CLINICAL TRIAL PROTOCOL

BNT111-01

Version:	7.0 **Date:** 09 FEB 2023
Sponsor:	BioNTech SE
Trial title:	Open-label, randomized Phase II trial with BNT111 and cemiplimab in combination or as single agents in patients with anti-PD-1/PD-L1-refractory/relapsed, unresectable Stage III or IV melanoma
Trial phase:	Phase II
Indication:	Melanoma (Stage III and IV)
Product:	BNT111, cemiplimab
Coordinating investigator:	Paolo Ascierto Istituto Nazionale Tumori IRCCS Fondazione Pascale, 80131, Naples, Italy
Trial sites:	This will be a multi-site trial with approximately 60 sites in up to 15 countries
Sponsor's responsible person:	Özlem Türeci, MD, Chief Medical Officer, BioNTech SE
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Clinical research organization (CRO):	ICON plc, South County Business Park, Leopardstown, Dublin 18, D18 X5R3, Ireland
Regulatory identifiers:	IND: 25176; EudraCT: 2020-002195-12; NCT: 04526899
Medical monitor:	Medical monitor name and contact information will be provided separately

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1 'Approved' means approval of the sponsor.
2 Created from global clinical trial protocol v2.0.

1 PROTOCOL SUMMARY

1.1 Trial synopsis

Trial number: BNT111-01 **Trial phase:** Phase II

Trial title

Open-label, randomized Phase II trial with BNT111 and cemiplimab in combination or as single agents in patients with anti-PD-1/PD-L1-refractory/relapsed, unresectable Stage III or IV melanoma.

Objectives and endpoints

Objectives	Endpoints
Primary objective	
Demonstrate the anti-tumor activity of BNT111 + cemiplimab (Arm 1) in terms of objective response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.	• ORR defined as the proportion of patients in whom a complete response (CR) or partial response (PR) is observed as best overall response by blinded independent central review (BICR).
Secondary objectives	
Assess the anti-tumor activity of each single agent (i.e., monotherapy of BNT111 and cemiplimab) in terms of ORR according to RECIST 1.1 (key secondary endpoint).	• ORR defined as the proportion of patients in whom a CR or PR is observed as best overall response by BICR.
Assess additional measures of anti-tumor activity of BNT111 + cemiplimab (Arm 1), and each single agent (i.e., monotherapy of BNT111 and cemiplimab) according to RECIST 1.1.	• Duration of response (DOR) defined as the time from first objective response (CR or PR) to first occurrence of objective tumor progression (progressive disease, PD) by BICR or death from any cause (whichever occurs first). • Disease control rate (DCR) defined as the proportion of patients in whom a CR, PR or stable disease (SD; assessed at least 6 weeks [wks] +/- 1 wk after first dose) is observed as best overall response by BICR. • Time to response (TTR) defined as the time from randomization to the first objective tumor response (CR or PR) by BICR. • Progression-free survival (PFS) defined as the time from randomization to first objective tumor progression (PD) by BICR or death from any cause (whichever occurs first). • ORR, DOR, DCR, TTR, PFS, as assessed by the investigator.
Assess overall survival (OS) of BNT111 + cemiplimab (Arm 1).	• OS defined as the time from randomization to death from any cause.

Objectives	Endpoints
Assess the safety and tolerability profile of BNT111 + cemiplimab (Arm 1), and each single agent (i.e., monotherapy of BNT111 and cemiplimab).	• Occurrence of treatment-emergent adverse events (TEAEs) within a patient including Grade ≥ 3, serious and/or fatal TEAEs by relationship. • Occurrence of immune-related adverse events (irAE). • Occurrence of dose reduction and discontinuation of trial treatment within a patient due to a TEAE. • Changes in laboratory parameters compared to baseline*. • Occurrence of abnormal laboratory parameters within a patient. • Changes in vital signs parameters compared to baseline*. • Occurrence of abnormal vital signs parameters within a patient.
Assess health-related quality of life (HRQoL) of patients treated with BNT111 + cemiplimab (Arm 1) and of patients receiving BNT111 and cemiplimab as single agents as measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items (EORTC QLQ-C30).	• Mean changes from baseline in the global health status score of the EORTC QLQ-C30*. • Mean changes from baseline in scores of the EORTC QLQ-C30 functional and symptoms scales*. • Time to first clinically meaningful deterioration in global health status score as measured by EORTC QLQ-C30*. • Time to first clinically meaningful deterioration in symptoms and functioning as measured by EORTC QLQ-C30*.
Exploratory objectives	
Assess the anti-tumor activity of BNT111 + cemiplimab (Arm 1) and each single agent (i.e., monotherapy of BNT111 and cemiplimab) according to immune-related RECIST (iRECIST).	• ORR, DOR, DCR, TTR, PFS as assessed by BICR and the investigator.
Assess additional measures of anti-tumor activity of BNT111 + cemiplimab (Arm 1), and each single agent (i.e., monotherapy of BNT111 and cemiplimab) according to RECIST 1.1 / iRECIST.	• Depth of response as defined by maximum percentage reduction from screening/baseline* in the size of the tumor as assessed by BICR and the investigator.
Assess the anti-tumor activity during add-on BNT111 + cemiplimab (Arm 2 and 3) according to RECIST 1.1/ iRECIST.	• ORR, DOR, DCR, TTR, PFS as assessed by BICR and the investigator.
Assess OS of each single agent (i.e., BNT111 and cemiplimab) with or without add-on treatment (Arm 2 and 3).	• OS.
Assess systemic induction/expansion of BNT111 antigen-specific T cells.	• Patients in biomarker sub-study (selected trial sites): Occurrence of *de novo* induction of increase in expansion of BNT111 antigen-specific T cells under treatment compared to screening/baseline* (Arms 1 and 2 and add-on treatment).

Objectives	Endpoints
Characterize the pharmacodynamic profile of BNT111 in combination with cemiplimab (Arm 1 and add-on treatment), and identify potential predictive biomarkers for efficacy.	• BNT111 target antigen expression, potential outcome-predictive biomarkers, immune signature molecules (e.g., PD-L1 expression), and potential prognostic factors in archival tumor tissue at screening and pharmacodynamics markers (e.g., cytokine levels) under treatment. Patients in selected trial sites: tumor infiltrating lymphocytes (TIL) and T cell receptor (TCR) repertoire characterization at screening/baseline* and under treatment. Cytotoxicity assays with autologous tumor cell lines and T cells.

* Baseline in the main study (Arm 1) encompasses all data collected before start of trial therapy on Visit C1D1.

Trial design

This is an open-label, randomized, multi-site, Phase II, interventional trial designed to evaluate the efficacy, tolerability, and safety of BNT111 + cemiplimab in anti-programmed death protein 1 (PD-1)/anti-programmed death ligand 1 (PD-L1)-refractory/relapsed patients with unresectable Stage III or IV melanoma (8th Edition of American Joint Committee on Cancer [AJCC] melanoma classification [Amin et al. 2017]). The contributions of BNT111 and cemiplimab will be delineated in single-agent calibrator arms.

Patients will be randomized in a 2:1:1 ratio to Arm 1 (BNT111 + cemiplimab) and calibrator Arm 2 (BNT111 monotherapy) and Arm 3 (cemiplimab monotherapy). Randomization will be stratified by metastatic status (M0, M1a, M1b vs M1c, M1d) and by number of prior lines of systemic treatment (1 vs 2 to 5).

Patients in Arms 2 and 3 who experience centrally verified disease progression under single-agent treatment, may be offered addition of the other compound to the ongoing treatment after re-consent.

The trial will take place in about 60 trial sites, in up to 15 countries.

For a summary of the trial as a flow diagram, see the Schema in Section 1.2.

For the planned assessments and visits, see the Schedule of Activities (SoA) in Section 1.3.

Trial duration

The planned duration of the trial is:

- Approximately 18 months of recruitment.
- Approximately up to 24 months of active treatment with BNT111 + cemiplimab or BNT111 or cemiplimab as single agents.

Approximately up to 48 months of OS follow-up from the randomization of the last patient.

Population

180 patients with anti-PD-1/PD-L1-refractory/relapsed, unresectable Stage III or IV melanoma.

Key inclusion criteria

Patients are only eligible to be enrolled in the trial if they meet the following criteria:

- Patients must have histologically confirmed, unresectable Stage III or IV (metastatic) cutaneous melanoma and measurable disease by RECIST 1.1.
- Patients must have confirmed disease progression on/after approved anti-PD-1/PD-L1 regimen for melanoma as defined by RECIST 1.1.
  - Previous exposure to approved anti-PD-1/PD-L1 containing regimen for at least 12 consecutive weeks **and**
  - Current radiological progression to be confirmed by two scans 4 to 12 wks apart. If progression is accompanied by new symptoms, or deterioration of performance status (PS) not attributed to toxicity, one scan is sufficient **and**
  - Inclusion into this trial must be within 6 months of confirmation of disease progression on anti-PD-1/PD-L1 treatment, regardless of any intervening therapy.
- Eastern Cooperative Oncology Group (ECOG) PS ≤ 1.
- Patients must have serum lactate dehydrogenase (LDH) ≤ upper limit of normal (ULN).

Key exclusion criteria

Patients are excluded from the trial if they present any of the following criteria:

- History of uveal, acral, or mucosal melanoma.
- Ongoing or recent evidence (within the last 5 years) of significant autoimmune disease that required treatment with systemic immunosuppressive treatments which may pose a risk for irAEs.
  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.
- Current use or use within 3 months prior to trial enrollment of systemic immune suppression including:
  - Use of chronic systemic steroid medication (up to 5 mg/day prednisolone equivalent is allowed); patients using physiological replacement doses of prednisone for adrenal or pituitary insufficiency are eligible,
  - Other clinically relevant systemic immune suppression.

Trial treatments

BNT111 will be given as intravenous (IV) injection at a dose of CCI µg total ribonucleic acid (RNA) for the first dose and subsequently at a dose of CCI µg total RNA. BNT111 will be given once-weekly for the first 6 wks, followed by treatments once every 3 wks (±3 d).

Cemiplimab will be given once every 3 wks (±3 d) as IV infusion at a dose of CCI mg.

Cemiplimab will be administered after administration of BNT111 with at least 30 min interval.

For further details of trial treatment schedules, see Section 6.2.

Statistics

The original sample size calculation for the BNT111 + cemiplimab group (Arm 1) is based on the following specifications and assumptions:

CCI

Based on these specifications, CCI

CCI

CCI patients are planned to be randomized into the BNT111 + cemiplimab group. The assumed true effect size for ORR is based on preliminary data of the ongoing Phase I Lipo-MERIT trial with a selected population of patients with melanoma.

After the originally planned interim analysis (first interim analysis [IA1]), where there were CCI patients in the BNT111 + cemiplimab group, one additional interim analysis (second interim analysis [IA2]) will be performed. IA2 will assess efficacy after CCI of the planned number of CCI patients are response evaluable (i.e., having at least two post-screening tumor assessments or discontinued before) in the BNT111 + cemiplimab group. Given CCI

CCI

The sample size calculation for the calibrator groups (i.e., single-agent BNT111 and cemiplimab, respectively) CCI

CCI

The primary analyses will be performed CCI

CCI

CCI The IA1 for efficacy has been performed after there were CCI of the planned number of CCI patients. IA1, which was based on CCI patients in the BNT111 + cemiplimab group, has been performed at a one-sided CCI significance level and required an ORR of at least CCI to show statistical significance. IA2 will be

performed after CCI of the planned number of CCI patients are response evaluable (i.e., having at least two post-screening tumor assessments or discontinued before). The minimal statistically significant ORR at IA2 would be CCI i.e., the smallest ORR that will result in a statistically significant p value of CCI The final analysis will be performed once all the planned CCI patients in Arm 1 are response evaluable (i.e., having at least three post-screening tumor assessments or discontinued before). The minimal statistically significant ORR at final analysis would be CCI i.e., the smallest ORR that will result in a statistically significant p value of CCI

Independent Data Monitoring Committee

Safety will be periodically reviewed and evaluated by an Independent Data Monitoring Committee (IDMC). The frequency will be based on the number of enrolled patients and will occur at least once every 3 months for the first year and every 6 months thereafter.

