting from Day 1 of Cycle 1 until Day 21 of Cycle 1 (21 days = 1 cycle). DLp has already been declared safe and no DLT assessment is required at this pre-conditioning dose.
- 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 IV administration of BNT151 in pre-conditioning Cycle in the first and the second patient, and between the second and the third patient.
- Hospitalization is required for the first 24 hours in Cycle 1 Day 1.

4.1.4.2 Backfilling

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

4.1.4.3 Further testing in a specific tumor type in the escalation stage

Enrollment of up to 10 additional patients in the escalation stage may be allowed if efficacy is seen in a specific tumor type.

4.1.4.4 Lower increment during dose escalation

If Grade 2 related AEs are observed at a given dose level, the increment to the next dose level may be reduced under SRC guidance, e.g., to 50% or lower of the planned increment. See also Section 4.1.2.

4.1.4.5 PK and PD sampling schedules

The PK and PD sampling schedules will start using Table 2a and Table 2b (for Part 1: Monotherapy with and without pre-conditioning), and Table 4a and Table 4b (for the Biomarker Cohort), however additional time points up to a total of 3 during the first 6 weeks may be added, or time points may be removed, based on the evolving PK and PD data.

4.1.4.6 Combination dose finding in Part 2

Once the monotherapy RP2D is established (with or without pre-conditioning) based on safety, efficacy, PK and PD, the trial will proceed with the Part 2 Expansion Phase.

4.1.4.6.1 Safety run-in

Safety run-in will be activated if no potential overlapping toxicities between BNT151 and SoC are anticipated based on the BNT151 monotherapy safety profile in Part 1. Guidance on assessment of overlapping toxicities is as follows:

- No occurrence of life-threatening adverse reactions (ARs) in Part 1.
- No occurrence of any related Grade ≥3 toxicities of BNT151, which are not amenable to standard clinical management overlapping with ARs known for SoC according to the ones listed in the USPI and SmPC.

Six patients eligible for any expansion cohorts will be enrolled and dosed with a combination of BNT151 and SoC as described in Section 4.1.4.6.2. The SRC will review all available safety data. Further enrollment into the expansion cohorts can continue when the SRC declares the combination to be safe. In the safety run-in patients, the dose of BNT151 will be the RP2D-1 in combination with SoC at its approved doses. Further patients dosed after safety run-in may receive the BNT151 RP2D if it is deemed safe.

In case pre-conditioning dose is identified in Part 1 (see Section 4.1.4.1), it will be applied for safety run-in with BNT151 with the same principle stated above.

4.1.4.6.2 Abbreviated dose escalation

If overlapping toxicity is observed as described above in Section 4.1.4.6, an abbreviated dose escalation of BNT151 in combination with SoC will be performed. Patients eligible for the expansion cohorts with BNT151 and SoC will be enrolled and dosed as follows.

The trial will continue with classical 3+3 design as described in Part 1, including staggered enrollment, overnight stay, and DLT observation period. At least 2 dose levels of BNT151 will be explored in combination with SoC given according to the Prescribing Information valid in a given country. The BNT151 dose will not exceed the monotherapy RP2D. The BNT151 starting dose will be one dose level below the monotherapy RP2D (i.e., RP2D-1). If safe, the BNT151 dose will be escalated to monotherapy RP2D. If the starting dose is declared too toxic according to the 3+3 design, dose levels with PK/PD activity below the starting dose can be explored in the combination.

In case pre-conditioning dose is identified in Part 1 (see Section 4.1.4.1), it will be applied for the abbreviated dose escalation with BNT151 with the same principle stated above.

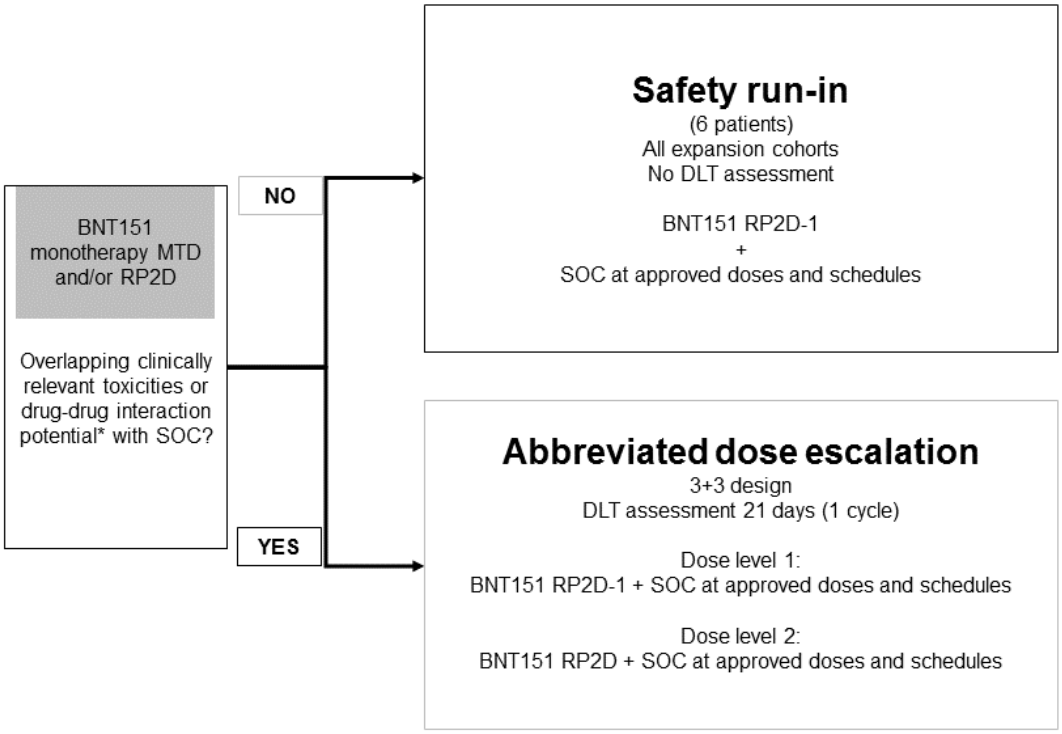

Figure 2: Decision for safety run-in versus abbreviated dose escalation

* Assessment of overlapping toxicities:
- No occurrence of life-threatening adverse reactions in Part 1.
- No occurrence of any related Grade ≥3 toxicities of BNT151, which are not amenable to standard clinical management overlapping with adverse reactions known for SoC according to the ones listed in the USPI and SmPC.

DLT = dose limiting toxicity; MTD = maximum tolerated dose; RP2D = recommended Phase II dose; SmPC = Summary of Product Characteristics; SoC/SOC = standard of care; USPI = US Prescribing Information.

4.1.5 Planned number of patients

In Part 1, the sample size will be up to 54 DLT-evaluable patients depending on the number of DLTs which may occur, with the possible enrollment of up to 10 additional

patients if efficacy is seen in a specific tumor type. The Biomarker Cohort will enroll approximately 20 patients.

The objective for the trial Part 2A and 2B is to further investigate the safety profile and to assess the efficacy of the IMP in different indications in combination with other approved anti-cancer agents. The design in Part 2A can either be a safety run-in of 6 patients or a short escalation at 2 dose levels according to the 3+3 trial design, therefore the sample size in Part 2A will range from 6 to 12 patients per cohort. The sample size in Part 2B may be based on either Simon two-stage design or one-stage design. The final sample size calculations will be introduced through protocol amendment.

4.1.6 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 BNT151.

4.2 Scientific rationale for the trial design

The first part (Part 1) of this trial is a FIH, open-label, dose escalation trial of BNT151 monotherapy in patients with different types of solid malignant tumors in order to determine the safety, PK and PD profile of BNT151. The second part (Part 2A) aims to determine the safety profile of BNT151 further in combination with SoC (Part 2B). Different treatment schedules may also be explored in Part 2A/2B.Part 1: Monotherapy dose escalation

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 [redacted] dose levels of BNT151 are assumed to induce no or minimal biological effects in humans and reflect precautions for the patient's safety while introducing a novel compound in humans. In case of occurrence of Grade ≥2 related toxicities, or DLTs observed or SRC decision which can also be informed by all available safety data and supportive PK/ PD data, the single-patient cohorts will be expanded to 3+3-patient cohorts. 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, PD and clinical efficacy data combined provide both more flexibility and better accuracy of the estimated RP2D while safeguarding the patient's safety. BNT151 is an LNP-formulated, single stranded, 5′-capped RNA that is translated into a human IL-2 variant fused to human serum albumin. Its mechanism of action is to stimulate the patient's IL-2-sensitive immune effector cells to kill tumor cells. Selected PD biomarkers, which inform about the immune activation status, such as soluble interleukin-2 receptor (sCD25), absolute lymphocyte count, cytokines and chemokines, can potentially be used to guide the dose escalation in Part 1 and if needed in Part 2A.

4.2.1 Option of monotherapy dose escalation with pre-conditioning

In preclinical studies, it was shown that mice better tolerated a higher dose of BNT151 after exposure to a lower dose in the previous cycle. This effect was most likely based on stimulation of NK cells by the translated IL-2 variant. The IL-2 variant mediates a transient activation and expansion of NK cells, which release cytokines such as IFN-γ as part of their innate immune function. These cytokines in turn may mediate the IL-2 AEs, such as temporary weight loss and lethargy observed in mice. NK cell numbers normalize within 14 days after BNT151 exposure. Therefore, their AE-mediating effect is self-limiting. Moreover, NK cells go into a transient refractory status. Re-challenges with BNT151, one to 3 weeks after the first treatment do not result in further NK cell stimulation or associated adverse effects such as weight loss in mice. In these mouse experiments NK cell expansion was BNT151 dose dependent and a low starting dose of BNT151 was better tolerated while it was still capable of inducing refractory NK cells, thereby increasing the tolerability of a subsequent high-dose.

To address this, preconditioning has been implemented in this trial. The reason for the preconditioning dose is to increase tolerability of subsequent BNT151 doses. As the preconditioning dose is low, it is not expected that the full therapeutic potential of the drug in terms of expansion of tumor-specific effector T-cells will be achieved. To achieve a meaningful expansion of tumor-specific cells as early as possible, a second dose will be administered soon after the preconditioning dose. Preclinical studies suggest that the preconditioning effect will be present as early as one week after dosing, thus administration of the second dose 1 week after the preconditioning dose is planned.

4.2.1.1 Biomarker Cohort

mRNA underlies an innovative and sophisticated drug platform to deliver a protein-based therapy but, ongoing data do potentially suggest an occurrence of interpatient variability especially in translation that can affect correct determination of effective dose, as well as establishing a confident safety profile of the product. Therefore, the implementation of the Biomarker Cohort to further elucidate the differences and understand the variabilities is justified. Dose levels that have been cleared by the SRC in the dose escalation will be investigated in the monotherapy Biomarker Cohort, in order to further investigate the mode of action of BNT151, to allow optimization of future combinations with other anti-cancer agents, and to assess the interpatient variability.

4.2.2 Part 2A: Combination dose finding

The monotherapy RP2D of BNT151 will be re-evaluated in combination with SoC by a safety run-in in Part 2 or by performing an expedited combination dose escalation. The decision for one option over the other depends on the potential overlapping toxicity between BNT151 and SoC.

The LNP-formulated RNA BNT151 codes for an IL-2 variant with prolonged half-life, increased capability to stimulate effector T cells and NK cells but abrogated activation of undesirable T_{reg} cells. As such, potential toxicities of BNT151 may encompass but are not limited to those toxicities observed for approved recombinant IL-2 (aldesleukin) and NKTR-214, a novel engineered IL-2 pathway agonist currently under clinical development:

Recombinant IL-2 (aldesleukin) exhibits a very short half-life in the range of minutes and requires high and frequent dosing, which in turn potentiates its side effects. Frequent AEs comprise changes in blood counts (reduced thrombocytes, erythrocytes and neutrophils), chills, pruritus, nausea, vomiting, diarrhea, and hypotension (Assier et al. 2004, Baluna and Vitetta 1997, Lotze et al. 1986, Rosenberg et al. 1987). CLS is the main DLT. CLS usually occurs 3-4 days after IL-2 treatment and results in decreased microcirculatory perfusion and interstitial edema especially in lung and liver.

NKTR-214 is an effector T-cell and NK cell biased human recombinant IL-2 that is attached to an average of 6 releasable polyethylene glycol (PEG) chains to alter both its receptor binding and PK. When fully PEGylated, NKTR-214 is a pro-drug that slowly releases the PEG chains *in vivo* to generate active cytokine species. Active NKTR-214 cytokine selectively increases the proliferation, activation, and effector function of effector T cells and NK cells, and is thus similar to the BNT151 translated IL-2 variant. Frequent AEs of NKTR-214 comprise fatigue, chills, pruritus, hypotension and rash (Bentebibel et al. 2019).

BNT151 is believed to yield higher efficacy as compared to recombinant IL-2 while ameliorating peak dose mediated toxicities. Furthermore, due to its beneficial PK properties, BNT151 requires less frequent dosing. Compared to NKTR-214, BNT151 translated IL-2 variant is not a pro-drug and does not require an additional processing step to be fully active. However, besides IL-2 mediated toxicities, potential toxicities of BNT151 can also be induced by the LNP-formulated RNA drug product.

Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. The safety profile of pembrolizumab has been documented from hundreds of clinical trials. Most commonly associated AEs are distinct immune-related AEs (irAEs).

The sponsor acknowledges that since BNT151 and pembrolizumab are both immunotherapies but with different mechanisms of action, the toxicities may not overlap. In such a case, a combination dose finding with a safety run-in phase is justified. The sponsor, however, also acknowledges the potential overlapping toxicities with the 2 compounds, thus a clear algorithm to trigger a typical combination dose escalation design is also outlined (see Section 4.1.4.6).

4.2.3 Part 2B: Expansion Phase

The trial design in the expansion cohorts are either Simon two-stage design or Khan one-stage design.

The Simon two-stage design is often used for Phase II cancer clinical trials. A trial proceeds to the second stage unless the null hypothesis, that the true tumor response rate is below some specified value, is already accepted at the end of stage one. This limits exposing more patients to a compound without sufficient anti-tumor activity.

The one-stage design per Khan et al. (2012) is used to examine several sample sizes for the same treatment effect and choose one that is the smallest. This would be especially

useful for trials of novel agents (where little is known about the treatment) or for rare disorders, where it is appropriate to minimize the sample size.

Further information and details on Part 2B will be done by protocol amendment.

4.3 Justification for dose

The proposed starting dose of BNT151 is in accordance with the ICH S9 recommendation (2009) for anti-cancer biopharmaceuticals with immune agonistic properties and integrates:

- Nonclinical data on pharmacological activity of the BNT151-translated IL-2-variant in human and cynomolgus macaque peripheral blood mononuclear cells (PBMCs) *in vitro.*
- The lymphoproliferation-based MABEL dose identified in BNT151-exposed cynomolgus macaques.
- The IL-2R activation-based MABEL identified in an accessory *in vitro* study to the non-GLP PK and tolerability study in cynomolgus macaques.
- Previous experience on interspecies scaling of LNP-transfection and RNA translation efficacy with liver-targeted LNP-formulated RNA.

