CLINICAL TRIAL PROTOCOL

First-in-human, dose titration and expansion trial to evaluate safety, immunogenicity and preliminary efficacy of W_pro1 (BNT112) monotherapy and in combination with cemiplimab in patients with prostate cancer

Protocol Number:	RN5609C00
Protocol Version:	6.0
Including Amendments:	1 to 5
Short Title / Acronym:	PRO-MERIT (**Pro**state Cancer **Me**ssenger **R**NA **I**mmuno**t**herapy)
Trial Phase:	1/2A
Compounds:	BNT112, cemiplimab
Sponsor:	BioNTech SE An der Goldgrube 12, 55131 Mainz, Germany
Clinical Research Organization:	Syneos Health 1030 Sync Street, Morrisville, NC 27560, USA
Coordinating Investigator:	Dr. Mark Linch FRCP PhD University College London Cancer Institute 72 Huntley Street, London, United Kingdom
Regulatory Agency Identifier Number(s):	EudraCT: 2018-004321-86; NCT04382898; IND: 26912
Approval Date:	23 FEB 2022

Statement of Compliance

GCP Compliance

This trial will be conducted in compliance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Guideline for Good Clinical Practice (ICH) E6(R2), and applicable regulatory requirements.

Confidentiality Statement

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Protocol Amendment Summary of Changes

DOCUMENT HISTORY	
Document	**Date**
Amendment 5	23 FEB 2022
Amendment 4_USA	06 APR 2021
Amendment 4_DEU	06 APR 2021
Amendment 4	06 APR 2021
Amendment 3.2	04 NOV 2020
Amendment 3.1	01 OCT 2020
Amendment 3	01 OCT 2020
Amendment 2	05 MAR 2020
Amendment 1	12 SEP 2019
Original Protocol	05 MAR 2019

Changes made to the protocol using the protocol amendments are described in detail in the document Protocol Amendment History which is available upon request. This Protocol Amendment History is filed together with the protocol in the trial master file. A short description of the changes made in each amendment are listed below.

Amendment 1 (12 SEP 2019)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

A new protocol template was implemented, and inconsistencies in the previous protocol version were corrected.

Amendment 2 (05 MAR 2020)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The dose-limiting toxicity section was updated, and inconsistencies in the previous protocol version were corrected.

Amendment 3 (01 OCT 2020)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

Amendment 3 implemented primarily cemiplimab-relevant information and changes reflecting feedback from the pre-IND meeting with the US Food and Drug Administration (FDA) regarding the newly diagnosed localized prostate cancer clinical setting. The company product code BNT112 for BNT112 cancer vaccine was introduced. Also, information relevant to Part 2 was corrected and actualized including the dose range confirmation.

Amendment 3.1 (01 OCT 2020) – Local amendment for Germany

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

Amendment 3.1 incorporated an additional exclusion criterion to the trial protocol in regards to mentally incapacitated patients, as requested by German authorities.

Amendment 3.2 (04 NOV 2020) – Local amendment for the United States

Overall Rationale for the Amendment:

Amendment 3.2 incorporated an additional exclusion criterion to the trial protocol in regards to mentally incapacitated patients, as requested by the United States authorities.

Amendment 4 (06 APR 2021)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

Amendment 4 implemented the option for patients with mCRPC on BNT112 monotherapy to switch to cemiplimab monotherapy after disease progression. Additional changes were incorporated following regulatory agency feedback.

Amendment 4_DEU (06 APR 2021) – Local amendment for Germany

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

Amendment 4_DEU incorporated an additional exclusion criterion to the amended global protocol (v5.0) in regards to mentally incapacitated patients, as previously requested by German authorities.

Amendment 4_USA (06 APR 2021) – Local amendment for the United States

Overall Rationale for the Amendment:

Amendment 4_USA incorporated an additional exclusion criterion to the amended global protocol (v5.0) in regards to mentally incapacitated patients, as previously requested by the United States authorities.

Amendment 5 (23 FEB 2022)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

Amendment 5 included the following substantial changes:

- Change of the immunogenicity secondary endpoint to an exploratory endpoint.
  - Immunogenicity assessments, within the context of the PRO-MERIT trial, support the generation of a hypothesis to investigate if there will be induction/expansion of vaccine antigen-specific T cells following treatment with BNT112 (W_pro1). The importance of induction of immunogenicity for the assessment of safety and preliminary clinical activity is not proven, which justifies re-classification of this endpoint.
- Additional exclusion criterion regarding mentally incapacitated patients, as previously requested by the United States and German authorities.
- The Schedule of Assessments was adapted to allow for additional blood draws at C1D8, C1D15, C2D8, and C2D15 for prostate-specific antigen level assessment.
  - This change is considered substantial as it affects one of the secondary objectives to evaluate anti-tumor activity based on levels of PSA and diagnostic or medical monitoring procedures. This change is likely to positively impact the scientific value of the trial as it may facilitate a deeper understanding of the pharmacological effects induced at the early stages of trial treatment.

Other changes included a terminology change from W_pro1 to BNT112 and the correction of inconsistencies.

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1. Protocol Summary

1.1. Synopsis

Title:	First-in-human, dose titration and expansion trial to evaluate safety, immunogenicity and preliminary efficacy of W_pro1 (BNT112) monotherapy and in combination with cemiplimab in patients with prostate cancer
Acronym:	PRO-MERIT (**Pro**state Cancer **Me**ssenger **R**NA **I**mmuno**t**herapy)
Sponsor's trial no.:	RN5609C00
EudraCT no.:	2018-004321-86
Clinical development:	Phase 1/2A
Trial design:	Open-label, multicenter, dose titration and expansion four-arm trial to evaluate the safety, tolerability, immunogenicity, and preliminary efficacy of BNT112 cancer vaccine (BNT112) monotherapy or in combination with cemiplimab in patients with metastatic castration-resistant prostate cancer (mCRPC: Part 1 and Part 2 Arms 1A and 1B) and in patients with high-risk, localized prostate cancer (LPC) eligible for treatment with androgen-deprivation therapy (ADT) followed by radical prostatectomy (LPC: Part 2 Arms 2 and 3)
Trial centers and investigators:	Approximately 30 investigational sites (trial centers)
Countries:	Up to 5 countries

Trial objectives and endpoints:

OBJECTIVES	ENDPOINTS
PRIMARY OBJECTIVE	**PRIMARY ENDPOINTS**
• (Part 1 and Part 2) Assess safety and tolerability profile of BNT112 monotherapy or in combination with cemiplimab	• Occurrence of dose-limiting toxicities (DLTs). • Occurrence of treatment-emergent adverse events (TEAEs) reported by relationship, grade, and seriousness according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0.
• (Part 2 Arms 1a and 1b) Evaluate preliminary anti-tumor activity of BNT112 monotherapy and in combination with cemiplimab in patients with mCRPC based on objective response rate (ORR)	• ORR, defined as the number of patients with a complete response (CR) or partial response (PR) per Prostate Cancer Working Group 3 (PCWG3) as determined by the investigator as best objective response divided by the number of patients in the analysis set.

OBJECTIVES	ENDPOINTS
SECONDARY OBJECTIVES	**SECONDARY ENDPOINTS**
• Evaluate anti-tumor activity based on levels of prostate-specific antigen (PSA)	• PSA decline of 0 to 25%, >25% to 50%, and >50% compared to baseline. • PSA doubling time (PSADT) post-treatment on C4D1 and D1 of every fourth subsequent cycle (e.g., C8D1, C12D1, etc.) in Part 1 and Part 2 Arms 1A and 1B, or on C4D1, C8D1, and end of treatment (EoT) in Part 2 Arms 2 and 3 compared to baseline. • PSA decline of ≥50% (according to the PCWG3).
• (Part 1) Evaluate preliminary anti-tumor activity of BNT112 monotherapy in patients with mCRPC based on ORR	• ORR, defined as the number of patients with a CR or PR per PCWG3 as determined by the investigator as best objective response divided by the number of patients in the analysis set.
• Evaluate preliminary anti-tumor activity of BNT112 monotherapy or in combination with cemiplimab in patients with newly diagnosed LPC	• Tumor response post-treatment compared to baseline.
EXPLORATORY OBJECTIVES	**EXPLORATORY ENDPOINTS**
• Determine systemic induction/expansion of BNT112 antigen-specific T cells for BNT112 monotherapy or in combination with cemiplimab	• Occurrence of *de novo* induction or increase of BNT112 antigen-specific T cells in peripheral blood under treatment on Cycle 3 Day 15 (C3D15), and/or C8D15, EoT, or safety follow-up compared to baseline.
• Evaluate preliminary anti-tumor activity of BNT112 monotherapy and in combination with cemiplimab in patients with mCRPC	• Duration of response (DoR), defined as the time from the first occurrence of a documented OR to the time of the first disease progression per PCWG3, as determined by the investigator, or death from any cause, whichever occurs first. • ORR and DoR, defined as above, using immune-modified Response Evaluation Criteria in Solid Tumors (iRECIST). • Progression-free survival (PFS), defined as the time from the first trial treatment to the first disease progression per PCWG3 as determined by the investigator, and per iRECIST determined by central reading, or death from any cause, whichever occurs first. • Overall survival (OS), defined as the time from first trial treatment until death from any cause. • Number of cycles received and relative dose intensity (RDI).

OBJECTIVES	ENDPOINTS
• Evaluate preliminary anti-tumor activity of cemiplimab in patients with mCRPC who have been previously treated with, and who have progressed after BNT112 monotherapy	• ORR, defined as the number of patients with a CR or PR per PCWG3 as determined by the investigator as best objective response (OR) divided by the number of patients in the analysis set. • DoR, defined as the time from the first occurrence of a documented OR to the time of the first disease progression per PCWG3, as determined by the investigator, or death from any cause, whichever occurs first. • ORR and DoR, defined as above, using iRECIST. • PFS, defined as the time from the first cemiplimab treatment to the first disease progression per PCWG3 as determined by the investigator, and per iRECIST determined by central reading, or death from any cause, whichever occurs first. • PFS2, defined as the time from the first trial treatment to the first disease progression after start of cemiplimab per PCWG3 as determined by the investigator, or death from any cause, whichever occurs first. • OS, defined as the time from first trial treatment until death from any cause. • Number of cycles received and RDI.
• Assess safety and tolerability profile of cemiplimab monotherapy in patients following progression after BNT112 monotherapy	• Occurrence of TEAEs reported by relationship, grade, and seriousness according to NCI CTCAE v5.0.
• Evaluate preliminary anti-tumor activity of BNT112 monotherapy or in combination with cemiplimab in patients with newly diagnosed LPC	• PFS, defined as the time from the first trial treatment to the first disease progression per PCWG3 as determined by the investigator, or death from any cause, whichever occurs first. • OS, defined as the time from first trial treatment until death from any cause.
• Preliminary assessment of biomarkers that might act as potential predictive, pharmacodynamics, anti-tumor, and safety indicators of activity of BNT112 monotherapy or in combination with cemiplimab	• Status of tumor mutational burden and immune-related gene expression (at the ribonucleic acid [RNA] level) in tumor tissue prior to treatment. • Change in protein expression pattern/levels of tumor microenvironment markers (e.g., CD3, CD8, MHC-I, PD-L1, etc.) and prostate tumor markers (e.g., PSA, PSAP, NKX3-1, etc.) in tumor tissue post-treatment compared to baseline.

OBJECTIVES	ENDPOINTS
	• Baseline status or change in RNA target expression of BNT112–encoded antigens in the post-treatment tissue compared to baseline. • Change in T cell clonality/diversity post-treatment compared to baseline. • Changes in blood biomarkers prior to and during trial treatment.

Abbreviations: C = cycle; CR = complete response; CTCAE v5.0 = Common Terminology Criteria for Adverse Events, version 5.0; D = day of cycle; DLT = dose-limiting toxicity; DoR = duration of response; EoT = end of treatment; iRECIST = immune-modified Response Evaluation Criteria in Solid Tumors; MHC = major histocompatibility complex; NCI = National Cancer Institute; NKX3-1 = NK3 homeobox 1; OR = objective response; ORR = objective response rate; OS = overall survival; PCWG3 = Prostate Cancer Working Group 3; PD-L1 = programmed cell death 1 ligand 1; PFS = progression-free survival; PR = partial response; PSA = prostate-specific antigen; PSADT = prostate-specific antigen doubling time; PSAP = prostate-specific acid phosphatase; RDI = relative dose intensity; TEAE = treatment-emergent adverse event.

Investigational medicinal products (IMPs):	
IMP 1:	BNT112 (previously referred to as W_pro1 in this and other trial-related documentation)
Composition:	BNT112 consists of messenger RNA (mRNA; further referred to as RNA) targeting 5 antigens expressed in *de novo* and metastatic prostate cancer that are separately complexed with liposomes to form serum-stable RNA lipoplexes
Administration:	Five slow intravenous (IV) bolus injections per administration (i.e., one injection per each antigen followed by a saline flush and separated from the next injection by at least 5 minutes)
Dosage regimen:	One cycle (C) is defined as 21 days The patients will receive the following treatments in the following dose and schedule: **Part 1 and Part 2 Arms 1A and 1B (mCRPC)** • IV administration of BNT112 on Day (D)1/8/15 of C1 (intra-patient dose titration) and C2, thereafter starting with D1 of C3 every 3 weeks (Q3W) until the EoT criterion is met • Part 1/Dose Titration - Three doses of BNT112 will be used for an intra-patient dose titration during C1: CCI µg, CCI µg, and CCI µg of total RNA, comprising CCI µg, CCI µg, and CCI µg of RNA of each of the 5 antigens encoded by BNT112, respectively • Part 2/Expansion - Recommended expansion dose range (REDR) was selected after the review of individual and cumulative safety data, and

Duration of treatment:	preliminary pharmacodynamic data of Part 1 by the Safety Review Committee (SRC). The selected dose range consists of a starting first dose of BNT112 of CCI µg, with an intra-patient dose titration to CCI µg in the second dose, and CCI µg of total RNA in the next doses. Total RNA of CCI µg, CCI µg and CCI µg comprise CCI µg, CCI µg, and CCI µg of RNA of each of the 5 antigens encoded by BNT112, respectively - Part 2 Arm 1A: Cemiplimab CCI mg IV Q3W - Part 2 Arm 1B: Following progression after BNT112 monotherapy, patients have the option to be treated with cemiplimab CCI mg IV Q3W monotherapy **Part 2 Arms 2 and 3 (LPC) – Part 2/Expansion ONLY** • IV administration of BNT112 on D1/8/15 of C1 (intra-patient dose titration) and C2, thereafter starting with D1 of C3 in a Q3W schedule until C8 followed by radical prostatectomy • Part 2 Arm 2: Cemiplimab CCI mg IV Q3W • Part 1 and Part 2 Arms 1A and 1B (mCRPC): The treatment with BNT112 will last until unacceptable toxicity or disease progression • Part 2 Arms 2 and 3 (LPC): The treatment with BNT112, cemiplimab will last until unacceptable toxicity or disease progression, or up to C8. • If either BNT112 or cemiplimab needs to be discontinued, treatment with either cemiplimab or BNT112 can continue upon investigator's and sponsor's agreement • If treatment with ADT (e.g., goserelin acetate) needs to be discontinued, cemiplimab and/or BNT112 also need(s) to be discontinued
IMP 2:	Cemiplimab (Libtayo)
Composition:	Programmed death receptor-1 (PD-1) blocking antibody
Dosage regimen and duration of treatment:	Refer to above description of IMP1 for dosage regimen and duration of treatment

Non-investigational medicinal product (NIMP):

Part 2 Arms 2 and 3 (LPC)

ADT, e.g., Goserelin acetate subcutaneous (SC) injection at a dose of 10.8 mg every 12 weeks (Q12W) or other ADT according the current prescribing information valid in a given country.

Product:	Goserelin acetate (Zoladex® LA 10.8 mg implant)
Composition:	Goserelin acetate (equivalent to 10.8 mg goserelin)
Administration:	SC
Dosage regimen:	One 10.8 mg depot injection given into the anterior abdominal wall Q12W

Duration of treatment:	Two injections (≤7 days C1D1 and 12 weeks after the first injection); treatment will last until unacceptable toxicity or disease progression, or up to C8

Treatment overview:

Part 1

Dose Titration[&]

	C1			C2			C3 →		
Day	1	8	15	1	8	15	1	8	15
BNT112[$]									
CCI µg IV	X								
CCI µg IV		X							
CCI µg IV			X						
dose*				X	X	X	X	→	Q3W

Part 2

Arm 1b[%] (BNT112 monotherapy in mCRPC)

Arm 3[#] (BNT112 monotherapy in LPC)

	C1			C2			C3 →		
Day	1	8	15	1	8	15	1	8	15
BNT112[$]									
CCI µg IV	X								
µg IV		X							
CCI µg IV			X	X	X	X	X	→	Q3W

Part 2

Arm 1a (BNT112 + cemiplimab in mCRPC)

Arm 2[#] (BNT112 + cemiplimab in LPC)

	C1			C2			C3 →		
Day	1	8	15	1	8	15	1	8	15
BNT112[$]									
CCI µg IV	X								
µg IV		X							
CCI µg IV			X	X	X	X	X	→	Q3W
Cemiplimab									
CCI mg IV Q3W	X			X			X	→	Q3W

Abbreviations and Footnotes:

LPC = localized prostate cancer; mCRPC = metastatic castration-resistant prostate cancer; Q3W = every three weeks.

& Recommended dose range (REDR) is confirmed in Part 1.

* Maximum administered dose CCI µg; minimum administered dose CCI µg; no dose re-escalation allowed.

\# In combination with ADT (e.g., goserelin).

$ From Day 1 of C1 onward, each patient will receive the individual standard dose (or the highest tolerated dose from Cycle 1) at each BNT112 administration.

% Following progression after BNT112 monotherapy, patients have the option to be treated with cemiplimab monotherapy CCI mg IV Q3W.

Background treatment:	Not applicable
Discontinuation-of-treatment criteria:	Unacceptable toxicity, evidence of tumor progression, consent withdrawal or patient's withdrawal from the trial at the discretion of the investigator may lead to termination of treatment.
Indication:	Prostate cancer (adenocarcinoma)
Number of patients:	There will be 3 to 9 patients in Part 1 (dose titration part, single arm) and up to 106 patients in Part 2 (expansion part, four arms: up to 33 patients in Arm 1A and Arm 1B, respectively, and approximately 20 patients in Arm 2 and Arm 3, respectively). Drop-outs may be replaced. In total, there will be approximately 115 patients.
Diagnosis and main criteria for inclusion:	Each potential participant must fulfill all of the following criteria at screening to be enrolled in the trial. In addition, all lab criteria must be fulfilled within 7 days prior to starting IMP. **Inclusion criteria for all patients** 1. Patients must be male and aged ≥18 years. 2. Patients must have histologically confirmed prostate adenocarcinoma. 3. Patients or their legally authorized representative (if applicable) must sign an informed consent form (ICF) indicating that they understand the purpose of the procedures required for the trial and are willing to participate. 4. Patients must have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0 or 1. 5. Patients must have adequate organ and bone marrow function, defined as: a. Bone marrow/hematological function: - Absolute neutrophil count ≥1.5 × 10^9/L. - Hemoglobin ≥9.0 g/dL. No transfusion is allowed within 2 weeks prior to trial treatment initiation. - Platelet count ≥100 × 10^9/L. b. Coagulation status: - International normalized ratio ≤1.5 upper limit of normal (ULN). Unless on therapeutic anticoagulants with values within therapeutic window. c. Renal function: - Glomerular filtration rate ≥45 mL/min/1.73 m² according to the abbreviated Modification of Diet in Renal Disease equation. 6. Patients who are sexually active with a woman of childbearing potential must agree to use a condom with spermicidal foam/gel/film/cream/suppository in addition to at least one form of highly effective contraception used by the patient or their partner during the trial starting after signing the ICF and for 90 days after receiving the last dose of BNT112 OR for 6 months after receiving the last dose of cemiplimab.

7. Patients should not donate sperm during the trial starting after signing the ICF and for 90 days after receiving the last dose of BNT112 OR for 6 months after receiving the last dose of cemiplimab.
8. Patients must be willing and able to adhere to the prohibitions and restrictions specified in this protocol.

In addition to the above inclusion criteria the following are mandatory for the different treatment arms:

Specific inclusion criteria for mCRPC patients (Part 1 and Part 2 Arms 1A and 1B)

9. Patients must have histologically confirmed mCRPC and have progressed after at least 2 but no more than 3 lines of life-prolonging systemic therapy (e.g., abiraterone or enzalutamide, docetaxel, cabazitaxel) or cannot tolerate or have refused any of these therapies. These lines of therapy include life-prolonging therapies administered in the metastatic hormone–sensitive setting.
10. Prior surgical or chemical castration with a serum testosterone <1.7 nmol/L (50 ng/dL). If the method of castration is luteinizing hormone-releasing hormone analogue (LHRHa), there must be a plan to maintain effective LHRHa therapy for the duration of the trial.
11. Patients must have documented mCRPC progression within 6 months prior to screening (assuming no subsequent change in treatments), as determined by the investigator, by means of 1 or more of the following criteria:
    a. PSA progression as defined by a minimum of 2 rising PSA levels with an interval of ≥1 week between each assessment where the PSA value at screening should be >2 ng/mL.
    b. Two rises out of 3 PSA sequential tests separated by at least 1 week also satisfies the criteria for baseline progression providing a new nadir is not established (i.e., upward trend).
    c. Radiographic disease progression in soft tissue based on modified Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1) with or without PSA progression.
    d. Radiographic disease progression in bone defined as the appearance of 2 or more new bone lesions on bone scan with or without PSA progression.
12. Patients must have adequate liver function defined as:
    a. Total bilirubin ≤1.5 × ULN (≤3 × ULN is acceptable for patients with known Gilbert disease).
    b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 × ULN.
        - For patients with hepatic metastases, total bilirubin <3 × ULN and AST or ALT <5 × ULN are acceptable.

	- For patients with bone metastases, alkaline phosphatase <5 × ULN and albumin ≥2.5 g/dL are acceptable. 13. Patients must agree to provide an archival pre-treatment formalin-fixed, paraffin-embedded tumor sample if available. **Specific inclusion criteria for newly diagnosed LPC patients (Part 2 Arms 2 and 3)** 14. Treatment-naïve patients with LPC (i.e., N0, M0). According to risk levels of the European Association of Urology Guidelines on Prostate Cancer (2018)[24], and in line with the U.S. National Comprehensive Cancer Network (NCCN 2020)[35], patients must have at least 1 of the following: a. PSA >20 ng/mL or b. Gleason Score >7 or c. Localized stage ≥cT2c, N0, M0 according to tumor, node, metastasis classification 15. Patients who intend to have and are suitable for a radical prostatectomy. 16. Patients must have adequate liver function defined as: a. Total bilirubin ≤1.5 × ULN (≤3 × ULN is acceptable for patients with known Gilbert disease) b. AST and ALT ≤2.5 × ULN 17. Patients must agree to provide tumor sample(s) from pre-treatment diagnostic biopsy and planned post-treatment surgery. 18. Patient must be eligible for up to 6 months of ADT treatment before prostatectomy.
Diagnosis and main criteria for exclusion:	**Exclusion criteria for all patients** <u>Medical Conditions</u> 1. Patients with uncontrolled intercurrent illness, including but not limited to: a. Ongoing or active infection which requires systemic treatment with antibiotics or corticosteroid therapy within 14 days before the first dose of IMP. b. Symptomatic congestive heart failure (Grade III or IV as classified by the New York Heart Association), myocardial infarction within 3 months before screening, unstable angina pectoris, or cardiac arrhythmia. c. Known recent history (in the past 5 years) or presence of significant pulmonary conditions such as uncontrolled chronic lung disease, or any evidence of interstitial lung disease, or active, non-infectious pneumonitis. d. Uncontrolled hypertension defined as systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥100 mmHg, despite optimal medical management.

e. Known primary immunodeficiencies, either cellular (e.g., DiGeorge syndrome, T cell negative severe combined immunodeficiency [SCID]) or combined T- and B-cell immunodeficiencies (e.g., T- and B-cell negative SCID, Wiskott Aldrich syndrome, ataxia telangiectasia, common variable immunodeficiency).

f. Ongoing or recent evidence (within the past year) of significant autoimmune disease that required treatment with systemic immunosuppressive treatments which may suggest risk for immune-related adverse events (AE).
Note: Patients with autoimmune-related hyperthyroidism, autoimmune-related hypothyroidism who are in remission, or on a stable dose of thyroid-replacement hormone, vitiligo, or psoriasis may be included.

g. Non-healing wound, skin ulcer (of any grade), or bone fracture.

h. Patients with prior allogeneic stem cell or solid organ transplantation.

i. Patients with the following risk factors for bowel perforation (e.g., history of acute diverticulitis or intra-abdominal abscess in the last 3 years; history of gastrointestinal obstruction or abdominal carcinomatosis).

j. Patients with uncontrolled type 1 diabetes mellitus.
Note: Patients controlled on a stable insulin regimen are eligible.

k. Patients with uncontrolled adrenal insufficiency.

l. Any other disease, metabolic dysfunction, physical examination finding, and/or laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or may render the patient at high-risk for treatment of complications.

2. Patients with a known history or current malignancy other than the inclusion diagnosis.
Note: Exceptions are patients with malignancies with a negligible risk of metastasis or death, that have been adequately treated, such as non-invasive basal cell or non-invasive squamous cell skin carcinoma, non-invasive, superficial bladder cancer, and any cancer with a CR that lasted more than 2 years may be included.

3. Patients who have had a splenectomy.

4. Patients who have had major surgery (e.g., requiring general anesthesia) within 4 weeks before screening, or have not fully recovered from surgery, or have a surgery planned during the time of trial participation, except for the radical prostatectomy planned for patients in Part 2 Arms 2 and 3.

5. Patients who have a known history of any of the following:

   a. HIV 1 or 2

   b. Hepatitis B (carrier or active infection)

c. Hepatitis C (unless considered cured 5 years post curative anti-viral therapy)

6. Patients with a known allergy, hypersensitivity, or intolerance to BNT112 or its excipients (all patients in Parts 1 and 2), cemiplimab or its excipients (patients in Part 2 Arm 1A, Arm 1B switch-over patients, and Arm 2 only), or to ADT (e.g., goserelin) or excipients thereof (patients in Part 2 Arms 2 and 3 only).
7. Patients with any condition for which, in the opinion of the investigator, participation would not be in the best interest of the patient (e.g., compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.
8. In situations where trial patients are not legally competent to provide consent (e.g., mentally incapacitated), these patients are not allowed to enter the trial.