In addition, an IDMC safety meeting is scheduled to occur once 10 patients in Arm 1 (BNT111 + cemiplimab combination therapy) have been treated for at least two cycles (6 wks) or have discontinued treatment for any reason during the first two cycles.

Specific stopping criteria will be based on the cumulative incidence of trigger events (TEs). TEs include all related serious adverse events (SAEs), related Grade 3 to 5 TEAEs/irAEs except for transient Grade 3 flu-like symptoms, clinically insignificant laboratory abnormalities and Grade 3 hypotension lasting for less than 6 h.

Furthermore, the occurrence of a single Grade 5 TEAE (unless clearly unrelated to study drug, e.g., due to underlying disease) or a cumulative incidence of ≥ 40% of TEs during the first two cycles of the first ten patients in Arm 1 will trigger an *ad hoc* meeting of the IDMC as well as an enrollment pause.

1.2 Schema (graphical representation of the trial)

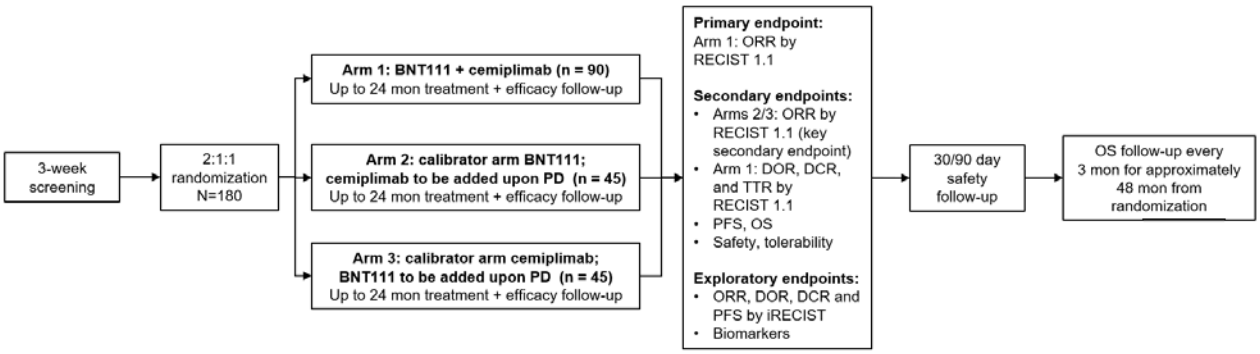

Figure 1: Trial schema

Abbreviations: DCR = disease control rate; DOR = duration of response; mon = months; N,n = number of patients; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors; TTR = time to response.

1.3 Schedules of activities

In light of the public health emergency related to coronavirus disease 2019 (COVID-19), the continuity of clinical trial conduct and oversight may require implementation of temporary or alternative mechanisms yet any effort should be made to adhere to the protocol as closely as possible. Examples of such mechanisms may include, but are not limited to, any of the following: phone contact, virtual visits, telemedicine visits, online meetings, non-invasive remote monitoring devices, use of local clinic or laboratory locations, and home visits by skilled staff. Additionally, no waivers to deviate from protocol enrollment criteria due to COVID-19 will be granted. All temporary mechanisms utilized, and deviations from planned trial procedures are to be documented as being related to COVID-19 and will remain in effect only for the duration of the public health emergency.

1.3.1 Schedule of activities for Arm 1, Arm 2, and Arm 3 patients (SOA1)

SOA1	Screening [a]		Treatment period							End of treatment [b]	Post-treatment follow-up period			
Cycle=21 d			Cycle 1			Cycle 2			Cycle 3 onward		Safety FU [c]		Efficacy FU [d]	Survival FU [e]
Visit			C1 D1	C1 D8*	C1 D15 *	C2 D1	C2 D8*	C2 D15 *	C3D1-CnD1 [f]	EoT	SFU 1	SFU2	EFU	LTFU
Day	≤ 21 d prior to randomization	≤ 10 d prior to randomization	1	8	15	22	29	36	X [g]	0 to 21 d after last dose	30 d after last dose	90 d after last dose	6/9/12 wks	Every 3 mon after last trial assessment
Visit window	-21 d	-10 d		±1 d	±1 d	±1 d	±1 d	±1 d	±3 d		+5 d	±7 d	±7/14 d	±14 d
Assessments and procedures														
Informed consent	X [h]													
Eligibility		X [i]												

SOA1	Screening [a]		Treatment period							End of treatment [b]	Post-treatment follow-up period			
Cycle=21 d			Cycle 1			Cycle 2			Cycle 3 onward		Safety FU [c]		Efficacy FU [d]	Survival FU [e]
Visit			C1 D1	C1 D8*	C1 D15 *	C2 D1	C2 D8*	C2 D15 *	C3D1-CnD1 [f]	EoT	SFU 1	SFU2	EFU	LTFU
Day	≤ 21 d prior to randomization	≤ 10 d prior to randomization	1	8	15	22	29	36	X [g]	0 to 21 d after last dose	30 d after last dose	90 d after last dose	6/9/12 wks	Every 3 mon after last trial assessment
Visit window	-21 d	-10 d		±1 d	±1 d	±1 d	±1 d	±1 d	±3 d		+5 d	±7 d	±7/14 d	±14 d
Demographic data	X													
Relevant medical history	X													
Underlying disease history	X [j]													
BRAF V600 mutation status [k]	X													
TNM staging at the time of trial entry		X [l]												
Concomitant medication and therapy [m]		X	X	X	X	X	X	X	X	X	X	X		

SOA1	Screening [a]		Treatment period							End of treatment [b]	Post-treatment follow-up period			
Cycle=21 d			Cycle 1			Cycle 2			Cycle 3 onward		Safety FU [c]		Efficacy FU [d]	Survival FU [e]
Visit			C1 D1	C1 D8*	C1 D15 *	C2 D1	C2 D8*	C2 D15 *	C3D1-CnD1 [f]	EoT	SFU 1	SFU2	EFU	LTFU
Day	≤ 21 d prior to randomization	≤ 10 d prior to randomization	1	8	15	22	29	36	X [g]	0 to 21 d after last dose	30 d after last dose	90 d after last dose	6/9/12 wks	Every 3 mon after last trial assessment
Visit window	-21 d	-10 d		±1 d	±1 d	±1 d	±1 d	±1 d	±3 d		+5 d	±7 d	±7/14 d	±14 d
Vital signs [n]		X	X	X	X	X	X	X	X	X	X			
Weight		X	X	X	X	X	X	X	X	X	X			
Height		X												
Physical examination [o]		X	X	X	X	X	X	X	X	X	X			
ECOG PS		X	X	X	X	X	X	X	X	X	X			
12-lead ECG [p]		X	Perform, if clinically indicated							X				
CT and/or MRI [q]	X [r]		X [q]										X [q]	
Brain imaging [s]	X		X										X	
Adverse events [t]	X	X	X	X	X	X	X	X	X	X	X	X		

SOA1	Screening [a]		Treatment period							End of treatment [b]	Post-treatment follow-up period			
Cycle=21 d			Cycle 1			Cycle 2			Cycle 3 onward		Safety FU [c]		Efficacy FU [d]	Survival FU [e]
Visit			C1 D1	C1 D8*	C1 D15 *	C2 D1	C2 D8*	C2 D15 *	C3D1-CnD1 [f]	EoT	SFU 1	SFU2	EFU	LTFU
Day	≤ 21 d prior to randomization	≤ 10 d prior to randomization	1	8	15	22	29	36	X [g]	0 to 21 d after last dose	30 d after last dose	90 d after last dose	6/9/12 wks	Every 3 mon after last trial assessment
Visit window	-21 d	-10 d		±1 d	±1 d	±1 d	±1 d	±1 d	±3 d		+5 d	±7 d	±7/14 d	±14 d
PRO/QoL assessments [u]			X			X			X	X	X			
PGIS			X						C4D1, C8D1	X				
PGIC									C4D1, C8D1	X				
Survival status														X
Subsequent anti-cancer therapy										X	X	X	X	X
Treatment arms														
Randomization [v]			X											
ARM 1														
BNT111 [w]			X	X	X	X	X	X	X					

SOA1	Screening [a]		Treatment period							End of treatment [b]	Post-treatment follow-up period			
Cycle=21 d			Cycle 1			Cycle 2			Cycle 3 onward		Safety FU [c]		Efficacy FU [d]	Survival FU [e]
Visit			C1 D1	C1 D8*	C1 D15 *	C2 D1	C2 D8*	C2 D15 *	C3D1-CnD1 [f]	EoT	SFU 1	SFU2	EFU	LTFU
Day	≤ 21 d prior to randomization	≤ 10 d prior to randomization	1	8	15	22	29	36	X [g]	0 to 21 d after last dose	30 d after last dose	90 d after last dose	6/9/12 wks	Every 3 mon after last trial assessment
Visit window	-21 d	-10 d		±1 d	±1 d	±1 d	±1 d	±1 d	±3 d		+5 d	±7 d	±7/14 d	±14 d
Cemiplimab (Q3W) [x]			X			X			X					
Treatment arms														
ARM 2														
BNT111 [w]			X	X	X	X	X	X	X					
ARM 3														
Cemiplimab (Q3W) [x]			X			X			X					
Laboratory assessments														
Hematology [y]		X	X	X	X	X	X	X	X	X	X			
Serology [z]	X													
Blood chemistry [aa]		X	X	X	X	X	X	X	X	X	X			

SOA1	Screening [a]		Treatment period							End of treatment [b]	Post-treatment follow-up period			
Cycle=21 d			Cycle 1			Cycle 2			Cycle 3 onward		Safety FU [c]		Efficacy FU [d]	Survival FU [e]
Visit			C1 D1	C1 D8*	C1 D15 *	C2 D1	C2 D8*	C2 D15 *	C3D1-CnD1 [f]	EoT	SFU 1	SFU2	EFU	LTFU
Day	≤ 21 d prior to randomization	≤ 10 d prior to randomization	1	8	15	22	29	36	X [g]	0 to 21 d after last dose	30 d after last dose	90 d after last dose	6/9/12 wks	Every 3 mon after last trial assessment
Visit window	-21 d	-10 d		±1 d	±1 d	±1 d	±1 d	±1 d	±3 d		+5 d	±7 d	±7/14 d	±14 d
Coagulation [bb]		X	Perform if clinically indicated							X	Perform if clinically indicated			
TSH and free T4 [cc]		X	X							X	X			
Pregnancy test [dd]		X	X			X			X	X	X			
Urinalysis [ee]		X	Perform if clinically indicated							X	X			
Cytokines [ff]			X			X			X [gg]					
Cellular immune responses [hh]		X [hh]							X [hh]	X				
HLA haplotyping [ll]		X [ll]												
Tumor biopsy [ii]		X [ii]							X [ii]	X [ii]				

SOA1	Screening [a]		Treatment period							End of treatment [b]	Post-treatment follow-up period			
Cycle=21 d			Cycle 1			Cycle 2			Cycle 3 onward		Safety FU [c]		Efficacy FU [d]	Survival FU [e]
Visit			C1 D1	C1 D8*	C1 D15 *	C2 D1	C2 D8*	C2 D15 *	C3D1-CnD1 [f]	EoT	SFU 1	SFU 2	EFU	LTFU
Day	≤ 21 d prior to randomization	≤ 10 d prior to randomization	1	8	15	22	29	36	X [g]	0 to 21 d after last dose	30 d after last dose	90 d after last dose	6/9/12 wks	Every 3 mon after last trial assessment
Visit window	-21 d	-10 d		±1 d	±1 d	±1 d	±1 d	±1 d	±3 d		+5 d	±7 d	±7/14 d	±14 d
Archival tumor sample [jj]	X													
Pharmaco-genomic analyses [kk]	X													

Note: On treatment days, all assessments should be performed prior to dosing unless otherwise specified.