The pharmacological data demonstrated that translated hAlb-hIL2var exhibits similar pharmacological activity in human and cynomolgus macaque PBMCs. Accordingly, the capability of hAlb-hIL2var to induce lymphoproliferation in cynomolgus monkeys was assessed as a PD marker of immune stimulation after IV BNT151 administration. Lymphocyte counts above pre-dose levels were first detected at a dose of CCI µg/kg BNT151 with a trend towards more pronounced lymphoproliferation in animals treated with CCI µg/kg. Due to the rather large dose increment in-between the CCI µg/kg cohorts, CCI **µg/kg BNT151** was defined as a conservative lymphoproliferation-based MABEL dose.

Figure 3: Lymphoproliferation-based MABEL projection

Dose-response of total lymphocyte counts as PD marker of immune stimulation in cynomolgus macaques treated with CCI µg/kg BNT151. Lymphocyte counts at pre-dose (test day 1) and at Test days 7 or 8 (TD7/TD8) are shown. Green rectangle indicates the dose range in which MABEL was reached.
MABEL = minimum anticipated biological effect level; PD = pharmacodynamics.

In a second, independent evaluation, the bioactivity of BNT151-exposed cynomolgus macaque serum, obtained as part of the non-GLP PK and tolerability study, was assessed on T_{regs} as most IL-2 sensitive immune cell subset in human PBMCs using signal transducer and activator of transcription 5 (STAT5) phosphorylation as a proxy for IL-2R activation (Lin and Leonard 2000, Parkes et al. 2018). STAT5 phosphorylation responses induced by individual sera were plotted as a function of cytokine serum levels, and the PK/PD correlation was modelled. Taking into account that prolonged duration (>30 h) rather than a transient pulse of IL-2R signaling is required to drive T-cell proliferation (Arneja et al. 2014, Rao et al. 2005), the CCI **µg/kg BNT151** dose level was identified as IL-2R activation-based MABEL dose.

Figure 4: IL-2R activation-based MABEL projection

(A) IL-2R activation on CD4+ T_{regs} in human PBMCs measured by phosphorylation of STAT5 as a function of cynomolgus macaque serum levels of BNT151-translated IL-2 variant. (B) Modelled PK/PD correlation making use of the recorded IL-2 variant PK data as well as the curve fit parameters derived from the IL-2R activation dose-response. The horizontal dashed line indicates the maximum obtainable effect level; the vertical dashed line indicates the threshold duration of IL-2R activation that is required to drive T-cell proliferation (Arneja et al. 2014).
CD4+ = cluster of differentiation 4 positive; IL-2(R) = interleukin 2 (receptor); hALB = human albumin; hIL-2 = human interleukin 2; MABEL = minimum anticipated biological effect; PBMC = peripheral blood mononuclear cells; PD = pharmacodynamics; PK = pharmacokinetic; (p)STAT5 = signal transducer and activator of transcription 5; T_{reg} = T regulatory.

Importantly, LNP-transfection efficacy and RNA translation is assumed to be comparable between cynomolgus monkeys and humans when applying body mass correction, as comparability has been reported for an small interfering RNA (siRNA) approach using a liver-targeted siRNA formulation similar in composition to the clinical formulation selected for BNT151 (Coelho et al. 2013). Hence, the identified MABEL dose for cynomolgus monkeys equals the anticipated MABEL dose for humans. Taking a conservative approach, an additional safety factor of 50 is added, to ensure patient safety. This results in a **proposed FIH dose of 0.4 µg/kg**.CCI

4.4 End of trial definition

The end of the trial will be declared at the time at which:

- All patients have discontinued IMP treatment; and
- All patients have completed safety follow-up assessment at Day 30/60 subsequent to last dose;

and/or

- The relevant authorities or sponsor discontinues the trial.

5 TRIAL POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion criteria

Each potential patient must fulfill all of the inclusion criteria provided in Section 5.1.1 and Section 5.1.2 to be enrolled in the trial.

5.1.1 Disease-specific inclusion criteria

For all Parts

1. Histological documentation of the original primary tumor via a pathology report.
2. Measurable disease per RECIST 1.1.

For Part 1:

3. Histologically confirmed solid tumor that is metastatic or of advanced unresectable stage and for whom there is no available standard therapy likely to confer clinical benefit, or patient who is not a candidate for such available therapy. If there is no contraindication, patients should have exhausted all SoC therapies before entering the trial, if possible.

For Part 2 (Including 2A and 2B):

Cohort 1: SCCHN

4. Histologically confirmed, R/M SCCHN with disease progression on or after a platinum-based therapy.

Cohort 2: HCC

5. Histologically confirmed unresectable or metastatic HCC who have been previously treated with a first-line systemic treatment.

Cohort 3: RCC

6. Histologically confirmed RCC eligible for pembrolizumab in combination with axitinib, for the first-line treatment of patients with advanced RCC.

Cohort 4: NSCLC

7. Histologically or cytologically confirmed NSCLC eligible for pembrolizumab in combination with pemetrexed and platinum chemotherapy for the first-line treatment

of patients with metastatic non-squamous NSCLC, with no *EGFR* or *ALK* genomic tumor aberrations.

Cohort 5: TNBC

8. Histologically confirmed TNBC eligible for atezolizumab in combination with paclitaxel protein-bound for the treatment of unresectable locally advanced or metastatic TNBC whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells of any intensity covering ≥1% of the tumor area), as determined by an FDA approved test.

5.1.2 Other inclusion criteria

For all Parts

9. ≥18 years of age.
10. Must sign an ICF indicating that he or she understands the purpose and procedures required for the trial and are willing to participate in the trial prior to any trial-related assessments or procedures.
11. ECOG performance status of 0 to 1.
12. Adequate coagulation function at screening as determined by:
    - INR or prothrombin time ≤1.5 × ULN; (unless on therapeutic anticoagulants with values within therapeutic window),
    - aPTT ≤1.5 × ULN (unless on therapeutic anticoagulants with values within therapeutic window).
13. Adequate hematologic function at screening as determined by:
    - White blood cell count (WBC) ≥3 × 10^9/L
    - ANC ≥1.5 × 10^9/L (patient may not use G-CSF or GM-CSF in the 7 days prior to trial treatment to achieve these WBC and ANC levels)
    - Platelet count ≥100 × 10^9/L
    - Hgb ≥9.0 g/dL.
14. Adequate hepatic function at screening as determined by:
    - TBili ≤1.5 mg/dL (or ≤2.0 mg/dL for patients with known Gilbert's syndrome or liver metastasis)
    - AST and ALT ≤2.5 × ULN; ≤3 × ULN for patients with liver metastasis.
15. Adequate renal function at screening as determined by:

    Glomerular filtration rate (GFR) ≥45 mL/min/1.73 m² –

    According to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, expressed as a single equation:

    $GFR = 141 \times \min(Scr/\kappa,1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] × 1.159 [if black]

Scr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.

- For creatinine assays using methods traceable to isotope dilution mass spectrometry (IDMS) assigned National Institute of Standards and Technology (NIST) certified reference materials (Levey et al. 2009).

16. Able and willing to attend trial visits as required by the protocol.
17. WOCBP must have a negative serum (β-hCG) test/value at screening. Patients who are postmenopausal or permanently sterilized (Section 10.4) can be considered as not having reproductive potential.
18. WOCBP must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the entire trial, until 6 months after last BNT151 treatment.
19. 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 BNT151 (refer Section 10.4 for information for further recommendations).
20. WOCBP must agree to use highly effective contraception during the trial and for 6 months after receiving the last dose of BNT151. Birth control methods are considered highly effective if they have a failure rate of less than 1% per year, when used consistently and correctly. Further guidance on contraceptive measures for female patients can be found in Section 10.4.

For the Biomarker Cohort:

21. At selected US sites only: at enrollment patients must agree to have one pre-dose biopsy and lesion that is deemed accessible by the investigator. If possible, at least one on-treatment biopsy should be accessible from same tumor lesion.

5.2 Exclusion criteria

Any potential patient who meets any of the following criteria will be excluded from participating in the trial.

Prior and concomitant therapy

1. Use of any IMP or device within 28 days before administration of first dose of trial treatment.
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. Ongoing participation in the active treatment phase of interventional clinical trial.
4. Receives concurrent systemic (oral or IV) steroid therapy >10 mg prednisone daily or its equivalent for an underlying condition.
5. Has had major surgery within the 4 weeks before the first dose of BNT151.
6. Ongoing or active infection requiring IV treatment with anti-infective therapy that has been administered less than 2 weeks prior to the first dose of BNT151.
7. Has ongoing side effects to any prior therapy or procedures for any medical condition not recovered to NCI CTCAE v5.0 Grade ≤1.

   Note: 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 metastases may be eligible if they:
   - had radiotherapy, surgery or stereotactic surgery for the brain metastases;
   - have no neurological symptoms (excluding Grade ≤2 neuropathy);
   - have stable brain metastasis on the CT or MRI scan within 4 weeks before signing the informed consent; and
   - are not undergoing acute corticosteroid therapy or steroid taper.

   Notes: Patients with central nervous system (CNS) symptoms should undergo a CT-scan or MRI of the brain to exclude new or progressive brain metastases. Spinal bone metastases are allowed, unless imminent fracture with cord compression is anticipated.
9. Has a history of a cerebrovascular accident or transient ischemic attack less than 6 months ago.
10. Effusions (pleural, pericardial, or ascites) requiring drainage.
11. History of autoimmune disease active or past including but not limited to inflammatory bowel disease, 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 patients with a history of Grave's disease with stable thyroid function. Patients with controlled hyperthyroidism must be negative for thyroglobulin, thyroid peroxidase antibodies, and thyroid stimulating immunoglobulin prior to administration of trial treatment.
12. Known history of seropositivity for HIV with CD4+ T-cell (CD4+) counts <350 cells/μL and with a history of AIDS-defining opportunistic infections.

13. Known history/positive serology for hepatitis B requiring active antiviral therapy (unless immune due to vaccination or resolved natural infection or unless passive immunization due to immunoglobulin therapy). Patients with positive serology must have HBV viral load below the limit of quantification.
14. Active HCV infection; patients who have completed curative antiviral treatment with HCV viral load below the limit of quantification are allowed.

    Note: 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).
15. Any contraindication to the combination therapies as per USPI or SmPC for patients receiving BNT151 in combination with other systemic anticancer agent(s).
16. 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 (including but not limited to 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 (for contact information see Section 8.12) in case of uncertainties.

Other comorbidities

17. Abnormal ECGs that are clinically significant, such as Fridericia-corrected QT prolongation >480 ms.
18. 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:
    - Ongoing or active infection requiring antibiotic/antiviral/antifungal therapy
    - Concurrent congestive heart failure (NYHA Functional Classification Class III or IV)
    - Concurrent unstable angina
    - Concurrent cardiac arrhythmia requiring treatment (excluding asymptomatic atrial fibrillation)
    - Acute coronary syndrome within the previous 6 months
    - Pulmonary embolism within the previous 3 months
    - Significant pulmonary disease (shortness of breath at rest or on mild exertion) for example due to concurrent severe obstructive pulmonary disease.
19. 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.
20. Is pregnant or breastfeeding.

5.3 Lifestyle considerations

Not applicable.

5.4 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, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Patients who do not meet the criteria for participation in this trial (screen failure) may be rescreened. Patients who fail their first screening for trial eligibility may qualify for 2 re-screening opportunities (for a total of 3 screenings per patient) at the investigator's discretion. Patients must re-sign the ICF prior to re-screening. Results of SoC 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 TREATMENTS

Trial treatment is defined as any investigational treatment(s), marketed product(s), or placebo intended to be administered to a trial patient according to the trial protocol.

6.1 Trial treatments administered

In this trial the trial treatments are: For Part 1, BNT151 monotherapy (refer to Table 9) and for Part 2, BNT151 and one of the combination therapies proposed in Section 2.2.2.2.

Potential treatment candidates will be described in an amendment to the protocol prior to the initialization of Parts 2A and 2B (Cohort 1 and 2).

Table 9: Trial treatments to be administered in Part 1

Treatment name	BNT151
Type	Biologic
Designation	Advance Therapy (FDA)/Advance Therapy Medicinal Product (EMA)
Dose formulation	Ampule
Unit dose strength(s)	IMP concentration (CCI mg/mL). Refer to the Pharmacy Manual for further information
Dosage level(s)	0.4 µg/kg RNA for the first dose, increments up to CCI µg/kg are described in more detail in Section 4.1.2 to 4.1.4 and Table 7
Route of administration	IV bolus injection/IV infusion (depending on the administered volume)
Use	Experimental (IMP)
Sourcing	Provided centrally by the sponsor
Packaging and labeling	IMP will be provided in a folding box. Each folding box and each vial will be labeled as required per country requirement

IMP = investigational medicinal product; IV = intravenous; RNA = ribonucleic acid.

In Part 1, BNT151 will be administered IV on Day 1 of each 3-week treatment cycle (21 days; or 7 days for the pre-conditioning cycle) after all required procedures and assessments before administration have been completed. Once eligibility is confirmed, administration of BNT151 can be delayed for up to 7 days unless otherwise approved by the sponsor medical monitor.

6.2 Preparation/handling/storage/accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all trial intervention received and any discrepancies are reported and resolved before use of the trial intervention.

Only patients enrolled in the trial may receive trial treatment and only authorized site staff may supply or administer trial intervention. All trial intervention 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.

The investigator, site, or the head of the site (where applicable) is responsible for trial treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused trial treatment are provided in the Pharmacy Manual and/or Clinical Trial Supply Manual.

6.3 Measures to minimize bias: randomization and blinding

This is an open-label trial.

6.4 Trial treatment compliance

Patients will receive trial treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered must be recorded in the source documents and recorded in the electronic case report form (eCRF). The dose of trial intervention 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 intervention. Fasting status at treatment will be recorded.

6.4.1 Concomitant medication and non-drug therapies

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 ICF, 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. Contact information for the medical monitor can be found in Section 8.12.

It is recommended that patients should abstain from taking nonprescription drugs (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) if not medically necessary before the start of trial intervention until completion of the follow-up visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the trial.

Concomitant antiemetics, antidiarrheal agents, IV fluids, or electrolyte replacement based on clinical or laboratory assessments and blood transfusions while on-treatment based on individual institutional guidelines will be allowed.

Palliative radiotherapy of, for example, painful bone metastases not defined as target lesions 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 either as IMP or one of the combination therapies in a given part of the trial (e.g., Part 1, Part 2A and Part 2B) proposed in Section 2.2.2.2.
- Other prohibited concomitant medications as listed in inclusion and exclusion criteria (Section 5.1 and Section 5.2).