Prior/Concomitant Therapy

9. Patients who have received or currently receive the following therapy/treatment:
   a. Chronic systemic immunosuppressive corticosteroid treatment (prednisone >5 mg daily orally [PO] or IV, or equivalent) during the trial.
      Note: Replacement therapy (e.g., physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is permitted.
   b. Prior treatment with other immune-modulating agents that was (a) within fewer than 4 weeks (28 days) or 5 half-lives (whichever is longer) prior to the first dose of cemiplimab, or (b) associated with immune-mediated AEs that were Grade ≥1 within 90 days prior to the first dose of cemiplimab, or (c) associated with toxicity that resulted in discontinuation of the immune-modulating agent.
   c. Prior treatment with other immune-modulating agents for any non-cancer disease within 4 weeks or 5 half-lives of the agent (whichever is longer) before the first dose of IMP.
   d. Prior treatment with live-attenuated vaccines within 4 weeks before the first dose of IMP and during treatment with IMP.
   e. Prior treatment with an investigational drug (including investigational vaccines) within 4 weeks or 5 half-lives of the agent (whichever is longer) before the planned first dose of IMP.
   f. Therapeutic PO or IV antibiotics within 14 days prior to enrollment.
      Note: Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or chronic obstructive pulmonary disease) may be enrolled.
   g. Concurrent use of herbal products that may decrease PSA levels (e.g., saw palmetto).

Other exclusion criteria for ALL patients

10. Patients who have previously been enrolled in this trial.
11. Patients with substance abuse or known medical, psychological, or social conditions that may interfere with the patient's participation in the trial or evaluation of the trial results.
12. Patients affiliated with the investigational site (e.g., a close relative of the investigator or dependent person, such as an employee or student of the investigational site)

Specific exclusion criteria for mCRPC patients (Part 1 and Part 2 Arms 1A and 1B)

Excluded medical conditions

13. Patients with toxicities from previous anti-cancer therapies that have not resolved to baseline levels or to Grade ≤1 according to NCI CTCAE v5.0 with the exception of alopecia, anorexia, vitiligo, fatigue, hyperthyroidism, hypothyroidism, and peripheral neuropathy. Anorexia, hyperthyroidism, hypothyroidism, and peripheral neuropathy must have recovered to Grade ≤2.
14. Patients with clinically active brain metastases.
    a. Patients with a history of symptomatic metastatic brain or meningeal tumors may be included, if the end of definitive therapy is >3 months before the first dose of BNT112 and the patients have no clinical or radiological evidence of tumor growth.
    b. Patients with brain metastases must not be undergoing acute or chronic corticosteroid therapy or steroid taper.
    c. Patients with central nervous system symptoms should undergo a computed tomography (CT) scan or magnetic resonance imaging (MRI) of the brain to exclude new or progressive brain metastases. Spinal cord metastasis is acceptable. However, patients with spinal cord compression should be excluded.

Excluded prior or concomitant anti-cancer therapies

15. Patients who have received or currently receive the following anti-cancer therapy/agent:
    a. Prior radiation therapy with curative intent within 14 days before the first dose of IMP.
    Note: Palliative radiotherapy is allowed.
    b. Prior treatment with an anti-cancer agent (within 4 weeks or for systemic therapies after at least 5 half-lives of the drug [whichever is longer] before the first dose of IMP).
    Note: Prior treatment with bone resorptive therapy, such as bisphosphonates (e.g., pamidronate, zoledronic acid, etc.) and denosumab, is allowed assuming that the patients have been on stable doses for ≥4 weeks prior to first dose of trial treatment.
    c. Prior treatment with anti-cancer immunomodulating agents, such as blockers of PD-1, programmed cell death 1 ligand 1 (PD-L1), tumor

	necrosis factor receptor superfamily member 9 (TNRSF9, 4-1BB, CD137), tumor necrosis factor receptor superfamily member 4 (OX-40), therapeutic vaccines, cytokine treatments, or any investigational agent within 4 weeks or 5 half-lives (whichever is longer) before the first dose of IMP. **Specific exclusion criteria for LPC patients (Part 2 Arms 2 and 3)** 16. Patients who are expected to be unable to undergo an mpMRI or MRI.
Coordinating investigator:	Dr. Mark Linch FRCP PhD, Consultant Medical Oncologist UCL-Cancer Institute, London, United Kingdom.
Methodology:	The trial consists of 2 parts: Part 1 – dose titration and Part 2 – expansion with four arms: Arms 1A and 1B (mCRPC) and Arms 2 and 3 (LPC). Each arm will have a screening period, a treatment period and a post-treatment follow-up period. Re-screening of patients is allowed. Part 1 and Part 2 Arms 1A and 1B will enroll patients with mCRPC. Part 2 Arms 2 and 3 will enroll patients with newly diagnosed LPC. Enrollment in Part 2 between Arms 1A and 1B and between Arms 2 and 3 will be randomized 1:1 to avoid enrollment bias. The safety of BNT112 in doses of CCI and CCI µg will be evaluated on the DLTs during the first treatment cycle (21 days) and the overall incidence of BNT112-related or potentially related AEs in all arms of the trial. The safety of concomitant administration of cemiplimab and/or ADT (e.g., goserelin acetate) will be evaluated based on the overall incidence of ADT (e.g., goserelin acetate) or cemiplimab-related or potentially related AEs in Part 2 Arms 2 and 3 of the trial, respectively, and will follow the same rules as Part 1, until the SRC reviews and confirms that the combination safety profile is acceptable. Based on the recommendation from the SRC, the sponsor will decide if enrollment should continue for the combination arms. More details are provided in the SRC charter. The dose titration part of the trial will employ a modified 3 + 3 + 3 design (adopted from Hamberg et al. 2010[13]) with cohorts of up to 9 evaluable patients. The safety will be evaluated by the SRC. The committee will consist of the investigators (especially those who have patients being treated at the dose under discussion), the BioNTech trial team including at a minimum, the medical monitor, and any other person the investigators/trial team consider necessary to assist with trial decisions such as a statistician. The SRC will make a recommendation to the sponsor after each meeting on how to proceed with the trial and whether to activate the respective expansion arms of the trial. The SRC will meet at least every 3 months throughout the trial. The efficacy in Part 1 and Part 2 Arm 1A and 1B will be assessed by on-treatment imaging every 8 weeks (±7 days) for 24 weeks, and then every 3 months (±7 days) thereafter until disease progression, the start of new anti-cancer therapy, withdrawal of consent, or death, whichever occurs first. The Prostate Cancer Working Group 3 (PCWG3) criteria, and immune-modified RECIST (iRECIST) criteria will be used for exploratory endpoint response evaluation. If the investigator considers radiographic changes secondary to drug-induced inflammation and not to tumor progression, the investigator may

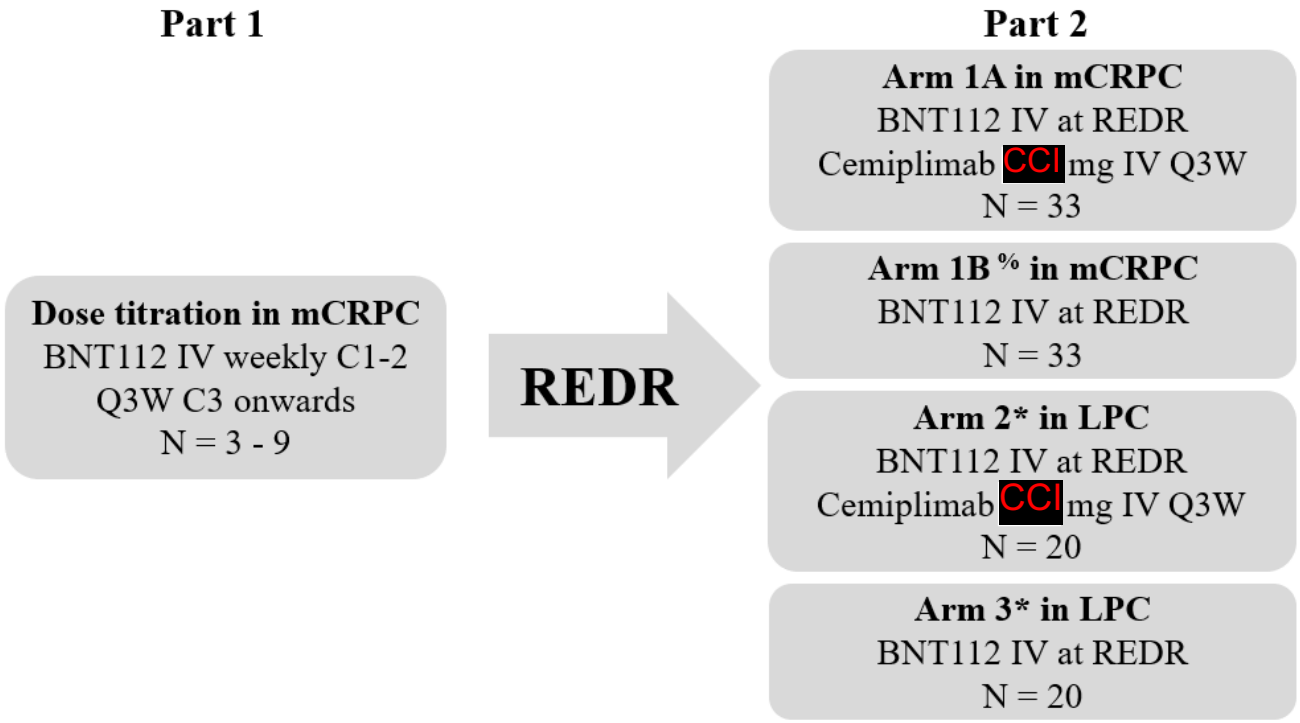
	postpone a diagnosis of progressive disease until the next radiographic evaluation in the trial. Following progression after BNT112 monotherapy, patients in Arm 1B have the option to be treated with cemiplimab monotherapy. The efficacy in Part 2 Arms 2 and 3 will be assessed by tumor measurement using mpMRI or MRI at baseline and prior to surgery (i.e., at the end of C8/EoT visit). The same imaging modality should be used at screening and at all subsequent assessments. Various blood- and tumor-based biomarkers will be analyzed in all arms.
Trial duration:	First patient was included on 19 December 2019. The end of the trial is defined as the date of last patient contact, whether in-person or by phone, for the last patient in the trial globally, including the efficacy follow-up for 12 months after the last dose of trial treatment.
Safety Review Committee (SRC):	The SRC will review all DLTs and suspected unexpected serious adverse reactions, make the REDR recommendation at the end of the Dose Titration Part (Part 1) and periodically review safety and efficacy in Part 2. The SRC will recommend when expansion arms may be initiated.

Plan for statistical analysis:	**Statistical Hypotheses** For each Part 2 Arm 1A and 1B the null hypothesis that the true response rate is 5% will be tested against a one-sided alternative (i.e., H_0: ORR=5% vs H_1: ORR>5%). There will be no formal comparison between treatment arms. No further statistical hypothesis is under test. **Sample Size Determination** The sample size for Part 1 is driven by the 3+3+3 trial design and will range from 3 to 9 DLT evaluable patients depending on the number of DLTs which may occur. The main objective for the Part 2 is to perform exploratory biomarker analyses in the LPC setting and to preliminary assess the efficacy in terms of response in the mCRPC setting. Simon's two-stage design (Simon, 1989[31]) based on the Minimax approach will be used for Part 2 Arm 1A and 1B separately. The null hypothesis that the true response rate is 5% will be tested against a one-sided alternative. In the first stage, 20 evaluable patients will be treated. Enrollment will continue following sponsor decision (upon recommendation from the SRC following review) and 13 additional evaluable patients may be treated for a total of 33 evaluable patients. If there is one or fewer responses in the first 20 evaluable patients, the enrollment for that arm may be stopped. The null hypothesis will be rejected if five or more responses are observed in 33 evaluable patients. This design yields a type I error rate of 2.5% and power of 80% when the true response rate is 20%. A patient will be considered as evaluable if included in the primary analysis set (mITT set) which is defined as all patients who are randomized to the IMP and

	have a baseline and at least one post-baseline (i.e., one on-treatment or post-treatment) tumor assessment (clinical or imaging assessment). No formal sample size calculation is performed for the LPC setting in Part 2 (Arms 2 and 3) due to its exploratory nature. However, 20 patients are planned to be enrolled into Arm 2 and Arm 3. Based on this sample size (N=20) the one-sided 95% CI of binary endpoints will have a width of up to +/-0.19 in each group depending on the observed effect size. **Primary Analysis** **DLTs and AEs** The primary endpoint is the occurrence of DLTs and AEs reported by relationship, grade, and seriousness according to NCI CTCAE v5.0. The number and percentage of patients with any DLT and/or AE will be presented for patients enrolled into Part 1 and for each arm in Part 2. Moreover, a patient listing will be provided with all relevant dose exposure data of all patients enrolled into Part 1 and for each arm in Part 2 and a listing of all recorded DLTs and/or AEs will be presented including the reported term and Medical Dictionary for Regulatory Activities (MedDRA®) Preferred Term (PT) and System Organ Class (SOC) term, its time of onset, relationship, NCI CTCAE grade, and seriousness including dose exposure data (e.g., BNT112 DL). **Objective Response Rate** For Arm 1A and 1B in Part 2, ORR is defined as primary efficacy endpoint. The ORR is defined as the number of patients with CR or PR as best objective response divided by the number of patients in the analysis set. Patients not meeting the criteria for CR or PR, including those without any post-baseline tumor assessments, will be considered as non-responders. The ORR will be summarized with absolute and relative frequencies along with two-sided 95% Clopper-Pearson confidence intervals by treatment group/cohort. The primary analysis will be performed using the mITT set. For Part 1, ORR is defined as secondary endpoint and will be analyzed descriptively.

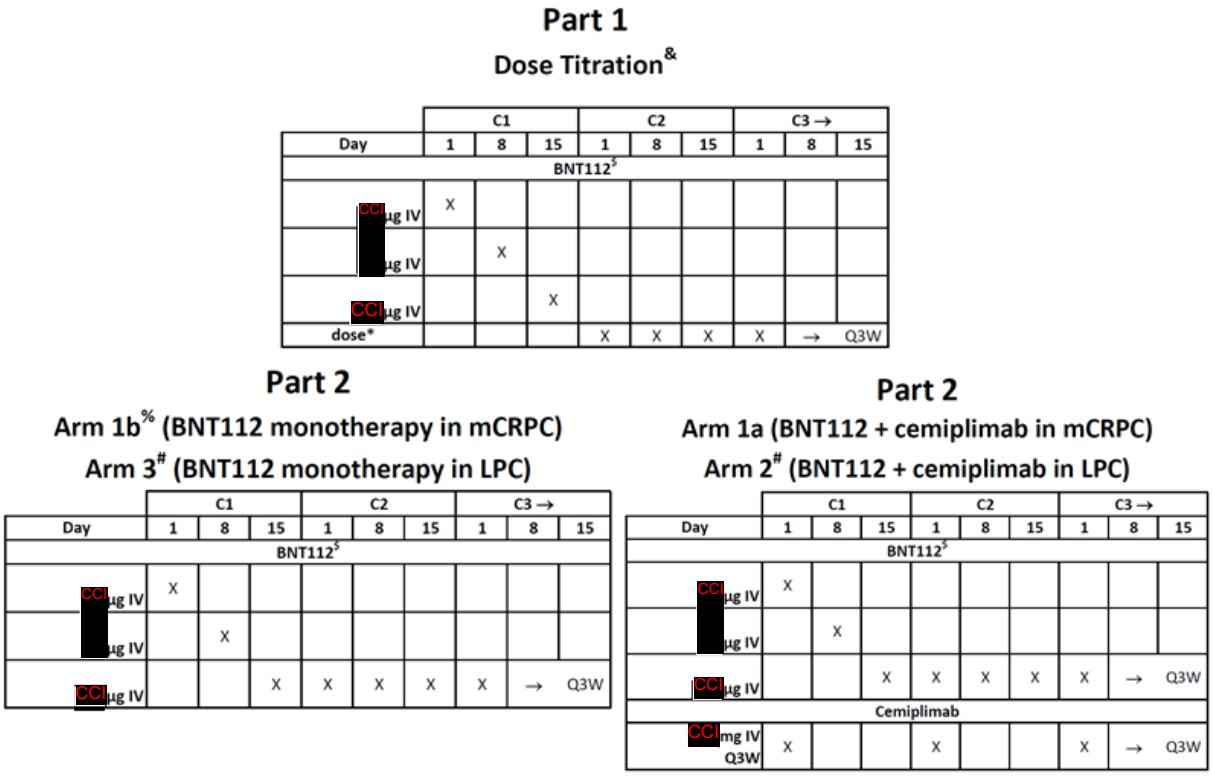
1.2. Schema

Figure 1-1: Trial Design



Abbreviations and Footnotes:
C = Cycle; IV = intravenous; LPC = localized prostate cancer; mCRPC = metastatic castration-resistant prostate cancer; Q3W = every 3 weeks; REDR = recommended expansion dose range.
* In combination with ADT (e.g., goserelin).
% Following progression after BNT112 monotherapy, patients in Arm 1b have the option to be treated with cemiplimab monotherapy CCI mg IV Q3W.

Figure 1-2: Treatment Administration – Part 1 and Part 2



Abbreviations and Footnotes:
LPC = localized prostate cancer; mCRPC = metastatic castration-resistant prostate cancer; Q3W = every three weeks.

& Recommended dose range (REDR) is confirmed in Part 1.

* Maximum administered dose CCI µg; minimum administered dose CCI µg; no dose re-escalation allowed.

\# In combination with ADT (e.g., goserelin).

$ From Day 1 of C1 onward, each patient will receive the individual standard dose (or the highest tolerated dose from Cycle 1) at each BNT112 administration.

% Following progression after BNT112 monotherapy, patients in Arm 1b have the option to be treated with cemiplimab monotherapy CCI mg IV Q3W.

1.3. Schedule of Activities: Part 1 and Part 2 Arms 1A and 1B

	Screening		Treatment																Follow-up (FU)			UV
1 cycle = 21 days			**C1[4]**			**C2**			**C3#**		**C4**	**C5**	**C6**	**C7**	**C8**		**≥C9#**	**EoT ***	**Safety FU ****	**Efficacy FU ****		
Visit	**≤28d**	**≤7d**	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**D1**	**D15**	**D1**	**D1**	**D1**	**D1**	**D1**	**D15**	**D1**		**D30 / D90**	**M6**	**M12**	
Visit window				**±1d**	**±1d**	**±1d**	**±1d**	**±1d**	**±1d**	**±3d**	**±1d**	**±1d**	**±1d**	**±1d**	**±1d**	**±3d**	**±3d**		**+7d**	**±14d**	**±14d**	
Patient information/consent[1]	X																					
Demographic data	X																					
Medical history[2] and body height	X																					
Body weight	X										X							X	X			
Physical examination[3]	X		X	X	X	X	X	X	X		X	X	X	X	X		X&	X	X			X[5]
ECOG PS	X		X&	X&	X&	X&	X&	X&	X&		X&	X&	X&	X&	X&		X&	X	X			X
Vital signs[4]	X	X	X&$	X&$	X&$	X&$	X&$	X&$	X&$	X	X&$	X&$	X&$	X&$	X&$	X	X&$	X	X			X
Single 12-lead ECG	X										X&			X&				X[5]	X[5]			X[5]
Concomitant treatment[6, 7]	X	X	X&	X&	X&	X&	X&	X&	X&	X	X&	X&	X&	X&	X&	X	X&	X	X	X	X	X[5]
Tumor response assessment[8]	X									X			X			X	X	X[5]				X
Archival FFPE tumor tissue sample	X																					
Tumor biopsy sample (optional)[10]																						X
Optional tumor sample[21]			(X)																			
Inclusion/Exclusion criteria	X	X	X&																			
Randomization[22]			X&																			
IMP Administration																						
Part 1 (monotherapy dose titration)																						
BNT112 (IMP)			X	X	X	X	X	X	X		X	X	X	X	X		X					
Part 2 Arm 1A (with cemiplimab)																						
BNT112 (IMP)			X	X	X	X	X	X	X		X	X	X	X	X		X					
Cemiplimab (IMP)			X			X			X		X	X	X	X	X		X					
Part 2 Arm 1B (monotherapy)																						
IMP 1 admin. Arm: BNT112			X	X	X	X	X	X	X		X	X	X	X	X		X					

	Screening		Treatment																Follow-up (FU)			UV
1 cycle = 21 days			**C1[4]**			**C2**			**C3#**		**C4**	**C5**	**C6**	**C7**	**C8**		**≥C9#**	**EoT ***	**Safety FU ****	**Efficacy FU ****		
Visit	**≤28d**	**≤7d**	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**D1**	**D15**	**D1**	**D1**	**D1**	**D1**	**D1**	**D15**	**D1**		**D30 / D90**	**M6**	**M12**	
Visit window				**±1d**	**±1d**	**±1d**	**±1d**	**±1d**	**±1d**	**±3d**	**±1d**	**±1d**	**±1d**	**±1d**	**±1d**	**±3d**	**±3d**		**+7d**	**±14d**	**±14d**	
Safety laboratory tests [11]																						
Serology	X																					
Hematology		X		X&	X&	X&	X&	X&	X&		X&	X&	X&	X&	X&		X&	X	X			X [5]
Coagulation		X				X&					X&		X&		X&		X&	X	X			X [5]
Blood chemistry		X		X&	X&	X&	X&	X&	X&		X&	X&	X&	X&	X&		X&	X	X			(X) [5]
Thyroid hormones [18, 20]		X				X					X		X		X		X20		X			(X)[5]
Urinalysis		X		X&	X&	X&	X&	X&	X&		X&	X&	X&	X&	X&		X&	X	X			(X) [5]
AE/TEAE [12, 13]	X	X	X&$	X&$	X&$	X&$	X&$	X&$	X&$	X	X&$	X&$	X&$	X&$	X&$	X	X&$	X	X			X
Survival/disease status [14]																				X	X	
Blood Biomarkers																						
Cytokines			X[15]	X[15]	X[15]	X[15]	X[15]	X[15]	X[15]		X[17]	X[17]	X[17]	X[17]	X[17]		X[17]	X	X			(X)
PSA		X	X[16]	X[16]	X[16]	X[16]	X [16]	X[16]	X[16]		X[16]	X[16]	X[16]	X[16]	X[16]		X[16]	X	X			(X)
Testosterone		X																				(X)
ELISpot and further immune monitoring		X[18]								X						X		X[19]	X[19]			(X)
HLA typing		X[18]																				
TCR profiling		X[18]														X		X[19]	X[19]			(X)
Circulating tumor cells [9]	(X)	(X)																				

Abbreviations and Footnotes:

X& = to be done before IMP administration; X$ = to be done after IMP administration; X&$ = to be done before and after IMP administration; (X) = optional; AE = adverse event; C = cycle (One cycle is defined as 21 days); D = day of cycle; d = day(s); DLT = dose-limiting toxicity; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; h = hour(s); ELISpot = enzyme linked immunospot (assay); EoT = End of Treatment; FFPE = formalin-fixed, paraffin-embedded; FU = follow-up; HLA = human leukocyte antigen; IMP = investigational medicinal product; PSA = prostate-specific antigen; SRC = Safety Review Committee; TCR = T cell receptor; TEAE = treatment-emergent AE; UV = unscheduled visit.

Starting with C3D1, treatment will be administered every 3 weeks until a discontinuation-of-treatment criterion is met. Planned visit schedule until C8 is shown in table. From Cycle 8 on, coagulation, blood chemistry, hematology, and urinalysis will be measured every second cycle (i.e., C8, C10, C12, etc.) unless clinically indicated.

* EoT assessments will be performed up to 21 days after administration of the last dose of IMP for patients who discontinued trial treatment, except if patient was lost to follow-up or died or the EoT visit may be combined with the Safety FU-D30 visit. For patients of Arm 1B who will optionally start cemiplimab monotherapy as outlined in the Schedule of Activities shown in Section 1.5, the EoT visit may be combined with visit CemC1 if both visits are to happen with less than 7 days difference.

** All patients (Part 1 and 2) will be actively followed up for safety (FU-D30) after last intake of BNT112. Patients in Part 2 Arm 1A will be followed up for safety (FU-D90) after last intake of cemiplimab or (FU-D30) after last intake of BNT112, whichever is later. All patients will be followed up for efficacy (FU-M6 after the last intake of IMP, FU-M12 after the last intake of IMP). Within 28 days after confirmation of disease progression, patients of Arm 1B can optionally start cemiplimab monotherapy and will follow the Schedule of Activities shown in Section 1.5 after performing the EoT for BNT112 treatment.

[1] The patient ICF for trial participation must be signed before any trial-related research procedures or interventions are performed, see Section 10.1.3. Patients who agree to additional optional tumor biopsy sample(s) in case these are taken at the time of disease progression must give written consent for this. Refusal to give consent for the optional tumor biopsy sample(s) does not exclude a patient from participation in the trial.

[2] Documentation of prostate cancer history and treatments, previous/ongoing concomitant diseases and tetanus vaccination status (see Section 8.3.2).

[3] A comprehensive physical examination will be performed at screening and abbreviated physical examinations (overall health judgment and change of symptoms) from C1D1 onwards prior to IMP administration, see Section 8.2.1.

[4] Vital signs (blood pressure, pulse rate, body temperature) should be assessed pre-treatment and 1 h (±15 min), 4 h (±1 h) and 6 h (±1 h) post-treatment and as clinically indicated during C1. Patients must be observed for at least 4 to 6 h after administration of BNT112 and vital signs collected pre-treatment, 4 to 6 h (±1 h) post-treatment and as clinically indicated.

[5] Only if clinically indicated.

[6] All prior prostate cancer-related drug treatment will be recorded; other prior medication only for the period of 28 days before the planned IMP administration.

[7] The period for documentation of concomitant treatment extends from C1D1 until Safety FU-D30 visit. Details of systemic anti-cancer treatments or non-drug anti-cancer therapies (e.g., radiotherapy, surgical therapeutic procedures) started after discontinuation of IMP will be recorded up to the end of the FU period (i.e., up to Efficacy FU-M12).

[8] Bone scans and CT/MRI of the chest, abdomen, and pelvis will be done at screening, every 8 weeks for the first 24 weeks and every 3 months thereafter (window for tumor assessment is ±7 days of respective visit day). PCWG3 and iRECIST guidelines for imaging will apply. See Section 8.1.1.1.

[9] Only if routinely performed locally.

[10] Patients in Part 1 and Part 2 Arm 1A and Arm 1B will be asked if they are willing to provide optional tumor biopsy sample(s) in case these are taken at the time of disease progression.

[11] For details on safety laboratory tests, see Section 10.2. If the time interval between screening laboratory tests and C1D1 (baseline) is more than 7 days, tests must be repeated at C1D1. Screening serum creatinine will be used to calculate patient's glomerular filtration rate required for inclusion criterion. If warranted by dipstick results, urine sediment will be microscopically examined. Serology can be done at earlier screening time point.

[12] At treatment visits, patients will also be monitored for TEAEs for at least 4 to 6 h post-treatment.