* Visits C1D8, C1D15, C2D8, and C2D15 are not to be conducted in patients in Arm 3 (cemiplimab only).

a Patients who do not meet the criteria for participation in this trial (screen failure) may be rescreened once. Patients must re-sign the ICF prior to re-screening, if the screening period exceeds 21 d. For both screening and re-screening, results of radiology scans performed prior to obtaining informed consent and within 28 d prior to randomization may be used. However, in case of signs of rapid progression, a new tumor evaluation may be necessary to obtain a reliable baseline assessment.

b Patients who discontinue trial treatment for whatever reason, will return to the clinic for EoT visit within 21 d after last dose. The visit at which response assessment shows (confirmed) progressive disease may be used as the EoT visit. The EoT visit and post-treatment follow-up period will only be performed after discontinuation of both trial drugs. The EoT visit and post-treatment follow-up period for patients in Arms 2 and 3 who will continue to receive add-on therapy will be performed as outlined in SOA2 (Section 1.3.2).

c All AEs will be reported until 90 d after the last dose of trial treatment or until a new anti-cancer therapy is started. Additionally, in case a new anti-cancer therapy is started within 90 d after last treatment, the safety follow-up visit should be performed just prior to starting the new anti-cancer therapy. Adverse events after start of new anti-cancer therapy do not need to be reported unless a causal relationship to BNT111-01 or cemiplimab is suspected.

d Patients who discontinue trial therapy prior to disease progression should continue to have regular efficacy assessments as scheduled per protocol, until disease progression, the start of next-line anti-cancer therapy, withdrawal of consent, or death, whichever occur first.

e After the last trial visit, information on survival status and new anti-cancer therapy will be collected via phone calls, patient medical records, and/or clinic visits approximately every 3 mon until death (unless the patient withdraws consent for survival follow-up or the sponsor terminates the trial). If a patient asks to be withdrawn from survival follow-up, this request must be documented in the source documents and signed by the investigator.

f "n" represents the number of the respective cycle (e.g., C4 means fourth cycle of treatment).

g Visit CnD1 should occur 21 (± 3) d after the first day (i.e., treatment visit) of the previous cycle.

h Informed consent must be documented before any trial-specific screening procedure is performed.

i Eligibility should be confirmed and documented in the eCRF. This should be performed when all screening results are available and within 21 d after initiation of screening.

j Underlying disease history should include histology, TNM stage at diagnosis (including which AJCC edition), prior anti-cancer therapies/procedures, date of last progression.

k BRAF V600 mutation status may be obtained from medical history data.

l TNM staging at the time of trial entry to be performed according to AJCC 8th edition.

m Concomitant medication and therapy includes any therapies (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated trial treatment from 28 d prior to initiation of trial treatment until the SFU2 visit.

n Vital signs (body temperature, pulse rate, respiratory rate, and blood pressure) should be measured within 60 min prior to the administration of the trial treatment(s) and at 30 (±10) min, 60 (±10) min, 4 h (±10 min), and 6 h (±10 min) after administration, or if clinically indicated (see Section 8.2.3 for guidelines on reduction or expansion of these time points).

o At screening and at EoT assessments must include a full physical examination. Record abnormalities observed on the respective eCRF pages as appropriate. For all subsequent physical examinations perform a limited, symptom-directed examination at specified time points and as clinically indicated at other time points. Record new or worsened clinically significant abnormalities on the AE eCRF.

p Single 12-lead ECG recordings will be obtained during screening, at EoT, and as clinically indicated at other time points. Patients should be resting in a supine position for ≥ 10 min prior to ECG recording. The interpretation of the ECG recording will be done locally by the investigator.

q Tumor response will be measured by RECIST 1.1 / iRECIST. Patients will undergo tumor assessments at screening, every 6±1 wks for the 3 mon after trial treatment start, every 9±1 wks for the next 9 mon, and every 12±2 wks thereafter, regardless of dose delays, until (confirmed) disease progression (even if the patients discontinue trial treatment for other reasons) or until the start of next-line anti-cancer therapy (whichever occurs first). An extra scan should be scheduled if clinically indicated. Patients in Arms 2 and 3 who experience (confirmed) disease progression under single-agent treatment may be offered addition of the respective other compound to the ongoing treatment. In such cases, tumor assessments are to continue, and additional images should be collected in accordance with the imaging schedule and modalities outlined in Section 1.3.2.

r All measurable and evaluable lesions should be assessed at screening and target as well as non-target lesions identified and documented following RECIST 1.1 criteria. Tumor assessments, including brain imaging, performed as standard of care prior to obtaining informed consent and within 28 d prior to randomization do not have to be repeated at screening. Radiological progression to be confirmed by two scans, 4 to 12 wks apart. If progression is accompanied by new symptoms or deterioration of PS not attributed to toxicity, one scan is sufficient.

s Any brain lesions present at screening must be stable as per eligibility criteria and should be followed and assessed at all subsequent tumor assessment visits. Brain imaging performed as standard of care prior to obtaining informed consent and within 28 d prior to randomization do not have to be repeated at screening. If no brain lesions are present at screening, brain imaging does not need to be repeated, only if clinically indicated as per investigator judgment. Brain imaging should be done by MRI, only in the case of a contra-indication for MRI, a contrast-enhanced CT brain scan will be acceptable.

t After informed consent has been obtained, all AEs will be documented on the eCRF, and all SAEs should be reported to the sponsor within the appropriate time frame. All AEs will be reported until 90 d after the last dose of trial treatment (i.e., SFU2 visit). In addition, the sponsor should be notified (even after SFU2 visit), if the investigator becomes aware of any SAE that is believed to be related to prior exposure to trial treatment or a trial procedure.

u Patient-reported outcomes/quality of life assessment questionnaires must be completed before any assessments are done or any treatment is given on the dosing day. Patients will provide PRO/QoL assessment during trial visits at baseline (C1D1 prior Treatment), C2D1, C3D1, C4D1, every 9±1 wks for the next 9 mon, and every 12±2 wks thereafter until SFU1.

v Randomization must be done before administration of trial treatment.

w Treatment with BNT111 must be initiated no later than 7 d after confirmed eligibility. After administration of BNT111, an initial observation time of at least 6 h is required (see Section 6.8.4.1). Treatment is to be continued up to 24 mon or until confirmed disease progression, patient withdrawal of consent or unacceptable toxicity.

x Treatment with cemiplimab must be initiated no later than 7 d after confirmed eligibility. Cemiplimab will be given according to the valid Prescribing Information in the country. The first administration of cemiplimab will be on Cycle 1 Day 1, followed by every 3 wks (±3 d) thereafter. Cemiplimab will be administered after administration of BNT111 with at least a 30 min interval (if feasible, both trial drugs should be given on the same day, a maximal window of 1 wk between administrations would be allowed). There should be an initial observation time of first administration of cemiplimab. From second administration of cemiplimab, no observation time is stipulated with reference to cemiplimab (local protocol should be followed). Treatment to be continued up to 24 mon or until confirmed disease progression, unacceptable toxicity, or patient withdrawal of consent.

y Hematology assessment should be performed at screening, ≤ 24 h prior to each drug administration, on treatment discontinuation, and at 30 d SFU1 or if clinically indicated (see Section 10.2 for assessments to be done). Samples should be assessed by both the central and local laboratory. Results of local laboratory assessments need to be reviewed prior to drug administration. Unscheduled assessments can be performed locally, or sent to the central laboratory.

z Serology assessments for patients will include HBsAG, anti-HBc, anti-HBs and anti-HCV. HIV (1/2) testing required if the patient has never been tested for HIV or if testing was prior to primary cancer diagnosis or performed ≥ 12 mon prior to trial start. Samples should be shipped to a central laboratory.

aa Chemistry panel should be performed at screening, ≤ 24 h prior to each drug administration, on treatment discontinuation, and at 30 d SFU1 or if clinically indicated (see Section 10.2 for assessments to be done). Samples should be assessed by both the central and local laboratory. Results of local laboratory assessments need to be reviewed prior to drug administration. Unscheduled assessments can be performed locally, or sent to the central laboratory.

bb Coagulation assessments to be performed at screening, at EoT and if clinically indicated (see Section 10.2 for assessments to be done). Samples should be shipped to a central laboratory; unscheduled assessments can be performed locally.

cc TSH and free T4 will be assessed at screening, once every two cycles, on treatment discontinuation, at SFU1, and as clinically indicated. Samples should be shipped to a central laboratory and, if required, to the local laboratory. Unscheduled assessments can be performed locally, or sent to the central laboratory.

dd All WOCBP will have a serum pregnancy test at screening, within 10 d prior to initiation of trial treatment. Urine or serum pregnancy test will be performed at the start of every cycle (starting from Cycle 2) or according to local requirements (in cases where more frequent testing is required) and at EoT and SFU1. If a urine pregnancy test is positive, hold dosing and confirm the result with a serum pregnancy test.

ee For urinalysis assessments dipsticks are to be used, microscopic evaluation should be performed per investigator's discretion. Tests will be done locally with material provided by the central laboratory.

ff Peripheral blood for assessment of cytokines will be drawn from all patients of Arms 1 and 2 prior to administration of BNT111 and 4 to 6 h post application. The tests will be performed centrally.

gg Only applicable for Cycle 3.

hh At selected trial sites, as part of the biomarker sub-study, blood for isolation of PBMCs for analysis of cellular immune responses should only be taken in patients randomized to Arm 1 or 2 at the following timepoints: prior to the first dosing with BNT111, on C3D1, C5D1, C8D1 and every six cycles afterwards, and at EoT. At C5D1, blood draws may be replaced by a leukapheresis.

ii At selected trial sites, as a part of the biomarker sub-study, three paired biopsies are to be taken in patients randomized to Arm 1 or 2 at the following timepoints: prior to the first dosing with BNT111, under treatment at approximately 6 to 8 wks after treatment start, and optionally at progression, if considered clinically feasible by the investigator. The tumor sample can be from a core biopsy or from resected tumor tissue. Fine needle aspirates and cytological specimens are not acceptable. For patients who are part of the biomarker sub-study, if a biopsy is not taken at baseline prior to the first dose of BNT111, no subsequent biopsies are to be taken during the trial as part of the biomarker sub-study procedures. It is recommended to perform the biopsy on progression only if 4 wks or more have elapsed since the last biopsy (on-treatment biopsy). If the time is shorter, no biopsy on progression should be taken.
For other trial sites, if any biopsies or resections are to be performed as part of standard clinical care, tissue samples from such procedures should be provided (if feasible) for the sponsor for biomarker testing.

jj All patients must provide a tumor tissue sample (formalin fixed paraffin-embedded [FFPE] blocks/slides) from a fresh biopsy collected before Visit C1D1, or archival tissue, which should be shipped to the central laboratory only following confirmation of eligibility. The archival tissue can be an FFPE block (not older than 3 years) or freshly cut slides (special storage conditions and immediate shipment to a specialty lab are required), with tissue preferably derived from advanced disease stage. The fresh or archival tissue must have been taken using core needle biopsy (18-gauge needle or larger) or surgical excision. Note: fine needle aspirate biopsies will not be acceptable.

kk Optional whole blood sampling at screening if patient has signed ICF for pharmacogenomic analyses.

ll At selected trial sites, as part of the biomarker sub-study, a blood sample for HLA typing should be taken which should be stored at -80°C.

Abbreviations: AJCC = American Joint Committee on Cancer; d = day; CT = computer tomography; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; d = day(s); eCRF = electronic case report form; EoT = end of treatment; FU = follow-up; h = hour(s); HBc = hepatitis B core antigen; HBs = hepatitis B surface antigen; HBsAG = hepatitis surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; ICF = informed consent form; LTFU = Lost to follow-up; mon = month; MRI = magnetic resonance imaging; PGIC= Patient Global Impression of Change; PGIS= Patient Global Impression of Severity; PRO/QoL = patient-reported outcomes/quality of life; SOA = schedule of activity; T4 = Thyroxine; TNM = tumor, node, metastasis; TSH = thyroid-stimulating hormone; wks = week(s); WOCBP = women of childbearing potential.

1.3.2 Schedule of activities for patients receiving add-on therapy (SOA2)

Patients with centrally verified PD on monotherapy in Arm 2 or 3 may enter add-on therapy where eligible patients will receive the other compound in addition to the continued initial trial therapy after re-consent.