For further guidance on prohibited and restricted medications, please refer to the IB for BNT151, and USPI or SmPCs for other approved agents used in combination with BNT151.

6.4.2 Premedication

Pre- and post-medications with antipyretics (e.g., acetaminophen, nonsteroidal anti-inflammatory drugs), antiemetics, proton-pump inhibitors and anxiolytics per institutional guidelines are allowed. If necessary, patients should be properly prehydrated before BNT151 treatment. Corticosteroid should not be used as a premedication for BNT151.

Patients who have experienced prior administration related Grade 2 or Grade 3 reactions in the trial should be premedicated. Premedication to prevent injection/infusion-related reactions (IRR) in subsequent administrations 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 [per os] or equivalent antihistamine), acetaminophen/paracetamol (e.g., acetaminophen 500-1000 mg *per os* or equivalent), and if considered necessary, patients should receive corticosteroids at a suggested maximum dose of 100 mg prednisone or equivalent.

All premedication must be reported on the concomitant medication page in the eCRF.

Further details on the administration of BNT151 in Cohort 3, 4 and 5 of Part 2 will be implemented by protocol amendment.

6.4.3 Rescue medication

There is no rescue medication for BNT151. For mitigation plans for particular AEs, refer to Section 6.5.4.

6.5 Dose modifications

6.5.1 Dose limiting toxicity

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

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 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 v5.0 will be used to grade the intensity of AEs.

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 (for contact information see Section 8.12).

Any other toxicity assessed as related to BNT151 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 and indefinitely.

6.5.2 DLTs for Part 1 and Part 2A (dose escalation)

During the first treatment cycle of both Part 1 and Part 2A (dose escalation) (during second treatment cycle if pre-conditioning dose is applied), a DLT is considered as any toxicity of Grade 3 and which does not resolve to Grade 1 or lower within a week despite the use of medical intervention, or that is of Grade 4 or Grade 5 (i.e., death), but with **exceptions as** follows:

- The following events occurring during the DLT period are also considered a DLT:
  - Hypotension of Grade 3 that persists for >4 hours and requires hospitalization.
  - 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 following events occurring during the DLT period ARE **NOT** considered a DLT:
  - Grade ≤3 nausea or vomiting controllable with antiemetics within 72 h.
  - Hypotension (systolic pressure <90 mm Hg) of Grade <3 that is of limited duration (less than 72 h) or can be managed with hydration measures.
  - Hypotension that requires a precautionary admission for observation after Grade 3 hypotension that persists for ≤4 h.
  - Grade 3 amylase and lipase elevations that are not accompanied by clinical signs/symptoms of pancreatitis.
  - Liver transaminase elevation lower than 8 × ULN or TBili lower than 3 × ULN.
  - 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.

6.5.3 Dose modification guidance/rules

6.5.3.1 DLTs

Patients who experience a DLT during the DLT observation period of any dose escalation/safety run-in period should permanently discontinue trial treatment.

6.5.3.2 Dose modifications after the DLT Observation Period has ended for patients in escalation/safety run-ins and for all patients in expansion cohorts

Patients who experience Grade 4 clinical AEs and clinically significant Grade 4 lab AEs attributed to BNT151 should permanently discontinue trial treatment. Should an individual patient show overwhelming evidence of clinical benefit at this time, continuation of trial treatment at a substantially reduced dose upon recovery may be discussed with the medical monitor.

Grade 3 clinical AEs and Grade 3 lab AEs attributed to BNT151 that are clinically significant should be handled as shown in Figure 5.

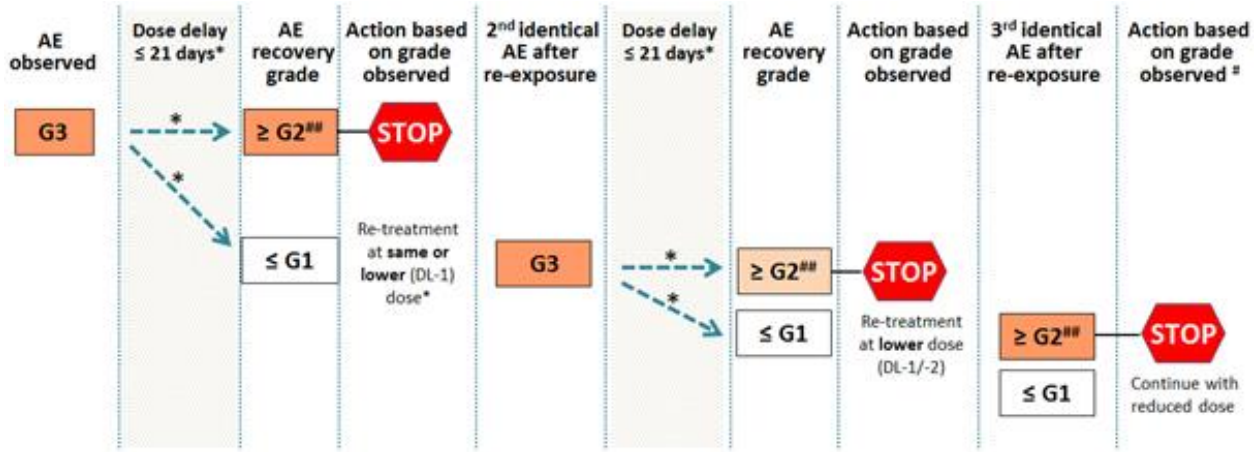

Figure 5: Handling of Grade 3 BNT151-related AEs outside of DLT periods

*Dose delay: Next dose of BNT151 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 treatment-related AEs will always lead to BNT151 discontinuation.
AE = adverse event; G = grade; DL = dose level; DLT = dose limiting toxicity.

First occurrence of Grade 3 AE:

- As a first measure, administration of BNT151 needs to be withheld.
- Investigator must contact sponsor for thorough discussion in order to decide whether the patient should be withdrawn from BNT151 treatment or next dosing should be delayed.
- Administration of BNT151 can be delayed for up to 21 days (i.e., one cycle) unless otherwise approved by the sponsor medical monitor (for contact information see Section 8.12). If the intensity resolves to Grade ≤1 or baseline within this period, re-treatment may be considered under the following:
  - Sponsor and investigator will discuss any safety concerns in order to decide whether the next dose of BNT151 should be administered at 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 BNT151:

- As a first measure, administration of BNT151 needs to be withheld.
- If re-treatment leads to an identical AE with same intensity, the next administration of BNT151 can be delayed for up to 21 days unless otherwise approved by the sponsor medical monitor (for contact information see Section 8.12). 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 BNT151 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 BNT151:

- As a first measure, administration of BNT151 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 treatment. 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 BNT151 should be administered at same reduced dose level (DL-1 or DL-2).

Please note:

- Re-escalation of BNT151 dose is not allowed for patients who have previously been dose reduced.
- BNT151 must be permanently discontinued if the patient experiences a Grade 3 AE that fails to resolve to Grade ≤1 within 21 days after the planned dosing date unless otherwise approved by the sponsor medical monitor (for contact information see Section 8.12).
- BNT151 must be permanently discontinued if more than 2 dose reductions are required.
- BNT151 must be permanently discontinued in case of a dose delay of more than 21 days due to toxicity possibly related to BNT151 unless otherwise approved by the sponsor medical monitor (for contact information see Section 8.12).
- The investigators are encouraged to contact the sponsor in case of any safety concern that needs thorough discussion and evaluation.
- If the causal relationship of AE cannot be attributed to either BNT151 or SoC, BNT151 should be discontinued; SoC should be dose modified as per the USPI or SmPC.

6.5.4 Mitigation plans for specific AEs

6.5.4.1 Injection/Infusion-related reactions (IRRs)

IRR is a general risk to be considered for any new compound administered IV irrelevant of its mechanism of action. An IRR is typically of immediate onset after the compound's administration. The risk of IRR cannot be excluded due to the given limited experience with BNT151.

The following treatment guidelines are provided below for patients who experience an IRR associated with administration of BNT151 treatment:

- Grade 1: If a Grade 1 IRR occurs, the administration does not need to be interrupted and can be continued at the investigator's discretion at half the injection/infusion rate under close medical supervision.
- Grade 2 or 3: If a Grade 2 or Grade 3 IRR occurs, the administration should be interrupted and appropriate medical management instituted. The administration may be re-started at the investigator's discretion at half the administration rate under close medical supervision if symptoms have resolved to Grade ≤1 within an hour.
  - Patients who have experienced prior administration related Grade 2 or Grade 3 reactions in the trial should be premedicated. Premedication to prevent IRR in subsequent administrations 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 [per os] or equivalent antihistamine), acetaminophen/paracetamol (e.g., acetaminophen 500-1000 mg per os 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 administration should be stopped and the patient should be withdrawn from treatment.
- Grade 4: If anaphylaxis or a Grade 4 IRR occurs, administration of BNT151 should be discontinued immediately and permanently, and appropriate medical therapy should be administered.

Please note:

- At all times during BNT151 administration, 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.

6.5.5 Safety stopping criteria

Across all patients in Both Part 1 and Part 2A, the following rules apply:

The trial will be paused for:

- Any death possibly related to BNT151
- Two Grade 4 AEs that are considered possibly, probably, or definitely related to BNT151

If a suspected DLT occurs, an 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 ethics committee (EC); or, with the sponsor's concurrence, whether the trial should be stopped.

In individual patients, treatment with BNT151 should be discontinued due to safety concerns under the following conditions:

- If the patient experiences an AE fulfilling the DLT criteria during the DLT observation period during any dose escalation or safety run-in part of the trial.
- If the patient experiences a BNT151-related Grade 4 clinical AE or Grade 4 clinically significant lab AE (after the DLT period has ended in the dose escalation/safety run-in parts of the trial or for any patient in the expansion cohorts).
- If the patient experiences a BNT151-related Grade 3 clinical AE or Grade 3 clinically significant lab AE that fails to resolve to Grade ≤1 within 21 days after the planned dosing date (after the DLT period has ended in the dose escalation/safety run-in parts of the trial or for any patient in the expansion cohorts).
- Any dose delay of more than 21 days due to toxicity possibly related to BNT151.
- If more than two dose reductions are required.
- In case of cytokine release syndrome (CRS) Grade 4, the patient should be discontinued from treatment.
- Second occurrence of an IRR of Grade ≥3 despite premedication prior to second administration.
- 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.
- Should an individual patient show overwhelming evidence of clinical benefit at the time of treatment-limiting AEs as defined above, continuation of trial treatment at a substantially reduced dose upon recovery may be discussed with the medical

monitor and must be approved by the medical monitor (for contact information see Section 8.12).

6.6 Treatment after the end of the trial - New anti-cancer treatment

New anti-cancer treatment according to SoC can be started after discontinuation from the trial treatment.

7 DISCONTINUATION OF TRIAL TREATMENT AND PATIENT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of trial treatment

Patients will receive BNT151 treatment until one of the predefined discontinuation of treatment criteria has been met:

- Radiographic disease progression per RECIST 1.1 (Section 12)
- Death
- Unacceptable AEs requiring BNT151 discontinuation (refer to safety stopping criteria Section 6.5.5)
- Investigator believes that it is in the best interest of the patient to stop BNT151 treatment
- Withdrawal of consent
- Pregnancy
- Lost to follow-up
- Trial termination by the sponsor

If BNT151 treatment is permanently discontinued for other reasons than radiographic disease progression, every effort should be made to continue tumor assessments.

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 1.3).

7.1.1 Temporary discontinuation

See Section 6.5.5.

7.1.2 Rechallenge (if applicable)

Not applicable.

7.2 Patient discontinuation/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 Section 1.3 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 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 BNT151. 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 ICF 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 SoAs for dose escalation (Section 1.3) and Part 2 (the SoA for this phase will be based on a substantial amendment based on the experiences from Part 1) of the trial. 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.

8.1 Efficacy assessments

8.1.1 Anti-tumor activity assessment – CT/MRI imaging

Anti-tumor activity will be evaluated according to RECIST 1.1 (Eisenhauer et al. 2009) (see Section 12). 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. The RECIST 1.1 criteria will be used for secondary endpoint response evaluation including PFS (Eisenhauer et al. 2009). All images obtained must be submitted to the central imaging vendor.

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., 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.

8.1.2 Survival follow-up

Survival follow-up starts 12 weeks after all other trial visits have been completed. Survival follow-up may be performed as telephone, e-mail, or clinic visit. Planned time points for Survival follow-up are provided in Section 1.3. Survival follow-up will continue until the patient dies, or the sponsor, whichever occurs earlier, closes the study.

8.2 Safety assessments

Planned time points for all safety assessments are provided in Section 1.3.

8.2.1 Physical examinations including height and body weight

Physical examinations will be performed (by inspection, palpation, and auscultation) by a physician at the trial site according to the SoA for Part 1 (Section 1.3) and Part 2 of the trial (table to follow with protocol amendment).

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 detected after signing the ICF have to be recorded on the AE page of the eCRF.

A limited, symptom-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.

8.2.2 Vital signs

Vital signs will be assessed by the appropriate trial personnel at the time points listed in the SoA for Part 1 (Section 1.3) and Part 2 of the trial (table to follow with protocol

amendment). The same methods for measuring vital signs such as body temperature should be used for one patient throughout the trial.

During dose escalation, body temperature, heart rate, respiratory rate, and blood pressure will be assessed as summarized in Table 10 on BNT151 administration days. On days when BNT151 is not administered, vital signs only need to be obtained once, at any time during the visit.

Blood pressure and heart rate 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 heart rate measurements should be preceded by at least 5 min 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 1 blood pressure measurement (if the blood pressure measurement is abnormal, 2 further measurements must be done at intervals of 1 minute and the average of the three measurement must be recorded on the eCRF).

Table 10: Vital signs during Part 1 (administration days)

Pre-administration
BNT151 pre-administration (up to 30 min before administration)
During administration:
If the IMP is given as an infusion, vital signs will be measured every 15 min during the infusion until infusion is completed (±5 min)
If the IMP is given as a bolus, vital signs will be measured 15 min after the injection (±5 min)
Post-administration:
30 min after end of administration (±5 min)
60 min after end of administration (±10 min)
120 min after end of administration (±15 min)

IMP = investigational medicinal product.

8.2.3 Electrocardiograms (ECGs)

12-lead ECG will be obtained as outlined in Section 1.3 using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and corrected QT (QTc) intervals. For the assessment the patients will be in the supine position, lying still and quietly for at least 10 minutes 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.

8.2.4 Clinical safety laboratory assessments

See Section 10.2 for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.

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 electronic 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 intervention 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.

8.2.5 Eastern Cooperative Oncology Group (ECOG)

ECOG performance status will be assessed at the time points indicated in Section 1.3 using the scale shown in Table 11.

Table 11: ECOG performance status scale

Grade	Eastern Cooperative Oncology Group (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.

8.2.6 Echocardiogram (ECHO)

Evaluation of left ventricular function by ECHO scan will be performed at screening, and as clinically indicated at other time points.