[13] For details on DLT assessment period and DLT criteria, see Sections 6.6.1.2 and 6.6.1.1.

[14] For details on patient's survival status and disease status, see Sections 10.9 and 8.1.

[15] Blood collection before and 4 h (±30 min) after administration of BNT112.

[16] Blood collection before administration of BNT112.

[17] Blood collection 4 h (±30 min) after administration of BNT112.

[18] Variable time point; either during screening ≤7 d or at C1D1 before administration of BNT112.

[19] A sample should be taken at EoT or at Safety FU and only if one has not previously been taken at C8D15.

[20] At screening for all patients, thereafter only for Arm 1A: thyroid hormones (thyroid stimulating hormone [TSH], free thyroxine [fT4] and triiodothyronine [T3]) will be performed at the times listed and every second cycle after C8 and when clinically indicated at the investigator's discretion.

[21] On-treatment tumor samples from biopsies or tumor resections done as part of the clinical management of the patient (e.g., palliative surgery) will optionally be provided for additional potential biomarker research.

[22] Randomization can be performed up to 1 day before C1D1.

1.4. Schedule of Activities: Part 2 Arms 2 and 3

	Screening		Treatment														Follow-up (FU)			UV	Surgery
1 cycle = 21 days			**C1**			**C2**			**C3**		**C4**	**C5**	**C6**	**C7**	**C8**		**EoT***	**Safety FU ****	**Efficacy FU ****			
Visit	**≤28d**	**≤7d**	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**D1**	**D15**	**D1**	**D1**	**D1**	**D1**	**D1**	**D15**		**D30/ D90**	**M6**	**M12**		
Visit window				**±1d**	**±1d**	**±1d**	**±1d**	**±1d**	**±1d**	**±3d**	**±1d**	**±1d**	**±1d**	**±1d**	**±1d**	**±3d**		**+7d**	**±14d**	**±14d**		
Patient information/ consent[1]	X																					
Demographic data	X																					
Medical history[2] and body height	X																					
Body weight	X										X&						X	X				
Physical examination[3]	X		X	X	X	X	X	X	X		X	X	X	X	X		X	X			X[5]	
ECOG PS	X		X&	X&	X&	X&	X&	X&	X&		X&	X&	X&	X&	X&		X	X			X	
Vital signs[4]	X	X	X&$	X&$	X&$	X&$	X&$	X&$	X&$	X	X&$	X&$	X&$	X&$	X&$	X	X	X			X	
Single 12-lead ECG	X										X&			X&			X[5]	X[5]			X[5]	
Concomitant treatment[6, 7]	X	X	X&	X&	X&	X&	X&	X&	X&	X	X&	X&	X&	X&	X&	X	X	X	X	X	X[5]	
Tumor response assessment[8, 13]	X														X		(X)				X	(X)
Tumor tissue (mandatory)[9]	X																					X
Optional tumor sample[22]			(X)																			
Inclusion/Exclusion criteria	X	X	X&																			
Randomization[23]			X&																			
IMP/NIMP administration:																						
Part 2 Arm 2 (with cemiplimab)																						
BNT112 (IMP)			X	X	X	X	X	X	X		X	X	X	X	X							
Cemiplimab (IMP)			X			X			X		X	X	X	X	X							
ADT (NIMP) [11]		X										X										

	Screening		Treatment															Follow-up (FU)			UV	Surgery
1 cycle = 21 days			C1			C2			C3		C4	C5	C6	C7	C8		EoT*	Safety FU **	Efficacy FU **			
Visit	**≤28d**	**≤7d**	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**D1**	**D15**	**D1**	**D1**	**D1**	**D1**	**D1**	**D15**		**D30/ D90**	**M6**	**M12**		
Visit window				**±1d**	**±1d**	**±1d**	**±1d**	**±1d**	**±1d**	**±3d**	**±1d**	**±1d**	**±1d**	**±1d**	**±1d**	**±3d**		**+7d**	**±14d**	**±14d**		
Part 2 Arm 3 (monotherapy)																						
BNT112 (IMP)			X	X	X	X	X	X	X		X	X	X	X	X							
ADT (NIMP) [11]		X										X										
Safety laboratory tests [12]																						
Serology	X																					
Hematology		X		X&	X&	X&	X&	X&	X&		X&	X&	X&	X&	X&		X	X			X[5]	
Coagulation		X				X&					X&		X&		X&		X	X			X[5]	
Blood chemistry		X		X&	X&	X&	X&	X&	X&		X&	X&	X&	X&	X&		X	X			X[5]	
Thyroid hormones [19, 21]		X				X					X		X		X			X			(X)[5]	
Urinalysis		X		X&	X&	X&	X&	X&	X&		X&	X&	X&	X&	X&		X	X			X	
AE/TEAE[14]	X	X	X&$	X&$	X&$	X&$	X&$	X&$	X&$	X	X&$	X&$	X&$	X&$	X&$	X	X	X			X	
Survival/disease status[15]																			X	X		
Blood Biomarkers																						
Cytokines			X[16]	X[16]	X[16]	X[16]	X[16]		X[16]		X[18]	X[18]	X[18]	X[18]	X[18]		X	X			(X)	
PSA		X	X[17]	X[17]	X[17]	X[17]	X[17]	X[17]	X[17]		X[17]	X[17]	X[17]	X[17]	X[17]		X	X	X	X	(X)	X [20]
ELISpot and further immune monitoring		X[19]								X						X	X[10]	X[10]			(X)	
HLA typing		X[19]																				
TCR profiling		X[19]														X	X[10]	X[10]			(X)	

Abbreviations and Footnotes

X& = to be done before IMP administration; X$ = to be done after IMP administration; X&$ = to be done before and after IMP administration; (X) = optional; ADT = androgen-deprivation therapy (e.g., goserelin acetate); AE = adverse event; C = cycle (One cycle is defined as 21 days); CT = computed tomography; D = day of cycle; d = day(s); ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; h = hour(s); ELISpot = enzyme linked immunospot (assay); EoT = End of Treatment; FFPE = formalin-fixed, paraffin-embedded; FU = follow-up; HLA = human leukocyte antigen; IMP = investigational medicinal product; mpMRI = multi-parametric magnetic resonance imaging; MRI = magnetic resonance imaging; NIMP = non-investigational medicinal product; PSA = prostate-specific antigen; REDR = recommended expansion dose range; TCR = T cell receptor; TEAE = treatment-emergent adverse event; UV = unscheduled visit; h = hour(s).

* EoT assessments will be performed up to 21 days after administration of the last dose of IMP for patients who discontinued trial treatment, except if patient was lost to follow-up or died or the EoT visit may be combined with the Safety FU-D30 visit.

** All patients (Part 1 and 2) will be actively followed up for safety (FU-D30) after last intake of BNT112. Patients in Part 2 Arm 2 will be followed up for safety (FU-D90) after last intake of cemiplimab or (FU-D30) after last intake of BNT112, whichever is later. Efficacy FU-M6 and M12 are performed for Part 2 Arms 2 and 3 after last IMP administration

[1] The patient ICF for trial participation must be signed before any trial-related research procedures or interventions are performed, see Section 10.1.3. Patients who agree to additional optional sampling must give written consent for this. Refusal to give consent for the optional sample(s) does not exclude a patient from participation in the trial, see Section 10.1.3.

[2] Documentation of prostate cancer history and treatments, previous/ongoing concomitant diseases and tetanus vaccination status (see Section 8.3.2).

[3] A comprehensive physical examination will be performed at screening and abbreviated physical examinations overall health judgment and change of symptoms) from C1D1 onwards prior to IMP administration, see Section 8.2.1.

[4] For all patients, vital signs (blood pressure, pulse rate, body temperature) should be assessed pre-treatment and 1 h (±15 min), 4 h (±1 h) and 6 h (±1 h) post-treatment and as clinically indicated during C1. Patients must be observed for at least 4 to 6 h after administration of BNT112 and vital signs collected pre-treatment, 4 to 6 h (±1 h) post-treatment and as clinically indicated.

[5] Only if clinically indicated.

[6] All prior prostate cancer-related drug treatment will be recorded; other prior medication only for the period of 28 days before the planned IMP administration.

[7] The period for documentation of concomitant treatment extends from C1D1 until Safety FU-D30 visit (Part 2 Arm 3) or FU-D90 (Part 2 Arm 2). Details of systemic anti-cancer treatments or non-drug anti-cancer therapies (e.g., radiotherapy, surgical therapeutic procedures) started after discontinuation of IMP will be recorded up to the end of the FU period (i.e., up to Efficacy FU-M12).

[8] Tumor measurement using mpMRI or MRI (window for tumor assessment is ±7 days of respective visit day). The same imaging modality should be used at screening and at all subsequent assessments. For details on tumor imaging and time points, see Section 8.1.1.

[9] An FFPE tumor sample from the diagnostic biopsy must be provided during screening. A fresh tissue sample must be provided from surgery; only if this is not feasible an FFPE tumor sample will be obtained.

[10] A sample should be taken at EoT or at Safety FU and only if one has not previously been taken at C8D15.

[11] The ADT administration should take place between 7 days before Day 1 and 12 weeks after the first administration.

[12] For details on safety laboratory tests, see Section 10.2. If time interval between screening laboratory tests and C1D1 (baseline) is more than 7 days, tests must be repeated at C1D1. Screening serum creatinine will be used to calculate patient's glomerular filtration rate required for inclusion. If warranted by dipstick results, urine sediment will be microscopically examined. Serology can be done at earlier screening time point.

[13] For details on response assessment, please refer to Section 8.1.1.2.

[14] At treatment visits, patients will also be monitored for TEAEs 4 to 6 h post-treatment.

[15] For details on patient's survival status and disease status, see Section 10.9 and Section 8.1.

[16] Blood collection before and 4 h after administration of BNT112.

[17] Blood collection before administration of BNT112.

[18] Blood collection 4 h (±30 min) after administration of BNT112.

[19] Variable time point; either during screening ≤7 d or at C1D1 before administration of BNT112.

[20] At 6 weeks (± 1 week) after the surgery (radical prostatectomy).

[21] Only for Arm 2 (and at screening for all patients if the patient is not yet randomized), thyroid hormones (thyroid stimulating hormone [TSH], free thyroxine [fT4] and triiodothyronine [T3]) will be performed at the times listed and as clinically indicated at the investigator's discretion.

[22] On-treatment tumor samples from biopsies or tumor resections done as part of the clinical management of the patient (e.g., palliative surgery) will optionally be provided for additional potential biomarker research.

[23] Randomization can be performed up to 1 day before C1D1.

1.5. Schedule of Activities: Part 2 Arm 1B – Optional Cemiplimab Treatment Following Progression after BNT112 Monotherapy

	Treatment#			Follow-up (FU)			UV
1 cycle = 21 days	**CemC1**	**≥CemC2**	**EoT ***	**Safety FU ****	**Efficacy FU ****		
Visit				**D90**	**M6**	**M12**	
Visit window	**≤28 d after progression in Arm 1b**	**±3d**		**+7d**	**±14d**	**±14d**	
Patient information/consent for cemiplimab monotherapy[1]	X@						
Physical examination[2]	X&	X&	X	X			X[3]
ECOG PS	X&	X&	X	X			X
Vital signs	X&$	X&$	X	X			X
Single 12-lead ECG	X&	X&[14]	X[3]	X[3]			X[3]
Concomitant treatment[5]	X&	X&	X	X	X	X	X[3]
Tumor response assessment[6]	X		X[3]				
Optional tumor sample[7]	(X)						
IMP Administration							
Cemiplimab (IMP)	X	X					
Safety laboratory tests [8]							
Hematology	X&	X&	X	X			X[3]
Coagulation[4]	X&		X	X			X[3]
Blood chemistry	X&	X&	X	X			(X)[3]
Thyroid hormones[4] [9]	X			X			(X)[3]
Urinalysis	X&	X&	X	X			(X)[3]
AE/TEAE [10]	X&$	X&$	X	X			X
Survival/disease status [11]					X	X	

	Treatment[#]			Follow-up (FU)			UV
1 cycle = 21 days	**CemC1**	**≥CemC2**	**EoT ***	**Safety FU ****	**Efficacy FU ****		
Visit				**D90**	**M6**	**M12**	
Visit window	**≤28 d after progression in Arm 1b**	**±3d**		**+7d**	**±14d**	**±14d**	
Blood Biomarkers							
PSA	X[&]	X[&]	X	X			(X)
Testosterone							(X)
ELISpot and further immune monitoring		X[12]					
TCR profiling		X[12]					
Circulating tumor cells [13]	(X)						

Abbreviations and Footnotes:

X[@] to be done before any CemC1-specific procedure or intervention; X[&] = to be done before IMP administration; X[$] = to be done after IMP administration; X[&$] = to be done before and after IMP administration; (X) = optional; AE = adverse event; CemC = cycle (One cycle is defined as 21 days); d = day(s); ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; h = hour(s); ELISpot = enzyme linked immunospot (assay); EoT = End of Treatment; FFPE = formalin-fixed, paraffin-embedded; FU = follow-up; IMP = investigational medicinal product; mCRPC = metastatic castration-resistant prostate cancer; PSA = prostate-specific antigen; SRC = Safety Review Committee; TCR = T cell receptor; TEAE = treatment-emergent adverse event; UV = unscheduled visit.

[#] Treatment will be administered every 3 weeks until a discontinuation-of-treatment criterion is met.

* EoT assessments will be performed up to 21 days after administration of the last dose of cemiplimab for patients who discontinued trial treatment, except if patient was lost to follow-up or died.

** All patients will be actively followed up for safety (FU-D90) after last intake of cemiplimab. All patients will be followed up for efficacy (FU-M6 after the last intake of IMP, FU-M12 after the last intake of IMP).

[1] The patient ICF for cemiplimab monotherapy must be signed before any trial-related research procedures or interventions are performed on CemC1, see Section 10.1.3. Patients who agree to additional optional sampling must give written consent for this. Refusal to give consent for the optional sample(s) does not exclude a patient from participation in this part of the trial, see Section 10.1.3.

[2] A comprehensive physical examination will be performed at CemC1 and abbreviated physical examinations (overall health judgment and change of symptoms) from CemC2 onwards prior to IMP administration, see Section 8.2.1.

[3] Only if clinically indicated.

[4] Assessments will be performed at CemC1 and then every second cycle (every 6 weeks)

[5] The period for documentation of concomitant treatment extends from CemC1 until Safety FU-D90 visit. Details of systemic anti-cancer treatments or non-drug anti-cancer therapies (e.g., radiotherapy, surgical therapeutic procedures) started after discontinuation of IMP will be recorded up to the end of the FU period (i.e., up to Efficacy FU-M12).

[6] Bone scans and CT/MRI of the chest, abdomen, and pelvis will be done every 3 months (window for tumor assessment is ±7 days of respective visit day). PCWG3 and iRECIST guidelines for imaging will apply. See Section 8.1.1.1.

[7] On-treatment tumor samples from biopsies or tumor resections done as part of the clinical management of the patient (e.g., palliative surgery) will optionally be provided for additional potential biomarker research.

[8] For details on safety laboratory tests, see Section 10.2. If warranted by dipstick results, urine sediment will be microscopically examined.
[9] Thyroid hormones (thyroid stimulating hormone [TSH], free thyroxine [fT4] and triiodothyronine [T3]) will be performed every 6 weeks, at Safety FU D90, or as clinically indicated at the investigator's discretion.
[10] At treatment visits, patients will also be monitored for TEAEs at site, according to local prescribing guidelines for cemiplimab.
[11] For details on patient's survival status and disease status, see Sections 8.1 and 10.9.
[12] Sampling at CemC3 or at EoT, whichever occurs first.
[13] Only if routinely performed locally.
[14] Assessments will be performed at CemC1, CemC4, CemC7 and when considered as clinically indicated by the investigator.

2. Introduction

2.1. Background

2.1.1. Overview of the Disease(s)

Prostate cancer is the second most common malignant neoplasm in men worldwide, with an estimated 1,276,106 incidences and 358,989 deaths in 2018. The incidence of prostate cancer has increased over the past 20 years (largely due to the wide availability of prostate-specific antigen [PSA] testing), and currently prostate cancer is the most frequently diagnosed cancer among men worldwide (13.5%); in Germany (18.9%), the United Kingdom (UK; 23.6%) and in the United States of America (USA; 18.5%). Although mortality rates do not follow those of incidence, prostate cancer is still the fifth cause of cancer-related death worldwide (6.7%) and the leading cause of cancer deaths among men in 46 less-developed countries.[5, 6]

PSA is a protein exclusively generated in prostate cells and high levels of PSA in the blood are often an indication of prostate cancer. Blood levels of PSA are commonly used to gauge the success of treatment, and the presence of recurrence. The risk of clinically significant prostate cancer is related to age, ethnicity, family history, PSA level, free/total PSA ratio, and findings from digital rectal examination.[32] PSA screening for prostate cancer reduces prostate cancer mortality by allowing early diagnosis of the disease and implementation of curative treatments in many patients.

In Western countries, most patients with prostate cancer are diagnosed with local disease and present with a low, intermediate, or high-risk of biochemical relapse. Approximately 15% of patients are classified as high-risk LPC.[24] These patients are at an increased risk of recurrence, need for secondary therapy, metastatic progression, and death from prostate cancer. These patients have a significant overall survival (OS) benefit from radical prostatectomy, with a relative risk reduction in mortality of 31%.[7] LPC remains a major cause of mortality, as the prostate cancer mortality worldwide during the 15 years after local treatment ranges from 6 to 121 deaths per 1000 persons per year, depending on the Gleason score.[32] Selection of an efficient treatment strategy is crucial for patients with high-risk LPC. Recently, multimodal treatment approaches that combine systemic and local therapies have been introduced and offer a promising strategy for improving the clinical outcomes of patients with LPC.[10] This includes chemotherapy, hormonal therapy, as well as newly introduced immune checkpoint inhibitors and anti-cancer vaccines.

In patients with recurrent or metastatic prostate cancer, there is initial benefit from hormonal therapies; however, patients invariably stop responding to ADT, a state known as castration-resistant prostate cancer (CRPC). Although multiple new agents have been approved for metastatic CRPC (mCRPC) over the last decade which prolong survival and provide palliative benefit[36], as of today there is no curative treatment for mCRPC available. The prognosis for patients with mCRPC is variable with median OS ranging from 16 to 34 months.

Despite advances in treatment of both LPC and mCRPC, the unmet medical need for these patients remains high and novel therapeutic approaches are being investigated.

According to the guidelines of the European Association of Urology - European Society for Radiotherapy & Oncology - International Society of Geriatric Oncology, the initial treatment with curative intent for LPC includes surgery (i.e., radical prostatectomy), or dose-escalated intensity-modulated radiation therapy in combination with ADT.[1] However, the latter treatment is associated with increased risk of death from cardiovascular diseases.[25] Radical prostatectomy as a single modality leaves about 30% of patients with positive surgical margins after radical prostatectomy and about 30% of these patients experience biochemical recurrence.

The benefit of combined ADT and radiotherapy in patients with locally advanced prostate cancer has been proved in randomized clinical trials.[22, 23, 33] This treatment modality is now also recommended in patients with high-risk LPC.[4] For example, goserelin acetate (Zoladex®) is approved as neoadjuvant treatment prior to radiotherapy and is also used prior to radical prostatectomy in patients with high-risk localized or locally advanced prostate cancer where Zoladex® has demonstrated improved disease-free survival (DFS). Neoadjuvant systemic treatments have been investigated for many years, so far without evidence from Phase 3 randomized trials regarding the benefit of neoadjuvant treatment in LPC patients. There are two outcomes for neoadjuvant treatment: (i) reduction of tumor volume facilitating complete surgical resection, providing the control of microscopic metastatic disease and to assess the treatment effect in the tissue performing accurate staging of the disease, Gleason score and surgical margins and (ii) a prolonged effect of neoadjuvant treatment on OS or its surrogate. A meta-analysis published in 2017 of randomized controlled trials in patients with LPC showed that metastasis-free survival is a strong surrogate of OS.[27]

In order to establish better neoadjuvant treatment options for patients with high-risk LPC, several Phase 1 and Phase 2 studies are ongoing that implement novel immunotherapies in combination with hormone deprivation therapies or chemotherapies.

The initial treatment of choice for metastatic prostate cancer is medical or surgical castration with hormonal therapy being the standard of care since the 1940s. However, prostate cancer inevitably progresses to CRPC after 16 to 34 months on ADT. Currently, mCRPC is usually treated with chemotherapy (docetaxel, mitoxantrone, and cabazitaxel) or secondary hormonal therapeutic agents such as abiraterone or enzalutamide.[26] Immunotherapy with sipuleucel-T has been employed in treating asymptomatic or minimally metastatic CRPC without visceral metastasis. Bone metastasis is managed with zoledronic acid, denosumab, or radium-223.[38] Radium-223 is used for symptomatic bone metastasis without visceral metastasis.[11] However, the effects of these treatments are less than satisfactory, and the need for novel agents in treating mCRPC is still present.

2.1.2. Introduction to the Investigational Medicinal Products

2.1.2.1. BNT112 (IMP 1)

BNT112 (previously referred to as W_pro1 in this and other trial-related documentation) consists of messenger RNA (mRNA; further referred to as RNA) targeting 5 antigens expressed in *de novo* and metastatic prostate cancer that are separately complexed with liposomes to form serum-stable RNA lipoplexes (RNA-LPXs). The RNA molecules are immune-pharmacologically optimized for high stability, translational efficiency and presentation on major histocompatibility complex (MHC) class I and II molecules.[17, 28, 18] Following preparation, the final products are administered as five separate, consecutive IV injections.

The MoA of RNA-LPX vaccination relies on the recruitment of antigen-specific T-lymphocytes after presentation of peptide-epitopes derived from the RNA-encoded antigens on MHC molecules by professional antigen-presenting cells (APCs), and toll-like receptor (TLR)-mediated immune-modulatory effects, which lead to cell activation and to the induction of pro-inflammatory cytokines such as type I interferons (IFNs), thereby enhancing the vaccination effects.[16]

The IV injected RNA-LPXs are selectively taken up by professional APCs in secondary lymphatic tissues including spleen, lymph nodes, and bone marrow. The RNA-encoded antigens are presented by APCs and induction of vaccine antigen-specific $CD8^+$ and $CD4^+$ T cell responses and T cell memory is initiated.[17] This is further supported by the local RNA-LPX–induced immune-modulation in the lymphoid compartments. In addition, BNT112 also has the potential to induce dendritic cell activation.

2.1.2.2. Cemiplimab (LIBTAYO®; IMP 2)

Cemiplimab is a high affinity IgG4P human antibody to the PD-1 receptor (PDCD1, CD279) that blocks PD-1/PD-L1-mediated T cell inhibition. Cemiplimab is approved in the US, European Union (EU), Canada and other countries for the treatment of advanced cutaneous squamous cell carcinoma (CSCC), patients with non-small cell lung cancer (NSCLC) expressing PD-L1 (in ≥50% tumor cells), and locally advanced or metastatic basal cell carcinoma (BCC)[41, 42, 43]. Additional background information on the trial drug and development program can be found in the latest version of the cemiplimab Investigator's Brochure (IB).

2.1.3. Non-Investigational Medicinal Products (NIMP)

2.1.3.1. Androgen-deprivation therapy followed by radical prostatectomy

Patients should be eligible for up to 6 months of ADT followed by radical prostatectomy. The sponsor will provide goserelin acetate if requested by the investigational site, however other types of ADT are allowed according to local clinical practice. In such cases, the investigational site will organize and reimburse the ADT of choice. The ADT can be interrupted any time prior to the radical prostatectomy and/or other clinically indicated treatment or intervention based on the investigator's decision.

Goserelin acetate (e.g., Zoladex® LA 10.8 mg implant): The luteinizing hormone-releasing hormone (LHRH) agonist Goserelin acetate, (synonym: D-Ser(But)6Azgly10-LHRH) is a synthetic analogue of the naturally occurring gonadotropin releasing hormone. Goserelin acetate 10.8 mg is indicated in the treatment of metastatic or locally advanced prostate cancer and as adjuvant treatment to radical prostatectomy or radiotherapy, and as neoadjuvant treatment prior to radiotherapy in patients with high-risk localized or locally advanced prostate cancer. Goserelin acetate is injected subcutaneously (SC) into the anterior abdominal wall every 12 weeks (Q12W). On chronic administration, goserelin acetate results in inhibition of pituitary luteinizing hormone secretion leading to a fall in serum testosterone concentrations in males and serum estradiol concentrations in females. This effect is reversible on discontinuation of therapy. Initially, goserelin acetate, like other LHRH agonists, may transiently increase serum testosterone concentration in men and serum estradiol concentration in women. In men, by around 21 days after the first depot injection, testosterone concentrations have fallen to within

the castrate range and remain suppressed with treatment Q12W. This inhibition leads to prostate tumor regression and symptomatic improvement in the majority of patients.

In the management of patients with metastatic prostate cancer, goserelin acetate has been shown in comparative clinical trials to give similar survival outcomes to those obtained with surgical castrations. In comparative trials, goserelin acetate has been shown to improve DFS and OS when used as an adjuvant therapy to radiotherapy in patients with LPC (T1-T2 and PSA of at least 10 ng/mL or a Gleason score of at least 7), or locally advanced (T3-T4) prostate cancer.

Very common (≥1/10) adverse drug reactions (ADRs) include hot flushes, hyperhidrosis, a decrease in libido and erectile dysfunction. These are pharmacological effects which seldom require withdrawal of therapy. Hyperhidrosis and hot flushes may continue after stopping goserelin acetate. For full details, see the Summary of Product Characteristics (SmPC) for Zoladex® LA 10.8 mg implant.[3]

Goserelin acetate is currently approved for the treatment of locally advanced prostate cancer. For the purposes of this trial, goserelin acetate is being used as a component of primary therapy for LPC, as outlined in the respective country prescribing information.

2.2. Trial Rationale

Over the last few years, immunotherapy has become a promising part of the treatment of various solid tumors. Since ipilimumab (Yervoy®, an anti-cytotoxic T-lymphocyte-associated protein [CTLA]-4 monoclonal antibody; Bristol-Meyer Squibb, Princeton, New Jersey, USA), was first approved in 2010 in the USA for late-stage melanoma, a number of new immunotherapy agents have entered development. Most notably, agents that block the programmed cell death receptor-1 (PD-1)/programmed cell death 1 ligand 1 (PD-L1) axis have been shown to prolong survival in patients with NSCLC, melanoma, kidney cancer, head and neck cancer, and others. Adoptive cellular therapy, mainly chimeric antigen receptor T cells, has shown activity in melanoma, lymphomas and leukemia. In prostate cancer, a vaccine-based active cellular therapy (sipuleucel-T [Provenge®]; Dendreon Corporation, Seattle, Washington, USA) is approved for mCRPC.