SOA2	Baseline add-on therapy	Treatment period							End of treatment [a]	Post-treatment follow-up period			
Cycle=21 d		Add-on Cycle 1			Add-on Cycle 2			Add-on Cycle 3 onward		Safety FU [b]		Efficacy FU [c]	Survival FU [d]
Visit		AOC1D1 [e]	AOC1D8	AOC1D15	AOC2D1	AOC2D8	AOC2D15	AOCnD1 [f]	EoT	SFU1	SFU2	EFU	LTFU
Day	≤ 10 d prior to AOC1D1	1	8	15	22	29	36	X [g]	0 to 21 d after last dose	30 d after last dose	90 d after last dose	6/9/12 wks	Every 3 mon after last trial assessment
Visit window			±1 d	±1 d	±1 d	±1 d	±1 d	±3 d		+5 d	±7 d	±7/14 d	±14 d
Assessments and procedures													
Concomitant medication and therapy [h]	X	X [i]	X	X	X	X	X	X	X	X	X		
Informed consent	X												
Vital signs [j]	X	X [i]	X	X	X	X	X	X	X	X			
Weight	X	X	X	X	X	X	X	X	X	X			
Physical examination [k]	X	X [i]	X	X	X	X	X	X	X	X			
ECOG PS	X	X [i]	X	X	X	X	X	X	X	X			
12-lead ECG [l]	X	Perform, if clinically indicated							X				
CT and/or MRI [m, n]	X [m]	X [n]										X [n]	
Brain imaging	X [o]	X [o]										X [o]	

SOA2	Baseline add-on therapy	Treatment period							End of treatment [a]	Post-treatment follow-up period			
Cycle=21 d		Add-on Cycle 1			Add-on Cycle 2			Add-on Cycle 3 onward		Safety FU [b]		Efficacy FU [c]	Survival FU [d]
Visit		AOC1D1 [e]	AOC1D8	AOC1D15	AOC2D1	AOC2D8	AOC2D15	AOCnD1 [f]	EoT	SFU1	SFU2	EFU	LTFU
Day	≤ 10 d prior to AOC1D1	1	8	15	22	29	36	X [g]	0 to 21 d after last dose	30 d after last dose	90 d after last dose	6/9/12 wks	Every 3 mon after last trial assessment
Visit window			±1 d	±1 d	±1 d	±1 d	±1 d	±3 d		+5 d	±7 d	±7/14 d	±14 d
Adverse events [p]	X	X [i]	X	X	X	X	X	X	X	X	X		
PRO/QoL assessments [q]		X			X			X	X	X			
PGIS		X						AOC4D1, AOC8D1	X				
PGIC								AOC4D1, AOC8D1	X				
Survival status													X
Subsequent anti-cancer therapy									X	X	X	X	X
BNT111 [r]		X	X [s]	X [s]	X	X [s]	X [s]	X					
Cemiplimab (Q3W) [t]		X			X			X					
Hematology [u]	X	X	X	X	X	X	X	X	X	X			
Blood chemistry [v]	X	X [i]	X	X	X	X	X	X	X	X			
Coagulation [w]	X	Perform, if clinically indicated							X	Perform, if clinically indicated			
TSH and free T4 [x]	X	X							X	X			

SOA2	Baseline add-on therapy	Treatment period							End of treatment [a]	Post-treatment follow-up period			
Cycle=21 d		Add-on Cycle 1			Add-on Cycle 2			Add-on Cycle 3 onward		Safety FU [b]		Efficacy FU [c]	Survival FU [d]
Visit		AOC1D1 [e]	AOC1D8	AOC1D15	AOC2D1	AOC2D8	AOC2D15	AOCnD1 [f]	EoT	SFU1	SFU2	EFU	LTFU
Day	≤ 10 d prior to AOC1D1	1	8	15	22	29	36	X [g]	0 to 21 d after last dose	30 d after last dose	90 d after last dose	6/9/12 wks	Every 3 mon after last trial assessment
Visit window			±1 d	±1 d	±1 d	±1 d	±1 d	±3 d		+5 d	±7 d	±7/14 d	±14 d
Pregnancy test [y]	X	X			X			X	X	X			
Urinalysis [z]	X	Perform, if clinically indicated							X	X			
Cytokines [aa]		X			X			X [bb]					
Cellular immune responses [cc]	X [cc]							X [cc]	X [dd]				
HLA haplotyping [ee]	X [ee]												
Tumor biopsy [ff]	X [ff]							X [ff]					

Note: On treatment days, all assessments should be performed prior to dosing unless otherwise specified.

a Patients who discontinue trial treatment for whatever reason will return to the clinic for EoT visit within 21 d after last dose. The visit at which response assessment shows (confirmed) progressive disease may be used as the EoT visit. The EoT visit and post-treatment follow-up period will only be performed after discontinuation of both trial drugs.

b All AEs will be reported until 90 d after the last dose of trial treatment or until a new anti-cancer therapy is started. Additionally, in case a new anti-cancer therapy is started within 90 d after last treatment, the safety follow-up visit should be performed just prior to starting the new anti-cancer therapy. Adverse events after start of new anti-cancer therapy do not need to be reported unless a causal relationship to BNT111-01 or cemiplimab is suspected.

c Patients who discontinue trial therapy prior to disease progression should continue to have regular efficacy assessments as scheduled per protocol, until disease progression, the start of next-line anti-cancer therapy, withdrawal of consent, or death, whichever occur first.

d After the last trial visit, information on survival status and new anti-cancer therapy will be collected via phone calls, patient medical records, and/or clinic visits approximately every 3 mon until death (unless the patient withdraws consent for survival follow-up or the sponsor terminates the trial). If a patient asks to be withdrawn from survival follow-up, this request must be documented in the source documents and signed by the investigator.

e Visit AOC1D1 shall occur no longer than 6 wks after confirmed disease progression on monotherapy in Arm 2 or 3.

f "n" represents the number of the respective cycle (e.g., AOC3 means the third cycle of add-on therapy).

g Visit X should occur 21 (± 3) d after the first day (i.e., treatment visit) of the previous cycle.

h Continued record of concomitant medication and therapy after add-on, includes any therapies (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated trial treatment until the SFU2 visit.

i If baseline and AOC1D1 are on the same day, assessment only needs to be taken once.

j Vital signs (body temperature, pulse rate, respiratory rate, and blood pressure) should be measured prior to the administration of the trial treatments, and at 30 (±10) min, 60 (±10) min, 4 h (±10 min), and 6 h (±10 min) after administration, or if clinically indicated (see Section 8.2.3 for guidelines on reduction or expansion of these time points).

k At baseline and at EoT assessments must include a full physical examination. Record abnormalities observed on the respective eCRF pages as appropriate. For all subsequent physical examinations perform a limited, symptom-directed examination at specified time points and as clinically indicated at other time points. Record new or worsened clinically significant abnormalities on the AE eCRF.

l Single 12-lead ECG recordings will be obtained during baseline, at EoT, and as clinically indicated at other time points. Patients should be resting in a supine position for at least 10 min prior to ECG recording. The interpretation of the ECG recording will be done locally by the investigator.

m Baseline image may not be older than 21 d prior to AOC1D1. Target lesions and non-target lesions can be redefined at baseline assessment for add-on therapy.

n Tumor response will be measured by RECIST 1.1 / iRECIST. Patients will undergo tumor assessments every 6±1 wks for the 3 mon after start of add-on treatment, every 9±1 wks for the next 9 mon, and every 12 ± 2 wks thereafter, regardless of dose delays, until (confirmed) disease progression (even if the patients discontinue trial treatment for other reasons) or until the start of next-line anti-cancer therapy (whichever occurs first). An extra scan should be scheduled if clinically indicated.

o Patients with new brain lesions identified at baseline for add-on therapy cannot continue with add-on therapy, patients with known brain lesions during monotherapy (Arm 2 or 3) should have stable brain lesions at baseline for add-on therapy, the lesions should be followed and assessed at all subsequent tumor assessments. If no brain lesions are present at baseline assessment for add-on therapy, brain imaging does not need to be repeated, only if clinically indicated as per investigator judgment.

p All AEs will be documented in the eCRF, and all SAEs should be reported to the sponsor within the appropriate time frame. All AEs will be reported until 90 d after the last dose of trial treatment (i.e., SFU2 visit). In addition, the sponsor should be notified (even after SFU2 visit), if the investigator becomes aware of any serious AE that is believed to be related to prior exposure to trial treatment or a trial procedure.

q Patient-reported outcomes/quality of life assessment questionnaire must be completed before any assessments are done or any treatment is given on the dosing day. Patients will provide PRO/QoL assessments during trial visits at baseline for add-on therapy, AOC2D1, AOC3D1, AOC4D1, every 9±1 wks for the next 9 mon, and every 12±2 wks thereafter until SFU1.

r After administration of BNT111, initially an observation time of at least 6 h is required (see Section 6.8.4.1). Treatment to be continued up to 24 mon or until confirmed disease progression, unacceptable toxicity or patient withdrawal of consent.

s Weekly dosing applicable to patients who have received cemiplimab monotherapy (Arm 3). Also applicable to patients who have received BNT111 monotherapy (Arm 2) if the patient has previously received ≤ 4 doses of BNT111.

t Cemiplimab will be given according to valid Prescribing Information in the country every 3 wks (±3 d). The first administration of cemiplimab will be on Cycle 1 Day 1, followed by every 3 wks (±3 d) thereafter. Cemiplimab will be administered subsequently after administration of BNT111 with at least 30 min interval. There should be an initial observation time of 6 h after administration of cemiplimab. From the second administration of cemiplimab, no observation time is stipulated with reference to cemiplimab (local protocol should be followed). Treatment to be continued up to 24 mon or until confirmed disease progression, unacceptable toxicity or patient withdrawal of consent.

u Hematology assessment should be performed at baseline for add-on therapy, ≤ 24 h prior to each drug administration, on treatment discontinuation, and at 30 d SFU1 or if clinically indicated (see Section 10.2 for assessments to be done). Samples should be assessed by both the central and local laboratory. Results of local laboratory assessments need to be reviewed prior to drug administration. Unscheduled assessments can be performed locally or sent to the central laboratory.

v Chemistry panel should be performed at baseline for add-on therapy, ≤ 24 h prior to each drug administration, on treatment discontinuation, and at 30 d SFU1 or if clinically indicated (see Section 10.2 for assessments to be done). Samples should be assessed by both the central and local laboratory. Results of local laboratory assessments need to be reviewed prior to drug administration. Unscheduled assessments can be performed locally or sent to the central laboratory.

w Coagulation assessments are to be performed at baseline for add-on therapy, at EoT, and if clinically indicated (see Section 10.2 for assessments to be done). Samples should be shipped to a central lab; unscheduled assessments can be performed locally.

x TSH and free T4 will be assessed at baseline for add-on therapy, once every two cycles, on treatment discontinuation, and at SFU1. Samples should be shipped to a central laboratory and, if required, to the local laboratory. Unscheduled assessments can be performed locally or sent to the central laboratory.

y All WOCBP will have a serum pregnancy test at baseline, within 10 d prior to initiation of trial treatment. Urine or serum pregnancy test will be performed at the start of every cycle (starting from Cycle 2) or according to local requirements (in cases where more frequent testing is required) and at EoT and SFU1. If a urine pregnancy test is positive, hold dosing and confirm the result with a serum pregnancy test.

z For urinalysis assessments dipsticks are to be used, microscopic evaluation should be performed per investigator's discretion.

aa Peripheral blood for assessment of cytokines will be drawn from all patients prior to administration of BNT111 and 4 to 6 h post application. The tests will be performed centrally. This is only applicable for the first three cycles with BNT111, if cytokines were collected in Arm 2 for three cycles, no further cytokines need to be collected.

bb Only applicable for Cycle 3.

cc At selected trial sites, as part of the biomarker sub-study, blood for isolation of PBMCs for analysis of cellular immune responses should be taken during baseline (unless previous blood draw was < 7 wks, then the baseline sample can be omitted) and on AOC3D1, AOC5D1, AOC8D1, every six cycles afterwards, and at EoT. This applies only to patients in Arm 2 and Arm 3 add-on therapy who have consented to the biomarker sub-study.

dd Should be done within 3 wks after BNT111 administration.

ee Only for patients entering Arm 3 add-on therapy who have not yet provided a sample for HLA typing: a blood sample for HLA typing should be taken which should be stored at -80°C.

ff At selected trial sites, as part of the biomarker sub-study, optional biopsies at baseline, under treatment and at progression will be performed. The tumor biopsy will be performed, if considered clinically feasible by the investigator. This applies only to patients in Arm 2 and Arm 3 add-on therapy who have consented to the biomarker sub-study. The tumor sample can be from a core biopsy or from resected tumor tissue. Fine needle aspirates and cytological specimens are not acceptable. In patients who have had biopsies taken during BNT111 monotherapy, the number of biopsies during add-on is to be adjusted as appropriate (up to three in total during the duration of the trial). It is recommended to perform the biopsy on progression only if 4 wks or more have elapsed since the last biopsy (on-treatment biopsy). If the time is shorter, no biopsy on progression should be taken.
For other trial sites, if any biopsies or resections are to be performed as part of standard clinical care, tissue samples from such procedures should be provided (if feasible) for the sponsor for biomarker testing.