8.2.7 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 Section 1.3 for the time points when pregnancy tests should be performed for WOCBP. 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. Refer to Section 10.4.3 for details of reporting pregnancies.

8.3 Adverse events (AEs) and serious adverse events (SAEs)

Definitions of AEs and SAEs can be found in Section 10.3. 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 all AEs and SAEs.

8.3.1 Time period and frequency for collecting AE and SAE information

All AEs and SAEs will be collected from signing of the ICF until the Safety Follow-up Visit 2 at the time points specified in the SoA (Section 1.3).

All SAEs (initial and follow-up reports) will be recorded and reported to the sponsor or designee **within 24 hours** after becoming aware of the event, as indicated in Section 10.3.1.12.

Investigators are not obligated to actively seek AE or SAE 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.

8.3.2 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 non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

8.3.3 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 and DLTs (as defined in Section 10.3 and 6.5.1) 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).

The investigator is obliged 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.

New or updated information will be recorded in the originally completed eCRF.

The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information

All ongoing AEs/SAEs will be followed until resolution, considered by the investigator to be stable or chronic (resolved with sequelae), the patient is lost to follow-up or the patient withdraws consent. If no final status is reached at the Safety Follow-up 2 Visit (Section 1.3), the investigator must confirm the unavailability of a final status.

Further information on follow-up procedures is provided in Section 10.3.

8.3.4 Regulatory reporting requirements for SAEs

Prompt notification by the investigator to the sponsor of a 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 (IRBs)/independent ethics committees (IECs), and investigators. The execution of expedited reporting to the different entities may be delegated as detailed in the trial-specific Safety Management Plan.

Safety reports will be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

For the IMPs, the sponsor or delegate will take care of the reporting of SUSAR Reports to the regulatory authority, the IEC and the other investigators as required by national law and applicable guidelines.

An investigator who receives a safety report describing a 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 IB and will notify the IRB/IEC, if appropriate according to local requirements.

Regulatory reporting requirements for SAEs in Part 2 of the trial will be added by amendment.

8.3.5 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).

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.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs (details defined in Section 10.4).

8.3.6 Death events

Any death that occurs within the observation period (please note details below) will be reported as an SAE (please note details below). Exemptions to the SAE definition as defined in Section 10.3.1.5 do also apply for fatal cases. A copy of an autopsy report should be submitted if available upon request. Date and cause of death will be recorded.

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 1 AE in a fatal case, only for the AE leading to death the outcome “fatal” should be selected. If the cause of death is unknown and cannot be ascertained at the time of reporting, “unexplained death” should be documented as event term.

In addition to reporting as SAE, the death page of the eCRF needs to be completed.

Deaths clearly related to the progression of the disease will not be documented as AEs, nor reported as SAEs. These deaths must be collected on the death page of the eCRF.

8.3.7 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 eCRF page in the patient’s eCRF.

NOTE: Symptoms resulting from the progression and clearly stated as related to the PD and fatal cases clearly related to the progression will not be documented as AEs nor reported as SAEs. 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, will have to be documented as AEs and reported as SAEs if applicable.

8.3.8 Adverse events of special interest

Not applicable.

8.4 Treatment of overdose

For this trial, an overdose is defined as a patient receiving a dose of BNT151 15% in excess of the intended dose specified in this protocol. For guidance on overdose for approved agents in combination with BNT151, refer to the relevant SmPC and USPI.

In the event of an overdose, the investigator should:

- Contact the medical monitor (for contact information see Section 8.12) immediately.
- Closely monitor the patient for any AE/SAE and laboratory abnormalities until BNT151 can no longer be detected systemically (at least 21 days).
- Document the quantity of the excess dose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor (for contact information see Section 8.12) based on the clinical evaluation of the patient.

8.5 Pharmacokinetics

Blood samples for (including but not limited to) maximum concentration (C_{max}), time to C_{max} (T_{max}), area under the curve (AUC_{0-T}), and half-life ($t_{1/2}$) analyses of BNT151 translated IL-2 variant will be collected according to the SoA (Section 1.3).

All samples will be analyzed centrally. For details, please see the Laboratory Manual.

Lipid PK samples will be drawn to enable potential further exploratory PK assessments. Refer to Table 4a and Table 4b (related to the Biomarker Cohort). Samples may be stored for up to 15 years (or according to local regulations) following the patient's last visit in the trial at a facility selected by the sponsor to enable analysis for lipid PK.

8.6 Exploratory pharmacodynamics

Details described in Section 8.8.2.

8.7 Genetics

Genetic as well as non-genetic analyses may be part of the biomarker investigations in this trial. Blood and tissue samples will only be used for genetic analysis if the patients have provided informed consent for this genetic analysis (see Section 10.1.3).

The genetic analyses comprise analysis of biomarker variants thought to play a role in the mechanism of action of BNT151.

All data generated using the samples, will be handled in accordance with applicable laws and regulations; this includes requirements applicable for data protection, for sample shipment, and a potential withdrawal of consent.

Samples will be analyzed according to the Laboratory Manual.

8.8 Biomarkers

See the SoA in Section 1.3 (for the dose esclatation Table 2a and Table 2b, for the Biomarker Cohort Table 4a and Table 4b) for planned time points of sample collection.

Sample handling and storage – details on the collection, processing, shipment and storage of samples will be provided in separate documents (e.g., Laboratory Manual). Samples

may be stored for a maximum of 15 years (or according to local regulations) following the end of the trial at a facility selected by the sponsor to enable further analyses.

Reporting – Some of the results of biomarker investigations may be reported separately (e.g., in a biomarker report).

Biomarker and related CRF data (e.g. clinical outcome) will be monitored regularly during the trial.

8.8.1 Tumor tissue

Tumor tissue collected at baseline or on-treatment or archival FFPE tumor blocks will be analyzed for biomarkers confirming and/or elucidating the mode of action, and to explore potential predictive factors as well as identify possible future combination therapies.

If feasible, all patients should provide a fresh biopsy (core needle biopsies preferred, aspirates are not acceptable) performed at screening or before the first dose and an on-treatment biopsy from the same lesion within the first two cycles, preferably in the time window C2D5-12 (see Table 2a and Table 2b, Table 4a and Table 4b). For patients enrolled in the Dose Escalation Cohort all biopsies are optional, for patients in the Biomarker Cohort the screening biopsy is required and the on-treatment biopsy is required if feasible. An additional biopsy upon treatment discontinuation in the trial is also requested if feasible. For each biopsy the trial site should provide a formalin-fixed paraffin embedded (FFPE) block (see Laboratory Manual) and only at selected US sites fresh tumor tissue cores for isolation of tumor infiltrating lymphocytes (TILs) (see the Laboratory Manual for instructions). In case the site and the patients are willing to provide biopsies on-treatment but cannot provide fresh biopsy during screening, archived material is allowed to be used as a screening sample (not allowed for the Biomarker Cohort).

8.8.2 Pharmacodynamic biomarkers

Pharmacodynamic biomarkers will be evaluated in samples collected before and during treatment in order to determine the impact of BNT151 in monotherapy or in combination therapy on these biomarkers.

Blood samples for PD biomarkers, which might act as anti-tumor, and safety indicators of activity of BNT151 monotherapy and in combination with SoC, will be collected as defined in detail in the SoA (Section 1.3). Relevant details on sample collection and handling will be documented in the Laboratory Manual.

Pharmacodynamic biomarkers in blood may include, but will not be limited to: absolute lymphocyte count, immune cell populations, e.g., T cells, regulatory T cells (T_{regs}), B cells and NK cells, as well as sCD25, and cytokines/chemokines as assessed by Flow cytometry and ELISA. The list of planned assessments may be subject to change dependent on the results obtained.

All samples will be analyzed centrally. For details, please see the Laboratory Manual.

8.8.3 Screening for predictive biomarkers

For consenting patients, candidate biomarkers in archived or fresh baseline tumor tissue will be evaluated for correlation with response to treatment to identify possible predictive biomarkers.

Predictive biomarkers may include but are not limited to presence of specific immune cell types and their respective abundance within the tumor immune microenvironment as may be assessed by immunohistofluorescence, immunohistochemistry, flow cytometry, and/or gene expression analysis (e.g., RNAseq) of archival or freshly obtained baseline FFPE biopsies. Predictive biomarker screening may also include specific tumor characteristics such as tumor mutational burden or tumor signatures assessed by Next Generation Sequencing (Whole Exome Sequencing and RNAseq) from the tumor tissue and cell pellet of the peripheral blood.

For withdrawal of consent from the use of biomarker samples refer to Section 10.1.3.1.

8.8.4 Additional biomarkers

In addition to the biomarkers described above, for consenting patients, further biomarkers related to, e.g., the mode of action or the safety of the trial intervention and similar drugs may be investigated by using longitudinal blood samples or serial biopsies. These biomarkers in serial biopsies may be specific immune cell types or specific tumor signatures as assessed by immunohistofluorescence, immunohistochemistry, flow cytometry, and/or gene expression analysis (e.g., RNAseq). The same applies to further biomarkers deemed relevant to cancer and associated health problems. These investigations may include e.g., diagnostic, safety, PD, monitoring, or potentially predictive biomarkers. For withdrawal of consent from the use of biomarker samples refer to Section 10.1.3.1.

8.9 Supplementary biomarker assessments

Blood sampling for immunophenotyping of peripheral immune cells will be (only) mandatory for consenting patients in the Biomarker Cohort as well as for trial sites where logistically manageable. For all other sites, the sampling is optional. The blood samples will be collected according to Table 2a and Table 2b (with and without pre-conditioning), Table 4a and Table 4b (for Biomarker Cohort with and without pre-conditioning). For withdrawal of consent from the use of biomarker samples refer to Section 10.1.3.1.

8.10 Immunogenicity assessments

Antibodies to PEG lipid and BNT151 translated IL-2 variant will be evaluated in serum samples, which will be collected from all patients according to Table 2a and Table 2b (with and without pre-conditioning), Table 4a and Table 4b (for Biomarker Cohort with and without pre-conditioning). These samples will be tested by the sponsor or sponsor's designee. An extra sample will be taken for retesting or retrospective testing if required.

Blood samples for immunogenicity analysis will be collected and handled as outlined in the Laboratory Manual. They will be analyzed centrally and batch-wise.

The detection and characterization of antibodies to PEG lipid and BNT151 translated IL-2 variant will be analyzed by or under the supervision of the sponsor. Samples may be stored for a maximum of 15 years (or according to local regulations) following the last patient's last visit for the trial at a facility selected by the sponsor to enable further analysis of immune responses to PEG lipid and BNT151 translated IL-2 variant.

8.11 Blood collection

Blood samples will be collected from all subjects for immunogenicity, PD and PK analysis. Additional blood will be collected for immunophenotyping for patients enrolled on the Biomarker cohort only. Additionally, for this cohort, the cell pellet, a byproduct from plasma preparation, will be collected once and used for genetic analysis. The total blood sampling volume for individual patients in this trial is up to approximately 770 mL for patients on the regular Dose Escalation Cohorts and 988 mL for patients in the Biomarker Cohort, within the first 6 months of the trial.

8.12 Medical monitor contact information

The site(s) may contact the medical monitor directly during normal German business hours (09:00am to 05:00pm central European time) via telephone or e-mail ([redacted]) for routine issues.

After normal business hours there will be a 24/7 Protocol Coverage for urgent protocol-related medical questions (see Section 8.13).

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, for discussion of urgent protocol Medical-related questions an on-call physician can be reached 24 hours per day, 7 days per week via Syneos 24/7 Call-Center:

- Telephone: [redacted] (chargeable US telephone number allowing a global reach from both landlines and mobile phones)
- [redacted]

On the above internet page, a list of country-specific toll-free access codes are provided. Call the direct access code, then enter: [redacted] (without the leading 0 from the direct access code).

It should be noted that not all countries globally have access to toll-free numbers. Countries without toll-free numbers need to dial the chargeable number as indicated above. Furthermore, there may be restrictions when dialing toll-free numbers from a mobile phone.

8.14 Collection of demographic and other baseline characteristics

8.14.1 Demographic data

At screening, the demographic data and baseline characteristics will be recorded for all trial patients.

8.14.2 Medical history

Medical history information will be recorded for at the times given in the SoA (Section 1.3).

9 STATISTICAL CONSIDERATIONS

9.1 Statistical hypotheses

The primary objectives of this trial Part 1 are to assess the safety profile and to identify the MTD and/or RP2D. The Biomarker Cohort examines the exploratory markers for the mechanism of action in the tumor and periphery. Hence, no statistical hypothesis is under test for trial Part 1. For trial Part 2A and 2B hypothesis testing for each expansion cohort may be introduced through protocol amendment.

9.2 Sample size determination

The sample size for Part 1 of the trial is driven by accelerated titration design of single-patient cohorts with a switch to the 3+3 trial design. In Part 1, the sample size will be up to 54 DLT-evaluable patients depending on the number of DLTs which may occur, with the possible enrollment of up to 10 additional patients if efficacy is seen in a specific tumor type.

In addition, approximately 20 patients will be enrolled in the Biomarker Cohort with paired biopsies. This sample size is based on the proportion of patients who have achieved at least 50% increase from baseline in lymphocytes (total lymphocytes, CD4+, CD8+, T_{regs}, and NK cells) upon treatment with BNT151. Twenty patients are estimated to have >80% chance to rule out a proportion of 10% if the true proportion is 40% at a 2-sided significance level of 0.05.

The objective for the trial Part 2A and 2B is to further investigate the safety profile and to assess the efficacy of the IMP in different indications in combination with other approved anti-cancer agents. The design in Part 2A can either be a safety run-in of 6 patients or a short escalation at 2 dose levels according to the 3+3 trial design, therefore the sample size in Part 2A will range from 6 to 12 patients per cohort. The sample size in Part 2B may be based on either Simon two-stage design or one-stage design. The final sample size calculations will be introduced through protocol amendment.

9.3 Analysis sets

Analysis sets are defined in Table 12.

Table 12: Analysis sets

Analysis set	Description
Screened	The screened set is defined as all patients who signed informed consent.
Treated set	The treated set is defined as all patients who received IMP (i.e., at least one dose of BNT151).
Safety	The safety set is defined as all patients who received IMP (i.e., at least one dose of BNT151).
Efficacy evaluable set	The efficacy evaluable set is defined as all patients who are assigned to IMP and have a baseline and at least one on-treatment/post-treatment tumor response assessment. This analysis set may only be used in Part 2 of the trial.
DLT evaluable set	The DLT evaluable set includes all patients from the safety set who either experienced a DLT during the DLT evaluation period (Cycle 1) or completed the DLT evaluation period. Patients who do not experience any DLT during the DLT observation period are considered to be evaluable if they have been observed for minimum 21 days following the first dose and are considered to have sufficient safety data to conclude that a DLT did not occur.
Pharmacodynamic	The pharmacodynamic set is defined as all patients with baseline and at least one valid on-treatment / post-treatment follow-up PD assessment.
Pharmacokinetic	The pharmacokinetic set is defined as all patients with baseline and at least one valid on-treatment / post-treatment follow-up pharmacokinetic assessment.