The new strategy of combining tumor vaccination with checkpoint inhibitors is being developed as potentially effective in cancer treatment. Nivolumab plus a multi-peptide vaccine (gp100, MART-1 [melanoma antigen recognized by T cells 1], and NY-ESO-1 [New York esophageal squamous cell carcinoma-1] with Montanide ISA 51 VG) has been investigated as adjuvant therapy in resected stage IIIC and IV melanoma patients in a Phase 1 trial, where the combination showed an acceptable safety profile. Despite this early success and the promise shown by the immune checkpoint inhibitors in other cancer types, immunotherapy in prostate cancer has been less effective than hoped for, with negative results in studies of checkpoint inhibitors[15] and those with other vaccines such as GVAX® (VITAL-1 and VITAL-2) and Prostvac (PROSPECT).

Immunotherapy for prostate cancer has many challenges to overcome, including lack of tumor immunogenicity as well as the major obstacle that prostate cancer is poorly infiltrated by T cells as compared to some of the more responsive tumor types where checkpoint inhibitors are already approved. The lack of efficacy of checkpoint inhibitors is probably caused by both the low expression of checkpoint ligands on prostate tumors and the low mutational burden in prostate cancers. Conversely, prostate cancer expresses several antigens restricted to the organ itself and

maintained in the process of malignant transformation (e.g., prostate-specific membrane antigen, PSA and prostatic acid phosphatase [PAP]), which makes it a good target for vaccines, potentially turning the "cold" tumors to "hot."

This Phase 1/2A safety, immunogenicity, pharmacodynamics, and efficacy trial with RNA-LPX vaccine targeting 5 tumor-associated antigens (TAAs) specific for *de novo* as well as metastatic prostate cancer, discovered and developed by BioNTech RNA Pharmaceuticals GmbH, predecessor of BioNTech SE (hereinafter referred to as "sponsor"), will be conducted in both neoadjuvant for LPC, and mCRPC settings. The clinical trial will initially start enrolling only mCRPC patients who have progressed after two prior lines of systemic therapy. After initial safety of the vaccine monotherapy is established, four expansion cohorts will be opened including two for newly diagnosed patients with high-risk LPC eligible for up to 6-month treatment with ADT (e.g., goserelin acetate) followed by radical prostatectomy. Patients with mCRPC will be given the option to be treated with cemiplimab monotherapy following progression after BNT112 monotherapy.

This clinical setting was selected based on the following rationale:

i. it provides a unique opportunity for the patients whose immune systems have not yet been exposed to prior hormonal and/or chemo/radiotherapy where an immunotherapy is believed to have the potential to stimulate long-lasting anti-tumor immune responses;
ii. the addition of BNT112 monotherapy and combination with cemiplimab does not interfere with the established clinical practice and will not delay the planned treatment for these patients (i.e., the hormonal therapy followed by planned radical prostatectomy);
iii. the addition of cemiplimab will begin to test the hypothesis that the immune response to tumor cells generated by the vaccine can be enhanced by the addition of a checkpoint inhibitor[39];
iv. the clinical setting provides a unique opportunity to study tumor-related biomarkers utilizing biopsies which are part of the established diagnostic work-up of the newly diagnosed patients;
v. careful safety monitoring including implementation of the SRC, which ensures the safety and well-being of the patients enrolled in this trial;
vi. it provides an opportunity for patients treated with BNT112 monotherapy to be treated with the anti-PD-1 cemiplimab after progression and to check the potential benefit of a sequential therapy.

The RNA-LPX cancer vaccine induces activation of both the adaptive immune system (vaccine antigen-specific $CD8^+/CD4^+$ T cell) as well as the innate immune system (TLR7-agonism of single-stranded RNA). The physiology of efficient induction, expansion and differentiation of antigen-specific T cells is associated with PD-1 upregulation on these T cells. Thus, the cancer vaccine is expected to have a synergistic MoA with anti-PD-1. One reason for treatment failure in patients treated with PD-1/PD-L1 blockade is the lack of preformed antigen-specific T-lymphocytes recognizing relevant tumor antigens. These are generated by the RNA-LPX cancer vaccine, which induces potent antigen-specific $CD4^+$ and $CD8^+$ T cell responses. These T cells not only execute direct anti-tumor activity by their cytotoxicity upon recognition of their target antigens on tumor cells, but they also induce inflammation (e.g., IFNγ secretion) in the tumor microenvironment thereby sensitizing tumor cells to the therapeutic effects of checkpoint inhibitors. The contribution of both mechanisms to anti-tumor efficacy is supported by non-

clinical studies in mice bearing syngeneic tumors treated with RNA-LPX vaccine alone or in combination with anti-PD-1/PD-L1 blockade.

In summary, the MoA of BNT112 both in monotherapy and in combination with the anti-PD-1 immune checkpoint inhibitor cemiplimab, together with carefully selected and refined clinical setting, presents a unique opportunity for patients with different stages of prostate cancer.

2.3. Benefit/Risk Assessment

The purpose of the PRO-MERIT trial is to test prostate cancer-associated antigens encoded in BNT112 for the first time in patients with different stages of prostate cancer.

As of today, the RNA-LPX based cancer vaccines have been administered in more than 270 patients with melanoma, triple negative breast cancer (TNBC), and human papilloma virus $(HPV)^{+}$ cancers and demonstrated a favorable safety and tolerability profile in different indications, different treatment settings (metastatic, post neo-adjuvant, adjuvant) and with different types of cancer vaccine antigens. In these clinical trials, no dose-limiting toxicities (DLTs) were reported during dose escalation, the TEAEs considered related to trial drug were transient, mostly Grade 1 and 2, and likely associated with the specific format of encoding and delivering the vaccine antigens, namely single-stranded RNA formulated as a DOTMA (1,2-di-O-octadecenyl-3-trimethylammonium propane)/DOPE (1,2-Dioleoyl-sn-glycero-3-phosphoethanolamine) lipoplex. In summary, the class-intrinsic safety profile of RNA-LPX *per se* appears to be dominated by mild-to-moderate, transient and manageable influenza-like AEs. These AEs are expected based on the distinct range of cytokines released by RNA-LPX. In addition, transient lymphopenia (by sequestration) observed in laboratory examinations is expected to be mediated by Type 1 IFN.

In addition to RNA-LPX class-intrinsic risks, potential risks related to the individual vaccine antigen targets are to be considered, which may potentially result in “on-target/off-tumor” toxicities mediated by the respective antigen-specific T cells. As the targets for the proposed prostate cancer trial were not used before in conjunction with the RNA-LPX format, the risk of on-target/off-tumor toxicity cannot be deduced from the ongoing trials. This risk is mitigated by selecting antigens with exquisitely cancer cell selective expression and lack of expression in vital normal tissues. The same pipeline has been used to select the cancer type specific vaccine antigens in the other ongoing RNA-LPX trials. Moreover, 2 of the 5 selected vaccine antigens have been used in trials by other sponsors in conjunction with other vaccine formats without indications of autoimmunity. Therefore, the risk of on-target/off-tumor toxicity is considered low.

Given that the Good Laboratory Practice (GLP) toxicology studies did not identify a no observed adverse effect level, the maximum dose (i.e., CCI µg total RNA) used safely in humans in the melanoma trials justifies the entire proposed dose range for the proposed trial.

The planned trial will address in the safety program potential risks of both the vaccine format (considered low based on aggregate data from all RNA-LPX trials conducted by the sponsor), and immunopathology associated with T cells induced against the individual vaccine targets (considered low based on the sponsor’s ongoing clinical trials and cumulative data in the public domain from other vaccine trials).

Part 1 (dose titration) of the PRO-MERIT trial has been performed in the UK and Hungary and enrollment has been completed with 9 patients dosed. The SRC reviewed the available safety data for patients in Part 1 on 17 MAY 2021. The safety profile observed indicates that BNT112 is a tolerable drug product with a manageable safety profile at the defined dose range (CCI to CCI µg) using the intra-patient step-up dose titration scheme. Observed AEs considered related to the IMP (including pyrexia, flu-like symptoms, hypertension, nausea, chills or headache), are in line with the innate immune activation by RNA-LPX, are transient in nature and manageable by analgesics, antipyretics or fluids at recommended and usual doses. The recommendation was to continue to Part 2 at the selected REDR (CCI µg) using the intra-patient step-up dose titration scheme.

The annual review of safety data for the IB update occurred on 20 MAY 2021 (data extraction date) and included safety data from patients in Part 1 as well as Part 2. Neither the safety profile nor the benefit-risk assessment were changed.

The sponsor's ongoing Lipo-MERIT Phase 1 clinical trial in melanoma (NCT02410733) has provided promising signals for single agent and anti-PD-1 combination activity of RNA-LPX cancer vaccine against melanoma-shared antigens in pretreated checkpoint inhibitor-experienced patients with high medical need and limited treatment options. It has further demonstrated that in almost every patient the vaccine executes its MoA, inducing T cells against at least one of the antigens. A considerable fraction of these immune responses was strong (measurable *ex vivo)* and both new T cells were primed and pre-existing T cells were expanded. Responses were both $CD8^+$, but also $CD4^+$, indicating that effector T cells received cognate T cell help in the priming process. It is expected that, in particular for patients that are refractory to anti-PD-1 (meaning that activation of pre-existing memory T cells only is not sufficient to mediate clinical activity), combining the vaccine with anti-PD-1 (which would rescue newly primed T cells specificities from exhaustion) is synergistic. This expectation is supported by data from non-clinical experiments.

Arm 1A and Arm 2 of the proposed clinical trial explores a combination of BNT112 and cemiplimab, anti-PD-1 antibody. Antibodies to PD-1/PDL-1 have been shown to be effective therapeutic options for cancer treatment. Cemiplimab is a fully human monoclonal antibody against PD-1 and is currently being evaluated in patients with advanced solid malignancies and B-cell lymphomas whose cancer are incurable and/or have failed to respond to or showed tumor progression despite standard therapy, or patients who are not candidates for standard therapy, or for whom no available therapy is expected to convey clinical benefit. Cemiplimab has demonstrated efficacy (based on ORR and DoR) and is approved in the U.S. for patients with advanced CSCC, NSCLC, and BCC. Patients in Arm 1b will be given the option to be treated with cemiplimab monotherapy after progression with BNT112 monotherapy.

In addition to the potential safety risks, there is a potential unknown risk related to a delayed radical prostatectomy in patients with newly diagnosed LPC. In order to address this risk, patients will be followed for up to 12 months after the last dose of either IMP and the treating physicians will be able to adjust the treatment also during the course of the trial in case earlier intervention is needed.

In summary, the potential benefits of the proposed trials include clinical responses and the generation of lasting T cells against prostate cancer TAAs both in BNT112 monotherapy and in combination with cemiplimab. This could potentially translate into clinically significant and

durable efficacy, which is of prime importance to patients and outweighs the potential risks outlined above. This warrants development of BNT112 in monotherapy and in combination with cemiplimab in patients with various stages of prostate cancer.

Furthermore, the clinical data generated with the RNA-LPX cancer vaccines thus far in melanoma, TNBC and HPV+ cancers in monotherapy and in combination with anti-PD-1 antibodies demonstrate a positive risk-benefit assessment and warrant further development of the RNA-LPX cancer vaccine in new indications, such as prostate cancer. The safety profile of cemiplimab is similar to the safety profile of other anti-PD-1/PD-L1. The important identified risks are immune-related AEs and injection-related reactions. Based on the currently available safety information for cemiplimab, safety information from other anti-PD-1 antibodies, the adequate risk identification and minimization described in the cemiplimab IB/protocols/ICFs, the emerging preliminary activity of cemiplimab on solid malignancies (including CSCC, NSCLC, and cervical cancer), the benefit-risk is considered favorable for continued clinical trials in these and other indications.

For further information about the known and potential risks of BNT112 and cemiplimab, refer to the latest version of the respective IB (BNT112 or cemiplimab).

3. Objectives and Endpoints

Trial objectives and endpoints are listed in Table 3-1.

Table 3-1: Objectives and endpoints of the clinical trial

OBJECTIVES	ENDPOINTS
PRIMARY OBJECTIVE	**PRIMARY ENDPOINTS**
• (Part 1 and Part 2) Assess safety and tolerability profile of BNT112 monotherapy or in combination with cemiplimab	• Occurrence of DLTs. • Occurrence of TEAEs reported by relationship, grade, and seriousness according to NCI CTCAE v5.0.
• (Part 2 Arms 1a and 1b) Evaluate preliminary anti-tumor activity of BNT112 monotherapy and in combination with cemiplimab in patients with mCRPC based on ORR	• ORR, defined as the number of patients with a CR or PR per PCWG3[29] as determined by the investigator as best objective response divided by the number of patients in the analysis set.
SECONDARY OBJECTIVES	**SECONDARY ENDPOINTS**
• Evaluate anti-tumor activity based on levels of PSA	• PSA decline of 0 to 25%, >25% to 50%, and >50% compared to baseline. • PSADT post-treatment on C4D1 and D1 of every fourth subsequent cycle (e.g., C8D1, C12D1, etc.) in Part 1 and Part 2 Arm 1A and 1B, or on C4D1, C8D1, and EoT in Part 2 Arms 2 and 3 compared to baseline.

OBJECTIVES	ENDPOINTS
	• PSA decline of ≥50% (according to the PCWG3).
• (Part 1) Evaluate preliminary anti-tumor activity of BNT112 monotherapy in patients with mCRPC based on ORR	• ORR, defined as the number of patients with a CR or PR per PCWG3[29] as determined by the investigator as best objective response divided by the number of patients in the analysis set.
• Evaluate preliminary anti-tumor activity of BNT112 monotherapy or in combination with cemiplimab in patients with newly diagnosed LPC	• Tumor response post-treatment compared to baseline.
EXPLORATORY OBJECTIVES	**EXPLORATORY ENDPOINTS**
• Determine systemic induction/expansion of BNT112 antigen-specific T cells for BNT112 monotherapy or in combination with cemiplimab	• Occurrence of *de novo* induction or increase of BNT112 antigen-specific T cells in peripheral blood under treatment on C3D15, and/or C8D15, EoT, or safety follow-up compared to baseline.
• Evaluate preliminary anti-tumor activity of BNT112 monotherapy and in combination with cemiplimab in patients with mCRPC	• DoR, defined as the time from the first occurrence of a documented OR to the time of the first disease progression per PCWG3[29], as determined by the investigator, or death from any cause, whichever occurs first. • ORR and DoR, defined as above, using iRECIST.[30] • PFS, defined as the time from the first trial treatment to the first disease progression per PCWG3,[29] as determined by the investigator, and per iRECIST[30] determined by central reading, or death from any cause, whichever occurs first. • OS, defined as the time from first trial treatment until death from any cause. • Number of cycles received and RDI.
• Evaluate preliminary anti-tumor activity of cemiplimab in patients with mCRPC who have been previously treated with, and who have progressed after BNT112 monotherapy	• ORR, defined as the number of patients with a CR or PR per PCWG3 as determined by the investigator as best objective response divided by the number of patients in the analysis set. • DoR, defined as the time from the first occurrence of a documented OR to the time of the first disease progression per PCWG3, as determined by the investigator, or death from any cause, whichever occurs first. • ORR and DoR, defined as above, using iRECIST. • PFS, defined as the time from the first trial treatment to the first disease progression per PCWG3, as determined

OBJECTIVES	ENDPOINTS
	by the investigator, and as per iRECIST determined by central reading, or death from any cause, whichever occurs first. • PFS2, defined as the time from the first trial treatment to the first disease progression after start of cemiplimab per PCWG3 as determined by the investigator, or death from any cause, whichever occurs first. • OS, defined as the time from first trial treatment until death from any cause. • Number of cycles received and RDI.
• Assess safety and tolerability profile of cemiplimab monotherapy in patients following progression after BNT112 monotherapy	• Occurrence of TEAEs reported by relationship, grade, and seriousness according to NCI CTCAE v5.0.
• Evaluate preliminary anti-tumor activity of BNT112 monotherapy or in combination with cemiplimab in patients with newly diagnosed LPC	• PFS, defined as the time from the first trial treatment to the first disease progression per PCWG3 as determined by the investigator, or death from any cause, whichever occurs first. • OS, defined as the time from first trial treatment until death from any cause.
• Preliminary assessment of biomarkers that might act as potential predictive, pharmacodynamics, anti-tumor, and safety indicators of activity of BNT112 monotherapy or in combination with cemiplimab	• Status of tumor mutational burden and immune-related gene expression (at the RNA level) in tumor tissue prior to treatment. • Change in protein expression pattern/levels of tumor microenvironment markers (e.g., CD3, CD8, MHC-I, PD-L1, etc.) and prostate tumor markers (e.g., PSA, PSAP, NKX3-1, etc.) in tumor tissue post-treatment compared to baseline. • Baseline status or change in RNA target expression of BNT112–encoded antigens in the post-treatment tissue compared to baseline. • Change in T cell clonality/diversity post-treatment compared to baseline. • Changes in blood biomarkers prior to and during trial treatment.

Abbreviations: AE = adverse event; C = Cycle; CR = complete response; CTCAE v5.0 = Common Terminology Criteria for Adverse Events, version 5.0; D = Day of cycle; DLT = dose-limiting toxicity; DoR = duration of response; EoT = End of Treatment; iRECIST = immune-modified Response Evaluation Criteria in Solid Tumors; MHC = major histocompatibility complex; NCI = National Cancer Institute; NKX3-1 = NK3 homeobox 1; OR = objective response; ORR = objective response rate; PCWG3 = Prostate Cancer Working Group 3; PD-L1 = programmed cell death 1 ligand 1; PFS = progression-free survival; PR = partial response; PSA = prostate-specific antigen; PSADT = prostate-specific antigen doubling time; PSAP = prostate-specific acid phosphatase; RDI = relative dose intensity.

4. Trial Design

4.1. Overall Design

The trial consists of 2 parts: Part 1 (dose titration) and Part 2 (dose expansion). Part 2 consists of four arms: Arms 1A and 1B (mCRPC patients) and Arms 2 and 3 (LPC patients).

Part 1 contains a dose titration for initial safety assessment and identification of the recommended expansion dose range (REDR). It will enroll mCRPC patients to receive BNT112 monotherapy at 3 predefined dose levels (DLs) until a discontinuation-of-treatment criterion is met (Section 7). Part 1 of the trial will employ a modified 3+3+3 design (adapted from Hamberg et al. 2010[13]) with up to 9 evaluable patients.

Once the REDR is defined, the trial will commence with Part 2 and enroll approximately 106 patients in four arms (the expansion part, Section 4.2). Part 2 Arms 1A and 1B will enroll patients with mCRPC to receive BNT112 monotherapy or BNT112 in combination with cemiplimab, and Part 2 Arms 2 and 3 will enroll patients with newly diagnosed LPC eligible for treatment with ADT (e.g., goserelin acetate) to receive BNT112 monotherapy or BNT112 in combination with cemiplimab.

Enrollment between Arms 1A and 1B in Part 2 and between Arms 2 and 3 will be randomized 1:1 to avoid enrollment bias.

The treatment in Part 2 Arms 1A and 1B will continue until a discontinuation-of-treatment criterion is met (Section 7). In Part 2 Arms 2 and 3 the treatment will be stopped at Cycle 8 Day 1 (C8D1) or until a discontinuation-of-treatment criterion is met (Section 7).

The safety of BNT112 in doses CCI µg, CCI µg, and CCI µg will be evaluated based on DLTs during the first treatment cycle (21 days) as well as the overall incidence of BNT112-related or potentially related TEAEs in both parts of the trial. The safety of concomitant administration of cemiplimab will be evaluated based on the overall incidence of cemiplimab-related or potentially related TEAEs in Part 2 Arms 1A and 2 of the trial and will follow the same rules as Part 1, until the SRC reviews and confirms that the combination safety profile is acceptable to continue with the enrollment for the combination arms. The safety will be evaluated by the SRC. For details, please refer to Section 9.6 and the SRC charter.

The efficacy measurement in mCRPC patients (i.e., Part 1 and Part 2 Arms 1A and 1B) will be tumor response assessment by on-treatment imaging every 8 weeks (±7 days) for 24 weeks, and then every 3 months (±7 days) thereafter until a discontinuation-of-treatment criterion is met (Section 7) as assessed by the investigator. The Prostate Cancer Working Group 3 (PCWG3) criteria[29] and immune-modified Response Evaluation Criteria in Solid Tumors (iRECIST) criteria[30] will be used for endpoint response evaluation. If the investigator considers radiographic changes secondary to drug-induced inflammation and not to tumor progression, the investigator may postpone a diagnosis of PD until the next radiographic evaluation in the trial.

Following progression after BNT112 monotherapy, patients in Arm 1B will have the option to be treated with cemiplimab monotherapy.

The efficacy in LPC patients (i.e., Part 2 Arms 2 and 3) will be assessed by tumor measurement using mpMRI or MRI consistently throughout the trial. The same imaging modality should be used at screening and at all subsequent assessments.

Various blood- and tumor-based biomarkers will be analyzed in both parts.

The trial will be conducted in approximately 30 trial centers in up to 5 countries.

Trial periods are provided in the Schedule of Activities (SoA).

4.1.1. Part 1

Trial Part 1 will identify the REDR of BNT112 monotherapy in patients with histologically confirmed mCRPC who progressed after at least 2 but no more than 3 lines of life-prolonging systemic therapy (e.g., abiraterone or enzalutamide, docetaxel, cabazitaxel) or who cannot tolerate or have refused any of these therapies.

Three doses of BNT112 cancer vaccine will be used for an intra-patient dose titration accommodating the inter- as well as intra-patient variability of the immune system activation:

- DL1 [starting dose]: CCI µg of total RNA CCI µg of RNA of each antigen)
- DL2 [intermediate dose]: CCI µg of total RNA (CCI µg of RNA of each antigen)
- DL3 [target dose]: CCI µg of total RNA (CCI µg of RNA of each antigen)

One additional DL of CCI µg of total RNA (with CCI µg of RNA of each antigen) can be used for dose reductions (see Section 6.6.1).

BNT112 will be given in the following dose schedule: D1, D8, and D15 of C1 and C2 and D1 from C3 onwards. The individual dose titration will be conducted during C1 with DL1 on D1, DL2 on D8 and DL3 on D15.

For the first 3 patients: (i) patients will be enrolled in a staggered manner with a safety monitoring interval of at least 1 week between the first and the second patient, and between the second and the third patient, and (ii) an overnight stay is required on C1D1, C1D8, and C1D15. On the 17 MAY 2021, the SRC recommended that patient monitoring can be limited to 4 to 6 h and no overnight stay is required.

A minimum of 3 patients will be evaluated for a DLT assessment period defined as 1 cycle (21 days), see Section 6.6.1.1. At the discretion of the investigator, the dose of BNT112 may be maintained at the current DL for 1 dose, i.e., intra-patient dose titration may be delayed (see Section 6.6.1.1). For these patients, the DLT assessment period is extended to 28 days.

The dose titration will be conducted according to the following rules (also refer to Table 4-1):

- If none of the first 3 DLT evaluable patients in Part 1 experience a DLT at any given DL (i.e., CCI µg, CCI µg, and CCI µg), the REDR will be confirmed and Part 2 will be initiated.
- If 1 of the first 3 DLT evaluable patients in the Part 1 experiences a DLT, 3 additional patients will be enrolled in Part 1.
- If fewer than 2 of 6 DLT evaluable patients in Part 1 experience a DLT/DLTs (i.e., no additional DLTs in the last 3 patients), Part 2 will be initiated.
- If 2 of the first 6 DLT evaluable patients in Part 1 experience a DLT, the cohort will be expanded to 9 patients.

- If 2 of the 9 DLT evaluable patients in Part 1 experience a DLT (no additional DLTs in the last 3 patients), Part 2 will be initiated.
- If 3 or more of up to 9 DLT evaluable patients in Part 1 experience DLTs, accrual will be halted. In this case, the REDR will have been exceeded and dose titration will stop. However, an intermediate DL below the REDR may be explored. If the REDR is exceeded, the highest dose at which fewer than 3 DLT evaluable patients experience a DLT will be declared the REDR.

In addition, if 2 or more patients in the first 3 patients cannot dose escalate to the target dose by C1D21 in the absence of a DLT, the cohort will be expanded to 6 patients (this situation will be regarded equivalent to an occurrence of 1 patient with DLT).

Each patient may experience a maximum of 2 dose titration steps. The highest tolerated dose given during dose titration should then become the standard dose for that patient to be given for the remainder of the trial unless dose reduction is required.

All patients will be closely monitored for TEAEs during the DLT assessment window. TEAEs identified as DLTs will be reported to the sponsor within 24 h. Any patient in Part 1 who does not complete the DLT assessment window for a reason other than a DLT will be considered non-evaluable for the REDR assessment and may be replaced by an additional patient. Any patient who received < 3 doses of BNT112 during the first cycle for a reason other than a DLT will be considered non-evaluable for the REDR assessment and may be replaced by an additional patient.

Table 4-1: Dose Titration Scenarios and Rules

Dose (µg)	**0 DLT scenario**	**1 DLT scenario**			**2 DLT scenarios**						**3 or more DLT scenarios**
CCI	0	0	0	1	0	0	2	0	1	1	> 2 DLTs across any DLs
	0	0	1	0	0	2	0	1	0	1	
	0	1	0	0	2	0	0	1	1	0	
Total number of patients required	3	Go to 6 or 9			9						
Action	Move to expansion	If 1/6 move to expansion; if additional DLT at any dose, go to 9 If 2/9 go to expansion. If >2/9 then hold and go to SRC.			If 2/9 move to expansion; if >2/9 then hold and go to SRC.						Hold and go to SRC.

Abbreviations: DLT = dose-limiting toxicity; SRC = Safety Review Committee.

After DLT assessment has been completed in Part 1, safety data will be reviewed by the SRC to determine the REDR. The SRC may recommend, on the basis of emerging clinical safety, and

pharmacodynamics data from this trial, that other DLs and dosing schedule of BNT112 may be evaluated in the trial.

4.1.2. Part 2

Part 2 will further explore the safety and pharmacodynamics of BNT112 at the REDR in patients with mCRPC (Arms 1A and 1B) and LPC (Arms 2 and 3) and to evaluate the preliminary clinical response. In all arms, BNT112 will be given in the following dose schedule: D1, D8, and D15 of C1 and C2 and D1 from C3 onwards. The individual dose titration will be conducted during C1 with DL1 on D1, DL2 on D8 and DL3 on D15. The highest tolerated dose given during dose titration should be administered for the remainder of the trial unless dose reduction is required. The treatment will continue until a discontinuation-of-treatment criterion is met (Section 7). In Part 2 Arms 2 and 3 the treatment will be stopped at C8D1.

Initially, patients will be monitored in the hospital overnight post-treatment at all visits in C1. On the 17 MAY 2021, the SRC recommended that patient monitoring can be limited to 4 to 6 h and no overnight stay is required.