Abbreviations: AOCnDn = add-on, cycle "n", day "n"; d = day; CT = computer tomography; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; d = day(s); eCRF = electronic case report form; EoT = end of treatment; FU = follow-up; h = hour(s); LTFU = Lost to follow-up; mon = month; MRI = magnetic resonance imaging; PGIC= Patient Global Impression of Change; PGIS= Patient Global Impression of Severity; PRO/QoL = patient-reported outcomes/quality of life; SOA = schedule of activity; T4 = Thyroxine; TSH = thyroid-stimulating hormone; wks = week(s); WOCBP = women of childbearing potential.

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TRIAL-SPECIFIC ABBREVIATIONS

Abbreviation	Explanation
APC	Antigen-presenting cell
BICR	Blinded independent central review
BRAF	B-Raf proto-oncogene
CPI	Checkpoint inhibitor
CR	Complete response
CSCC	Cutaneous squamous cell carcinoma
DCR	Disease control rate
DOR	Duration of response
HLA	Human leukocyte antigen
IB	Investigator's brochure
IFN	Interferon
IL	Interleukin
irAEs	Immune-related adverse events
IRR	Injection-related reaction
LDH	Lactate dehydrogenase
MAPK	Mitogen-activated protein kinase
MEK	Mitogen-activated protein kinase kinase
MHC	Major histocompatibility complex
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed death protein 1
PD-L1	Programmed death ligand 1
PFS	Progression-free survival
PR	Partial response
SD	Stable disease
RNA	Ribonucleic acid
RNA-LPX	RNA lipoplex
TAA	Tumor-associated antigen
TCR	T cell receptor

Abbreviation	Explanation
TIL	Tumor infiltrating lymphocytes
TSH	Thyroid-stimulating hormone
TTR	Time to response
ULN	Upper limit of normal

For standard abbreviations, see Section 10.9.

NOTES FOR THE READER

The BioNTech group is a holding comprising several subsidiaries including BioNTech SE, the sponsor of this clinical trial.

2 INTRODUCTION

2.1 Background

Overview of the disease

Melanoma is a malignant tumor of melanocytes. Most melanomas arise in the skin, but they may also arise from mucosal surfaces or at other sites to which neural crest cells migrate, including the uveal tract. Mucosal and uveal melanomas differ significantly from cutaneous melanoma in incidence, prognostic factors, molecular characteristics and treatment. The word melanoma, unless specified otherwise, will only refer to cutaneous melanoma in this protocol.

Melanoma is the 19th most common malignancy worldwide, with an estimated age-standardized incidence rate of 3.0 per 100,000. Approximately 287,700 new cases of melanoma and 60,700 deaths were estimated worldwide in 2018 (Ferlay et al. 2019). In North America, melanoma is the fifth most common cancer in males and sixth most common cancer in females (Siegel et al. 2018). In the United States (US), approximately 106,110 patients will be diagnosed and there will be about 7,180 estimated deaths in 2021. The incidence has been increasing over the past 30 years. Invasive melanoma represents about 1% of skin cancers but results in the most deaths (ACS 2021). In Europe, melanoma is less common, being the seventh most common cancer (GLOBOCAN 2020). Five-year survival for patients with early stage disease (i.e., localized) is achieved in approximately 99% of patients. However, 5-year survival for patients with distant disease is approximately 27% (NCI 2019). There is an increasing appreciation of the variations in specific genetic alterations among distinct clinical subtypes of melanoma, some of which have different therapeutic implications (NCCN 2021).

2.1.1 Treatment option overview for unresectable Stage III and Stage IV and recurrent melanoma

Advanced or metastatic melanoma (unresectable Stage III and Stage IV) remains a lethal disease with a high proportion of patients being resistant to approved therapies. Furthermore, there are limited treatment options for patients who progress on targeted therapy or immunotherapy. Therefore, there is a high unmet medical need justifying the development of novel therapies for advanced melanoma patients who have failed existing therapies.

Systemic treatment

There are two approaches for systemic treatment of unresectable Stage III/IV and recurrent melanoma. Either immune checkpoint inhibition (CPI) or targeting the mitogen-activated protein kinase (MAPK) pathway, they have both demonstrated improvement in PFS and OS in randomized trials.

Immune checkpoint inhibitors

CPIs targeting cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4; e.g., ipilimumab) and PD-1, e.g., nivolumab and pembrolizumab, have been approved for the treatment of

advanced or metastatic melanoma as single agents or in combination. In first-line therapy, nivolumab and ipilimumab combination therapy is associated with an improved ORR (57% vs 19% vs 44%) and median PFS (11.5 months vs 2.9 months vs 6.9 months) compared with single-agent ipilimumab or nivolumab, respectively. However, the combination is associated with substantial toxicity and the impact of combination therapy on OS is not yet fully established (Wolchok et al. 2017). In addition, Opdualag® was approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) in 2022 for the treatment of melanoma (Opdualag US Prescribing Information; Opdualag Summary of Product Characteristics). Opdualag is a fixed dose combination of nivolumab and relatlimab, a LAG-3 inhibitor. Monotherapy treatment with PD-1 inhibitors (e.g., pembrolizumab or nivolumab) or cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) inhibitors (e.g., ipilimumab) is also an option for patients who are not candidates for combination therapy.

Signal transduction inhibitors

Approximately 50% patients with metastatic cutaneous melanoma harbor an activating mutation of proto-oncogene B-Raf (BRAF), an intracellular signaling kinase in the MAPK pathway. BRAF inhibitors (e.g., vemurafenib and dabrafenib) have shown clinical activity in BRAF V600-mutated melanoma. BRAF inhibitors have monotherapy efficacy in patients with BRAF-mutated melanoma, but half of patients relapse within approximately 6 months due to development of drug resistance. Combination therapy with BRAF and MEK inhibitors circumvents resistance and has superior efficacy (i.e., improved ORR, DOR, PFS, and OS) when compared to BRAF inhibitor monotherapy in patients with previously untreated unresectable or metastatic disease. Nevertheless, 50% of patients who respond to combination therapy still progress within the first 12 months (Mackiewicz et al. 2018; Gellrich et al. 2020). Pembrolizumab and nivolumab are also approved as first-line treatments for patients with BRAF-mutated melanoma. For patients with BRAF V600-mutated tumors that do not progress quickly, the currently recommended therapeutic sequence is immunotherapy (e.g., with an anti-PD-1 inhibitor) followed by targeted therapy with BRAF/MEK inhibitors (Michielin et al. 2019).

Intralesional therapy

Talimogene laherparepvec (T-vec, tradename Imlygic) is a genetically modified oncolytic viral therapy indicated for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery. T-vec is a modified type 1 herpes simplex virus (HSV-1) that has undergone genetic modifications, e.g., insertion of two copies of the human cytokine granulocyte-macrophage colony-stimulating factor (GM-CSF) gene to promote selective viral replication in tumor cells, while reducing viral pathogenicity and promoting immunogenicity. In a randomized Phase III trial, intratumoral T-vec compared to subcutaneous GM-CSF showed an ORR of 26% vs 5.7%. However, the difference seen in OS did not reach statistical significance and the response rate in visceral lesions was poor (Rehman et al. 2016). Therefore, this treatment will only be an option for selected patients.

Other therapies

Treatment options for patients with advanced or metastatic melanoma who have progressed on targeted therapy or immunotherapy may include high-dose interleukin (IL)-2 or other cytotoxic therapies (e.g., dacarbazine, carboplatin/paclitaxel, albumin-bound paclitaxel). These agents have modest response rates of less than 20% in the first- and second-line settings, but no data exist in post-PD-1 settings. Furthermore, little consensus exists regarding optimal standard chemotherapy (NCCN 2021). The first promising results were shown for a c-kit-inhibitor with an ORR of 23.3% (Guo et al. 2011) whereas the multi-kinase-inhibitor sorafenib targeting both the MAPK-cascade as well as the vascular endothelial growth factor and platelet-derived growth factor cascades did not improve median PFS when compared to placebo in a Phase III, randomized, double-blind, placebo-controlled trial in combination with carboplatin and paclitaxel (Hauschild et al. 2009).

2.1.2 Introduction to the investigational treatments

BNT111

BNT111 is a fixed set of four liposome-formulated protein-encoding ribonucleic acids (RNAs; henceforward referred to as RNA-lipoplexes [RNA-LPX]). The four RNAs are individually complexed with liposomes and administered separately via IV injections. The RNA-LPX formulation is designed for specific targeting of antigen-presenting cells (APCs) in lymphoid organs.

The RNA components of BNT111 code for four tumor-associated antigens (TAAs), namely New York esophageal squamous cell carcinoma-1 (NY-ESO-1), tyrosinase, melanoma antigen A3 (MAGE-A3), and transmembrane phosphatase with tensin homology (TPTE). All target antigens are known to be immunogenic and, with the exception of TPTE, have already been extensively studied as TAAs in numerous diverse clinical settings (Chen et al. 2005; Shackleton et al. 2004; Slingluff et al. 2003; Sanderson et al. 2005; Marchand et al. 2003; Carrasco et al. 2008; Brichard et al. 2007; Tyagi et al. 2009; Banchereau et al. 2005; Toungouz et al. 2001; Oshita et al. 2012; Weide et al. 2009; Wilgenhof et al. 2011). BNT111 is currently being tested in Germany in an ongoing first-in-human dose-escalation, multi-site, open-label interventional and sequential Phase I trial in patients with advanced melanoma (NCT02410733; further referred to as the Lipo-MERIT trial).

The RNA design is optimized for the induction of strong antigen-specific immune responses. The RNA sequence contains naturally occurring sequence elements at 3’ and 5’ untranslated regions that significantly increase the intracellular half-life and the translational efficiency of the molecule (Holtkamp et al. 2006). The encoded proteins are flanked by natural peptide tags which improve the processing of the antigens resulting in efficient presentation of antigen-derived peptide epitopes on major histocompatibility complex (MHC) class I and II molecules (Kreiter et al. 2008). These tags include a secretory signal peptide for translocation of the nascent polypeptide chain into the endoplasmic reticulum and the transmembrane and cytoplasmic domain of the MHC class I molecule. The synthetic cap structure (beta-S-ARCA) increases the resistance of the RNA molecules to degradation by extracellular and intracellular ribonucleases (Kuhn et

al. 2010). The TAAs are fused to the tetanus toxoid epitopes (P2P16), which are well-known universal T helper epitopes to break immune tolerance.