DLT = dose limiting toxicity; IMP = investigational medicinal product.

The DLT evaluable set will be used for the evaluation of DLTs in order to assess the MTD and RP2D. The safety set will be used for all other safety analyses. The treated set will be used for efficacy analyses.

9.4 Statistical analyses

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

The SAP will be finalized prior to database lock for the main analysis and it will include a more technical and detailed description of the statistical analyses described in this section. Any deviations from the planned analyses described in the final SAP will be described and justified in the clinical trial report. 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 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 (1982) and the first and third quartile will be presented for each cohort. Survival rates (including two-sided 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 IMP.

Data up to and including the clinical cut-off date for the statistical analysis will be taken into account for the statistical analysis.

9.4.2 Primary endpoints

Primary endpoints include the occurrence of DLTs within a patient during the DLT evaluation period to identify the MTD and/or RP2D, and the occurrence of TEAE as well as the occurrence of dose reduction and discontinuation of IMP due to TEAE to assess the safety and tolerability of the IMP. The analysis of these endpoints is described in Section 9.4.5.

9.4.3 Secondary endpoints

Secondary endpoints include evaluation of anti-tumor activity in terms of ORR, disease control rate (DCR), and DOR.

Objective response rate (ORR)

ORR is defined as the proportion of patients in whom a CR or partial response (PR) is observed as best overall response. Patients not meeting the criteria for CR or PR, including those without any post-baseline tumor assessments, will be considered as non-responders.

ORR will be summarized with absolute and relative frequencies along with two-sided 95% Clopper-Pearson confidence intervals by cohort using the treated set. Statistical hypotheses for expansion cohorts may be introduced by protocol amendment prior to the start of Expansion Phase. For Part 2, a sensitivity analysis will be performed using the efficacy evaluable set.

Disease control rate (DCR)

DCR is defined as the proportion of patients in whom a CR or PR or stable disease (SD) (SD assessed at least 6 weeks after first dose) is observed as best overall response. Patients not meeting the criteria for CR or PR or SD, including those without any post-baseline tumor assessments, will be considered as non-responders.

DCR will be summarized with absolute and relative frequencies along with two-sided Clopper-Pearson 95% confidence intervals by cohort.

Duration of response (DOR)

DOR is defined as the time from first objective response (CR or PR) to first occurrence of objective tumor progression (PD), or death from any cause, whichever occurs first. Only patients in whom a CR or PR has been confirmed will be analyzed for DOR.

DOR will be analyzed using Kaplan-Meier methodology by cohort. Patients alive and without disease progression at data cut-off date or patients lost to follow-up will be censored at the day of their last tumor assessment. Additional censoring rules will be defined in the SAP.

9.4.4 Exploratory endpoints

Exploratory endpoints include analysis of PK parameters (including but not to be limited to AUC, C_{max}, T_{max}, and $t_{1/2}$), and changes of peripheral (cytokines or other soluble proteins or cell types) and intratumoral biomarkers (immune cells, or tumor signatures) that might act as PD, anti-tumor, and safety indicators.

The analysis of these exploratory endpoints including PFS and OS will be described in the SAP.

9.4.5 Safety analyses

All safety analyses will be made on the safety set.

Adverse events

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.

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

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, its time of onset, duration, and outcome, relationship, NCI CTCAE grade, and seriousness including dose exposure data.

9.4.6 Other analyses

Other analyses will be described in the SAP.

9.5 Interim analyses

No formal interim analysis is planned. However, data will be reviewed after each cohort.

The main analysis of the trial will be performed based on all available data from a clinical data cut-off that will occur when all patients have been followed up for at least 6 months of treatment or discontinued before.

A final analysis will be performed when the last patient has discontinued from the trial.

9.6 Data Monitoring Committee

A DMC is not planned. An SRC is planned, for details see Section 10.1.5.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Regulatory, ethical, and trial oversight considerations

This trial will be conducted in according to this protocol, the ethical principles that have their origin in the Declaration of Helsinki, Good clinical practice (GCP), and applicable regulatory requirements.

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 GCP Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, IB, and other relevant documents, will be submitted to the relevant regulatory authorities as required by applicable regulations. If required, approval for conducting the trial will be obtained from regulatory authorities in accordance with relevant regulatory requirements.

The protocol, protocol amendments, ICF, IB, 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 (if applicable), and all other applicable local regulations.

The principal investigator, any investigator(s), the sponsor, or personnel at other establishments, must cooperate with any inspection of the documents, facilities, records, and other resources deemed appropriate by the inspecting authorities to be related to the trial and that may be located at the trial site, at the sponsor, or at other establishments.

The sponsor must be notified as soon as possible about any upcoming regulatory authority inspection.

10.1.2 Financial disclosure

All 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 will be required to sign a statement of informed consent that meets the requirements of local regulations (e.g., 21 CFR 50), ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or trial site.

The medical record must include a statement that written informed consent was obtained using an ICF 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 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 re-screened (see Section 5.4) must sign and date a new ICF.

A separate Biomarker Cohort ICF will also include genetics that will need to be signed and dated by consenting patients.

10.1.3.1 Withdrawal from the use of biomarker 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 (up to five years following reporting of trial results), or as per local standards, whichever comes first. Samples for future exploratory research will be shipped to the sponsor and will be stored for up to 15 years (or according to local regulations) following the patient's last visit.

10.1.4 Data protection

All data collected and processing during this trial will be performed in accordance with the applicable data protection requirements.

Patients will be assigned a unique identifier by the investigator according to the sponsor specifications on unique identifier assignment. 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 laws. 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 their medical records may be examined by sponsor 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 Committees structure – SRC

An 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 adaptive trial design as well as for the recommended dose for pre-conditioning if needed and for Parts 2A and 2B 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 SRC Charter.

If a toxic dose is reached, the medical monitor will e-mail the investigators and site staff to inform them that recruitment has been suspended pending review by the SRC. If the e-mail 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 e-mail update of all SRC decisions within 24 hours of each meeting.

10.1.6 Dissemination of clinical trial data

All information concerning the product as well as any information such as clinical indications for the IMP, its formula, methods of manufacture and other scientific data relating to it, that have been provided by the sponsor or designee, and are unpublished, are confidential, and must remain the sole property of the sponsor. The investigator will agree to use the information only for the purposes of carrying out this trial and for no other purpose unless prior written permission from the sponsor is obtained. The sponsor has full ownership of the eCRFs completed as part of the trial.

10.1.7 Data quality assurance

Pseudonymized patient data obtained during the trial as a result of the trial procedures, as well as relevant data from the medical history of the patient, findings as they occur, and other relevant data must be reported to the sponsor by the investigator. Data must be reported in the eCRF or other media approved by the sponsor.

Different eCRF accounts are available for investigator site staff and other users (e.g., clinical research associates [CRAs], data managers, etc.). Roles and rights of the site personnel responsible for entering the clinical data into the eCRF or approving them will be defined in advance and documented on the delegation form. All data must be entered in English.

The site team and other users will be trained on the eCRF. Completion of the training to be performed by each individual is to be documented appropriately and only afterwards the individual account valid for the trial-specific database is received. eCRF completion guidelines should be provided to the investigator sites.

During the trial, all data will be reported in pseudonymized form and will be identified by the assigned patient identification code. The investigator site will keep a patient identification code list, which is only available to the investigator site staff. The eCRFs must be completed, and electronically approved, by the investigator or sub-investigator in a timely manner after the patient visits. Corrections and clarification requested by the CRA, the Data Manager or other qualified people should be resolved/answered in an adequate time period. This will be audit-trailed by the eCRF system, meaning that the name of the person who entered/updated data, and date/time are captured. The investigator must keep the eCRFs in good order and up-to-date so that they always reflect the latest observations on the patients enrolled in the trial.

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 Clinical Monitoring Plan.

The sponsor assumes accountability for actions delegated to other patients (e.g., Contract Research Organizations).

Trial monitors will perform ongoing source data verification (SDV) 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 archived by the investigator and the sponsor for a duration in accordance with the national law, but not less than 15 years after trial completion unless local regulations or institutional policies require a longer retention period. The content of the clinical trial master file must be archived for at least 25 years after the end of the clinical trial. 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.

10.1.8 Source documents

The CRA will compare source data (original or certified copy) documents to data entered in the eCRF. For this trial, 100% SDV will be performed.

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.

Source documents are original documents, data and records (e.g., hospital records, laboratory notes, evaluation checklist, pharmacy dispense records, drug accountability logs per patient, and recorded data from automated instruments, CT and MRI results, and discharge letters).

10.1.9 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 considered as the trial start date.

The sponsor 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 CRO(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.

10.1.10 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 BioNTech's publication policy, which follows the International Committee of Medical Journal Editors authorship requirements.

The sponsor or designee will prepare a final report on the trial. The investigator's right to publish or present any information on the trial, and publication procedures to be followed, will be defined in the investigator site agreement.

10.1.11 Protocol preparation and approval

This protocol has been prepared, reviewed and approved, including wet ink sign-off by the sponsor's responsible person, in accordance with the sponsor's standard operating procedures (SOP). Documentation of this process is filed in the trial master file (TMF).

10.2 Clinical laboratory tests

- The tests detailed in Table 13 will be performed according to the SoA presented in Section 1.3.
- Protocol-specific requirements for inclusion or exclusion of patients are detailed in Section 5 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 13: Protocol-required safety laboratory assessments

Laboratory assessments	Parameters			
Hematology[1]	Platelet count	RBC Indices: MCV MCHC %Reticulocytes	White blood cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
	Red blood cell (RBC) count	Hemoglobin	Hematocrit	
Coagulation factors[1]	• Activated partial thromboplastin time • Prothrombin time • International normalized ratio			
Blood chemistry[1,2]	Blood urea nitrogen (BUN) or urea[3]	Potassium	Aspartate Aminotransferase (AST)	Total bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)	Lactate dehydrogenase
	Glucose [Indicate if fasting, or nonfasting]	Calcium	Alkaline phosphatase	C-reactive protein
	Bicarbonate or carbon dioxide	Chloride	Total protein	Pre-albumin
	Phosphorus	Magnesium	Ferritin	Albumin
Routine urinalysis[1]	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)			
Endocrine tests (thyroid function tests)[1]	• TSH, free-T3 and free-T4			

Laboratory assessments	Parameters
Pregnancy test (females of childbearing potential only)[1]	• Urine human chorionic gonadotropin (hCG) • Serum β-hCG (at screening only and if a urine hCG is equivocal or positive during the remainder of the trial)
Serum autoantibody analysis[1]	• Anti-nuclear antibody • Anti-double-stranded-DNA • Circulating anti-neutrophil cytoplasmic antibody • Perinuclear anti-neutrophil cytoplasmic antibody

[1] Local laboratory testing.
[2] Time points and content of the reduced blood chemistry panel are detailed in Section 1.3.
[3] Depending on the country.
MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; T3 = triiodothyronine, T4 = thyroxine; TSH = thyroid stimulating hormone.

10.3 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, administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this 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 trial treatment.

10.3.1.1 Events meeting the AE definition

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.

Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

New conditions or worsening of pre-existing conditions detected or diagnosed after signing the ICF.

Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

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.

10.3.1.2 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 expected 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 that may 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.

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.

Disease-Related Events and/or Disease-Related Outcomes not Qualifying as AEs or SAEs are further specified in Section 8.3.7.

10.3.1.3 Treatment emergent adverse events (TEAE)

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

10.3.1.4 Suspected adverse reaction (suspected AR)

All untoward and unintended responses to an IMP related to any dose administered.

- The definition covers also medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product.
- The definition implies a reasonable possibility of a causal relationship between the event and the IMP. This means that there are facts (evidence) or arguments to suggest a causal relationship.

10.3.1.5 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

An SAE is defined as any untoward medical occurrence that, at any dose:

- Results in death
- 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.
- 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.
- 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.
- Is a congenital anomaly/birth defect.
- Other situations:
  - 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.

10.3.1.6 Suspected unexpected serious adverse reaction (SUSAR)

All suspected ARs related to an IMP (the tested drugs and comparators) that occur in this trial, and that are both unexpected and serious are “suspected unexpected serious adverse reaction,” or SUSAR. SUSARs are subject to expedited reporting.

10.3.1.7 Use of the terms “severe” and “serious”

The terms “severe” and “serious” are not synonymous. Severity refers to the intensity of an AE (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE; see Section 10.3.1.8 for guidance on the assessment of intensity; the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be assessed independently for each AE recorded on the eCRF.

SAEs must be reported by the investigator to the sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 10.3.1.12 for reporting instructions).

10.3.1.8 Recording and follow-up of AEs and/or SAEs

AE and SAE recording

The investigator needs to assess and document any AE regardless of association with the use of the trial treatment during the period of observation (from signing of ICF until 60 days after the patient receives the last dose of BNT151).

- Data pertaining to AEs will be collected during each trial visit, either based on the patient’s spontaneous description or investigator’s inquiry, or discovered in the course of examinations performed during the visit. The clinical significance of any sign or symptom needs to be evaluated by the investigator.
- Clinically significant findings need to 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 AE.
- The investigator will then record all relevant AE information in the eCRF and perform an assessment on:
  - Intensity according to CTCAE v5.0
  - Seriousness
  - Outcome
  - Causal relationship of the AE to the trial treatment
  - Any trial treatment action and/or any other action taken
- All assessments as well as AE term (diagnosis/description), start date and time of onset, end date and time need to be documented in the eCRF.
- There may be instances when copies of medical records for certain cases are requested by the sponsor. In this case, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before submission to the sponsor.
- To avoid colloquial expressions, the AE should be reported in standard medical terminology. 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. If a definitive diagnosis is not possible, the individual signs and symptoms should be recorded.

Assessment of intensity

The intensity of an AE (i.e., severity of organ toxicity) will be graded according to the NCI CTCAE v5.0. AEs that are not listed in CTCAE v5.0 should be classified according to the investigator's discretion as close as possible to CTCAE v5.0, based on the comparison with the most severe case encountered in past training and clinical experience.

The investigator will make an assessment of intensity for each AE and SAE reported during the trial and assign it to one of the following categories:

- Grade 1 - Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.
- 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 of self-care ADL. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- Grade 4 - Life-threatening consequences; urgent intervention indicated.
- Grade 5 - Death related to AE.

With regards the intensity of an AE the following needs to be documented in the eCRF:

- Initial intensity of the AE
- For each change of intensity:
  - New Grade of intensity
  - Date of change (= start of new Grade of intensity)
  - Time of change (only if relevant)

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 CTCAE criteria).

An event is defined as "serious" when it meets at least one of the predefined seriousness criteria as described in the definition of an SAE, NOT when it is rated as severe.

Actions taken by the investigator

Actions taken by the investigator as a result of an AE have to be documented.