Part 2 Arms 1A and 1B (mCRPC)

Approximately 66 (33 per arm) patients with histologically confirmed mCRPC, who progressed after at least 2 but no more than 3 lines of life-prolonging systemic therapy (e.g., abiraterone or enzalutamide, docetaxel, cabazitaxel) or who cannot tolerate or have refused any of these therapies will be enrolled in Part 2 Arms 1A and 1B. Enrollment between Arms 1A and 1B will be randomized 1:1 to avoid enrollment bias.

Following progression after BNT112 monotherapy, patients in Arm 1B will have the option to be treated with cemiplimab monotherapy.

Part 2 Arm 2 and Arm 3 (LPC)

Treatment-naïve patients with LPC (i.e., N0, M0), defined according to European Association of Urology Guidelines on Prostate Cancer (2018)[23] and in line with the U.S. National Comprehensive Cancer Network (NCCN 2020)[35], who are eligible for treatment with ADT (e.g., goserelin acetate) followed by radical prostatectomy will be enrolled in Part 2 Arms 2 and 3. Enrollment between Arms 2 and 3 will be randomized 1:1 to avoid enrollment bias.

4.2. Planned Number of Patients

There will be 3 to 9 patients in Part 1 (dose titration part, single arm) and up to 106 patients in Part 2 (expansion part, four arms: up to 33 patients in Arm 1A and Arm 1B, respectively, and approximately 20 patients in Arm 2 and Arm 3, respectively). Drop-outs may be replaced. In total, there will be approximately 115 patients.

Re-screening of patients is allowed.

4.3. Trial Design Rationale

This trial is designed to evaluate the safety, tolerability, immunogenicity, and preliminary efficacy of BNT112 in monotherapy and in combination with cemiplimab in mCRPC and LPC patients eligible for treatment with ADT (e.g., goserelin acetate) followed by radical prostatectomy.

In Part 1, a modified 3+3+3 design (adapted from Hamberg et al. 2010[13]) will be applied with approximately 3 to 9 patients enrolled. This modified 3+3+3 design is used to reduce the chance of incorrectly ceasing enrollment at a certain step-up DL, when inter- and intra-patient variability is expected and the true DLT rate may be <5%. If > 1 patient of the first 3 patients or > 2 patients of the first 6 patients experiences a DLT, no additional patients will be enrolled at that DL, in order to avoid patients being treated at DLs with unacceptable toxicities. Furthermore, intra-patient dose titration is implemented and is justified in detail in the next section.

Patients eligible for Part 1 and Part 2 Arms 1A and 1B of this trial will have histologically confirmed mCRPC and have progressed after at least 2 but no more than 3 lines of life-prolonging systemic therapy (e.g., abiraterone or enzalutamide, docetaxel, cabazitaxel) or cannot tolerate or have refused any of these therapies. These lines of therapy include life-prolonging therapies administered in the metastatic hormone–sensitive setting. This description defines a population in which it is ethically acceptable and feasible to evaluate the safety, tolerability, immune response, and pharmacokinetics of novel therapies intended for the treatment of patients with advanced malignancies.

Immune therapies based on antigen-specific T cells have the highest probability of success in patients with low tumor burden and at an early stage of the tumor's life cycle. Therefore, patients eligible for Part 2 Arms 2 and 3 of this trial will have a newly diagnosed LPC and will be candidates for neoadjuvant treatment with LHRH agonist or antagonist followed by radical prostatectomy. LPC patients will be enrolled only after the initial safety assessment in the dose titration part of Part 1 is completed and the REDR is defined (for further details please also refer to Section 2.2).

Both clinical trial populations were selected and refined together with clinical experts from the field to enable the real-life clinical setting where the benefit for the patients might be the highest. The clinical setting is further justified by several factors recognized as relevant and important for development of cancer vaccines, also listed in the FDA Guidance for Industry "Clinical Considerations for Therapeutic Cancer Vaccines".[34] These include the time to develop an anti-tumor response, which is generally longer for immunotherapies, and the higher chance for a cancer vaccine to show efficacy in lower tumor burden patients and patients with limited prior therapy exposure.

All patients in Part 2 Arms 2 and 3 will receive up to 3 DLs of BNT112 during the C1 intra-patient dose titration based on the REDR defined in Part 1, thereby allowing for a safe combination with cemiplimab. The safety of this combination is further supported by data from the ongoing Lipo-MERIT trial where no differences were seen between RNA-LPX monotherapy and combination with anti-PD-1 or BRAF/MEK (serine/threonine-protein kinase B-Raf/mitogen-activated protein kinase kinase) inhibitors. All combinations in that trial indicate a well-tolerated safety profile of these combinations with Lipo-MERIT vaccine doses ranging from CCI µg to CCI µg. Safety of the treatment arms with BNT112 and cemiplimab combination will be reviewed and will follow the same rules as Part 1, until the SRC reviews and confirms that the combination safety profile is acceptable. Based on the recommendation from the SRC, the sponsor will decide if enrollment should continue for the combination arms. More details are provided in the SRC charter.

Randomization in a 1:1 ratio between Part 2 Arms 1A and 1B and between Part 2 Arms 2 and 3 is included to avoid enrollment bias.

Eligibility criteria are based primarily on clinical safety data from the Lipo-MERIT trial as well as standard eligibility criteria for mCRPC and LPC. [22, 25] Eligibility criteria for the Part 2 Arm 2 (combination with cemiplimab) of the trial are, in addition, based on available safety data for cemiplimab as well as studies with anti-CTLA-4 and with anti-PD-1 treatments. [2, 37]

4.4. Dose and Schedule Rationale

One of the purposes of early phase trials is to determine the optimal dose and schedule for a particular treatment. For classical chemotherapy and targeted agents, the highest tolerated dose will usually be the most effective and is often taken forward in later stage studies. For checkpoint inhibitors, the anti-tumor effect may reach a plateau after which an increased dose confers neither increased toxicity nor improved benefit. In contrast, for cancer vaccines, a maximum tolerated dose (MTD) is rarely reached, the effective range may be very broad, and there usually is some minimum threshold that elicits an immune response.[9] The impact of antigen dose on immune response is controversial. A trial evaluating the immunologic response to high, medium, and low doses of a human epidermal growth factor receptor 2 (HER2)/neu intracellular domain protein-based vaccine showed differences in the kinetics of the expansion of an antigen-specific T cell response, but no difference in the overall magnitude of the T cell response, antibody response or avidity.[12] There is evidence that different doses of peptide vaccines selectively stimulate expansion of T cells with different levels of avidity and cytotoxicity.[20, 8] Moreover, the impact of different vaccine administration schedules on immune response has not been thoroughly explored. Most studies do not explore different vaccine dosing schedules and, therefore, the ideal vaccine dosing schedule has not been identified. The dose titration part as well as the expansion cohorts will investigate potential large differences in immune response and preliminary anti-tumor efficacy of DLs below the MTD/maximum administered dose alone or in combination with ADT (e.g., goserelin acetate) with or without cemiplimab in order to inform dose and schedule in pivotal studies.

BNT112: The proposed starting dose and dosing schedule of BNT112 as a single agent is based primarily on the safety, immunogenicity, preliminary efficacy, and generated in the ongoing clinical trials with the sponsor's RNA-LPX as well as on an integrated assessment of the proposed MoA (i.e., generation of a T cell response to a tumor shared antigen), efficacy in murine tumor models, and *in vivo* safety in the GLP toxicity studies conducted in mice.

Based on preliminary analysis of safety, efficacy and immunogenicity data of the Lipo-MERIT trial as well as the other ongoing Phase 1 clinical trials, a dose range of CCI , and CCI µg was proposed to be tested in the Part 1 dose titration part of this trial.

The step-up dose titration follows the approach implemented in the ongoing clinical trials with RNA cancer vaccine IMPs and allows for optimal dose management on an individual basis, and accounts for inter- and intra-individual variability of the immune system. Step-up dosing may offer advantages over flat dosing, including the potential mitigation of a hypothetical first dose phenomenon (i.e., allowing the patient to acclimate to gradually increasing doses of BNT112) with the lower starting dose acting as a "lead-in" dose potentially mitigating immune system activation-related AEs. This approach was confirmed in the previous and ongoing sponsor trials with RNA-encoded cancer vaccines. The dosing schedule proposed in this trial is based primarily on the Lipo-MERIT trial (6 weekly vaccinations followed by 2 bi-weekly vaccinations followed by continuous treatment with the maximum individually tolerated dose given every 28 days for

patients without PD). The dosing schedule in the proposed prostate cancer trial includes the intensified weekly dosing in C1 and C2 followed by the treatment with the maximum individually tolerated dose every 21 days. The schedule also fits the dosing schedule for cemiplimab (every 21 days) and both are easily incorporated in the standard dosing of the ADT (e.g., goserelin acetate is given Q12W).

Part 1 (dose titration) of the PRO-MERIT trial has been performed in the UK and Hungary and enrollment has been completed with 9 patients dosed. The SRC reviewed the available safety data for patients in Part 1 on 17 MAY 2021. The safety profile observed indicates that BNT112 a tolerable drug product with a manageable safety profile at the defined dose range CCI µg) using the intra-patient step-up dose titration scheme. Observed AEs considered related to the IMP (including pyrexia, flu-like symptoms, hypertension, nausea, chills or headache), are in line with the innate immune activation by RNA-LPX, are transient in nature and manageable by analgesics, antipyretics or fluids at recommended and usual doses. The recommendation was to continue to Part 2 at the selected REDR (CCI to CCI µg) using the intra-patient step-up dose titration scheme. The annual review of safety data for the IB update occurred on 20 MAY 2021 (data extraction date) and included safety data from patients in Part 1 as well as Part 2. Neither the safety profile nor the benefit-risk assessment were changed.

Cemiplimab is given at a dose of CCI mg as an IV infusion over 30 minutes every 3 weeks.

Goserelin acetate is administered at a dose of 10.8 mg as an SC injection into the anterior abdominal wall Q12W, according to the current SmPC (e.g., Zoladex® LA 10.8 mg implant).[3] In order to facilitate interpretation of toxicities with suspected relationship to the IMP, goserelin acetate is to be administered anytime within 7 days prior to the start of BNT112 treatment. In case another ADT is used, it is to be administered in line with the current prescribing information valid in a given country.

4.5. End of Trial Definition

The end of the trial is defined as the date of last patient contact, whether in-person or by phone, for the last patient in the trial globally, including the efficacy follow-up for 12 months after the last dose of trial treatment.

In addition, the sponsor may decide to terminate the trial at any time. If the sponsor decides to terminate the trial, patients who are still receiving trial treatment or undergoing survival follow-up may be enrolled in an extension trial or a non-interventional trial, if available (Section 10.1.9).

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 participant must fulfill all of the following criteria to be enrolled in the trial.

1. Patients must be male and aged ≥18 years.
2. Patients must have histologically confirmed prostate adenocarcinoma.

3. Patients or their legally authorized representative (if applicable) must sign an ICF indicating that they understand the purpose of the procedures required for the trial and are willing to participate.
4. Patients must have an ECOG PS score of 0 or 1.
5. Patients must have adequate organ and bone marrow function, defined as:
    a. Bone marrow/hematological function:
        – Absolute neutrophil count (ANC) ≥1.5 × 10^9/L.
        – Hemoglobin ≥9.0 g/dL. No transfusion is allowed within 2 weeks prior to trial treatment initiation.
        – Platelet count ≥100 × 10^9/L.
    b. Coagulation status:
        – International normalized ratio ≤1.5 ULN. Unless on therapeutic anticoagulants with values within therapeutic window.
    c. Renal function:
        – Glomerular filtration rate ≥45 mL/min/1.73 m² according to the abbreviated Modification of Diet in Renal Disease equation.
6. Patients who are sexually active with a woman of childbearing potential must agree to use a condom with spermicidal foam/gel/film/cream/suppository in addition to at least one form of highly effective contraception used by the patient or their partner (for details, see Section 10.4) during the trial starting after signing the ICF and for 90 days after receiving the last dose of BNT112 OR for 6 months after receiving the last dose of cemiplimab.
7. Patients should not donate sperm during the trial starting after signing the ICF and for 90 days after receiving the last dose of BNT112 OR for 6 months after receiving the last dose of cemiplimab.
8. Patients must be willing and able to adhere to the prohibitions and restrictions specified in this protocol.

In addition to the above inclusion criteria, the following are mandatory for the different treatment arms:

Specific inclusion criteria for mCRPC patients (Part 1 and Part 2 Arms 1A and 1B)

9. Patients must have histologically confirmed mCRPC and have progressed after at least 2 but no more than 3 lines of life-prolonging systemic therapy (e.g., abiraterone or enzalutamide, docetaxel, cabazitaxel) or cannot tolerate or have refused any of these therapies. These lines of therapy include life-prolonging therapies administered in the metastatic hormone–sensitive setting.
10. Prior surgical or chemical castration with a serum testosterone <1.7 nmol/L (50 ng/dL). If the method of castration is luteinizing hormone-releasing hormone analogue (LHRHa), there must be a plan to maintain effective LHRHa therapy for the duration of the trial.

11. Patients must have documented mCRPC progression within 6 months prior to screening (assuming no subsequent change in treatments), as determined by the investigator, by means of 1 or more of the following criteria:
    a. PSA progression as defined by a minimum of 2 rising PSA levels with an interval of ≥1 week between each assessment where the PSA value at screening should be >2 ng/mL.
    b. Two rises out of 3 PSA sequential tests separated by at least 1 week also satisfies the criteria for baseline progression providing a new nadir is not established (i.e., upward trend) – see Section 10.9.
    c. Radiographic disease progression in soft tissue based on modified Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1) with or without PSA progression.
    d. Radiographic disease progression in bone defined as the appearance of 2 or more new bone lesions on bone scan with or without PSA progression.
12. Patients must have adequate liver function defined as:
    a. Total bilirubin ≤1.5 × ULN (≤3 × ULN is acceptable for patients with known Gilbert disease).
    b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 × ULN.
        – For patients with hepatic metastases, total bilirubin <3 × ULN and AST or ALT <5 × ULN are acceptable.
        – For patients with bone metastases, alkaline phosphatase <5 × ULN and albumin ≥2.5 g/dL are acceptable.
13. Patients must agree to provide an archival pre-treatment formalin-fixed, paraffin-embedded tumor sample if available.

Specific inclusion criteria for newly diagnosed LPC patients (Part 2 Arms 2 and 3)

14. Treatment-naïve patients with LPC (i.e., N0, M0). According to risk levels of the European Association of Urology Guidelines on Prostate Cancer (2018)[24] and in line with the US National Comprehensive Cancer Network (NCCN 2020)[35] patients must have at least one of the following:
    a. PSA >20 ng/mL or
    b. Gleason Score >7 or
    c. Localized stage ≥cT2c, N0, M0 according to tumor, node, metastasis (TNM) classification[7]
15. Patients who intend to have and are suitable for a radical prostatectomy.
16. Patients must have adequate liver function defined as:
    a. Total bilirubin ≤1.5 × ULN (≤3 × ULN is acceptable for patients with known Gilbert disease)

b. AST and ALT ≤2.5 × ULN

17. Patients must agree to provide tumor sample(s) from pre-treatment diagnostic biopsy and planned post-treatment surgery.
18. Patient must be eligible for up to 6 months of ADT treatment before prostatectomy.

5.2. Exclusion Criteria

Each potential participant is not eligible to be included in the trial if any of the following criteria at screening to be enrolled in the trial. In addition, all lab criteria must be fulfilled within 7 days prior to starting IMP.

Medical Conditions

1. Patients with uncontrolled intercurrent illness, including but not limited to:
    a. Ongoing or active infection which requires systemic treatment with antibiotics or corticoid therapy within 14 days before the first dose of IMP.
    b. Symptomatic congestive heart failure (Grade III or IV as classified by the New York Heart Association), myocardial infarction within 3 months before screening, unstable angina pectoris, or cardiac arrhythmia.
    c. Known recent history (in the past 5 years) or presence of significant pulmonary conditions such as uncontrolled chronic lung disease, or any evidence of interstitial lung disease, or active, non-infectious pneumonitis.
    d. Uncontrolled hypertension defined as systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥100 mmHg, despite optimal medical management.
    e. Known primary immunodeficiencies, either cellular (e.g., DiGeorge syndrome, T-cell negative severe combined immunodeficiency [SCID]) or combined T- and B-cell immunodeficiencies (e.g., T- and B-cell negative SCID, Wiskott- Aldrich syndrome, ataxia telangiectasia, common variable immunodeficiency).
    f. Ongoing or recent evidence (within the past year) of significant autoimmune disease that required treatment with systemic immunosuppressive treatments which may suggest risk for immune-related AEs.
    Note: Patients with autoimmune-related hyperthyroidism, autoimmune-related hypothyroidism who are in remission, or on a stable dose of thyroid-replacement hormone, vitiligo, or psoriasis may be included.
    g. Non-healing wound, skin ulcer (of any grade), or bone fracture.
    h. Patients with prior allogeneic stem cell or solid organ transplantation.
    i. Patients with the following risk factors for bowel perforation (e.g., history of acute diverticulitis or intra-abdominal abscess in the last 3 years; history of gastrointestinal obstruction or abdominal carcinomatosis).
    j. Patients with uncontrolled type 1 diabetes mellitus.
    Note: Patients controlled on a stable insulin regimen are eligible.
    k. Patients with uncontrolled adrenal insufficiency.

l. Any other disease, metabolic dysfunction, physical examination finding, and/or laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or may render the patient at high-risk for treatment of complications.

2. Patients with a known history or current malignancy other than the inclusion diagnosis. *Note: Exceptions are patients with malignancies with a negligible risk of metastasis or death, that have been adequately treated, such as non-invasive basal cell or non-invasive squamous cell skin carcinoma, non-invasive, superficial bladder cancer, and any cancer with a complete response (CR) that lasted more than 2 years may be included.*
3. Patients who have had a splenectomy.
4. Patients who have had major surgery (e.g., requiring general anesthesia) within 4 weeks before screening, or have not fully recovered from surgery, or have a surgery planned during the time of trial participation, except for the radical prostatectomy planned for patients in Part 2 Arms 2 and 3.
5. Patients who have a known history of any of the following:
    a. HIV 1 or 2
    b. Hepatitis B (carrier or active infection)
    c. Hepatitis C (unless considered cured 5 years post curative anti-viral therapy)
6. Patients with a known allergy, hypersensitivity, or intolerance to BNT112 or its excipients (all patients in Parts 1 and 2), cemiplimab or its excipients (patients in Part 2 Arm 1A, Arm 1B switch-over patients, and Arm 2 only), or to ADT (e.g., goserelin) or excipients thereof (patients in Part 2 Arms 2 and 3 only).
7. Patients with any condition for which, in the opinion of the investigator, participation would not be in the best interest of the patient (e.g., compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.
8. In situations where trial patients are not legally competent to provide consent (e.g., mentally incapacitated), these patients are not allowed to enter the trial.

Prior/Concomitant Therapy

9. Patients who have received or currently receive the following therapy/treatment:
    a. Chronic systemic immunosuppressive corticosteroid treatment (prednisone >5 mg daily PO or IV, or equivalent) during the trial.
    Note: Replacement therapy (e.g., physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is permitted.
    b. Prior treatment with other immune-modulating agents that was (a) within fewer than 4 weeks (28 days) or 5 half-lives (whichever is longer) prior to the first dose of cemiplimab, or (b) associated with immune-mediated AEs that were Grade ≥1 within 90 days prior to the first dose of cemiplimab, or (c) associated with toxicity that resulted in discontinuation of the immune-modulating agent.

c. Prior treatment with other immune-modulating agents for any non-cancer disease within 4 weeks or 5 half-lives of the agent (whichever is longer) before the first dose of IMP.

d. Prior treatment with live-attenuated vaccines within 4 weeks before the first dose of IMP and during treatment with IMP.

e. Prior treatment with an investigational drug (including investigational vaccines) within 4 weeks or 5 half-lives of the agent (whichever is longer) before the planned first dose of IMP.

f. Therapeutic PO or IV antibiotics within 14 days prior to enrollment.
Note: Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or chronic obstructive pulmonary disease) may be enrolled.

g. Concurrent use of herbal products that may decrease PSA levels (e.g., saw palmetto).

Other Exclusion Criteria for All Patients

10. Patients who have previously been enrolled in this trial.
11. Patients with substance abuse or known medical, psychological, or social conditions that may interfere with the patient's participation in the trial or evaluation of the trial results.
12. Patients affiliated with the investigational site (e.g., a close relative of the investigator or dependent person, such as an employee or student of the investigational site).

Specific Exclusion Criteria for mCRPC Patients (Part 1 and Part 2 Arms 1A and 1B)

<u>Excluded medical conditions</u>

13. Patients with toxicities from previous anti-cancer therapies that have not resolved to baseline levels or to Grade ≤1 according to NCI CTCAE v5.0 with the exception of alopecia, anorexia, vitiligo, fatigue, hyperthyroidism, hypothyroidism, and peripheral neuropathy. Anorexia, hyperthyroidism, hypothyroidism, and peripheral neuropathy must have recovered to Grade ≤2.
14. Patients with clinically active brain metastases.
    a. Patients with a history of symptomatic metastatic brain or meningeal tumors may be included, if the end of definitive therapy is >3 months before the first dose of BNT112 and the patients have no clinical or radiological evidence of tumor growth.
    b. Patients with brain metastases must not be undergoing acute or chronic corticosteroid therapy or steroid taper.
    c. Patients with central nervous system symptoms should undergo a CT scan or MRI of the brain to exclude new or progressive brain metastases. Spinal cord metastasis is acceptable. However, patients with spinal cord compression should be excluded.

Excluded prior or concomitant anti-cancer therapies

15. Patients who have received or currently receive the following anti-cancer therapy/agent:
    a. Prior radiation therapy with curative intent within 14 days before the first dose of IMP.
    Note: Palliative radiotherapy is allowed.
    b. Prior treatment with an anti-cancer agent (within 4 weeks or for systemic therapies after at least 5 half-lives of the drug [whichever is longer] before the first dose of IMP).
    Note: Prior treatment with bone resorptive therapy, such as bisphosphonates (e.g., pamidronate, zoledronic acid, etc.) and denosumab, is allowed assuming that the patients have been on stable doses for ≥4 weeks prior to first dose of trial treatment.
    c. Prior treatment with anti-cancer immunomodulating agents, such as blockers of PD-1, PD-L1, tumor necrosis factor receptor superfamily member 9 (TNRSF9, 4-1BB, CD137), OX-40, therapeutic vaccines, cytokine treatments, or any investigational agent within 4 weeks or 5 half-lives (whichever is longer) before the first dose of IMP.

Specific exclusion criteria for LPC patients (Part 2 Arms 2 and 3)

16. Patients who are expected to be unable to undergo an mpMRI or MRI.

5.3. Screen Failures

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

Patients who do not meet the criteria for participation in this trial (screen failures) may be rescreened.

6. Trial Treatment

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.

(If applicable) NIMP ADT is to be administered first, thereafter BNT112, and then cemiplimab.

Investigational medicinal products (IMPs):	
IMP 1:	BNT112 (previously referred to as W_pro1 in this and other trial-related documentation)
Composition:	BNT112 consists of messenger RNA (mRNA; further referred to as RNA) targeting 5 antigens expressed in de novo and metastatic prostate cancer that are separately complexed with liposomes to form serum-stable RNA lipoplexes
Administration:	Five slow IV bolus injections per administration (i.e., one injection per each antigen followed by a saline flush and separated from the next injection by at least 5 minutes)
Dosage regimen:	One cycle (C) is defined as 21 days The patients will receive the following treatments in the following dose and schedule: **Part 1 and Part 2 Arms 1A and 1B (mCRPC)** • IV administration of BNT112 on Day (D)1/8/15 of C1 (intra-patient dose titration) and C2, thereafter starting with D1 of C3 every 3 weeks (Q3W) until end of treatment criterion is met • Part 1/Dose Titration - Three doses of BNT112 will be used for an intra-patient dose titration during C1: CCI µg, CCI µg, and CCI µg of total RNA, comprising CCI µg, CCI µg, and CCI µg of RNA of each of the 5 antigens encoded by BNT112, respectively. • Part 2/Expansion - REDR was selected after the review of individual and cumulative safety data, and preliminary pharmacodynamic data of Part 1 by the SRC. The selected dose range consists of a starting first dose of BNT112 of CCI µg, with an intra-patient dose titration to CCI µg in the second dose, and CCI µg of total RNA in the next doses. Total RNA of CCI µg, CCI µg and CCI µg comprise CCI µg, CCI µg, and CCI µg of RNA of each of the 5 antigens encoded by BNT112, respectively - Part 2 Arm 1A: Cemiplimab CCI mg IV Q3W - Part 2 Arm 1B: following progression after BNT112 monotherapy, patients will have the option to be treated with cemiplimab CCI mg IV Q3W monotherapy

Duration of treatment:	**Part 2 Arms 2 and 3 (LPC) – Part 2/Expansion ONLY** • IV administration of BNT112 on D1/8/15 of C1 (intra-patient dose titration) and C2, thereafter starting with D1 of C3 in a Q3W schedule until C8 followed by radical prostatectomy • Part 2 Arm 2: Cemiplimab CCI mg IV Q3W • Part 1 and Part 2 Arms 1A and 1B (mCRPC): The treatment with BNT112 will last until unacceptable toxicity or disease progression • Part 2 Arms 2 and 3 (LPC): The treatment with BNT112, cemiplimab will last until unacceptable toxicity or disease progression, or up to C8 • If either BNT112 or cemiplimab needs to be discontinued, treatment with either cemiplimab or BNT112 can continue upon investigator and sponsor agreement • If treatment with ADT (e.g., goserelin acetate) needs to be discontinued, cemiplimab and/or BNT112 also need(s) to be discontinued
IMP 2:	Cemiplimab (LIBTAYO)
Composition:	Programmed death receptor-1 (PD-1) blocking antibody
Dosage regimen and duration of treatment:	Refer to above description of IMP1 for dosage regimen and duration of treatment

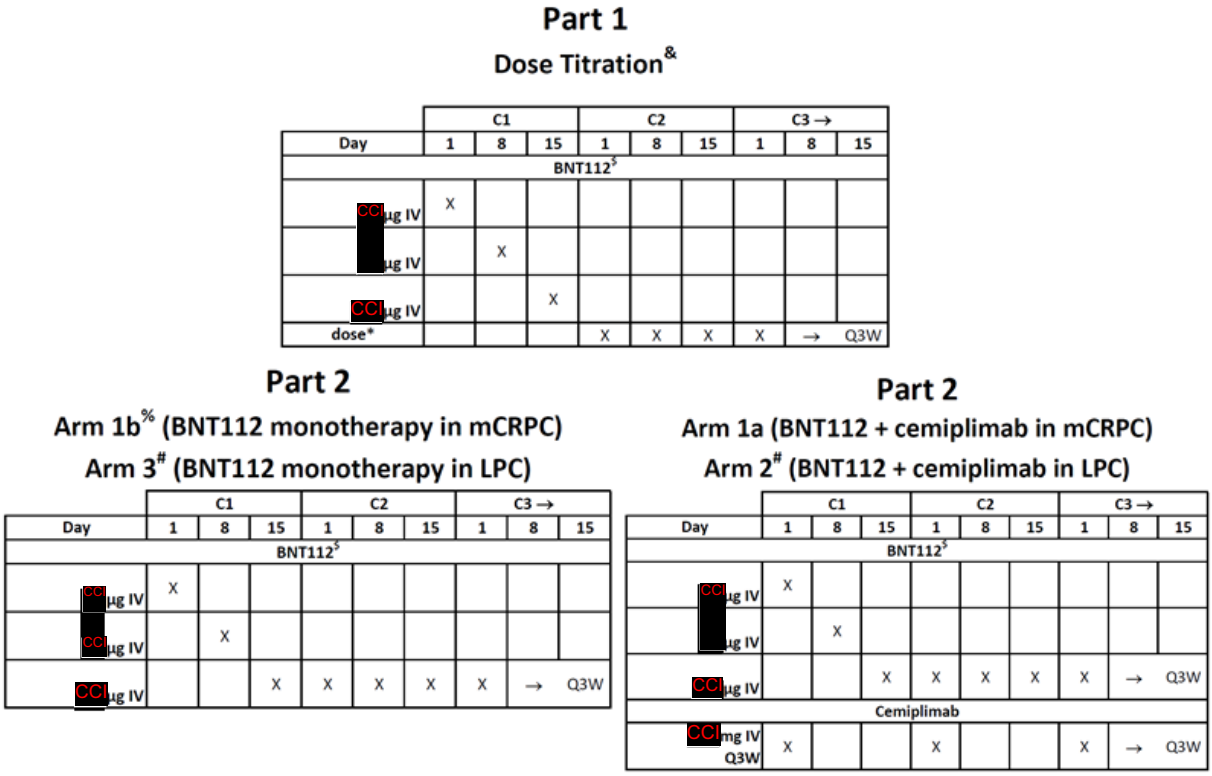
Non-investigational medicinal product (NIMP):

Part 2 Arms 2 and 3 (LPC)

ADT, e.g., Goserelin acetate subcutaneous (SC) injection at a dose of 10.8 mg every 12 weeks or other ADT according the current prescribing information valid in a given country.