The liposome formulation of BNT111 is designed to deliver mRNA that encode the antigens into dendritic cells in lymphoid organs and exploits anti-viral innate and adaptive immune mechanisms for induction of highly potent antigen-specific T cell responses. IV injected RNA-LPX home to secondary lymphatic tissues, e.g., spleen, lymph nodes, and bone marrow, are rapidly taken up by resident professional APCs. The proteins translated from the RNA components of the BNT111 vaccine are processed and presented on the patient's individual set of both human leukocyte antigen (HLA)-class I and HLA-class II molecules (Kranz et al. 2016). The close proximity of APCs to T cells in lymphoid tissues is the ideal microenvironment for efficient priming and amplification of $CD8^+$ and $CD4^+$ T cell responses (Zinkernagel et al. 1997). RNA-LPX activate APCs via toll-like receptor signaling, which results in a pulsatile release of pro-inflammatory cytokines, such as interferon (IFN)-α, IL-6, IFN-γ, and interferon gamma-induced protein 10 (IP-10). The secretion of type I IFN concomitant to efficient antigen presentation stimulates immune cells and directly inhibits regulatory T cells (Srivastava et al. 2014) which, in combination with cognate $CD4^+$ T cell help, is necessary for overcoming tolerance to self-antigens. Based on this mechanism of action, the repeated application of RNA-LPX cancer vaccines allows potent priming and fast amplification of antigen-specific $CD8^+$ T cell responses.

The RNA-LPX-based cancer vaccines have 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 the Lipo-MERIT trial, 108 patients were treated and the TEAEs considered related to trial treatment were transient, mostly Grade 1 and 2, and associated with the specific format of encoding and delivering the vaccine antigens, namely single-stranded RNA formulated as a DOTMA/DOPE lipoplex. The identified risks consisted of mild-to-moderate, transient and manageable flu-like aEs and transient lymphopenia (by sequestration). In 8% of patients, Grade 2 or 3 hypotension (as per National Cancer Common Terminology Criteria for Adverse Events [NCI-CTCAE]) was seen within the first hours after vaccination, sometimes with a sudden onset, and in general patients responded well to fluids.

The Lipo-MERIT trial has provided promising signals for single-agent and anti-PD-1 combination activity of BNT111 in pre-treated CPI-experienced patients with high medical need and limited treatment options. It was further demonstrated that in the majority of patients, the vaccine displays its expected mechanism of action and induces T cells against at least one of the TAAs. 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 (Sahin et al. 2020).

It is expected that in particular for patients that are refractory to or relapsing after anti-PD-1 therapy (meaning that activation of pre-existing memory T cells only is not sufficient to mediate clinical activity) combining the vaccine with a PD-1 inhibitor (which would rescue newly primed T cells specificities from exhaustion) is synergistic as supported by

preclinical treatment studies in syngeneic and xenograft mouse tumor models (see the BNT111 investigator's brochure [IB]).

Cemiplimab

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 (LIBTAYO®) is approved in several countries worldwide for the treatment of advanced cutaneous squamous cell carcinoma (CSCC), basal cell carcinoma (BCC), cervical cancer, and non-small cell lung cancer (NSCLC).

The clinical activity of cemiplimab has been shown in multiple cancer indications and, given the activity of other immune checkpoint inhibitors in melanoma, it is thus reasonable to expect activity of cemiplimab in this indication. Additional background information on the trial drug and development program can be found in the cemiplimab IB.

2.2 Trial rationale

This trial is designed to address the high unmet medical need of patients with unresectable Stage III or IV melanoma (8th Edition of AJCC melanoma classification [Amin et al. 2017]) who failed anti-PD-1/PD-L1 therapy. Due to the mechanisms of action of BNT111 and cemiplimab, it is expected that the combination of the two agents will have a synergistic anti-tumor effect in patients that have failed previous anti-PD-1/PD-L1 therapy.

Both compounds have single-agent activity in melanoma or other tumors. Cemiplimab has been approved based on its single-agent activity in advanced CSCC. For BNT111, preliminary indications of single-agent activity have been observed in the ongoing Lipo-MERIT Phase I trial testing pre-treated CPI-experienced patients with unresectable/metastatic melanoma Stages IIIB, IIIC and IV.

Activation, expansion and differentiation of naïve T cells, particularly in the context of persistent antigen encounter, is physiologically associated with induction of PD-1 expression, which contributes to regulation of the immune responses. PD-1 blockade acts by re-activation and expansion of pre-existent antigen-specific T cells of the patient directed particularly against mutation-derived neo-antigens. More than half of the patients with metastatic melanoma have a moderate to low mutational burden. These patients are less likely to have pre-formed neo-antigen-specific T cells and thus at higher risk of anti-PD-1 treatment failure and progression (Hugo et al. 2016). BNT111 has been shown to prime, activate and expand $CD4^+$ and $CD8^+$ T cell specificities and thus generate a complementary pool of T cell specificities directed against non-mutant TAAs that are frequently expressed in human melanoma irrespective of the mutational burden of the tumor. In patients with melanoma treated with BNT111, induction of antigen-specific T cells has been shown to correlate with upregulation of PD-1 expression. Thus, mechanistically, anti-PD-1 blockade is expected to augment vaccine-induced T cell responses. This is supported by preclinical data in mice inoculated with syngeneic melanoma cells and by an early efficacy signal observed in the BNT111/anti-PD-1 (nivolumab, pembrolizumab) combination cohort of the Lipo-MERIT trial. Thus, we consider the combination of cemiplimab and BNT111 to be synergistic and anticipate that

patients who failed prior anti-PD-1 treatment will be sensitized by the BNT111 vaccine to respond to the anti-PD-1 component in the combination.

2.3 Benefit/risk assessment

More detailed information about the known and expected benefits and risks, and reasonably expected adverse events (AEs) for this trial are given in Section 6.2 of the BNT111 IB and Section 6.4 of the cemiplimab IB.

2.3.1 Risk assessment

Expected adverse drug reactions (ADR) for BNT111 are fever, chills, lymphopenia, increase of cytokines and dizziness, not considered to have a significant impact on the risk-benefit profile of the product. NCI-CTCAE Grade 2 or 3 hypotension was seen in 8% of patients within 4 to 6 h after BNT111 administration, typically after the first or second vaccination, and patients with hypotension responded well to fluids. In rare cases, more severe events of cytokine release syndrome associated with pyrexia, hypotension, and hypoxia of higher NCI-CTCAE grades occurred. The onset was sometimes sudden; vital signs should therefore be carefully monitored for 6 h after at least the first three vaccinations.

Immune-related adverse reactions can occur with cemiplimab. Most of these, including severe reactions, resolved following initiation of appropriate medical therapy or withdrawal of cemiplimab. The most common immune-related adverse reactions seen in clinical trials (591 patients) were hypothyroidism (7.1%), pneumonitis (3.7%), immune-related skin adverse reactions (2.0%), hyperthyroidism (1.9%) and hepatitis (1.9%). Adverse reactions were serious in 8.6% patients and led to permanent discontinuation of cemiplimab in 5.8% of patients. See Section 6.8.4.2 for special warnings and precautions.

BNT111 has been given in combination with anti-PD-1 therapy in the Lipo-MERIT trial, no increase of AEs for any of the components was seen for the combination therapy compared to monotherapy. Safety data from the BNT111-01 trial interim analysis was in line with that observed in the Lipo-MERIT trial (Section 5.2 of the BNT111 IB). Based on the available safety data on TESAEs and treatment-emergent deaths, no safety signal was detected which would change the safety profile or benefit/risk assessment of BNT111 established in Lipo-MERIT trial. This was supported by the outcome of all IDMC meetings that recommended to continue the trial without modification.

Table 1: Summary of important, potential risks and mitigation actions taken

Potential risks	Actions taken
General safety	An IDMC manages all potential safety concerns in this trial.
Risks related to cancer vaccine antigen targets or anti-PD-1 therapy	Patients with clinically relevant autoimmune diseases are excluded from the trial.
Risks related to transient cytokine increase	Cytokines in patients' blood samples are monitored for early identification of systemic immune activation. Recommendations for detection and management of acute reactions are provided. Either as treatment modification or pre-medication with paracetamol and/or other antipyretic drugs.
Risks related to lipid accumulation in liver and other organs	Liver parameters are monitored.
Risks related to pharmaceutical issues arising from incorrect preparation or dilution	Pharmacy and trial site staff are trained to prevent incorrect preparation or dilution of BNT111 and correct preparation of cemiplimab. The lipid-to-RNA ratio of BNT111 was selected with a broad safety window for the formation of correct RNA-LPX particles.
General risks for parenteral medicinal product	Careful evaluation of patients with previous drug-induced allergic reactions that can lead to an increased risk of hypersensitivity reactions during infusion. Patients are educated on the possible infusion-related reactions that may occur during their course of therapy. Mild-to-moderate infusion reactions may be managed with antihistamines for symptom management, and/or by adding corticosteroids. Drug administration must be stopped immediately if the patient experiences noticeable chest pain, cardiac issues, or anaphylaxis. Patients are treated at trial sites equipped to handle life-threatening reactions and institutional treatment protocol should be followed. At the first sign of an anaphylactic reaction, the therapy should be stopped with prompt intervention by the medical and trial site staff.

IDMC = Independent data monitoring committee; RNA-LPX = RNA lipoplex.

2.3.2 Benefit assessment

Advanced or metastatic melanoma (unresectable Stage III and Stage IV) remains to be a lethal disease with a high proportion of patients being either resistant to approved therapies or relapsing on therapy. Furthermore, there are limited treatment options for patients who progress on targeted therapy or immunotherapy. Therefore, there is a high unmet medical need justifying the development of novel therapies for advanced melanoma patients who are resistant to approved therapies. Patients who failed prior anti-PD-1/PD-L1 therapy may benefit from the combination of cemiplimab and BNT111 as BNT111 is expected to sensitize them to the anti-PD-1 component in the combination.

2.3.3 Risk/benefit assessment of COVID-19 vaccination

2.3.3.1 Risk assessment

BNT111

BNT111-induced adaptive immune responses are expected to be highly specific and limited to the TAAs (see Section 2.1.2). Similarly, available European and US approved COVID-19 vaccines elicit a specific response towards the selected severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antigens. It is thought that adaptive immune responses driven by these entirely distinctive antigens (melanoma and SARS-CoV-2) should not cross-react with each other. Consequently, BNT111 administration is not expected to impact COVID-19 vaccine efficacy and vice versa.

In parallel to the activation of the adaptive immune response mechanisms, BNT111, as observed with other RNA-LPX-based cancer vaccines, also induces an innate immune response and its administration is expected to be followed by a pulsatile release of cytokines with peaks observed at approximately 6 h after dosing and values returning to baseline by 24 h or earlier. Similarly, COVID-19 vaccination is expected to trigger a transient elevation of cytokine concentration in the peripheral blood. A 7 d interval between COVID-19 and BNT111 vaccination is therefore recommended to mitigate the risk of increased, cumulative toxicity related to cytokines release.

Cemiplimab

As outlined in Section 2.1.2, cemiplimab is a high-affinity human monoclonal antibody that belongs to the class of PD-1/PD-L1 inhibitors. By targeting and binding to PD-1, cemiplimab blocks PD-1/PD-L1-mediated inhibitory signaling in helper and cytotoxic T cells, thus releasing cytotoxic T cells to target cancer cells (for more information, refer to the cemiplimab IB). This mechanism may potentially lead to breaking of peripheral tolerance towards self-antigens and induction of unwanted immune responses towards a patients' own tissues. COVID-19 vaccination induces adaptive immune responses to the selected SARS-CoV-2 antigens and has no identified cross-reactivity with human antigens. Therefore, increased autoimmune toxicity is unlikely, although clinical data is needed to support this hypothesis. The efficacy of COVID-19 vaccination is not expected to be adversely impacted by concomitant administration of PD-1 inhibitors as PD-1/PD-L1 blockade would circumvent T cell deactivation.

BNT111 and cemiplimab combination

Based on the single-agent mechanism of action of BNT111 and cemiplimab, it is expected that the efficacy of COVID-19 vaccination will not be decreased when administered in this treatment setting. In the Lipo-MERIT trial, BNT111 was given in combination with PD-1 inhibitor therapy (nivolumab or pembrolizumab) and no increase of toxicities or AEs for any of the components was observed for the combination therapy when compared to monotherapy, and no overlapping toxicities or safety concerns were reported with the combination therapy. However, confirmation with clinical observation that the safety profile remains unchanged in patients with concomitant COVID-19 vaccination is required.