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

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

*Note: If an increase of trial treatment dosage is intended according to the trial protocol and the dosage is kept in comparison to last administration of trial treatment, it needs to be documented as “Dose reduced.”

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
- Initiation/termination of a non-drug therapy
- Other (please specify)

Outcome

The investigator has to assess the outcome of an AE (and not the patient’s outcome) at the time of documentation based on the following criteria:

- Recovered/resolved* (= complete resolution of the AE)
- Recovering/resolving (= AEs which are improving but not yet resolved completely, e.g., decrease in an intensity grade)
- Not recovered/not resolved (= AEs which are ongoing without improving or still present when the patient deceases due to another cause)
- Recovered/resolved with sequelae* (= patient recuperated but retained pathological conditions resulting from the AE; the sequelae should be indicated)
- Fatal** (= death due to the AE)
- Unknown (e.g., in case the patient is lost to follow-up)

* Generally, an AE is defined as recovered/resolved if all symptoms have ceased, no medication for treatment of the event is taken anymore and no other measures (e.g., hospitalization) are ongoing.

If the patient has developed permanent or chronic symptoms or if the event requires long term medication(s), the AE is defined as recovered/resolved with sequelae as soon as no changes of symptoms and/or medication(s) are expected anymore.

An AE that is documented as a worsening of a medical condition already known at baseline, is defined as recovered as soon as the medical condition has returned to baseline status.

** 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”. All other AEs ongoing at the time of death will be attributed with the outcome “not recovered/not resolved”. A copy of an autopsy report should be submitted if available.

Assessment of causality

The investigator is obligated to assess the relationship between trial treatment/trial procedure 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.

It is sufficient to document the causality in the source data and eCRF as:

- Related (= there is a reasonable possibility of a causal relationship) or
- Not related (= there is no reasonable possibility of a causal relationship)

Relationship to trial treatment

The relationship or association of an AE or SAE to a trial treatment will be made by the investigator after having evaluated all accessible data and, if necessary, he/she will re-evaluate the case as new information becomes available.

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 IMPs itself should be documented as suspected ARs but not events caused by the procedure of trial treatment administration.

How the investigator should assess the relationship between anti-cancer agents used in combination with BNT151 and each occurrence of each AE/SAE will be specified by amendment.

Relationship to trial procedures

In this trial, it cannot be excluded that during the course of the trial some procedures give rise to AEs which are related to the trial procedure and not to the trial treatment. Procedure-related AEs can occur on the site of injection of the trial treatment e.g.,

redness, swelling, hematoma or itching or during or after trial-specific procedure, e.g., discomfort after blood drawing. These events have to be reported in the eCRF on Adverse Event pages as “related to trial procedure” with the causing procedure specified. The intensity of these AEs will be characterized according to the NCI CTCAE v5.0.

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 makes 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.

10.3.1.9 SAE exemptions

In general, SAEs are defined according to ICH Topic E2A (CPMP/ICH/377/95), EU Directive 2001/20/EC and ENTR/CT-3 (see Section 10.3.1.5).

In the present trial, some events are excluded from the SAE definition given in Section 10.3.1.5. The following events do not need to be reported as SAEs:

- AEs and SAEs occurring later than 60 days after the last dose of trial treatment must only be reported by the investigator to the sponsor if a relationship to trial drug or trial procedure is suspected.
- Hospitalizations for respite care will not be considered as reportable SAE.
- Hospitalizations solely for coordination of care, including hospice arrangements, will not be considered as reportable SAE.
- Hospitalizations that were necessary solely because of patient requirement for outpatient care outside of normal outpatient clinic operating hours will not be considered as reportable SAE.
- Planned hospitalizations required by the protocol (e.g., for trial drug administration or insertion of access device for trial drug administration) will not be considered as reportable SAE.
- Hospitalizations for procedures or interventions of a pre-existing condition of the patient (elective surgery = planned, non-emergency surgical procedure) will not be considered as a reportable SAE.
  - If it was planned and documented in patient record before the trial-specific patient informed consent was signed (ICF for trial participation, see Section 10.1.3), or
  - If it was scheduled during the trial when elective surgery became necessary and the patient has not experienced an AE.

Nevertheless, this kind of hospitalization should be avoided during trial treatment.

- The progression of underlying disease (e.g., new metastases) during trial participation is not considered as AE. 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 will have to be documented as AEs and reported as SAEs if applicable.
- Routine treatment or monitoring of the underlying disease not associated with any deterioration in the patient's condition.

10.3.1.10 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 eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be documented as AE.
- If vomiting results in severe dehydration, both events should be documented as AEs separately.

Abnormal laboratory results and vital signs values:

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

- If a laboratory/vital signs abnormality is a sign of a disease or syndrome, the laboratory/vital signs abnormality is clinically significant and only the diagnosis of the causing disease or syndrome needs to be documented as AE.
- If a laboratory/vital signs abnormality results in specific symptoms but no diagnosis of a disease or syndrome can be made, the laboratory/vital signs abnormality is clinically significant and only the symptoms need to be documented as AEs.
- If a laboratory/vital signs abnormality 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, the laboratory/vital signs abnormality is clinically significant and must be documented as AE.

AEs associated with an overdose or error in drug administration:

For definition and treatment of overdose, please refer to Section 8.4.

An overdose or incorrect administration of a drug is not itself an AE, but it may result in an AE. All AEs associated with an overdose or incorrect administration should be documented as AE in the eCRF and reported as SAE if applicable.

10.3.1.11 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 (contacts given in Section 10.3.1.12) with a copy of any post mortem findings including histopathology.
- 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 10.3.1.12 within 24 hours of receipt of the information.

10.3.1.12 Reporting of SAEs

All SAEs which occur in a patient during the observation period (defined in Section 10.3.1.5), whether considered to be associated with trial medication or not, must be reported by the investigator **to the sponsor within 24 hours following knowledge of the event**.

All SAEs occurring after the end of the period of observation only have to be reported to the sponsor if the investigator suspects a relationship to trial medication or procedure.

SAE reporting to sponsor using a Paper (SAE Report) Form

For the period of observation please refer to Section 8.3.1.

The investigator needs to complete the paper Serious Adverse Event Form which must be sent to the sponsor via one of the following reporting lines:

- Safety Report Fax No.: [redacted]
- Safety Report E-Mail Address: [redacted]

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 patient (patient number)
- A suspected medicinal product
- An identifiable reporting source (investigator/trial site identification)
- An event or outcome that can be identified as serious

SAE follow-up information should be sent to the sponsor (indicating that this is a “follow-up” report using the SAE Form or the Additional Information and Follow-Up Form) without delay as described above and accompanied by appropriate anonymous supporting documentation (e.g., discharge letters, medical reports or death certificates), until a final

outcome and date are available. All confidential information (name, address, full day of birth) needs to be blackened before sending. In addition to a medical record, the investigator should complete an Additional Information and Follow Up Form, which contains the SAE term and patient number.

A copy of the submitted SAE report must be retained on file by the investigator. If explicitly required according to national legislation, the investigator must submit copies of the SAEs to the IRB/IEC or authority and retain documentation of these submissions in the Investigator's site file (ISF).

In case an investigator or any other trial team member has questions on safety reporting the sponsor may be contacted via:

- E-Mail: [redacted]

For medical questions, the medical monitor for this trial should be contacted.

10.4 Contraceptive guidance and collection of pregnancy information

Definition of reproductive potential and measures of contraception for BNT151 are detailed below. Further guidance for other trial treatment agents should be according to the authorized product information (for approved concomitant medications).

10.4.1 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 BNT151.

Female patients of reproductive potential must agree to use adequate contraception during and for 6 months after the last BNT151 administration. Adequate contraception is defined as highly effective methods of contraception (Table 14). 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 14: 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 BNT151, 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 Clinical Trial Facilitation Group (CTFG)-meeting in Rome 2014' (CTFG 2014).

10.4.2 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 BNT151.

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 BNT151. 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 BNT151.

10.4.3 Collection of pregnancy information

Pregnancy information will only be collected after obtaining written informed consent from the pregnant female patient (or if a male patients' partner becomes pregnant, written informed consent from both).

Pregnancy information will be collected for pregnancies that occurred after the start of trial treatment and until 90 days after the last dose for pregnant patients (or until 28 days after the last dosing of the male patient for pregnant female partners).

The initial and follow-up information must be documented on the paper-based Pregnancy Reporting Form and submitted to the sponsor within 24 h of learning of a patient's pregnancy/partner's pregnancy. The completed form needs to be sent to the sponsor using either the Safety Report Fax number: [redacted] or the e-mail address: [redacted] Completed pregnancy forms must 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 patient/patient'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 IMP. 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 treatment by the investigator will be reported to the sponsor. While the Investigator is not obligated to actively seek this information in former trial patients, he or she may learn of an SAE through spontaneous reporting.

10.5 Genetics

See Section 8.7.

10.6 Liver safety: Suggested actions and follow-up assessments

Potential cases of drug induced liver injury (DILI)

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed "tolerators", while those who show transient liver injury, but adapt are termed "adaptors". In some cases, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Patients who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are an "adaptor" or are "susceptible."

LFTs are not required as a routine safety monitoring procedure for all participants in this trial. However, should an investigator deem it necessary to assess LFTs because a participant present with clinical signs/symptoms, such LFT results should be managed and followed as described below.

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (i.e., AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential

DILI. Therefore, abnormal elevations in either AST or ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the patient's individual baseline values and underlying conditions. Patients who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST or ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

For patients with baseline AST or ALT or TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN or if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The patient should return to the investigator site and be evaluated as soon as possible, preferably within 48 h from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin (PT)/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a co-formulated product in prescription or over the counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (e.g., biliary tract) and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if

no other reason for the LFT abnormalities has yet been found. Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

10.7 Investigators and trial administrative structure

10.7.1 Investigators and trial site personnel

There must be an investigator at each trial site.

Note: Country-specific criteria for Germany: There must be an investigator and deputy to the investigator at each trial site.

If the trial is conducted by a team of individuals at the trial site, the investigator leading and responsible for the team is called the principal investigator.

All persons assigned responsibility as principal investigator must sign a declaration of their responsibilities and their agreement to this protocol before any trial-related procedure is performed.

Curriculum vitae and/or other relevant documents confirming the current qualification of the investigators must be provided to the sponsor. This should include any previous training in the principles of GCP, experience obtained from work with clinical trials, and experience with patient care.

Documentation of all involved investigators must be maintained according to GCP and applicable regulatory requirements.

10.7.2 Trial site personnel assigned trial-related duties

The principal investigator may define appropriately qualified personnel at a trial site to perform significant trial-related procedures and/or to make trial-related decisions under his/her supervision. In this case, the principal investigator must maintain a signed list of the persons to whom they delegate significant trial-related duties/responsibilities; the delegated trial-related duties/responsibilities must be specified in the list.

When personnel or responsibility changes are made, the principal investigator must ensure that the relevant documentation is updated before any trial-related activities are performed.

Documentation of all involved trial site personnel performing significant trial-related procedures and/or making trial-related decisions must be maintained according to GCP and applicable regulatory requirements.

10.7.3 Contract research organizations

Documentation of all involved CROs must be maintained according to GCP and applicable regulatory requirements. This includes documentation of any delegation of responsibilities to CROs.

10.7.4 The sponsor and sponsor's personnel

The trial sponsor listed on the title page accepts the responsibilities of the sponsor according to GCP and applicable regulatory requirements.

The sponsor must designate appropriately qualified personnel to advise on trial-related topics. The trial site will be provided with contact details for these personnel before any trial-related procedure is performed.

A list of key sponsor personnel involved in the preparation of this protocol and the conduct of the trial, including their full names, titles, roles, and responsibilities, must be maintained.

10.8 Country-specific requirements

Country-specific requirements will be met. For information regarding country-specific requirements, refer to Appendix 2: Country-specific information.

10.9 Other standard abbreviations and definitions

For trial-specific abbreviations, see the list of trial-specific abbreviations.

For definitions related to safety, see Section 10.3.

Abbreviation	Explanation
AE	Adverse Event
CRA	Clinical research associate
CRO	Clinical research organization
CTP	Clinical trial protocol
GCP	Good Clinical Practice
h	Hour(s)
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Conference on Harmonization (of technical requirements for registration of pharmaceuticals for human use)
IEC	Independent ethics committee
IMP	Investigational medicinal product
IRB	Institutional review board
ISF	Investigator's site file
MedDRA®	Medical Dictionary for Regulatory Activities
min	Minute(s)
ms	Millisecond
PT	Preferred Term
SAE	Serious adverse event
SoA	Schedule of activities
SRC	Safety Review Committee
SUSAR	Suspected unexpected serious adverse reaction

Abbreviation	Explanation
TEAE	Treatment emergent adverse event
TMF	Trial master file
US	United States (of America)

10.10 Protocol amendments

10.10.1 Update to protocol version 8.0 (from version 7.0)

Detailed description of changes

See the table for a summary of the reasons for major changes compared to the previous version. Inserted text is red; deleted text is struck out.

Section	Changes:	Reason for change
Title page	Sponsor's responsible person updated: Goran Babić, MD, Director Clinical Development ~~Hariz Hassan, MD, Senior Director Clinical Development~~	Update
10.3.1.12 Reporting of SAEs and 10.4.3	Contact information updated: • Safety Report Fax No.: [redacted] • Safety Report E-Mail Address: [redacted]	Updated contact information for SAE reporting

10.10.2 Update to protocol version 7.0 (from version 6.0)

Amendment rationale

This update describes changes made in order to add Biomarker Cohort details, and to improve clarity of the SOAs.

A comparison of every new sponsor approved protocol version with the next approved version is filed together with the protocol in the TMF.

Detailed description of changes

See the table for a summary of the reasons for major changes compared to the previous version.

Section	Reason for change
1.3 Schedule of activities	Tables restructured. Cohorts with and without preconditioning now combined in the same tables. Former Cycle 1 of the "with pre-conditioning" cohort renamed "pre-conditioning cycle", and subsequent cycle numbers now aligned between the different cohorts Sampling points added
3 Objectives and endpoints	Inclusion of exploratory endpoints: potentially predictive biomarkers, and incidence of ADAs
4.1.4 Adaptive trial design elements	Update of cycle numbering in alignment with change to SoAs Clarification of C1D1 dose
4.2.1 Option of monotherapy dose escalation with pre-conditioning	Explanation of rationale behind pre-conditioning dose

5 Inclusion criteria	Criterion 3 updated from "histologically confirmed solid tumor that is metastatic (Stage IV) or unresectable…" to "histologically confirmed solid tumor that is metastatic or of advanced unresectable stage…"
6.4 Trial treatment compliance	Fasting status at treatment will be recorded
6.4.1 Concomitant medication and non-drug therapies	Instruction that patients should abstain from taking nonprescription drugs updated to recommendation
8.8 Biomarkers	Details added regarding Biomarker Cohort: Biomarker and related CRF data (e.g. clinical outcome) will be monitored regularly during the trial. Clarification of tumor tissue sampling Definition of sequencing procedure
9.3 Analysis sets	Definition of DLT evaluable set updated to reflect change in cycle nomenclature for "with pre-conditioning" cohort
10.1.3.1 Withdrawal from the use of biomarker samples	Specification of maximum time limit for storage of samples.
10.2 Clinical laboratory tests	Addition of serum antibody analysis to table of protocol-required safety laboratory assessments
12.5 Appendix 5	Previous administration of COVID-19 vaccine should be documented on the prior and concomitant medication form

10.10.3 Update to protocol version 6.0 (from version 5.0)

Amendment rationale

This update describes changes made in order to add Biomarker Cohort details.