Product:	Goserelin acetate (Zoladex® LA 10.8 mg implant)
Composition:	Goserelin acetate (equivalent to 10.8 mg goserelin)
Administration:	SC
Dosage regimen:	One 10.8 mg depot injection given into the anterior abdominal wall every 12 weeks (Q12W)
Duration of treatment:	Two injections (C1D1 and C5D1); treatment will last until unacceptable toxicity or disease progression, or up to C8

Figure 6-1: Treatment Administration – Part 1 and Part 2



Abbreviations and Footnotes:
LPC = localized prostate cancer; mCRPC = metastatic castration resistant prostate cancer; Q3W = every three weeks.

& Recommended dose range (REDR) is confirmed in Part 1.

* Maximum administered dose CCI µg; minimum administered dose CCI µg; no dose re-escalation allowed.

\# In combination with ADT (e.g., Goserelin).

$ From Day 1 of C1 onward, each patient will receive the individual standard dose (or the highest tolerated dose from Cycle 1) at each BNT112 administration.

% Following progression after BNT112 monotherapy, patients in Arm 1b will have the option to be treated with cemiplimab monotherapy CCI mg IV Q3W.

6.1. Trial Treatments Administered

The details of **BNT112 (test product)** are presented in Table 6-1.

Table 6-1: Identity and Properties of IMP1: BNT112 (IMP)

Generic name/INN (brand name):	Not applicable
Substance code name:	BNT112
Formulation:	Injectable solution
Route of administration:	IV injection
Composition:	Active ingredients Five RNA-encoded prostate cancer-specific antigens
Strength (amount of drug per unit):	CCI mg/mL of RNA of each antigen in a single use vial
Concentration after appropriate dilution:	Individually diluted with isotonic sodium chloride and complexed with liposomes to form RNA-LPX products
Storage conditions:	RNA drug products must be stored at –20±5°C (further descriptions are given in the current Pharmacy Manual) in a locked area with restricted access and handled in accordance with the manufacturer's instruction. Liposomes and NaCl solution must be stored at 5±3°C.
Marketing authorization holder:	Not applicable

Abbreviations: INN = international nonproprietary name; IV = intravenous; RNA = ribonucleic acid; RNA-LPX = RNA-lipoplex.

The details of the PD-1 blocking antibody cemiplimab (concomitant IMP) are presented in Table 6-2.

Table 6-2: Identity and Properties of IMP2: Cemiplimab

Generic name/INN (brand name):	Cemiplimab (Libtayo)
Class:	PD-1 blocking antibody
Formulation:	Liquid in vial
Route of administration:	IV
Composition:	Active ingredient: Cemiplimab CCI mg/mL and CCI mg/mL DP are formulated in an aqueous buffered solution at pH 6.0 Other ingredients: 10 mM histidine, 5% (w/v) sucrose, 1.5% (w/v) L proline, and 0.2% (w/v) polysorbate 80.
Strength (amount of drug per unit):	CCI mg/7 mL (CCI mg/ml)
Storage conditions:	Must be stored at 2°C to 8°C.
Marketing authorization holder:	Regeneron Ireland DAC.

Abbreviations: INN = international nonproprietary name.

The details of the LHRH agonist **goserelin acetate** (NIMP) are presented in Table 6-3.

Table 6-3: Identity and Properties of NIMP: Goserelin Acetate

Generic name/INN (brand name):	Goserelin acetate (e.g., Zoladex® LA 10.8 mg implant)
Class:	LHRH agonist (gonadotropin releasing hormone analogue)
Formulation:	Implant (depot)
Route of administration:	Deep SC injection into the anterior abdominal wall below the navel line
Composition:	Active constituent goserelin acetate equivalent to 10.8 mg goserelin per depot Other Constituents Lactide-glycolide copolymer to total weight 36.0 mg per depot
Strength (amount of drug per unit):	10.8 mg goserelin in pre-filled sterile ready-to-use syringe [a]
Storage conditions:	Do not store above 25 °C
Marketing authorization holder:	Astra Zeneca UK Limited (Luton, LU1 3LU, UK)

Abbreviations: INN = international nonproprietary name; LHRH = luteinizing hormone-releasing hormone; UK = United Kingdom; SC = subcutaneous.
[a] Zoladex® LA 10.8 mg implant is supplied as a single dose SafeSystem™ syringe applicator with a protective sleeve in a sealed pouch which contains a desiccant.

6.2. Preparation/Handling/Storage/Accountability

6.2.1. IMP 1 - BNT112

For instructions on dilution of the IMP BNT112, stability of the diluted solution, and administration details, please refer to the Pharmacy Manual provided in the Pharmacy Trial File.

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all BNT112 received and any discrepancies are reported and resolved before use of the supplied BNT112. Only patients enrolled in the trial may receive BNT112 and only authorized site staff may supply or administer BNT112. All BNT112 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, institution, or the head of the medical institution (where applicable) is responsible for BNT112 accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused IMP are provided in the trial-related Pharmacy Manual.

6.2.2. IMP 2 - Cemiplimab

Based on data from ongoing long-term, accelerated, and stress stability studies, the cemiplimab IMP is considered stable for use.

Cemiplimab IMP must be stored at the trial centers at 2°C to 8°C. The temperature of storage in the refrigerator should be checked and recorded at least daily as prescribed in the Pharmacy Manual.

Details on storage and preparation for cemiplimab IMP for IV administration are provided in the Pharmacy Manual.

Storage of the infusion solution: cemiplimab IMP should be stored at room temperature (≤25°C for no more than 8 h from the time of preparation to the end of infusion, or at 2°C to 8°C for no more than 24 h from the time of preparation to the end of infusion.

6.3. Measures to Minimize Bias: Randomization and Blinding

At screening, patients will be assigned a unique number (patient identification code), regardless of whether they actually receive trial treatment.

In Part 2, patients with mCRPC treated in Arm 1A or Arm 1B, and patients with LPC treated in Arm 2 or Arm 3, will be randomized in 1:1 ratio. Central randomization will be used to reduce potential investigator bias.

The site will contact the central randomization service prior to the start of trial treatment administration for each patient. The treatment assignment will be recorded on the applicable electronic case report form (eCRF), as required.

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 in the clinic will be recorded in the

source documents and recorded in the eCRF. The dose of trial treatment and trial patient identification will be confirmed at the time of dosing by a member of the trial center staff other than the person administering the trial treatment.

6.5. Concomitant Therapy

Any background therapy for cancer or concomitant diseases/disorders not defined as NIMP and any non-drug cancer treatment (e.g., palliative radiotherapy/any supportive treatment) that is ongoing at the time of first IMPs administration (C1D1) or newly started after C1D1 is defined as concomitant treatment. Administration of concomitant treatment must be reported in the appropriate section of the eCRF.

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care except for those medications identified as "prohibited" (Section 6.5.2).

- Palliative radiotherapy during the trial will be allowed for local pain control provided that (i) in the opinion of the investigator, the patient does not have PD AND (ii) no more than 10% of the patient's bone marrow is irradiated AND (iii) the radiation field does not encompass a target lesion.
- Granulocyte-colony stimulating factor and other hematopoietic growth factors may be used in the management of acute toxicity, such as febrile neutropenia, when clinically indicated or at the investigator's discretion.
- Blood cell transfusion is allowed during the trial if clinically indicated. No transfusion is allowed within 2 weeks prior to trial treatment initiation.
- Steroid treatment is permitted to modulate symptoms of an immune-related AEs at the discretion of the investigator. Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is permitted. However, whenever possible corticosteroid treatment (prednisone >5 mg daily PO or IV, or equivalent) should be avoided as it counteracts with the MoA of the vaccine.
- Bisphosphonates (e.g., pamidronate, zoledronic acid, etc.) and denosumab.
- Multivitamins, vitamin D, calcium, and supplements in prevention of weight loss.
- For further details, please refer to the SoA: Section 1.3 (Part 1 and Part 2 Arms 1A and 1B), Section 1.4 (Part 2 Arms 2 and 3), and Section 1.5 (Part 2 Arm 1B [switch-over patients]).

6.5.1. Treatment of AEs Related to Treatment with BNT112 based on the RNA-LPX Class Profile

The class-intrinsic safety profile of RNA-LPX *per se* appears to be dominated by mild-to-moderate, transient and manageable influenza-like drug-related AEs (i.e., ADRs). The AEs are manageable by analgesics or antipyretics at recommended commonly used doses. Treatment of these events is dependent on the discretion of the treating physician with treatment suggestions provided below.

- Treat fever with acetaminophen or non-steroidal anti-inflammatory drugs (NSAIDs) with a dose per institution's recommendation.

- After the first occurrence of influenza-like symptomatology, patients can be premedicated with standard therapeutic dose of acetaminophen, or NSAIDs, at least 60 minutes before BNT112 administration followed by a second dose 5 to 8 h after BNT112.
- Corticosteroid treatment (prednisone >5 mg daily PO or IV, or equivalent) should be avoided as either prophylaxis or treatment as it counteracts the effects of BNT112.
- Ensure adequate hydration of patients on the day of BNT112 administration. Consider administering IV isotonic fluid (e.g., normal saline 500 to 1000 mL) within approximately 1 h following the dose of BNT112 per institutional standard.

In addition to clinically manifested AEs described above, a transient reversible lymphopenia is mentioned above which was observed in laboratory examinations – there is no clinical manifestation of this event and no treatment required.

For further information about the known and potential risks of BNT112 refer to the latest version of the IB.

6.5.2. Prohibited Concomitant Therapy

The following concomitant therapies and medications are not allowed from C1D1 until the Safety Follow-Up (FU)-D30 visit (for Part 1 and Part 2 Arm 1B and Arm 3) and from C1D1 until Safety FU-D90 visit (for Part 2 Arm 1A, Arm 1B switch-over patients, and Arm 2):

- Any concomitant systemic anti-cancer therapy defined as any agent or combination of agents with clinically proven antineoplastic activity that achieves non-negligible systemic bioavailability after being administered by any route for affecting the malignancy, either directly or indirectly, including palliative and therapeutic objectives except for the concomitant use of cemiplimab (Part 2 Arms 1A and 2) and ADT (e.g., goserelin acetate) (Part 2 Arms 2 and 3).
- Immunosuppressive or maintenance therapy with systemic corticosteroids (PO or IV prednisone > 5 mg per day, or its equivalent) **unless required per investigator's decision**.
- Note: Replacement therapy (e.g., physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is permitted.
- Immunization with live-attenuated vaccines within 28 days prior to the first dose of IMP and during treatment with IMP. In addition, patients should not receive any live-attenuated vaccines within 3 months after the last dose of IMP.
- Use of herbal products that may decrease PSA levels (e.g., saw palmetto).

If a patient receives any of these during the trial, the sponsor must be notified for evaluation of whether the patient can continue treatment or not.

6.6. Dose Modifications

6.6.1. BNT112 (IMP/test product)

The DLs of BNT112 used in this trial include the 3 DLs for intra-individual patient dose titration (CCI and CCI µg) and 1 additional dose of CCI µg (with CCI µg of RNA of each antigen) which can be used for dose reduction in case of toxicities. A maximum of 2 subsequent dose reductions is allowed. Re-escalation to a higher dose level is not allowed.

For further information about the known and potential risks of BNT112 refer to the latest version of the IB.

6.6.1.1. Dose-Limiting Toxicities – Part 1

For the purpose of intra-patient dose titration, TESAEs, TEAEs ≥Grade 3 and clinically significant abnormal lab values at least possibly related to BNT112 cancer vaccine will be collected and assessed for DLTs during the first cycle (21 days) of the dose titration part (DLT observation period). NCI CTCAE v.5.0 will be used to grade the intensity of TEAEs. At the discretion of the investigator, the dose of BNT112 cancer vaccine may be maintained at the current DL for one dose, i.e., intra-patient dose titration may be delayed. For these patients, the DLT assessment period is extended to 28 days.

DLT criteria are defined below:

- Any TEAE of Grade 5 intensity.

Hematological

- Grade 3 and 4 febrile neutropenia (i.e., ANC $<1.0 \times 10^9$ cells/L with a single temperature of >38.3°C or a sustained temperature of ≥38°C for more than 1 h).
- Grade 4 thrombocytopenia ($<25.0 \times 10^9$ platelets/L) for minimal duration of 7 days.
- Grade 3 and 4 hemorrhage associated with thrombocytopenia of Grade ≥3.
- Grade 4 anemia.

Non-hematological

- Grade 4 cytokine release syndrome (CRS) according to Lee et al. 2019[19] (also refer to Table 10-5).
- Grade 3 CRS according to Lee et al. 2019[19] (also refer to Table 10-5), which has NOT improved to Grade 1 or resolved within 48 h.
- Any Grade ≥3 non-hematological TEAE at least possibly related which occurs during the first BNT112 cancer vaccine treatment cycle excluding:
  - Grade 3 CRS according to Lee et al. 2019[19] (refer to Table 10-5) which has improved to Grade 1 or resolved within 48 h.
  - Grade 3 fever (>40.0°C for ≤24 h).
  - Grade 3 hypotension (resolving within 24 h).
  - Related Grade 3 hypertension resolving within 24 h and considered as not clinically significant by the SRC.

- Grade 3 infusion-related reactions that resolve to Grade ≤1 within 24 h.
- Non-hematological laboratory abnormalities that have no clinical consequences and resolve to Grade ≤2 within 14 days (this also includes electrolyte abnormalities that respond to medical intervention).
- Grade 3 diarrhea that responds to optimal antidiarrheal treatment within 3 days.
- Grade 3 vomiting that responds to optimal antiemetic treatment within 3 days.
- Grade 3 nausea that responds to optimal antiemetic treatment within 7 days.
- Grade 3 fatigue/asthenia when fatigue/asthenia was present at baseline or that lasts for <14 days after the last administration of BNT112 cancer vaccine.
- Grade 3 irTEAEs that improve to Grade ≤1 in <7 days by appropriate care or with corticosteroids.
- Any related Grade 3 AE resolving within 24 h and considered as not clinically significant by the SRC.

All patients will be closely monitored for TEAEs during the DLT assessment period of Part 1.

TEAEs fulfilling the DLT criteria must be reported to the sponsor **within 24 h** as described in Section 10.3.3.

6.6.1.2. Handling of TEAEs

Administration of BNT112 may be delayed for up to 21 days at the discretion of the investigator in order to adequately manage TEAEs.

TEAEs that fulfill the DLT criteria both within and outside the DLT period should be handled as shown in Figure 6-2.

Grade 4 TEAEs fulfilling DLT criteria will always lead to BNT112 cancer vaccine discontinuation.

First occurrence of a TEAE of CTCAE Grade 3 fulfilling the DLT criteria:

- Investigator must contact the sponsor's medical monitor (MM) for thorough discussion in order to decide whether the patient should be withdrawn from BNT112 treatment or the next BNT112 dosing should be delayed.
- Administration of BNT112 can be delayed for up to 21 days (i.e., 1 cycle) unless otherwise approved by the sponsor's MM. If the intensity resolves to Grade ≤1 or baseline within this period, re-treatment may be considered under the following condition:
  - Sponsor and investigator will discuss any safety concerns in order to decide whether the next dose of BNT112 should be administered at the same DL or 1 DL below the current dose (i.e., 1 DL below the level of DLT occurrence: DL-1). In case investigator and sponsor disagree, the SRC must be consulted.

Second occurrence in the same patient of an identical TEAE of CTCAE Grade 3 after re-exposure to BNT112:

- If re-treatment leads to an identical TEAE with same intensity, the next administration of BNT112 can be delayed for up to 21 days unless otherwise approved by the sponsor's

MM. If the intensity of the TEAE resolves to Grade ≤1 or baseline within this period, re-treatment may be considered under the following conditions:

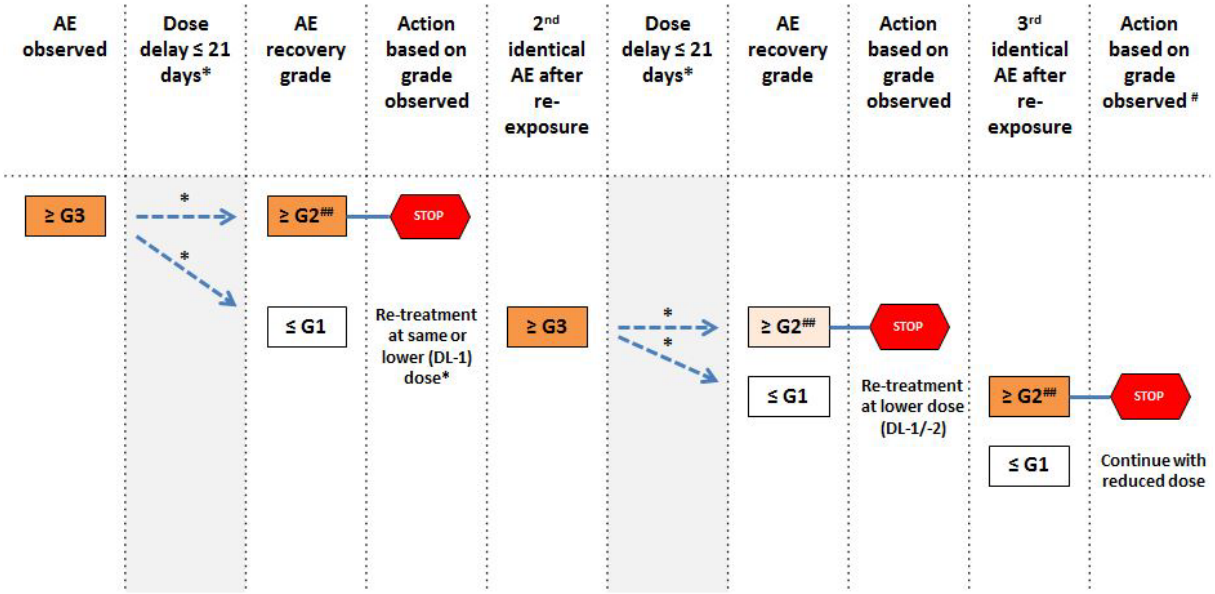
– Next dose of BNT112 should be administered 1 DL below the level of TEAE recurrence (DL-1 or DL-2).

Third occurrence of an identical TEAE of Grade ≥2 after re-exposure to BNT112:

- If re-treatment at a lower dose leads to a third identical TEAE with intensity Grade ≥2, the patient must permanently discontinue BNT112 treatment. No dose delay is allowed.

See Figure 6-2 for a decision tree for possible dose reductions and dosing delays required for TEAEs that fulfill the DLT criteria both within the DLT period and outside the DLT period.

Figure 6-2: Handling of TEAEs fulfilling the DLT criteria



Abbreviations and Footnotes:
AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; G = grade, grading according to CTCAE v5.0; TEAE = treatment-emergent adverse event.

* Dose delay: Next dose of BNT112 can be delayed by a maximum of 21 days unless approved otherwise by the sponsor's MM.

\# No delay for recovery from CTCAE Grade ≥2 allowed.

\## Unless baseline CTCAE Grade was ≥2 and TEAE has resolved to baseline grade.

Please note:

- Re-escalation of BNT112 dose is not allowed for patients that previously have been dose-reduced based on investigator's, sponsor's, and SRC's decision.
- BNT112 must be permanently discontinued if the patient experiences an AE fulfilling the DLT criteria during any period of the trial even if outside the DLT period that fails to

resolve to Grade ≤1 within 21 days after the planned dosing date unless otherwise approved by the sponsor's MM.

- BNT112 must be permanently discontinued if > 2 dose reductions are required.
- BNT112 must be permanently discontinued in case of a dose delay of > 21 days due to toxicity possibly related to BNT112 unless otherwise approved by the sponsor MM.

6.6.2. Cemiplimab (IMP)

No dose reduction of cemiplimab is recommended.

Cemiplimab should be withheld in the following conditions:

- Grade 2 pneumonitis
- Grades 2 or 3 colitis
- Hepatitis (aspartate transaminase [AST] or alanine [ALT]) increased >3 and ≤10 times the upper limit of normal [ULN], or total bilirubin increased ≤3 times the upper limit of normal)
- Grades 2–4 endocrinopathies (withhold if clinically necessary)
- Other immune-mediated Grade 3 adverse reactions involving a major organ

Cemiplimab should be permanently discontinued in the following conditions:

- Grades 3 or 4 pneumonitis
- Grade 4 colitis
- Hepatitis (AST or ALT increased >10 times the ULN or total bilirubin increased >3 times the ULN)
- Grades 3 or 4 infusion-related reactions
- Recurrent or persistent immune-mediated adverse reactions (persistent for ≥ 12 weeks after the last dose or requiring prednisone ≥ 10 mg/day or the equivalent for ≥12 weeks after last cemiplimab dose)

Additional and more detailed information about when cemiplimab should be withheld or discontinued in order to manage TEAEs are described in the relevant country label or SmPC.

For further information about the known and potential risks of cemiplimab refer to the latest version of the IB.

6.6.3. ADT (e.g., Goserelin acetate; NIMP)

No dose modification is allowed for goserelin acetate. Patients receiving goserelin acetate will remain on the assigned dose of goserelin acetate (10.8 mg Q12W) throughout the course of the trial or until 1 of the predefined discontinuation-of-treatment criteria defined in has been met (see Section 7). In case another ADT is given instead of goserelin acetate, respective prescribing information valid in a given country should be followed for dose modifications or until 1 of the predefined discontinuation-of-treatment criteria defined has been met (see Section 7).

6.7. Treatment After the End of the Trial

No trial treatment is currently envisioned beyond the end of the trial treatment period as defined in the SoA for the respective treatment arms (i.e., Month 12).

7. Discontinuation of Trial Treatment and Patient Discontinuation/Withdrawal

7.1. Discontinuation of Trial Treatment

In rare instances, it may be necessary for a patient to permanently discontinue (definitive discontinuation) trial treatment.

Patients will be withdrawn from the trial treatment if any of the following applies:

- Patient withdraws his consent to trial participation.
- Unacceptable toxicity.
- Evidence of clinical disease progression as defined by PCWG3 criteria[29] (Part 1 and Part 2 Arms 1A and 1B). Part 2 Arm 1B: following progression after BNT112 monotherapy, patients will have the option to be treated with cemiplimab CCI mg IV Q3W.
  Note: If the investigator considers radiographic changes secondary to drug-induced inflammation and not due to tumor progression, the investigator may postpone a diagnosis of PD until the next radiographic evaluation in the trial.
- Part 2 Arms 2 and 3: the planned surgery for prostate cancer can be performed at any time during the 6 months' treatment at the discretion of the investigator.
- Development of any intercurrent illness or situation which may, in the judgment of the investigator, affect assessments of clinical status and trial endpoints to a relevant degree.
- Development of a second malignancy that requires a different treatment.
- Substantial non-compliance with trial procedures.
- Use of illicit drugs, prohibited concomitant treatment, or other substances that may, in the opinion of the investigator, have a reasonable chance of contributing to toxicity or otherwise confound the results.
- Patient is lost to follow-up.

If either BNT112 or cemiplimab needs to be discontinued, treatment with either cemiplimab or BNT112 can continue upon investigator's and sponsor's agreement. As ADT has been selected as the backbone therapy for patients with LPC in this trial, if treatment with ADT (e.g., goserelin acetate) needs to be discontinued, cemiplimab and/or BNT112 also need(s) to be discontinued to minimize the risk of the delay of the radical prostatectomy.

See the SoA for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

7.2. Patient Discontinuation/Withdrawal from the Trial

A patient may withdraw from the trial at any time at his own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.

At the time of discontinuing from the trial, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of trial discontinuation and follow-up and for any further evaluations that need to be completed.

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 may request destruction of any samples taken and not tested, and the investigator must document this in the site trial records.

7.3. Lost to Follow-up

A patient will be considered lost to follow-up if he repeatedly fails to return for scheduled visits and is unable to be contacted by the trial center.

The following actions must be taken if a patient fails to return to the clinic for a required trial visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the trial.
- Before a patient is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, he will be considered to have withdrawn from the trial.

Discontinuation of specific sites or of the trial as a whole are described in Section 10.1.9.

8. Trial Assessments and Procedures

Trial procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue trial treatment.

Adherence to the trial design requirements, including those specified in the SoA, is essential and required for trial conduct.

All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the patient's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

8.1. Efficacy Assessments

8.1.1. Clinical Monitoring of Tumor Lesions

8.1.1.1. Prostate Cancer Imaging

The efficacy in mCRPC (Part 1 and Part 2 Arms 1A and 1B) will be assessed by radiographic progression as defined in PCWG3 guideline and iRECIST guideline and/or unequivocal clinical progression. The efficacy in neoadjuvant LPC (Part 2 Arms 2 and 3) will be assessed by tumor measurement using mpMRI or MRI. The same imaging modality should be used at screening and at all subsequent assessments.