Melanoma (disease-specific section)

There are no specific data from clinical trials on COVID-19 vaccine safety and efficacy in cancer patients, and in particular those with advanced malignant melanoma. Based on clinical experience with other vaccines, and depending on the type of vaccine, efficacy and/or safety might be affected in immunocompromised cancer patients (Rieger et al. 2018).

2.3.3.2 Benefit assessment

It is generally assumed that cancer patients may be at an increased risk of severe COVID-19 due to immunosuppression that may result from both anti-cancer treatment and the malignancy itself (Cook et al. 2020; Dai et al. 2020; Liang et al. 2020). As for the entire population, immunization with COVID-19 vaccine reduces the likelihood of SARS-CoV-2 infection as well as severity of disease in patients with cancer. Additionally, decreasing the likelihood of SARS-CoV-2 infection by COVID-19 vaccination may allow better adherence to anti-cancer therapeutic regimens and in doing so potentially increase treatment efficacy.

2.3.3.3 Risk/benefit summary of COVID-19 vaccination

Based on the available non-clinical and clinical data, the sponsor considers that the potential benefits of COVID-19 vaccination in patients with melanoma treated with BNT111 either as monotherapy or in combination with cemiplimab outweigh the anticipated risks.

The following recommendations are proposed to mitigate potential risks:

- Patients with prior COVID-19 vaccination may be allowed to enter the trial with a wash-out period of at least 7 d since the last COVID-19 vaccine dose.
- Patients who are already enrolled in the clinical trial and still receiving trial treatment may be allowed COVID-19 vaccination if it is ensured that there are at least 7 d between individual doses of COVID-19 vaccine and trial treatment.
- In terms of the risk/benefit of COVID-19 vaccination, the final decision for individual patients should be taken by the investigator in accordance with individual country guidance on vaccination in patients with active cancer.
- Patients treated with BNT111 should not be immunized directly prior to and during the trial with live-attenuated vaccines, as per prohibited concomitant therapy (see Section 6.7.2).

2.3.4 Overall benefit/risk conclusion

Based on the available clinical and non-clinical data, the poor prognosis and the unmet medical need for melanoma patients, the potential anticipated benefits of the RNA-based immunotherapy BNT111 in combination with cemiplimab outweigh the anticipated limited risks of this approach. This benefit/risk evaluation remains unchanged after having enrolled about 50% of originally planned patients based on the input of the IDMC.

Overall, the sponsor considers the benefit/risk ratio to be acceptable for a trial of this type.

3 OBJECTIVES AND ENDPOINTS

Objectives and endpoints

Objectives	Endpoints
Primary objective	
Demonstrate the anti-tumor activity of BNT111 + cemiplimab (Arm 1) in terms of objective response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.	• ORR defined as the proportion of patients in whom a complete response (CR) or partial response (PR) is observed as best overall response by blinded independent central review (BICR).
Secondary objectives	
Assess the anti-tumor activity of each single agent (i.e., monotherapy of BNT111 and cemiplimab) in terms of ORR according to RECIST 1.1 (key secondary endpoint).	• ORR defined as the proportion of patients in whom a CR or PR is observed as best overall response by BICR.
Assess additional measures of anti-tumor activity of BNT111 + cemiplimab (Arm 1), and each single agent (i.e., monotherapy of BNT111 and cemiplimab) according to RECIST 1.1.	• Duration of response (DOR) defined as the time from first objective response (CR or PR) to first occurrence of objective tumor progression (progressive disease, PD) by BICR or death from any cause (whichever occurs first). • Disease control rate (DCR) defined as the proportion of patients in whom a CR, PR or stable disease (SD; assessed at least 6 weeks [wks] +/- 1 wk after first dose) is observed as best overall response by BICR. • Time to response (TTR) defined as the time from randomization to the first objective tumor response (CR or PR) by BICR. • Progression-free survival (PFS) defined as the time from randomization to first objective tumor progression (PD) by BICR or death from any cause (whichever occurs first). • ORR, DOR, DCR, TTR, PFS, as assessed by the investigator.
Assess overall survival (OS) of BNT111 + cemiplimab (Arm 1).	• OS defined as the time from randomization to death from any cause.
Assess the safety and tolerability profile of BNT111 + cemiplimab (Arm 1), and each single agent (i.e., monotherapy of BNT111 and cemipilmab).	• Occurrence of treatment-emergent adverse events (TEAEs) within a patient including Grade ≥ 3, serious and/or fatal TEAEs by relationship. • Occurrence of immune-related adverse events (irAE). • Occurrence of dose reduction and discontinuation of trial treatment within a patient due to a TEAE. • Changes in laboratory parameters compared to baseline*. • Occurrence of abnormal laboratory parameters within a patient. • Changes in vital signs parameters compared to baseline*. • Occurrence of abnormal vital signs parameters within a patient.

Objectives	Endpoints
Assess health-related quality of life (HRQoL) of patients treated with BNT111 + cemiplimab (Arm 1) and of patients receiving BNT111 and cemiplimab as single agents as measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items (EORTC QLQ-C30).	• Mean changes from baseline in the global health status score of the EORTC QLQ-C30*. • Mean changes from baseline in scores of the EORTC QLQ-C30 functional and symptoms scales*. • Time to first clinically meaningful deterioration in global health status score as measured by EORTC QLQ-C30*. • Time to first clinically meaningful deterioration in symptoms and functioning as measured by EORTC QLQ-C30*.
Exploratory objectives	
Assess the anti-tumor activity of BNT111 + cemiplimab (Arm 1) and each single agent (i.e., monotherapy of BNT111 and cemiplimab) according to iRECIST.	• ORR, DOR, DCR, TTR, PFS as assessed by BICR and the investigator.
Assess additional measures of anti-tumor activity of BNT111 + cemiplimab (Arm 1), and each single agent (i.e., monotherapy of BNT111 and cemiplimab) according to RECIST 1.1 / iRECIST.	• Depth of response as defined by maximum percentage reduction from screening/baseline* in the size of the tumor as assessed by BICR and the investigator.
Assess the anti-tumor activity during add-on BNT111 + cemiplimab (Arm 2 and 3) according to RECIST 1.1/ iRECIST.	• ORR, DOR, DCR, TTR, PFS as assessed by BICR and the investigator.
Assess OS of each single agent (i.e., BNT111 and cemiplimab) with or without add-on treatment (Arm 2 and 3).	• OS.
Assess systemic induction/expansion of BNT111 antigen-specific T cells.	• Patients in biomarker sub-study (selected trial sites): Occurrence of *de novo* induction of increase in expansion of BNT111 antigen-specific T cells under treatment compared to screening/baseline* (Arms 1 and 2 and add-on treatment).
Characterize the pharmacodynamic profile of BNT111 in combination with cemiplimab (Arm 1 and add-on treatment), and identify potential predictive biomarkers for efficacy.	• BNT111 target antigen expression, potential outcome-predictive biomarkers, immune signature molecules (e.g., PD-L1 expression), and potential prognostic factors in archival tumor tissue at screening and pharmacodynamics markers (e.g., cytokine levels) under treatment. Patients in selected trial sites: tumor infiltrating lymphocytes (TIL) and T cell receptor (TCR) repertoire characterization at screening/baseline* and under treatment. Cytotoxicity assays with autologous tumor cell lines and T cells.

* Baseline in the main study (Arm 1) encompasses all data collected before start of trial therapy on Visit C1D1.

4 TRIAL DESIGN

4.1 Overall design

Patients with anti-PD-1/PD-L1-refractory/relapsed, unresectable Stage III or IV melanoma will be screened for the trial and 180 patients will be randomized in a 2:1:1 ratio to Arm 1 (BNT111 + cemiplimab) and calibrator Arm 2 (BNT111 monotherapy), and Arm 3 (cemiplimab monotherapy). Randomization will be stratified by metastatic status (M0, M1a, M1b vs M1c, M1d) and by number of prior lines of systemic treatment (1 vs 2 to 5).

Patients in Arms 2 and 3 who experience centrally verified disease progression under single-agent treatment may be offered addition of the respective other compound to the ongoing treatment after re-consent.

4.1.1 Screening period

Screening procedures will be performed within 21 d before the start of treatment on Day 1 of Cycle 1.

A signed informed consent form (ICF) must be obtained before any screening procedure may begin.

4.1.2 Treatment period

Patients will be randomized to receive either BNT111 + cemiplimab combination therapy (Arm 1), BNT111 monotherapy (Arm 2) or cemiplimab monotherapy (Arm 3).

Treatments with BNT111 will be given once-weekly for the first 6 wks, followed by treatments once every 3 wks (±3 d). Cemiplimab will be given once every 3 wks (±3 d) throughout the trial.

The treatment period starts on Day 1 of Cycle 1 and continues for up to 24 months or until confirmed progression of disease, withdrawal of consent or unacceptable toxicity.

4.1.3 Add-on therapy for patients in Arm 2 or 3

Patients who experience disease progression under monotherapy may continue with add-on therapy. Disease progression must be verified centrally. The eligibility of patients for the add-on therapy needs to be checked based on the inclusion criteria (Section 5.1.3) and exclusion criteria (Section 5.1.4). Patients need to re-consent for participation in the add-on therapy.

Patients in Arm 2 (add-on of cemiplimab to BNT111): Cemiplimab will be given once every 3 wks (±3 d). BNT111 will be continued according to the planned schedule; a patient must have received a total of 6 weekly injections during the initial trial treatment and the add-on therapy before moving to a once every 3 wk schedule of injections.

Patients in Arm 3 (add-on of BNT111 to cemiplimab): BNT111 will be given once-weekly for the first 6 wks of add-on therapy, followed by treatments once every 3 wks (±3 d). Cemiplimab will continue to be given once every 3 wks (±3 d).

Treatments will continue up to a total treatment duration (monotherapy and add-on therapy) of 24 months.

4.1.4 Safety follow-up

The treatment period is followed by a safety follow-up period with visits after 30 and 90 days after last treatment to assess AEs. If the patient is not able to visit the clinic/hospital, the AE assessment will be done by phone call.

In cases where a new anti-cancer therapy is started within 90 days after last treatment, the safety follow-up visit should be performed just prior to starting the new anti-cancer therapy. Adverse events after start of new anti-cancer therapy do not need to be reported unless a causal relationship to BNT111-01 or cemiplimab is suspected.

4.1.5 Efficacy follow-up

Patients whose last disease assessment on trial treatment was CR, PR or SD will continue to have efficacy assessments.

Efficacy is assessed with regular efficacy assessments every 6 wks for the first 3 months after treatment start, then every 9 wks for the next 9 months and every 12 wks thereafter until PD, start of a new anti-cancer therapy, withdrawal of consent, death or lost to follow-up.

4.1.6 Survival follow-up

Patients will be followed for survival every 3 months for approximately up to 48 months of OS follow-up from the randomization of the last patient.

4.1.7 Planned number of patients

180 patients with anti-PD-1/PD-L1-refractory/relapsed, unresectable Stage III or IV melanoma.

4.2 Scientific rationale for the trial design

Proposed patient population:

Currently, the treatment paradigm in unresectable Stage III and Stage IV melanoma is either to treat first-line with a combination of nivolumab and ipilimumab, which is associated with significant toxicities for the patient, or to treat with either nivolumab or pembrolizumab monotherapy. However, approximately 40 to 45% of patients experience no response to initial therapy, showing primary resistance, and another 30 to 40% experience an initial response but eventually progress, having secondary resistance (Mooradian and Sullivan 2019). This subset of CPI-failed patients represents a population with a very high unmet medical need. It is expected that a vaccine and anti-PD-1 combination which addresses several of the potential reasons for primary or acquired non-responsiveness to a CPI may provide clinical benefit. Based on available non-clinical data of the melanoma cancer vaccine in combination with anti-PD-1, as well as the preliminary efficacy data, BNT111 can work synergistically with anti-PD-1 by overcoming resistance

and refractoriness to CPI therapy, which is expected to result in higher ORR compared to current standard of care.

Patients with ECOG PS 0 and 1 and LDH ≤ ULN are eligible. The reason for this criterion is the higher potential for a cancer vaccine to show efficacy in patients with a good PS and with lower tumor burden. This is further supported by data from the Lipo-MERIT trial (NCT02410733), where all patients with clinical benefit (PR or SD) presented with LDH ≤ ULN.