Detailed description of changes

Editorial changes are made. Those are not listed below.

Changed text **(inserted text is blue; deleted text is red/struck out)** **Where appropriate, a simple description is provided.**	**Rationale**
Sections 1.1 Trial synopsis and 3 Objectives and endpoints: **Exploratory objectives:** Identify exploratory PD markers. • Changes in selected cytokines and other soluble innate and adaptive immune system 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 and tumor microenvironment analysis ~~of immune cells in peripheral blood, absolute and relative changes compared to baseline in tissues and/or PBMCs~~).	To simplify the exploratory endpoints.
Sections 1.1 Trial synopsis and 4.1 Overall design:	To include Biomarker Cohort.

Changed text **(inserted text is blue; deleted text is red/struck out)** **Where appropriate, a simple description is provided.**	**Rationale**
The Part 1 of the trial also plans to implement a dedicated biomarker cohort in BNT151 monotherapy: • The Biomarker Cohort will recruit patients at selected sites in the US only. The objective of the cohort is to observe PD activity and drug-induced changes in the blood and tumor. The gathered data are expected to inform on the drugs mechanism of action and further refine selection of monotherapy dose. This cohort will only enroll patients that are capable and willing to donate serial biopsies. Patients will only be dosed at dose levels at the RP2D level or lower, which have been cleared safe in the monotherapy dose escalation, and where pharmacodynamics activity is expected. Approximately, 20 patients will be enrolled in this cohort. • Part 2 will start once Part 1 monotherapy dose escalation is completed (exception: Biomarker Cohort in Part 1 can continue enrolling as long as a BNT151 monotherapy dose is established in the dose escalation). **Population** In addition, approximately 20 patients will be enrolled in the Biomarker Cohort	
Sections 1.1 Trial synopsis and 5.1 Inclusion criteria: 21. At selected US sites only: at enrollment patients must agree to have one pre-dose biopsy and lesion that is deemed accessible by the investigator. If possible, at least one on-treatment biopsy should be accessible from same tumor lesion.	Inclusion criterion added specific to Biomarker Cohort.
Sections 1.1 Trial synopsis and 9.1 Statistical hypotheses: **Statistics** The primary objectives of this trial Part 1 are to assess the safety profile and to identify the MTD and/or ~~recommended RP2D~~ RP2D. The Biomarker Cohort examines the exploratory markers for the mechanism of action in the tumor and periphery.	Details added to include Biomarker Cohort.
Sections 1.1 Trial synopsis and 9.2 Sample size determination: In addition, approximately 20 patients will be enrolled in the Biomarker Cohort with paired biopsies. This sample size is based on the proportion of patients who have achieved at least 50% increase from baseline in lymphocytes (total lymphocytes, CD4+, CD8+, T_{regs}, and NK cells) upon treatment with BNT151. Twenty patients are estimated to have >80% chance to rule out a proportion of 10% if the true proportion is 40% at a 2-sided significance level of 0.05.	Details added to include Biomarker Cohort.
Sections 1.2 Schema (graphical representation of the trial):	Updated to include Biomarker Cohort.
Section 1.3 Schedule of activities: Table 5: Schedule of activities and procedures – Part 1: Biomarker Cohort without pre-conditioning Table 6: Schedule of PK, exploratory PD, cytokines/chemokines and immunogenicity and biopsies for Biomarker Cohort: Monotherapy without pre-conditioning in selected US sites only Table 7: Schedule of activities and procedures – Part 1: Biomarker Cohort with pre-conditioning Table 8: Schedule of PK, exploratory PD, cytokines/chemokines and immunogenicity and biopsies for Biomarker Cohort: Monotherapy with	Updated to include tables for Biomarker Cohort.

Changed text **(inserted text is blue; deleted text is red/struck out)** **Where appropriate, a simple description is provided.**	**Rationale**
pre-conditioning in selected US sites only	
Sections 2.1 Trial rationale and 4.2.1.2 Biomarker Cohort: mRNA underlies an innovative and sophisticated drug platform to deliver a protein-based therapy but, ongoing data do potentially suggest an occurrence of interpatient variability especially in translation that can affect correct determination of effective dose, as well as establishing a confident safety profile of the product. Therefore, the implementation of the Biomarker Cohort to further elucidate the differences and understand the variabilities is justified. Dose levels that have been cleared by the SRC in the dose escalation will be investigated in the monotherapy Biomarker Cohort, in order to further investigate the mode of action of BNT151, to allow optimization of future combinations with other anti-cancer agents, and to assess the interpatient variability.	Added rationale to include Biomarker Cohort.
Section 4.1.2.1 Biomarker Cohort: For the Biomarker Cohort at selected US sites only: at enrollment patients must agree to have one pre-dose biopsy and lesion that is deemed accessible by the investigator. If possible, at least one on-treatment biopsy (preferred C2D5-12) should be accessible from same tumor lesion. Patients will be screened within 3 weeks prior to the beginning of treatment. Patients will be treated with treatment cycles lasting 21 days until progression, or treatment discontinuation of BNT151 due to other factors. Following discontinuation, and a safety follow-up period of 60 days, patients will be followed up for survival every 12 weeks until death.	Updated trial design to include Biomarker Cohort information.
Section 4.1.5 Planned number of patients: In Part 1, the sample size will be up to 54 DLT-evaluable patients depending on the number of DLTs which may occur, with the possible enrollment of up to 10 additional patients if efficacy is seen in a specific tumor type. The Biomarker Cohort will enroll approximately 20 patients.	Updated planned number of patients to include Biomarker Cohort information
Section 8.5 Pharmacokinetics: Lipid PK samples will be drawn to enable potential further exploratory PK assessments. Refer to Table 2 and Table 6 (related to Biomarker Cohort), or in case of pre-conditioning Table 4 and Table 8 (related to the Biomarker Cohort). Samples may be stored for up to 5 years (or according to local regulations) following the patient's last visit in the trial at a facility selected by the sponsor to enable analysis for lipid PK.	Updated to include reference to Tables 5 and 6.
Section 8.6 Exploratory Pharmacodynamics: Details described in Section 8.8.2.	Updated to include Biomarker Cohort.
Section 8.7 Genetics: Genetic as well as non-genetic analyses may be part of the biomarker investigations in this trial. Blood and tissue samples will only be used for genetic analysis if the patients have provided informed consent for this genetic analysis (see Section 10.1.3). The genetic analyses comprise analysis of biomarker variants thought to play a role in the mechanism of action of BNT151, especially within the tumor immune microenvironment. All data generated using the samples, will be handled in accordance with applicable laws and regulations; this includes requirements applicable for data protection, for sample shipment, and a potential withdrawal of consent. Samples will be analyzed according to the Laboratory Manual.	Updated to include Biomarker Cohort.

Changed text (inserted text is blue; deleted text is red/struck out) Where appropriate, a simple description is provided.	Rationale
Section 8.8 Biomarkers: See the SoA in Section 1.3, Table 5, and Table 6 for planned time points of sample collection. Sample handling and storage – details on the collection, processing, shipment and storage of samples will be provided in separate documents (e.g., Laboratory Manual). Samples may be stored for a maximum of 5 years (or according to local regulations) following the end of the trial at a facility selected by the sponsor to enable further analyses. Reporting – Some of the results of biomarker investigations may be reported separately (e.g., in a biomarker report). **Section 8.8.1 Tumor tissue** Tumor tissue collected at baseline or on-treatment or archival FFPE tumor blocks will be analyzed for biomarkers confirming and/or elucidating the mode of action, and to explore potential predictive factors as well as identify possible future combination therapies. If feasible, all patients should provide a fresh biopsy (core needle biopsies preferred, aspirates are not acceptable) performed at screening or before the first dose and an on-treatment biopsy from the same lesion within the first two cycles, preferably in the time window C2D5-12 (see Table 6). For patients enrolled in the Biomarker Cohort the screening biopsy is required and the on-treatment biopsy is required if feasible. An additional biopsy upon treatment discontinuation in the trial is also requested if feasible. For each biopsy the trial site should provide a formalin-fixed paraffin embedded (FFPE) block (see Laboratory Manual) and only at selected US sites a fresh core for isolation of tumor infiltrating lymphocytes (TILs), see the Laboratory Manual for instructions. In case the site and the patients are willing to provide biopsies on-treatment but cannot provide fresh biopsy during screening, archived material is allowed to be used as a screening sample (not allowed for the Biomarker Cohort). **Section 8.8.2 Pharmacodynamic biomarkers** Pharmacodynamic biomarkers will be evaluated in samples collected before and during treatment in order to determine the impact of BNT151 in monotherapy or in combination therapy on these biomarkers. Blood samples for PD biomarkers, which might act as anti-tumor, and safety indicators of activity of BNT151 monotherapy and in combination with SoC, will be collected as defined in detail in the SoA (Section 1.3). Relevant details on sample collection and handling will be documented in the Laboratory Manual. Pharmacodynamic biomarkers in blood may include, but will not be limited to: absolute lymphocyte count, immune cell populations, e.g., T cells, regulatory T cells (T_{regs}), B cells and NK cells, as well as sCD25, and cytokines/chemokines as assessed by Flow cytometry and ELISA. The list of planned assessments may be subject to change dependent on the results obtained. All samples will be analyzed centrally. For details, please see the Laboratory Manual. **Section 8.8.3 Screening for predictive biomarkers** For consenting patients, candidate biomarkers in archived or fresh baseline tumor tissue will be evaluated for correlation with response to treatment to identify possible predictive biomarkers. Predictive biomarkers may include but are not limited to presence of	Updated to include Biomarker Cohort.

Changed text **(inserted text is blue; deleted text is red/struck out)** **Where appropriate, a simple description is provided.**	**Rationale**
specific immune cell types and their respective abundance within the tumor immune microenvironment as may be assessed by immunohistofluorescence, immunohistochemistry, and/or gene expression analysis (e.g., RNAseq) of archival or freshly obtained baseline FFPE biopsies. Predictive biomarker screening may also include specific tumor characteristics such as tumor mutational burden or tumor signatures assessed by Next Generation Sequencing. For withdrawal of consent from the use of R&D and biomarker samples refer to Section 10.1.3.1. **Section 8.8.4 Additional biomarkers** In addition to the biomarkers described above, for consenting patients, further biomarkers related to, e.g., the mode of action or the safety of the trial intervention and similar drugs may be investigated by using longitudinal blood samples or serial biopsies. These biomarkers in serial biopsies may be specific immune cell types or specific tumor signatures as assessed by immunohistofluorescence, immunohistochemistry, and/or gene expression analysis (e.g., RNAseq). The same applies to further biomarkers deemed relevant to cancer and associated health problems. These investigations may include e.g., diagnostic, safety, PD, monitoring, or potentially predictive biomarkers. For withdrawal of consent from the use of R&D and biomarker samples refer to Section 10.1.3.1.	
Section 8.9 Supplementary R&D assessments: Blood sampling for ~~supplementary R&D assessments of~~ immunophenotyping of peripheral immune cells will be (only) mandatory for consenting patients in the Biomarker Cohort as well as for trial sites ~~in Germany~~ where logistically manageable. For all other sites, the sampling is optional and should only be collected if logistically manageable. The blood samples will be collected according to Table 2, Table 4 (in case of pre-conditioning), and Table 6 (for Biomarker Cohort). For withdrawal of consent from the use of R&D and biomarker samples refer to Section 10.1.3.1.	Updated to include reference to Table 6: Biomarker Cohort.
Section 8.11 Blood collection: Only for the Biomarker Cohort, a total volume of 820 mL of blood will be collected for immunophenotyping, cytokine analysis, and PK.	Updated to include blood volume collected for Biomarker Cohort.
Section 8.14 Collection of demographic and other baseline characteristics: Section 8.14.1 Demographic data At screening, the demographic data and baseline characteristics will be recorded for all trial patients. Section 8.14.2 Medical history Medical history information will be recorded for at the times given in the SoA (Section 1.3).	Added missing sections which were part of the SoA.
Section 9.4.4 Exploratory endpoints: Exploratory endpoints include analysis of PK parameters (including but not to be limited to AUC, C_{max}, T_{max}, and $t_{1/2}$), and changes of peripheral (cytokines or other soluble proteins or cell types) and intratumoral ~~the preliminary assessment of~~ biomarkers (immune cells, or tumor signatures) that might act as PD, anti-tumor, and safety indicators ~~(in terms of changes in selected cytokines and other activation markers compared to baseline and changes in systemic and intra-tumoral immune response [e.g., immunophenotyping of immune cells in peripheral blood, absolute and relative changes compared to baseline in tissues and/or PBMCs] in blood and tumor tissue compared to baseline)~~.	Reworded exploratory endpoint.

Changed text (inserted text is blue; deleted text is red/struck out) Where appropriate, a simple description is provided.	Rationale
Section 10.1.3 Informed consent process: Patients who are re-screened (see Section 5.4) must sign and date a new ICF. A separate Biomarker Cohort ICF will also include genetics that will need to be signed and dated by consenting patients.	Updated to include Biomarker Cohort.

10.10.4 Update to protocol version 5.0 (from version 4.0)

Amendment rationale

This update describes changes made in response to feedback from various health authorities from US, UK, and Spain.

Detailed description of changes

Editorial changes are made. Those are not listed below.

Changed text (inserted text is blue; deleted text is red/struck out) Where appropriate, a simple description is provided.	Rationale
Sections 1.1 Trial Synopsis and 3 Objectives and endpoints: (Part 1: Dose escalation only)	Added clarification that the objectives and endpoints defined are for Part 1 of the trial.
Sections 1.1 Trial Synopsis and 3 Objectives and endpoints:<br~~The TTP is defined as the time from first dose of IMP to objective tumor progression (PD per RECIST 1.1).~~	TTP is similar to PFS but not an equally useful efficacy measurement as PFS. Hence, deleted.
Sections 1.1 Trial Synopsis, 1.3 Schedule of activities (tables 1, 3: footnote#11), 4.1 Overall design and 8.1.1 anti-tumor activity assessment<br~~Regardless of whether patients start new anti-cancer therapy~~	Deleted sentence, as we won't use the tumor assessment on new anti-cancer therapy.
Sections 1.1 Trial Synopsis and 5.1 Inclusion criteria: Inclusion criterion #13 Hemoglobin (Hgb) ≥9.0 g/dL ~~(may not transfuse or use erythropoietin to obtain this Hgb level in the past 7 days)~~.	After eligibility has been confirmed, inclusion/exclusion criteria are not taken into account anymore.
Sections 1.1 Trial Synopsis and 5.2 Exclusion criteria: Inclusion criterion #15 15. Glomerular filtration rate (GFR) ≥45 mL/min/1.73 m² –According to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, expressed as a single equation: GFR = 141 * min(Scr/κ,1)α ×* max(Scr/κ, 1)-1.209 ×* 0.993Age ×* 1.018 [if female] ×* 1.159 [if black] Scr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.	Heidelberg Ethics Committee comment: The use of the MDRD formula for creatinine values, which have been measured with a non-standardised assay, is foreseen. Such assays are no longer standard. Instead of this, the CKD-EPI formula should be used, which has generally become recognised as standard in the meantime.