If the investigator considers radiographic changes secondary to drug-induced inflammation and not due to tumor progression, the investigator may postpone a diagnosis of PD until the next radiographic evaluation in the trial.

Additional CT-scans or MRI-scans should be performed at the investigator's discretion to confirm response or potential progression of the disease (e.g., patients with confirmed PSA doubling during trial treatment).

Same imaging modalities should be kept throughout the trial to optimize the reproducibility of the assessment and preserve the accuracy of the assessment of response or progression. An Imaging Acquisition Guideline will be provided for guidance. All records and films of responding patients (CR, PR, and stable disease [SD]) must be available for eventual extramural review of the tumor.

mCRPC patients (Part 1 and Part 2 Arms 1A and 1B)

Bone scintigraphy (bone scans) and CT/MRI chest, abdomen, and pelvis should be performed at the following time points:

- During the screening period (within 28 days before C1D1 [baseline])
- At C3D15 (± 7 days)
- Then every 8 weeks (±7 days) for 24 weeks, i.e., between C6D1 and C8D15
- And every 3 months (±7 days) thereafter, i.e., from C11D15 until disease progression is assessed by the investigator or the start of new anti-cancer therapy or withdrawal of consent, or death, whichever occurs first
- At EoT visit (only if clinically indicated); not required if previous imaging was performed within ≤9 weeks before the EoT visit

Patients in Arm 1B who move to treatment with cemiplimab monotherapy following progression after BNT112 monotherapy, should have radiographic assessments performed every 3 months (±7 days) thereafter, until disease progression is assessed by the investigator or the start of new anti-cancer therapy or withdrawal of consent, or death, whichever occurs first.

LPC patients (Part 2 Arms 2 and 3)

Tumor measurement using mpMRI or MRI will be used consistently for assessment. The same imaging modality should be used at screening and at all subsequent assessments. Tumor measurements should be performed at the following time points:

- During the screening period (within 28 days before C1D1 [baseline])
- Prior to surgery (i.e., at the end of C8/EoT visit).

For guidance on the mpMRI, see the Imaging Acquisition Guideline.

8.1.1.2. Tumor Response Assessment

Part 1 and Part 2 Arms 1A and 1B

In patients with mCRPC, response to treatment with BNT112 as monotherapy or in combination with cemiplimab will be assessed for the following outcome measures based on post-baseline radiographic images as defined above.

- ORR (CR or PR) using PCWG3 criteria[29] and iRECIST criteria[30]
- DoR, using PCWG3 criteria[29]
- PFS using PCWG3 criteria[29] and iRECIST criteria[30]
- Criteria for disease response assessment are provided in Appendix 9.

The PCWG3 criteria[29] will be used for endpoint response evaluation as well as follow-up tumor assessment and will be done by a local radiologist.

The iRECIST criteria[30] will be used for exploratory endpoint response evaluation and will be done retrospectively centrally by an imaging laboratory.

Patients in Arm 1B will be given the option to be treated with cemiplimab monotherapy following progression on BNT112 monotherapy treatment and will be assessed for the same outcome measures as listed above, where the last measurement prior to start of cemiplimab treatment will serve as baseline measurement and the time-to-event endpoints (DoR, and PFS) will start from first dose of cemiplimab treatment. In particular, the last radiographic tumor assessment prior to cemiplimab treatment will re-define target and non-target lesions as basis for tumor response assessment on cemiplimab treatment. Additionally, PFS2 will be evaluated based on initial treatment.

Part 2 Arms 2 and 3

In patients with LPC, response to neoadjuvant treatment with BNT112 plus cemiplimab (Part 2 Arm 2) and BNT112 alone (Part 2 Arm 3) will be assessed for the following outcome measure based on post-baseline radiographic images as defined above:

- mpMRI or MRI tumor assessment post-treatment compared to baseline.

The tumor assessment will be used for endpoint response evaluation and will be done by a local radiologist; in addition, based on the sponsor's decision, a central read by an imaging laboratory can be added. The same imaging modality should be used at screening and at all subsequent assessments.

8.1.2. Survival Status and Biochemical Recurrence

Survival status will be assessed at month 6 and month 12 (±14 days), beginning from the day of last IMP dose and continues until the patient dies or withdraws from the trial. Patients may be contacted by telephone, E-Mail, or visit. Survival status may be requested more frequently around the time of a database lock. Patients or whose designated family members are not available for this assessment should be entered as "lost to follow-up".

Biochemical recurrence after radical prostatectomy based on post-treatment PSA levels at month 12 will be assessed for patients in Part 2 Arms 2 and 3.

8.2. Safety Assessments

8.2.1. Physical Examination

Physical examinations will be performed (by inspection, palpation, and auscultation) by a physician at the trial center at the time points specified in Section 1.3 (Part 1 and Part 2 Arms 1A and 1B), Section 1.4 (Part 2 Arms 2 and 3), and Section 1.5 (Part 2 Arm 1B [switch-over patients]). Comprehensive physical examinations will be performed at screening. During the treatment the investigators should make an overall health judgment and make only in-depth examinations if clinically indicated.

Depending on timing (before or after signing the ICF for trial participation), the clinically significant findings of the physical examination have to be recorded as medical/surgical history or as AEs (see Section 10.3.3).

Comprehensive physical examination

At a minimum, the following aspects/regions need to be assessed:

- General appearance
- Skin
- Eyes
- Ears, nose, throat
- Head and neck
- Lungs
- Heart
- Abdomen (pain, tenderness, peristaltic, ascites, organomegaly)
- Lymph nodes
- Musculoskeletal system (including extremities and spine)
- Neurologic findings

The following will be examined by specialists, if applicable:

- Genito-urinary system
- Anus/Rectum

If a patient states any symptoms that might be related to prostatitis or other prostate-related condition, further investigations like digital rectal examination, ultrasound should be initiated.

Abbreviated physical examination

The abbreviated physical examination includes an overall health judgment and brief interim history (change of symptoms). In-depth physical examinations are required if obvious pathological signs are visible or in the case the patient states any signs or symptoms.

For details regarding the measurement of body weight/height and vital signs (blood pressure, pulse, body temperature), please refer to Sections 8.2.2 and 8.2.5.

8.2.2. Clinical Laboratory Tests

Details on safety laboratory tests are provided in Table 10-1.

8.2.3. Vital Signs

Vital signs (blood pressure, pulse rate, body temperature) will be measured by a member of the investigator's team at the time points specified in Section 1.3 (Part 1 and Part 2 Arms 1A and 1B), Section 1.4 (Part 2 Arms 2 and 3), and Section 1.5 (Part 2 Arm 1B [switch-over patients]).

- Patient's systolic/diastolic blood pressure is measured in mmHg and pulse rate in bpm in sitting or supine position after at least 5 minutes rest.
- Body temperature will be measured in °C.

The same method of measurement should be used for the patient during the course of the trial.

8.2.4. Electrocardiogram

A single standard 12-lead electrocardiogram (ECG) will be recorded at the time points specified in Section 1.3 (Part 1 and Part 2 Arms 1A and 1B), Section 1.4 (Part 2 Arms 2 and 3), and Section 1.5 (Part 2 Arm 1B [switch-over patients]).

ECG will be evaluated by the investigator and will be documented in the eCRF.

8.2.5. Body Weight and Height

Patient's body weight (in kg) and height (in cm) will be measured by a member of the investigator's team at the time points specified in Section 1.3 (Part 1 and Part 2 Arms 1A and 1B) and Section 1.4 (Part 2 Arms 2 and 3).

8.2.6. ECOG PS

Patient's ability to manage activities of daily living will be appraised utilizing the performance status scale developed by the Eastern Cooperative Oncology Group published in 1982 (see Appendix 7).

The patient's ECOG PS will be estimated by a physician of the investigator's team at the time points specified in Section 1.3 (Part 1 and Part 2 Arms 1A and 1B), Section 1.4 (Part 2 Arms 2 and 3), and Section 1.5 (Part 2 Arm 1B [switch-over patients]). An ECOG PS score of 0 or 1 is required for trial inclusion (see Section 10.6).

Planned time points for all safety assessments are provided in the SoA.

8.3. Other Assessments

8.3.1. Demographic Data

At screening, the following demographic data will be recorded for all patients enrolled in this trial: age, gender (must be male), and ethnic group. The patients of all races/ethnicity can participate in the trial provided that they meet all eligibility criteria.

8.3.2. Medical History

At screening, the following relevant information on patient's medical history will be recorded:

- Documentation of prostate cancer history:
  - Month/year of initial diagnosis
  - Prior cancer treatment and previous diagnostic and therapeutic procedures
  - Tumor stage (TNM system), tumor grade (Gleason score) and risk group according to European Association of Urology Guidelines on Prostate Cancer
  - PSA at diagnosis
  - Documentation for confirmation of inclusion diagnosis: histopathology report, radiology report of bone scan, CT/MRI performed <2 months before screening (see Section 5.1: inclusion criteria)
- Documentation of relevant concomitant diseases/disorders and surgeries (start/stop date or ongoing)
- Tetanus vaccination status

8.3.3. Surgery-related Assessments

In this trial, newly diagnosed LPC patients randomized to Arms 2 and 3 will be given neoadjuvant treatment with BNT112 up to Cycle 8 (week 21) before surgery (radical prostatectomy).

The surgery is scheduled after the EoT visit and is not part of this trial. However, the following trial-related procedures/assessments are required and will be documented in the eCRF:

Pre-surgery:

- Prostate cancer imaging

During surgery:

- Date of surgery
- Fresh tumor tissue sample(s) taken intraoperatively for tumor marker analysis; if no fresh tissue sample is available, a formalin-fixed, paraffin-embedded (FFPE) sample of the tumor will be obtained

8.4. AEs and SAEs

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

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

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs will be collected from signing of the ICF until the safety FU visit at the time points specified in the SoA (Section 1.3 [Part 1 and Part 2 Arms 1A and 1B], Section 1.4 [Part 2 Arms 2 and 3], and Section 1.5 [Part 2 Arm 1B, switch-over patients]).

All SAEs will be collected from signing of the ICF until the safety FU visit at the time points specified in the SoA (Section 1.3 [Part 1 and Part 2 Arms 1A and 1B], Section 1.4 [Part 2 Arms 2 and 3], and Section 1.5 [Part 2 Arm 1B, switch-over patients]).

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 h, as indicated in Section 10.3.4. The investigator will submit any updated SAE data to the sponsor within 24 h of it being available.

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.

8.4.2. 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.

8.4.3. 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 AEs/SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.3.

8.4.4. 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 (IRB)/Independent Ethics Committees (IEC),

and investigators. The execution of expedited reporting to the different entities may be delegated as detailed in the trial-specific Safety Management Plan.

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

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

All AEs suspected to be related to the NIMP should be sent by the investigator to the national competent authority in the country where it occurred (according to the national legislation) or to the marketing authorization holder of the NIMP, but not to both to avoid duplicate submissions (ENTR/CT-3, GVP Module VI EMA/873138/2011 Rev 2).

An investigator who receives an investigator 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 respective IB (BNT112 or cemiplimab) and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5. Pregnancy

Only males will be included. After signing the ICF, patients who are sexually active with a woman of childbearing potential must agree to use a condom with spermicidal foam/gel/film/cream/suppository. Additionally, patients or their partners are required to use at least one form of highly effective contraception (please refer to Table 10-3). This must be adhered to for the duration of trial treatment and for 90 days after receiving the last dose of BNT112 OR for 6 months after the last dose of cemiplimab.

Details of all pregnancies in female partners of male patients will be collected after the start of trial treatment and until 90 days after the last dose of BNT112 and 6 months after the last dose of cemiplimab.

If a pregnancy of a female partner is reported, the investigator should inform the sponsor within 24 h of learning of the pregnancy and should follow the procedures outlined in Section 10.4.

Patients should not donate sperm during the trial starting after signing the ICF and for 90 days after receiving the last dose of BNT112 OR for 6 months after receiving the last dose of cemiplimab.

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

8.4.6. Death

Any death that occurs within the observation period will be reported as an SAE. Exemptions to the SAE definition as defined in Section 10.3.3 do also apply for fatal cases. A copy of an autopsy report should be submitted if available. 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.

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

The progression of underlying disease (e.g., new metastases, increase of PSA value) during trial participation is not considered as AE. The following disease-related event (DRE) is common in patients with prostate cancer and can be medically relevant and/or serious/life-threatening:

- The progression of prostate cancer (e.g., new metastases, PSA increase)

Because disease progression is common for patients with cancer, it will not be reported according to the standard process for expedited reporting of SAEs 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. This DRE will be monitored by an SRC on a routine basis. See Section 9.6.
Note: However, specific symptoms at time of progression that are considered that may be caused by other reasons, and fatal cases where other reasons rather than the PD may not be discarded, will have to be documented as AEs and reported as SAEs if applicable.

8.5. Treatment of Overdose

For this trial, any dose of trial treatment greater than 110% of the intended dose of either BNT112 or cemiplimab specified in the protocol will be considered an overdose.

The sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

- Contact the MM immediately.
- Closely monitor the patient for any AE/SAE and laboratory abnormalities (at least 21 days).
- Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

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

8.6. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this trial.

8.7. Pharmacodynamics

Potential pharmacodynamic parameters are evaluated in this trial and described in the next Section 8.8.

8.8. Biomarkers

Blood samples and tumor samples for biomarker analysis will be collected from patients with mCRPC (Part 1 and Part 2 Arms 1A and 1B) and LPC (Part 2 Arms 2 and 3) at the time points shown in the SoA (Section 1.3, Section 1.4, and Section 1.5 respectively).

The selected biomarkers will be used as follows:

- For tracking the progression of prostate cancer (diagnostic markers, e.g., PSA); therefore, patient's blood samples will be tested for levels of PSA.
- To monitor the safety of investigational treatment (e.g., cytokines).
- To investigate immuno-pharmacodynamics of BNT112 to evaluate the MoA and identify the optimal dosage regimen for guiding treatment strategies (MoA/Pharmacodynamics biomarkers). As an exploratory endpoint, T cell responses against each of the vaccine antigens in patient's blood samples will be analyzed.
- Additionally, potential pharmacodynamic and predictive biomarkers that may identify patients that can benefit from therapy may be addressed:
  - Blood and tumor samples will be collected in order to perform profiling of T cell receptors (TCR profiling) in the periphery and tumor as potential predictive marker as well as surrogate for pharmacodynamics.
  - Tumor samples may also be investigated with regards to intratumoral changes of infiltrating immune cells by immunohistochemistry.
  - Furthermore, fresh tumor samples (non-FFPE material) will be collected in order to investigate anti-tumor specific activity within the tumor by functional T cell tests (such as ELISpot) and phenotypic characterization of tumor-antigen-specific T cells. For the latter, the patient's blood has to be characterized with regards to the respective human leukocyte antigen (HLA) type.
  - Furthermore, i) the mRNA expression of vaccine antigens in the tumor may be investigated, as well as ii) specific mutations in tumor DNA in order to evaluate tumor mutational burden, and iii) the identification of RNA expression pattern of immune-relevant genes. For these analyses, patient's tumor samples will be collected.

The biomarker parameters will be analyzed by different laboratories (central laboratory and specialty laboratories). Detailed information about the handling, labeling, and shipment of blood samples for biomarker analysis will be provided in a separate document (i.e., Laboratory Manual).

Optional samples for biomarker research that should be collected from patients in the trial where possible are the following:

- Blood and tumor tissue (analyses as described above will be performed with these additional samples)
- On-treatment tumor samples from biopsies or tumor resections done as part of the clinical management of the patient (e.g., palliative surgery) will optionally be provided for additional potential biomarker research.

In addition, samples will be stored and analysis may be performed on biomarker variants thought to play a role in the MoA of BNT112 including, but not limited to, blood and tumor tissue biomarkers to evaluate their association with observed clinical responses to BNT112 alone, or in combination with cemiplimab and/or ADT (e.g., goserelin acetate).

Other samples may be used for research to develop methods, assays, prognostics and/or companion diagnostics related BNT112 alone, or in combination with cemiplimab and/or ADT (e.g., goserelin acetate) in prostate cancer.

Biomarker samples may be stored up to 5 years after the trial ends. Biomarker analyses may be deferred or not performed, if during or at the end of the trial, is becomes clear that the analysis will not have sufficient scientific value for biomarker evaluation, or if there are not enough samples to allow adequate evaluation. In the event the trial is terminated early or shows poor clinical efficacy, completion of biomarker assessments is based on justification and intended utility of the data.

The results of this additional research may not be presented in the Clinical Study Report (CSR). These results may be presented outside of the CSR.

8.9. Immunogenicity Assessments

Immunogenicity will be assessed using relevant biomarkers (refer to details in Section 8.8).

9. Statistical Considerations

9.1. Statistical Hypotheses

For each Part 2 Arm 1A and 1B the null hypothesis that the true response rate is 5% will be tested against a one-sided alternative (i.e., H_0: ORR=5% vs H_1: ORR>5%). There will be no formal comparison between treatment arms. No further statistical hypothesis is under test.

9.2. Sample Size Determination

The sample size for Part 1 is driven by the 3+3+3 trial design and will range from 3 to 9 DLT evaluable patients depending on the number of DLTs which may occur. The main objective for the Part 2 is to perform exploratory biomarker analyses in the LPC setting and to preliminary assess the efficacy in terms of response in the mCRPC setting.

Simon's two-stage design (Simon, 1989[31]) based on the Minimax approach will be used for Part 2 Arm 1A and 1B separately. The null hypothesis that the true response rate is 5% will be tested against a one-sided alternative. In the first stage, 20 evaluable patients will be treated. Enrollment will continue following sponsor decision (upon recommendation from the SRC following review) and 13 evaluable patients may be treated for a total of 33 evaluable patients. If there is one or fewer responses in the first 20 evaluable patients, the enrollment for that arm may be stopped. The null hypothesis will be rejected if five or more responses are observed in 33 evaluable patients. This design yields a type I error rate of 2.5% and power of 80% when the true response rate is 20%.

A patient will be considered as evaluable if included in the primary analysis set (mITT set, see Section 9.3) which is defined as all patients who are randomized to the IMP and have a baseline

and at least one post-baseline (i.e., one on-treatment or post-treatment) tumor assessment (clinical or imaging assessment).

No formal sample size calculation is performed for the LPC setting in Part 2 (Arms 2 and 3) due to its exploratory nature. However, 20 patients are planned to be enrolled into Arm 2 and Arm 3. Based on this sample size (N=20) the one-sided 95% CI of binary endpoints will have a width of up to +/-0.19 in each group depending on the observed effect size.

9.3. Analyses Sets

The following analysis sets are defined:

Population	Description
Screened	The screened analysis set is defined as all patients who sign the ICF.
Intent-to-Treat (ITT)	The ITT set is defined as all patients who are randomized to the IMP.
Modified Intent-to-Treat (mITT)	The mITT set is defined as all patients who are randomized to the IMP and have a baseline and at least one post-baseline (i.e., one on-treatment or post-treatment) tumor assessment (clinical or imaging assessment).
DLT Evaluation	The DLT evaluation set includes all patients from the safety set who either have completed the DLT evaluation period and meet the minimum exposure criterion or have experienced a DLT during C1. Patients who do not experience any DLTs during C1 are considered to be evaluable if they have been observed for minimum of 21 days following the first dose and are considered to have sufficient safety data to conclude that a DLT did not occur. A patient is considered to have met the minimum exposure criterion if the RDI of BNT112 in C1 is at least 90%.
Safety	The safety set is defined as all patients who received IMP (i.e., at least 1 dose of BNT112 and/or cemiplimab).
Pharmacodynamic	The Pharmacodynamic analysis set is defined as all patients with baseline and at least 1 on-treatment/post-treatment follow-up pharmacodynamic assessment.

The DLT evaluation set will be used for the evaluation of DLTs in order to assess the REDR. The safety set will be used for all other safety analyses, while the mITT set will be used for efficacy analyses. Arm 1b will be additionally analyzed for patients who received cemiplimab (i.e., at least 1 dose of cemiplimab) after progression to BNT112 monotherapy.

All safety analyses will be based on the treatment actually taken by the patient ("as treated"). All other analyses will be based on the treatment the patient was assigned/randomized to ("as randomized"), unless stated otherwise.

9.4. Statistical Analyses

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

9.4.1. General Considerations

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

In general, the statistical analysis will be performed by trial part (i.e., Part 1 and Part 2, respectively) and by treatment group in Part 2 (i.e., Arm 1A, Arm 1B, Arm 2 and Arm 3).

Continuous variables will be summarized by treatment group using the following descriptive statistics: n, mean, standard deviation, median, minimum, and maximum.

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

Time-to-event-endpoints (DoR, PFS, and OS) will be analyzed using Kaplan-Meier methodology and censored in accordance with the FDA Guidance: "Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics." Censoring rules will be defined in the SAP. Number of patients with events, censored and under risk as well as the median, first and third quartile of time-to-event (including 95% confidence limits according to Brookmeyer and Crowley) will be presented. Survival rates including 95% confidence interval based on Greenwood's formula will be displayed after 3 months, after 6 months and after 12 months.

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

In the following sections basic statistical analyses will be described. Further details of statistical analyses will be provided in the SAP. Additional statistical analyses may be added in the SAP.

9.4.2. Primary Endpoints

DLTs and AEs

The primary endpoint is the occurrence of DLTs and AEs reported by relationship, grade, and seriousness according to NCI CTCAE v5.0. The number and percentage of patients with any DLT and/or AE will be presented for patients enrolled into Part 1 and for each arm in Part 2. Moreover, a patient listing will be provided with all relevant dose exposure data of all patients enrolled into Part 1 and for each arm in Part 2 and a listing of all recorded DLTs and/or AEs will be presented including the reported term and Medical Dictionary for Regulatory Activities (MedDRA®) PT and SOC term, its time of onset, relationship, NCI CTCAE grade, and seriousness including dose exposure data (e.g., BNT112 DL).

Objective Response Rate

For Arm 1A and 1B in Part 2, ORR is defined as primary efficacy endpoint.

The ORR is defined as the number of patients with CR or PR as best objective response divided by the number of patients in the analysis set. Patients not meeting the criteria for CR or PR, including those without any post-baseline tumor assessments, will be considered as non-responders. The ORR will be summarized with absolute and relative frequencies along with two-sided 95% Clopper-Pearson confidence intervals by treatment group/cohort.

The primary analysis will be performed using the mITT set.

For Part 1, ORR is defined as secondary endpoint ORR and will be analyzed descriptively.

9.4.3. Secondary Endpoints

PSA Decline

PSA decline of 0 to 25%, >25% to 50%, and >50% compared to baseline will be summarized with absolute and relative frequencies (n and %) of patients in each category. PSA decline of ≥50% (according to the PCWG3) will be summarized with absolute and relative frequencies (n and %) of patients in each category.

PSA Doubling Time

The number and percentage of patients per PSADT under-treatment compared to baseline.

Tumor Response

For Arm 2 and 3 in Part 2, tumor response is defined as secondary efficacy endpoint.

Secondary efficacy analyses will be performed using the mITT set.

9.4.4. Exploratory Endpoints

Exploratory Immunogenicity Analyses

Exploratory immunogenicity analyses will be further defined in the SAP.

BNT112 antigen-specific T cells

Occurrence of *de novo* induction or increase of BNT112 antigen-specific T cells in peripheral blood under treatment on C3D15 and/or C8D15, EoT, or safety follow-up compared to baseline will be summarized with absolute and relative frequencies (n and %) of patients in each category.

Exploratory Efficacy Analyses

Exploratory efficacy analyses will be performed using the mITT set.

Exploratory efficacy endpoints comprise ORR (in the mCRPC arms and only per iRECIST), DoR, PFS, and OS. Tumor assessments will be performed using PCWG3 and iRECIST. DoR and PFS will be analyzed separately for PCWG3 and iRECIST.

Exploratory efficacy analyses will also be performed on patients in Arm 1B who are treated with cemiplimab monotherapy following progression after BNT112 monotherapy. These exploratory analyses will comprise ORR, DoR, PFS (per PCWG3 and iRECIST) on cemiplimab monotherapy based on last tumor assessment prior to start of cemiplimab treatment and OS. PFS2 will be analyzed as well. Further details will be described in the SAP.

Duration of Response

The DoR is defined as the time from the date of first radiographic documented OR to the date of first disease progression. Only patients who experience a confirmed CR or PR will be analyzed for DoR. DoR will be analyzed using the Kaplan-Meier method. 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.

Progression-free Survival

PFS is defined as the time from the date of first dose of IMP/randomization to the date of first disease progression, or death from any cause, whichever occurs first. PFS will be analyzed using the Kaplan-Meier method. Patients alive and without disease progression at the data cut-off date or patients lost to follow-up will be censored at the day of their last tumor assessment. If no baseline or post-baseline tumor assessment is available, the patient will be censored at the date of first dose of IMP/randomization. Additional censoring rules will be defined in the SAP.

Overall Survival

OS is defined as the time from the date of first dose of IMP/randomization to the date of death from any cause. OS will be analyzed using the Kaplan-Meier method. Patients alive or patients lost to follow-up at the date of analysis cut-off will be censored at the day of their last date known to be alive. Additional censoring rules will be defined in the SAP.

9.4.5. Safety Analyses

Safety data that will be summarized include exposure, AEs, clinical laboratory assessments, vital signs and ECGs. All safety analyses will be based on the safety set and will be summarized by treatment group unless otherwise stated.

Treatment Exposure

The following dose exposure variables will be derived and analyzed for each compound:

- Number of cycles
- Treatment duration (weeks) defined as follows:
    - (Date of last administration - date of first administration + planned duration)/7, whereas the Planned Duration (days) is defined as the planned time between two consecutive administrations.
- Cumulative Dose (µg [BNT112] / mg [cemiplimab]) defined as sum of all administered doses
- Dose Intensity (DI) defined as Cumulative Dose/Treatment Duration
- Relative Dose Intensity (RDI) defined as follows:

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

whereas

$$\text{(Actual) Dose Intensity} = \frac{\text{(Actual) Cumulative Dose}}{\text{(Actual) Treatment Duration}}$$

$$\text{Planned Dose Intensity} = \frac{\text{Planned Cumulative Dose}}{\text{Planned Treatment Duration}}$$

$$\text{Dose Index} = \frac{\text{Total Administered Dose}}{\text{Total Planned Dose}}$$

$$\text{Time Index} = \frac{\text{Planned Treatment Duration}}{\text{Actual Treatment Duration}}$$

AEs

AEs will be coded using the most recent version of MedDRA® coding system to get a SOC and PT for each AE and graded for severity using NCI CTCAE v5.0.