Changed text **(inserted text is blue; deleted text is red/struck out)** **Where appropriate, a simple description is provided.**	**Rationale**
– For creatinine assays using methods traceable to isotope dilution mass spectrometry (IDMS) assigned National Institute of Standards and Technology (NIST) certified reference materials (Levey et al. 2009). – ~~GFR ≥45 mL/min/1.73 m² – according to the abbreviated MDRD equation:~~ = ~~GFR = 186 × (Screatinin-1.154) × (age-0.203)~~ ~~(where Screatinin, the serum creatinine level, is expressed in mg/dL; multiply it by 0.742 if the patient is female; multiply it by 1.212, if the patient is African-American [Levey et al. 1999]).~~	
Section 1.3 Schedule of activities (Tables 1 and 3): 29 Cycle 2 dose should not be given during DLT observation period, which lasts for 21 days.	A clarification added as footnote #29, to avoid administration of the second dose while the DLT period is still ongoing.
Sections 1.3 Schedule of activities (Tables 1 and 3) and 8.1.2 Survival follow-up: Survival follow-up starts 12 weeks after all other trial visits have been completed.	Survival follow-up definition added.
Sections 1.3 Schedule of activities (Tables 1 and 3; footnote#28): If feasible, patients ~~must~~ should provide a fresh ~~FFPE~~ biopsy (aspirates are not acceptable) performed at screening and treatment discontinuation in the trial. Further serial biopsy during treatment and/or at progression will be performed in the same patients if feasible. The trial site should either provide FFPE (block/~~curls~~ slides) or provide fresh formalin fixed tumor biopsy for sponsor processing into FFPE. In case the site and the patients are willing to provide biopsies on-treatment but cannot provide fresh biopsy during screening, archived material is allowed to be used as a screening sample.	Clarification added.
Sections 1.1 Trial synopsis and 6.1 Trial treatment administered: In Part 1, BNT151 will be administered IV on Day 1 of each 3-week treatment cycle (21 days) after all required procedures and assessments before administration have been completed. Once eligibility is confirmed, administration of BNT151 can be delayed for up to 7 days unless otherwise approved by the sponsor medical monitor	To avoid protocol deviations a clarification added that C1D1 may also be postponed for 7 days.
Section 8.5 Pharmacokinetics: Samples may be stored for up to 5 years (or according to local regulations) following the patient's last visit in the trial at a facility selected by the sponsor to enable analysis for lipid PK.	Missing information added
Section 8.6 Exploratory pharmacodynamics: Relevant details on sample collection and handling will be documented in a suitable Laboratory Manual.	Correction made

Changed text **(inserted text is blue; deleted text is red/struck out)** **Where appropriate, a simple description is provided.**	**Rationale**
Exploratory PD markers will include, but will not be limited to: absolute lymphocyte count, immune cell populations e.g., T cells, T_{regs}, B cells and NK cells, as well as sCD25, and cytokines / chemokines. The list of planned assessments may change, i.e., listed assessments maybe deleted or new assessments added, depending on the results obtained. ~~Exploratory PD markers include absolute lymphocyte count, immune cell populations such as e.g. T cells, Tregs, B cells and NK cells, as well as (sCD25, and cytokines/chemokines.~~ If feasible, patients should provide a fresh biopsy (aspirates are not acceptable) performed at screening and treatment discontinuation in the trial. Further serial biopsy during treatment and/or at progression will be performed in the same patients if feasible. The trial site should either provide FFPE (block/slides) or provide fresh formalin-fixed tumor biopsy for sponsor processing into FFPE. In case the site and the patients are willing to provide biopsies on-treatment but cannot provide fresh biopsy during screening, archived material is allowed to be used as a screening sample. The exploratory PD biomarker data generated used in support of the defined clinical trial objectives will be reported in suitable biomarker reports and reported in accordance with the requirements of applicable regulations and laws.	
Section 8.10 Immunogenicity assessments Blood samples for immunogenicity analysis will be collected and handled as outlined in the Laboratory Manual. They will be analyzed centrally and batch wise.	Further clarification added.
Section 9.3 Analysis set: **Treated set** The treated set is defined as all patients who received IMP (i.e., at least one dose of BNT151). ~~Modified intent-to-treat: The modified intent-to-treat (mITT) set is defined as all patients who are assigned to IMP and have a baseline and at least one on-treatment / post-treatment tumor response assessment.~~ ~~This analysis set may only be used in Part 2 of the trial.~~ **Efficacy evaluable set** The efficacy evaluable set is defined as all patients who are assigned to IMP and have a baseline and at least one on-treatment/post-treatment tumor response assessment. This analysis set may only be used in Part 2 of the trial. ~~Per Protocol~~ ~~The per protocol set (PPS) is defined as all patients who received IMP and fulfill the following criteria:~~ • ~~The absence of any important protocol deviations that could affect the primary efficacy analysis~~ • ~~The completion of a minimal exposure to the treatment of 1 cycle of the IMP~~ • ~~Availability of baseline and at least one on-treatment / post-treatment tumor assessment~~ ~~Important deviations will lead to an exclusion of patients from the PPS and will be agreed at the data review meeting prior to database snapshot for the primary analysis. Protocol deviations that may be considered important will be specified in the statistical analysis plan (SAP).~~	Updated analysis sets definition for clarity.

Changed text (inserted text is blue; deleted text is red/struck out) Where appropriate, a simple description is provided.	Rationale
~~This analysis set may only be used in Part 2 of the trial~~.	
Section 12.3: Appendix 3: Management recommendations in case of a potential cytokine release syndrome (CRS)	Toxicity management plan added as per German Ethics Committee request.
Section 12.4: Appendix 4: Risk-benefit assessment of COVID-19 vaccination in BNT151 01 trial	Added as per MHRA guidance.
Section 12.5: Appendix 5: COVID-19 vaccination in BNT151-01 trial during the pandemic	Added as requested by investigators.

10.11 Data collection and management

The trial documentation must be adequate for the reconstruction of the trial.

10.11.1 Case report forms (CRFs)

CRFs will be completed through use of an electronic data capture (EDC) system. Different eCRF accounts are available for Investigator site staff and other users (e.g., CRAs, Data Managers, etc.). Roles and rights of the site personnel responsible for entering the clinical data into the eCRF or approving them will be defined in advance and documented on the delegation form. Trial site personnel and other users will receive training and have access to a manual for appropriate eCRF completion (eCRF completion guidelines).

All eCRFs should be completed by designated, trained trial site personnel. eCRFs should be reviewed, verified, and then electronically signed and dated by the investigator or a designee. All data must be entered in English.

At the end of the trial, the investigator will receive trial subject data for his/her trial site in a readable format that must be kept with the trial records. Acknowledgement of receipt and readability of the trial subject data will be required.

10.11.2 Data management

The sponsor or designee is responsible for the data management of this trial. Data Management will be performed in accordance to the respective data management plan (DMP).
Data management is responsible for eCRF design and development, data imports from external data sources (e.g., central laboratory), data reconciliations, data cleaning, data coding, data exports and database lock.

eCRF design and development
The eCRF is set up in accordance to the SoA, reviewed, and tested via user acceptance test before it is pushed to production. Different roles/accounts with different access rights will be set up during this process.

Data Cleaning
Data Cleaning includes quality checking the data for completeness and consistency, in accordance with an edit check specifications document, via programmed or manual review checks. In case of discrepancies, queries will be generated accordingly in the eCRF as

appropriate. Additional reviews by the qualified team (e.g., medical review, SAE reconciliation, etc.) may also lead to queries. All discrepancies and queries need to be resolved prior to database lock.

Data Coding
In order to code medical conditions, AEs and non-drug therapies, the MedDRA® will be used throughout the trial.

In order to code medications, the World Health Organization Drug Dictionary (WHO-DD) will be used with product group/level codes assigned according to the anatomical, therapeutic and chemical classification system.

At least before database lock, MedDRA® and WHO-DD will be updated to the most recent version and coding will be re-checked, reviewed, and approved by the sponsor representative.

Database Lock
Prerequisite for database lock is that all required data are entered in the eCRF, queries are addressed and closed appropriately, all terms are coded, all external data is imported/reconciled, pages are verified/re-verified, and upon resolution of all issues, principal investigator signoff/approval of eCRF pages is obtained.

10.11.3 Investigator's Site File (ISF) and the Trial Master File (TMF)

The principal investigator is responsible for the filing of all essential documents in an ISF. The sponsor is responsible for the timely filing of all essential documents in the TMF. As applicable, these files must be available at monitoring visits and during audits or regulatory inspections.

After trial completion, the principal investigator must ensure that all source data/documentation related to the trial is recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification. The principal investigator must take measures to prevent accidental or premature destruction of these documents.

The principal investigator must keep the ISF, the source data/documentation arising from the trial according to the prescribed record retention period in the country and/or according to the hospital/investigational site's policy, but at least until informed by the sponsor that the trial-related records are no longer required.

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12 APPENDICES

12.1 Appendix 1: 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 7.1). 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 1.1. 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 IMP therapy if investigators consider that patients continue to benefit from treatment.

Evaluation of overall response

For the overall response based on RECIST 1.1, 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. 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 1.1). 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 15 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 15: 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[1]	Complete response	No	Complete response
Complete response	Not evaluable[2]	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)[2]	No	Partial response
Stable disease	Non-progressive disease and not evaluable (or no non-target lesion)[2]	No	Stable disease
Not all evaluated	Non-progressive disease	No	Not evaluable
No target lesion[1]	Not all evaluated	No	Not evaluable
No target lesion[1]	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[1]	Unequivocal progressive disease	Yes/No	Progressive disease
No target lesion[1]	Any	Yes	Progressive disease

[1] Defined as no target lesion at baseline.
[2] Not evaluable is defined as when either no or only a subset of lesion measurements are made at an assessment.

12.2 Appendix 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 anti-HCV, antibody against HIV-1 and -2 (anti-HIV 1/2).
- There must be an investigator and deputy to the investigator at each trial site.

12.3 Appendix 3: Management recommendations in case of a potential 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 NCI CTCAE v5.0 as shown in Table 16.

Table 16: CRS grading per NCI CTCAE v5.0

Grading system	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
NCI 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 is a disorder characterized by fever, tachypnea, headache, tachycardia, hypotension, rash, and/or hypoxia caused by the release of cytokines.

CRS = cytokine release syndrome; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; FiO2 = fraction of inspired oxygen.

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 17 (Lee et al. 2019).

Table 17: 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 lowflow- 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)

[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.

BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; CRS = cytokine release syndrome.

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

For the management of CRS, the following guidelines should apply (Table 18):

Table 18: Guidelines for management of cytokine release syndrome

ASTCT CRS Grade	Management
Grade 1	• Antipyretics and IV hydration • Diagnostic work-up to rule out infection • Consider growth factors and antibiotics if neutropenic
Grade 2	• Supportive care as in Grade 1 • IV 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 IV q6h or its equivalent of methylprednisolone
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

ASTCT = American Society for Transplantation and Cellular Therapy (previously known as: ASBMT, American Society for Bone Marrow Transplant); CRS = cytokine release syndrome; ICU = intensive care unit; IV = intravenous; q6h = every 6 hours.

Source: Neelapu 2019.

12.4 Appendix 4: Risk-benefit assessment of COVID-19 vaccination in BNT151-01 trial

BNT151 is a single stranded, pharmacologically optimized, 5′-capped messenger RNA coding for an IL-2/serum albumin fusion construct. IL-2 is a key cytokine in T-cell homeostasis and pivotal for the differentiation, proliferation, survival and effector functions of T cells (Bamford et al. 1994, Blattman et al. 2003, Gillis and Smith 1977, Kamimura and Bevan 2007). BNT151 may also stimulate other cells of the immune system (e.g., NK cells). 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 BNT151.

At this time, there are three COVID-19 vaccines authorized and recommended in the United States: The Pfizer-BioNTech, Moderna, and Johnson & Johnson/Janssen vaccines. These vaccines are described on the US centers for disease control and prevention (CDC)'s vaccine page. In the EU, the same vaccines are authorized and recommended with the addition of the COVID-19 vaccine by AstraZeneca. The Pfizer-BioNTech and Moderna vaccines are mRNA vaccines, whereas both Johnson & Johnson/Janssen and AstraZeneca 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 for COVID-19 vaccination even in oncology patients under active treatment. As to this date, there is no clear or specific guidance for patients enrolled in interventional oncology clinical trials and should be taken as per case-by-case basis.

Recently results of 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 due to COVID-19 in patients with cancer who are being treated, data supports current guidelines and call for vaccination of patients being treated with immune checkpoint inhibitors, especially during pandemic surges.

The interaction of BNT151 with all the vaccines approved in the US and EU are not known. It is unlikely that there will be any data of IL-2 in combination with any of the COVID-19 vaccines. However, the sponsor assesses the risk of significant side effects of BNT151 in combination with COVID-19 vaccine to be low. 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 BNT151 is still under development in Phase 1 trial without comprehensive clinical data, the protocol would recommend at least a few days of interval between COVID-19 vaccine and administration of BNT151 as a precaution. The 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, BNT151 is anticipated to strongly boost COVID-19 vaccine induced T-cell responses. On one hand this can result in an improved efficacy of the vaccine but on the other hand 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, we would recommend at least a 7-day interval between BNT151 treatment and COVID-19 vaccination.

However, a longer interval may be necessary during the DLT observation period, because the dose of BNT151 has not yet 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).

12.5 Appendix 5: COVID-19 vaccination in BNT151-01 trial during the pandemic

BioNTech as the sponsor of the BNT151-01 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, CDC, 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 at least 7 days between individual dose of COVID19 vaccine and trial treatment dose are ensured.
- COVID-19 vaccination during 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 BNT151-01 trial should be documented as a concomitant medication.
- Previous administration of COVID-19 vaccine should be documented on the prior and concomitant medication form. Past confirmed infection of COVID-19 by reverse transcription polymerase chain reaction (RT-PCR) before enrolment in the BNT151-01 trial should be documented in the medical history.