A TEAE is defined as any AE with an onset date on or after the first administration of IMP (if the AE was absent before the first administration of IMP) or worsened after the first administration of IMP (if the AE was present before the first administration of IMP). AEs with an onset date more than 30 days or 90 days, respectively for BNT112 or cemiplimab, after the last administration of IMP will be considered as treatment-emergent only if assessed as related to the IMP by the investigator. TEAEs will be summarized overall and by treatment arm.

For Arm 1B, the analysis of AEs will be additionally performed for each IMP separately, i.e. TEAEs from first dose of BNT112 until last dose of BNT112 +30 days and TEAEs from first dose of cemiplimab until last dose of cemiplimab +90 days, respectively.

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
- AEs leading to dose delays or dose reduction
- AE leading to permanent discontinuation-of-treatment

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

Laboratory Assessments

Clinical laboratory data to be summarized include hematology, blood chemistry, and urinalysis. The clinical laboratory parameters to be assessed are listed in Section 10.2 and the scheduled time points for assessment are tabulated in the SoA.

Clinical laboratory parameters at each time point and change from baseline to each post-baseline time point will be summarized using descriptive summary statistics for each parameter by treatment group.

Clinical laboratory results will be classified according to of NCI CTCAE v5.0. Laboratory results not corresponding to an NCI CTCAE term will not be graded. Shift tables from baseline to worst grade on-treatment will be provided for each laboratory parameter.

Vital Signs

Vital sign parameters and the scheduled time points for assessment are presented in the SoA.

Vital sign parameters at each time point and change from baseline to each post-baseline time point will be summarized using descriptive summary statistics for each parameter by treatment group.

ECG

ECGs parameters and the scheduled time points for assessment are presented in the SoA.

ECGs will be judged by the investigator as clinically significant (yes/no). The number and percentage of patients with clinically significant ECG findings will be summarized by treatment group for each time point.

9.4.6. Other Analyses

Biomarker Analyses

Cellular immune responses, cytokines, and further immunological parameters as represented in SoA will be analyzed using the pharmacodynamics analysis set. Details of these analyses will be presented in the SAP.

Other analyses may include analyses of assessments, which are not defined as endpoints, that need to be pre-specified and not necessarily be reported in the clinical trial report such as, but not limited to, immunogenicity, biomarkers, population pharmacokinetics, health care utilization endpoints and health technology assessment related endpoints.

9.5. Interim and Final Analyses

An interim statistical analysis for futility is planned for Arm 1A and Arm 1B based on the Simon's two-stage design (Simon, 1989[31]) (see Section 9.2).

The interim analysis will be performed based on all available data from a clinical data cut-off that will occur when the required number of patients in the respective arm have performed the first post-baseline tumor assessment or have been diagnosed with unequivocal clinical progression.

The final analysis of the trial will be performed based on all available data from a clinical data cut-off that will occur after patients in the respective setting of Part 2 (Arms 1A, 1B, and 2, 3, respectively) have completed 8 cycles of treatment or discontinued. An analysis update will be performed when the last patient discontinues from the trial.

9.6. Data Monitoring Committee/Safety Review Committee

An Independent Data Monitoring Committee is not planned for this trial.

The patient's safety will be monitored throughout the trial by the SRC. The SRC will be chaired by the sponsor's MM and membership will include at a minimum the trial principal investigators, members of the sponsor medical and safety departments, as well as additional staff as appropriate. Please refer to the current SRC charter.

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

This trial will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable ICH GCP Guidelines
- Applicable laws and regulations

The clinical trial 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 substantial 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 Code of Federal Regulation (CFR), ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the trial to the patient or his legally authorized representative and answer all questions regarding the trial.

Patients must be informed that their participation is voluntary. Patients or their legally authorized representative (if applicable) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or trial center.

The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the trial and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Patients must be re-consented to the most current version of the ICF(s) during their participation in the trial.

A copy of the ICF(s) must be provided to the patient or the patient's legally authorized representative.

Separate ICFs will be used in this trial:

- Main ICF for trial participation of mCRPC patients (Part 1 and Part 2 Arms 1A and 1B)
- Main ICF for trial participation of LPC patients including mandatory tumor tissue sample (Part 2 Arms 2 and 3)
- Pregnant partner ICF
- Additional ICFs will be used if required by local regulations
- Optional (in main ICF): tumor sample ICF (Patients in Part 1 and Part 2 Arms 1A and 1B will be asked if they are willing to provide optional tumor biopsy sample(s) in case these are taken at the time of disease progression)
- Optional (in main ICF): Under certain circumstances the collection of additional blood samples might be indicated for a given patient
- Optional ICF for trial participation of mCRPC patients in Arm 1B who wish to be treated with cemiplimab monotherapy following progression after to BNT112 monotherapy

10.1.4. Data Protection

During data entry, processing and analysis by the sponsor or designated CRO, all requirements of the data protection act will be taken into account. Access to data is strictly limited to authorized persons. Data are protected against unauthorized access according to current federal legislation and regulations.

The sponsor will ensure that all safeguards are in place to minimize any eventual risk of breaches, and complies otherwise with the requirements of EU General Data Protection Regulation (GDPR Regulation [EU] 2016/679). The sponsor will regularly check all procedures relevant to the processing of personal data, as to ensure privacy by design and compliance with GDPR.

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 personal trial-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient who will be required to give consent for their data to be used as described in the informed consent.

The patient must be informed that his medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

In this clinical trial, an SRC is being implemented. For further details, see the SRC charter.

10.1.6. Dissemination of Clinical Trial Data

A final report integrating all trial results will be prepared by the sponsor.

This trial will be registered and trials results be publicly posted on publicly accessible trial registries (e.g., ClinicalTrials.gov, EudraCT) in accordance with the applicable regulations.

10.1.7. Data Quality Assurance

All patient data relating to the trial will be recorded on printed or eCRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The investigator must permit trial-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

The sponsor or designee is responsible for the data management of this trial including quality checking of the data. The sponsor assumes accountability for actions delegated to other parties (e.g., CROs).

Trial monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the trial is being conducted in accordance with the currently approved protocol and any other trial agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this trial must be retained by the investigator for 30 years after trial completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8. Source Documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the trial. Also, current medical records must be available.

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 enrollment of patients.

The sponsor or applicable health authority may terminate the trial for reasonable cause.

Trial centers will be closed upon trial completion. A trial center 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 center 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.
- Discovery of an unexpected, serious or unacceptable risk to patients enrolled in the trial.
- Inadequate recruitment of patients by the investigator.
- Discontinuation of further trial treatment development.

The sponsor or health authority may terminate the trial for reasonable cause. Conditions that may warrant termination of the trial include, but are not limited to:

- Discovery of an unexpected, serious or unacceptable risk to patients enrolled in the trial.
- Sponsor decision to suspend or discontinue testing, evaluation, or development of the trial drug.
- Failure of the investigator to comply with the approved clinical trial protocol, pertinent guidelines, and or regulations.

If the trial is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the trial of the reason for termination or suspension, as specified by the applicable

regulatory requirements. The investigator shall promptly inform the patient and should assure appropriate patient therapy and/or follow-up.

10.1.10. 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 International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

For further details, please refer to the Laboratory Manual provided by the central laboratory.

Table 10-1: Local Safety Laboratory Tests (Blood and Urine) - Overview

Parameters (by group)
Hematology:
Hemoglobin, hematocrit, red blood cell count, white blood cell count and differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), platelet count
Coagulation:
International normalized ratio, activated partial thromboplastin time, fibrinogen
Blood chemistry:
Alkaline phosphatase (ALP), creatinine, ferritin, C-reactive protein, albumin, alanine aminotransferase (ALT), amylase, aspartate aminotransferase (AST), gamma glutamyl transpeptidase, total bilirubin, blood urea nitrogen, glucose, lipase, sodium, potassium, calcium, and thyroid function (thyroid stimulating hormone [TSH], free thyroxine [fT4] and triiodothyronine [T3])
Urinalysis:
Dipstick: specific gravity, pH, glucose, protein, ketones, blood
Microscopic urinalysis: If warranted by dipstick results, urine sediment will be microscopically examined for presence of red blood cells, white blood cells, casts, crystals, epithelial cells, and bacteria
Circulating tumor cells

Table 10-2: Central Blood Biomarker Assessment - Overview

Rationale	Test
Eligibility	Testosterone
Eligibility	Serology i.e., HBsAG, anti-HBc, anti-HBs, anti-HCV, anti-HIV 1/2
Safety	Cytokines
MoA/PD	PSA
MoA/PD	Antigen-specific T cells (ELISpot and further immune monitoring)
MoA/PD	HLA typing
MoA/PD	TCR profiling

ELISpot = enzyme linked immunospot (assay); HBc = hepatitis B core antigen; HBs = hepatitis B surface antigen; HBsAG = hepatitis surface antigen; HCV = hepatitis C virus; HLA = human leukocyte antigen; ICS = intracellular cytokine staining; MoA/PD = mechanism of action/pharmacodynamics; TCR = T cell receptor.

Please refer to the trial-specific Laboratory Manual for further details.

10.3. Appendix 3: AEs: 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 use of a medicinal product, whether or not considered related to the medicinal product. • 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 30 days or 90 days, respectively (and at screening for all patients if the patient is not yet randomized), after the last administration of IMP will be considered as treatment-emergent only if assessed as related to the IMP by the investigator.

Events <u>Meeting</u> 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 detected or diagnosed after trial treatment administration even though it may have been present before the start of the trial. • 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 treatment. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. “Lack of efficacy” or “failure of expected pharmacological action” will not be reported as an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than 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. • DREs and/or disease-related outcomes not qualifying as AEs or SAEs are further specified in Section 8.4.7.

Adverse Reaction (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.

10.3.2. 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.

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Is another medically important condition:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical treatment to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE; see Section 10.3.3; 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 are required to be reported by the investigator to the sponsor immediately (i.e., no more than 24 h after learning of the event; see Section 10.3.4 for reporting instructions).

SUSARs

Any serious adverse reaction that is classified as unexpected by the sponsor.

An AR is classified as unexpected when the nature or severity is not consistent with the applicable product information (reference safety information [RSI], i.e., IB for an unauthorized investigational product or SmPC for an authorized product). The term severity is used here to describe the intensity of a specific event. This has to be distinguished from the term serious.

The expectedness of an AR is determined by the sponsor according to the RSI. This should be done from the perspective of events previously observed, not based on what might be anticipated from the pharmacological properties of a medicinal product.

If the RSI is contained in an IB, the IB should contain a clearly identified section to expected ARs.

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

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 ICF until FU-D30 for Part 1 and Part 2 Arm 1B and Arm 3, and FU-D90 visit for Part 2 Arm 1A, Arm 1B switch-over patients, and Arm 2).

- 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 done during the visit, 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
  - Drug 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 on the source data and eCRF.
- It is not acceptable for the investigator to send photocopies of the patient's medical records to the sponsor in lieu of completion of the AE eCRF page.
- 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)*. An event that causes sufficient discomfort and interferes with normal everyday activities.
- 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 event that prevents normal everyday activities. 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

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

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

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

- Initial intensity of the AE
- Maximum intensity of the AE
- For each change of intensity:
    - New grade of intensity
    - Date of change (= start of new grade of intensity)
    - 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 treatment (IMPs) by the investigator:

- Dose not changed (= continuation of trial treatment 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 trial treatment has not yet started or event starts after last trial treatment administration)

*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 therapy for the treatment of the AE
- Termination of a concomitant treatment (please specify; e.g., if this might be the cause of the AE)
- Change of the dose of a concomitant treatment
- Hospitalization or prolongation of hospitalization (please complete SAE-Form)
- 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.*

All ongoing AEs will be followed until resolution, considered by the investigator to be stable or chronic (resolved with sequelae), new systemic anti-cancer treatment (outside the protocol) is initiated, the patient is lost to follow-up or the patient withdraws consent. If no final status is reached at Safety FU-D30 (for all Part 1 patients and Part 2 Arm 1B and Arm 3) or Safety FU-D90 visit (for Part 2 Arm 1A, Arm 1B switch-over patients, and Arm 2), the investigator must confirm the unavailability of a final status.

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.
- The following table can be taken as guidance:

Causality Term	Assessment Criteria	Assessed as
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically)	Related

	• Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognized pharmacological phenomenon) • Rechallenge satisfactory, if necessary	
Probable/ Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required	Related
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear	Related
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations	Not related

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

- Related, or
- Not related.

For an event considered "related to trial treatment" there is a **reasonable possibility** of a causal relationship.

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

Relationship to trial treatment (BNT112 and Cemiplimab)

- 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 ADRs but not events caused by the NIMP or the procedure of trial treatment administration

Relationship to trial procedures

- In this first-in-human 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 AE can occur at 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.

Relationship to prostate cancer surgery

- For patients in Part 2 Arms 2 and 3 the investigator should also assess the relationship of the event to the prostate cancer surgery. These events have to be reported in the eCRF on Adverse Event pages as "related to prostate cancer surgery".
- The investigator will also consult the respective IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always 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 a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

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

- AEs and SAEs occurring later than 30 days (for Part 1 and Part 2 Arm 1B and Arm 3) and 90 days (for Part 2 Arm 1A, Arm 1B switch-over patients, and Arm 2) after the last administration of trial medication must only be reported by the investigator to the sponsor if a relationship to trial treatment 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 treatment administration or insertion of access device for trial treatment 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 (e.g., prostate cancer surgery planned for patients in Part 2 Arms 2 and 3)
    - 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.

- Hospitalization of a patient for monitoring and symptomatic treatment for up to 24 h due to a transient inflammatory reaction of Grade 1 or 2 will not be considered as a SAE (but needs to be documented as AE).
- The progression of underlying disease (e.g., new metastases, increase of PSA value) during trial participation is not considered as AE. However, specific symptoms at time of progression that are considered that may be caused by other reasons, and fatal cases where other reasons 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

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 source data and 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.

Death:

- Any death that occurs within the observation period will be reported as an SAE. Exemptions to the SAE definition as defined above do also apply for fatal cases. A copy of an autopsy report should be submitted if available. 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 one 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.

AEs associated with an overdose or error in drug administration:

An overdose is the accidental or intentional use of a drug in an amount (per administration or cumulatively) higher than the dose being studied (for the trial treatment) or higher than the maximum recommended dose according to the authorized product information (for approved concomitant treatments). 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 source data and eCRF and reported as SAE if applicable.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- If a patient dies during participation in the trial or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any post-mortem findings including histopathology.
- 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 h of receipt of the information as described in Section 10.3.4.

10.3.4. Reporting of SAEs

SAE Reporting to Sponsor

The period of observation for each patient extends **from signing ICF until Safety FU-D30 (for all Part 1 patients and Part 2 Arm 1B and Arm 3) or Safety FU-D90 visit (for Part 2 Arm 1A, Arm 1B switch-over patients, and Arm 2)**.

All SAEs which occur in a patient during the observation period, whether considered to be associated with trial medication or not, must be reported by the investigator **to the sponsor immediately but at the latest within 24 h 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 the trial procedure.

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

Safety Report Fax No.:

Safety Report E-Mail Address:

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 center 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) 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 Site Trial File. In case an investigator or any other trial team member has questions on **safety reporting** to the sponsor, these can be addressed to:

E-Mail:

Please note that for medical questions the MM for this trial should be contacted.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Contraception Guidance

After signing the ICF, patients who are sexually active with a woman of childbearing potential must agree to use a condom with spermicidal foam/gel/film/cream/suppository. Additionally, patients or their partners are required to use at least one form of highly effective contraception for the time period between signing the ICF and 90 days after the last administration of BNT112 OR for 6 months after the last dose of cemiplimab. Highly effective contraception methods are listed in Table 10-3. Birth control methods are considered highly effective if they have a failure rate of less than 1% per year, when used consistently and correctly.

All patients must also not donate sperm during the trial starting after signing the ICF and for 90 days after receiving the last dose of BNT112 OR for 6 months after receiving the last dose of cemiplimab.

Table 10-3: 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 some concomitant medications, which may reduce the efficacy of the contraception method.
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 childbearing potential (trial patient) and that the vasectomized partner has received medical assessment of the surgical success.
4. In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

Table adapted from 'Recommendations related to contraception and pregnancy testing in clinical trials. Advisory non-binding guidance represented at the CTFG-meeting in Rome 2014[40].

Collection of Pregnancy Information

Male patients with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male patient's female partner who becomes pregnant after the male patient's start of trial treatment and until 90 days after the last dose of BNT112 and 6 months after the last dose of cemiplimab.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the paper-based **Pregnancy Reporting Form** and submit it to the sponsor within 24 h of learning of the partner's pregnancy. The completed form needs to be sent to the Safety Report Fax number or E-Mail Address mentioned in Section 10.3.4. The female partner will also be followed to determine 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 trial treatment.

10.5. Appendix 5: Declaration of Helsinki

World Medical Association (WMA) Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013.

10.6. Appendix 6: ECOG PS

Developed by the Eastern Cooperative Oncology Group, Robert L. Comis, MD, Group Chair.*

The Eastern Cooperative Oncology Group is now part of the ECOG-ACRIN Cancer Research Group.

Table 10-4: ECOG PS

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all 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	Dead

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

10.7. Appendix 7: Graphical Illustration of PSA Progression for Trial Eligibility

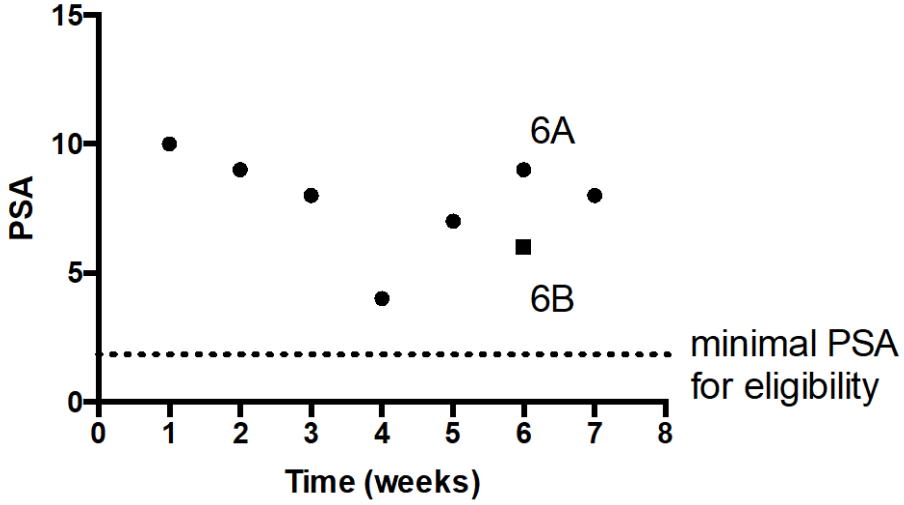


Figure 10-1: Graphical Illustration of PSA Progression for Trial Eligibility

The Prostate Cancer Working Group Criteria 3[29] states that for PSA eligibility for a trial there should be 2 sequential rises (value in Week 5 and 6A) in PSA above the baseline (seen above at Week 4) separated by ≥ 1 week with the baseline PSA being above 2 ng/mL. If after 1 rise in PSA there is a decrease with the value remaining above baseline (e.g., 6B), a further rise is required (as seen in Week 7).

10.8. Appendix 8: Consensus Grading for Cytokine Release Syndrome

Table 10-5: ASTCT CRS Consensus grading

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

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

a. 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.

b. 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.

c. 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.

ASTCT = American Society for Transplantation and Cellular Therapy; BiPAP = Bilevel Positive Airway Pressure; CPAP = continuous positive airway pressure; CRS = cytokine release syndrome; CTCAE = Common Terminology Criteria for Adverse Events.

Source: Lee et al. 2019.[19]

10.9. Appendix 9: Criteria for Disease Response Assessment

1. MEASURES OF PROGRESSION AFTER COMMENCMENT OF TREATMENT:

Progression will be documented by confirmed radiograph progression (bone and/or CT/MRI scan with a subsequent confirmatory scan) and/or unequivocal clinical progression. Patients should **not discontinue treatment on the basis of PSA progression alone** and instead this should guide the investigator to potentially expedite radiological investigations.

The criteria for disease progression are considered met if one or more of the following conditions occur:

a) Radiological progression per PCWG3:

- Soft tissue/visceral disease progression:
  - A patient will be determined to have progressed if they have progression of target lesions (sum of diameter increase to nadir of ≥20% and by ≥5 mm), clear progression of existing non-target lesions, or the appearance of 1 or more new lesions. **Lymph nodes have to be ≥ 1.5 cm in short axis to be deemed measurable.**
  - The scan for confirmation of progression may be performed ≥4 and ≤8 weeks after the initial scan demonstrating progression. Patients who have a repeat scan earlier than scheduled and do not confirm progression do not need to undergo the next scheduled imaging if it is <4 weeks after the confirmation scan. Patients will return to their regular imaging schedule starting with the next time point.
- Bone disease progression
  - On the C3D15 scan, ≥2 new lesions compared with baseline confirmed by a second scan ≥6 weeks later that also shows an additional ≥2 new bone lesions (2+2 rule, i.e., a total of ≥4 new lesions compared with the baseline bone scan).
  - On subsequent scans (>16 weeks), ≥2 new bone lesions compared with the previous scan with the confirmatory scan at ≥6 weeks demonstrating at least persistence of the progression noted on the previous scan.

b) Unequivocal evidence of clinical progression

c) PSA Progression

- ≥25% increase and an absolute ≥2 ng/mL rise This rise must be confirmed by a second measurement ≥3 weeks later and the date of progression is denoted as the first measurement to meet these criteria. Ignore early rises (before 12 weeks) in determining PSA progression.
- If the PSA has risen during the first 12 weeks and then decreased, the ≥25% increase and an absolute ≥2 ng/mL rise is required above the new decreased value (nadir value), confirmed by a second measurement at least 3 weeks later.
- If the PSA has risen during the first 12 weeks with no decline, the date of progression is backdated to the date when ≥25% increase and an absolute ≥2 ng/mL rise (from Baseline value) was first observed.

2. MEASURES OF RESPONSE:

The PCWG3 criteria for disease response in a patient are considered met if 1 or more of the following conditions occur:

a) PSA response:

- PR: ≥50% decline in PSA from baseline confirmed at least 4 weeks later
- SD: Serial PSA measurements that do not meet the criteria for PR or PD

b) Radiological response:

- Soft tissue/visceral disease:
  - CR: Disappearance of all target lesions. A reduction in short axis to <10 mm must be seen in any pathological lymph nodes. No new lesions.
  - PR: 30% decrease in the sum of the longest diameter of target lesions.
  - SD: No evidence of PD, CR or PR.
- Bone disease response
  - Bone scan is not used as part of the response criteria. Bone scans will be evaluated for progression only.

c) Circulating tumor cell (CTC) response:

- Conversion of CTC ≥5/7.5 mL to <5/7.5 mL at 9 weeks. If there is a CTC response, this must be confirmed by an additional <5/7.5 mL result at least 4 weeks later.

10.10. Appendix 10: Abbreviations

Abbreviation	Definition
ADL	Activities of daily living
ADR	Adverse drug reaction
ADT	Androgen-deprivation therapy
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
APC	Antigen presenting cell
AR	Adverse reaction
AST	Aspartate aminotransferase
C	Cycle
CFR	Code of Federal Regulation
CR	Complete response
CRO	Contract research organization
CRPC	Castration-resistant prostate cancer
CRS	Cytokine release syndrome
CT	Computed tomography
CTC	Circulating tumor cell
CTCAE v5.0	Common Terminology Criteria for Adverse Events, version 5.0
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
D	Day of cycle
DFS	Disease-free survival
DI	Dose intensity
DL	Dose level
DLT	Dose-limiting toxicity
DoR	Duration of response
DRE	Disease-related event
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic case report form

Abbreviation	Definition
EoT	End of treatment
EU	European Union
FU	Follow-up (Visit)
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GLP	Good Laboratory Practice
h	Hour(s)
HPV	Human papilloma virus
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IFN	Interferon
IMP	Investigational medicinal product
IMP 1	BNT112
IMP 2	Cemiplimab
IRB	Institutional Review Board
iRECIST	Immune-modified Response Evaluation Criteria in Solid Tumors
ITT	Intent-to-treat
IV	Intravenous(ly)
LHRH	Luteinizing hormone-releasing hormone
LHRHa	Luteinizing hormone-releasing hormone analogue
LPC	Localized prostate cancer
mCRPC	Metastatic castration-resistant prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
MHC	Major histocompatibility complex
MHRA	Medicines & Healthcare products Regulatory Agency of the United Kingdom
min	Minute(s)
mITT	Modified intent-to-treat

Abbreviation	Definition
MM	Medical Monitor
MoA	Mechanism (mode) of action
mpMRI	Multi-parametric MRI
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
mRNA (or RNA)	Messenger ribonucleic acid
NCI	National Cancer Institute
NIMP	Non-investigational medicinal product
NSAID	Non-steroidal anti-inflammatory drug
OR	Objective response
ORR	Objective response rate
OS	Overall survival
PAP	Prostatic acid phosphatase
PCWG3	Prostate Cancer Working Group 3
PD	Progressive disease
PD-1	Programmed death receptor-1
PD-L1	Programmed cell death 1 ligand 1
PFS	Progression-free survival
PO	Oral(ly); per os
PR	Partial response
PSA	Prostate-specific antigen
PSADT	Prostate-specific antigen doubling time
PT	Preferred Term
Q12W	Every 12 weeks
Q3W	Every 3 weeks
RDI	Relative dose intensity
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
REDR	Recommended expansion dose range
RNA-LPX	Nanoparticulate formulation of lipid-complexed ribonucleic acid
RSI	Reference safety information
SAE	Serious adverse event

Abbreviation	Definition
SAP	Statistical analysis plan
SC	Subcutaneous(ly)
SCID	Severe combined immunodeficiency
SD	Stable disease
SmPC	Summary of Product Characteristics
SoA	Schedule of activities
SOC	System Organ Class
SRC	Safety Review Committee
SUSAR	Suspected unexpected serious adverse reaction
TAA	Tumor-associated antigen
TEAE	Treatment-emergent adverse event
TI	Time index
TLR	Toll-like receptor
TNBC	Triple negative breast cancer
TNRFSF9	Tumor necrosis factor receptor superfamily member 9; 4-1BB; CD137
TNM	Tumor node metastasis
ULN	Upper limit of normal
US FDA	United States Food and Drug Administration
USA	United States of America
W_pro1	Previously used term for BNT112 cancer vaccine (BioNTech IMP)
WMA	World Medical Association

10.11. Appendix 11: Protocol Amendment History

Changes made to the protocol using the substantial protocol amendments are described in detail in the document Protocol Amendment History which is available upon request. This Protocol Amendment History is filed together with the protocol in the trial master file.

A comparison of the protocol after implementation of each amendment, e.g., a comparison between the protocol after amendment 1.0 and the protocol after implementation of amendment 2.0, are available upon request.

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