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'. These include the time to develop an anti-tumor response, which is generally longer for immunotherapies; there is a higher chance for a cancer vaccine to show efficacy in patients with a lower tumor burden and with limited prior therapy exposure.

Proposed trial design and trial endpoints:

The primary endpoint of ORR by RECIST 1.1 and BICR as well as secondary endpoints for testing the BNT111 + cemiplimab combination were selected based on the FDA Guidance for Industry 'Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics'. The guideline specifically states that tumor response is widely accepted by oncologists in guiding cancer treatments. As ORR is directly attributable to drug effect, single-arm trials conducted in patients with refractory tumors where no available therapy exists provide a justifiable assessment of efficacy. The proposed target population fulfils both criteria of refractory tumors without available therapy. To delineate the contribution of components in the same well-defined patient population, the ORR of each single agent is assessed in two calibrator arms and the trial is randomized. Randomization will be stratified by metastatic status (M0, M1a, M1b vs M1c, M1d) and by number of prior lines of systemic treatment (1 vs 2 to 5).

Add-on therapy for patients in Arm 2 or 3:

Addition of the respective single-agent treatment in Arms 2 and 3 to the BNT111 + cemiplimab combination upon disease progression is justified and strengthens equipoise and the requirement for patients to have LDH ≤ ULN mitigates risk by ensuring low tumor burden. Specifically, this is the case for the cemiplimab monotherapy arm, because the patient population per definition has failed on prior anti-PD-1 therapy and for the BNT111 monotherapy arm as BNT111-induced T cells are expected to be blunted by natural PD-1-upregulation.

BNT111 dose and schedule:

BNT111 will follow a prime and boost schedule: 6 once-weekly doses (Q1W) followed by once every 3 wks (± 3 d) (Q3W) up to 24 months and until confirmed disease progression, patient withdrawal of consent or unacceptable toxicity. BNT111 is administered repeatedly to reflect the prime/boost paradigm as referred to in the FDA Guidance for Industry 'Clinical Considerations for Therapeutic Cancer Vaccines'. The first 6-wkly doses are for priming and subsequent efficient expansion of naïve $CD4^+$ and $CD8^+$ T cells. This is

followed by 3-wkly administrations from Cycle 3 onwards to maintain the expanded T cell specificities at a high level and obtain durable immune responses.

4.3 Justification for dose

4.3.1 BNT111

The dose range of BNT111 chosen for this Phase II trial is based on the established recommended Phase II dose range from Phase I dose finding and dose expansion in the Lipo-MERIT trial. The starting dose is CCI µg followed by CCI µg target dose for each patient, and CCI µg dose for dose reduction.

The following preliminary observations were made in the Lipo-MERIT trial:

1. PRs with BNT111 alone or in combination with anti-PD-1 occurred in patients treated with BNT111 at target doses of CCI µg
2. BNT111 + anti-PD-1 combination induced clinical and radiological responses clustered in the CCI µg cohort
3. Target doses of BNT111 at CCI µg induced robust $CD4^+$ and $CD8^+$ T cell immune responses, the magnitude of which was not dose-dependent
4. BNT111 in the range of CCI µg gives rise to secondary immune response-supporting cytokines (e.g., IL12).

Thus, the proposed dose range of CCI µg is expected to be within the efficacious dose range. The intra-patient dose titration reflects the individual needs of a patient in light of high inter-patient variability of the innate immune sensor-signaling-associated immune-related effects.

4.3.2 Cemiplimab

The cemiplimab dose and schedule of CCI mg Q3W is the FDA-approved dose for advanced CSCC, basal cell carcinoma, and non-small cell lung cancer (LIBTAYO®) and for all ongoing registrational trials in the cemiplimab program including CSCC, basal cell carcinoma, and cervical cancer indications.

4.4 End of trial definition

A patient is considered to have completed the trial if he/she has completed all phases of the trial including survival follow-up.

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

- all patients have discontinued trial treatment; and
- all patients have completed safety follow-up assessment at day 90 subsequent to last dose; and
- all patients have been followed-up for at least 24 months subsequent to first dose;

or

- the sponsor discontinues the trial.

5 TRIAL POPULATION

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

5.1 Inclusion and exclusion criteria

5.1.1 Inclusion criteria initial treatment

Patients are eligible to be included in the trial only if all the following general criteria apply:

1. Patients must sign the written ICF before any screening procedure.
2. Patients must be aged ≥ 18 years on the date of signing the ICF.
3. Patients must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests, and other requirements of the trial.
4. Patients must have histologically confirmed unresectable Stage III or IV (metastatic) cutaneous melanoma and measurable disease by RECIST 1.1.
5. Patients must have confirmed disease progression on/after an approved anti-PD-1/PD-L1 regimen for melanoma as defined by RECIST 1.1
   a. Previous exposure to approved anti-PD-1/PD-L1 containing regimen for at least 12 consecutive weeks **and**
   b. Current radiological progression to be confirmed by two scans 4 to 12 wks apart. If progression is accompanied by new symptoms, or deterioration of PS not attributed to toxicity, one scan is sufficient **and**
   c. Inclusion into this trial must be within 6 months of confirmation of disease progression on anti-PD-1/PD-L1 treatment, regardless of any intervening therapy
6. Inclusion criterion 6 was deleted.

7. Patients should have received at least one but no more than five lines of prior therapy for advanced disease (see Section 8.1.1 for definition of line of therapy).
8. Patients must be able to tolerate additional anti-PD-1/PD-L1 therapy (i.e., did not permanently discontinue anti-PD-1/PD-L1 therapy due to toxicity).
9. Patients must have known BRAF mutation status.
10. Patients with BRAF V600-positive tumor(s) should have received prior treatment with a BRAF inhibitor (alone or in combination with a MEK inhibitor).

    Note: Considering the possible negative impact of a prior BRAF/MEK therapy on immune system targeting therapies, patients with BRAF V600-positive tumors with no clinically significant tumor-related symptoms or evidence of rapid PD may be eligible for participation. This should be based on investigator assessment AND provided they are ineligible for, intolerant to, or have refused BRAF V600 mutation targeted therapy after receiving the information on possible other therapies including BRAF/MEK inhibitor-based therapy during the informed consent process.

11. Patients must have an ECOG PS ≤ 1.
12. Adequate bone marrow function as defined by hematological parameters:
    a. Absolute neutrophil count (ANC) ≥ 1.5 × 10^9/L achieved without the use of granulocyte colony-stimulating factor (G-CSF).
    b. Hemoglobin ≥ 9.0 g/dL (5.59 mmol/L). No transfusion is allowed within 1 wk prior to treatment initiation.
    c. Platelet count ≥ 100 × 10^9/L.
13. Patients must have serum LDH ≤ ULN.
14. Patient should have adequate hepatic function, as determined by:
    a. aspartate aminotransferase (AST) ≤ 3 × ULN; alanine aminotransferase (ALT) ≤ 3 × ULN (regardless of liver involvement);
    b. serum bilirubin ≤ 1.5 × ULN, except in patients with Gilbert's Syndrome who must have a total bilirubin < 3 mg/dL.
15. Patient should have adequate kidney function, assessed by the estimated glomerular filtration rate (eGFR) ≥ 30 mL/min using the chronic kidney disease epidemiology collaboration (CKD-EPI) equation.
16. Patient should be stable with adequate coagulation, as determined by:
    a. international normalized ratio (INR) or prothrombin time ≤ 1.5 × ULN (unless on therapeutic anticoagulants with values within therapeutic window), and
    b. activated partial thromboplastin time (aPTT) ≤ 1.5 × ULN (unless on therapeutic anticoagulants with values within therapeutic window).
17. Patients must provide the following biopsy samples:
    a. All patients: must provide a tumor tissue sample (formalin fixed paraffin-embedded [FFPE] blocks/slides) from a fresh biopsy collected before Visit C1D1, or archival tissue. The archival tissue can be an FFPE block (not older than 3 years) or freshly cut slides (special storage conditions and immediate shipment to specialty lab are required), preferably derived from advanced disease stage.

b. Patients at selected trial sites: After additional consent, patients should be amenable to pre-treatment and on-treatment PBMC sampling and optional biopsy. If amenable, patients should provide a PBMC sample and optionally a biopsy which contains tumor tissue after failure/stop of last prior trial treatment.

18. Women of childbearing potential (WOCBP) must have a negative serum (beta-human chorionic gonadotropin [beta-hCG]) at screening. Patients that are post-menopausal or permanently sterilized can be considered as not having reproductive potential. For a definition of WOCBP, see Section 10.4.
    a. Female patients of reproductive potential must agree to use highly effective contraception during and for 6 months after the last trial drug administration (Section 10.4).
19. WOCBP must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during trial starting at screening, during the trial and for 6 months after receiving the last trial treatment.
20. A man who is sexually active with a WOCBP and has not had a vasectomy must agree to use a barrier method of birth control, e.g., either condom with spermicidal foam/gel/film/cream/suppository or partner with occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository, and all men must also not donate sperm during the trial and for 6 months after receiving the last trial treatment. For a definition of adequate contraception, see Section 10.4.

5.1.2 Exclusion criteria initial treatment

Patients are not eligible to be included in the trial only if any of the following criteria apply:

Medical conditions:

1. Patients must not be pregnant or breastfeeding.
2. Patients must not have history of uveal, acral, or mucosal melanoma.
3. Patients must have no ongoing or recent evidence (within the last 5 years) of significant autoimmune disease that required treatment with systemic immunosuppressive treatments which may pose a risk for irAEs.
   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.
4. Patients must have no 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 negative SCID, Wiskott Aldrich syndrome, ataxia telangiectasia, common variable immunodeficiency).
5. Patients with uncontrolled type 1 diabetes mellitus or with uncontrolled adrenal insufficiency are not eligible.

6. Patients must have no uncontrolled infection with human immunodeficiency virus, hepatitis B or hepatitis C infection; or diagnosis of immunodeficiency that is related to, or results in chronic infection. Mild cancer-related immunodeficiency (such as immunodeficiency treated with gamma globulin and without chronic or recurrent infection) is allowed.
   a. Patients with known HIV who have controlled infection (undetectable viral load and CD4 count above 350 either spontaneously or on a stable anti-viral regimen) are permitted. For patients with controlled HIV infection, monitoring will be performed per local standards.
   b. Patients with known hepatitis B virus (HBV) who have controlled infection (serum hepatitis B virus DNA PCR that is below the limit of detection AND receiving anti-viral therapy for hepatitis B) are permitted. Patients with controlled infections must undergo periodic monitoring of HBV DNA per local standards. Patients must remain on anti-viral therapy for at least 6 months beyond the last dose of trial treatment.
   c. Patients who are known hepatitis C virus (HCV) antibody positive who have controlled infection (undetectable HCV RNA by PCR either spontaneously or in response to a successful prior course of anti-HCV therapy) are permitted.
   d. Patients with HIV or hepatitis must have their disease reviewed by the specialist (e.g., infectious disease specialist or hepatologist) managing this disease prior to commencing and throughout the duration of their participation in the trial.

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

7. Patients with another primary malignancy that has not been in complete remission for at least 2 years, with the exception of those with a negligible risk of metastasis, progression or death (such as adequately treated carcinoma *in situ* of the cervix, basal or squamous cell skin cancer, localized prostate cancer, non-invasive, superficial bladder cancer or breast ductal carcinoma *in situ*).

   Note: should be discussed with medical monitor in case of uncertainties.

Prior/concomitant therapy:

8. Current use or use within 3 months prior to trial enrollment of systemic immune suppression including:
   a. use of chronic systemic steroid medication (up to 5 mg/day prednisolone equivalent is allowed); patients using physiological replacement doses of prednisone for adrenal or pituitary insufficiency are eligible,
   b. other clinically relevant systemic immune suppression.
9. Treatment with other anti-cancer therapy including chemotherapy, radiotherapy, or investigational or biological cancer therapy within 3 wks prior to the first dose of trial treatment (6 wks for nitrosureas). Adjuvant hormonotherapy used for breast cancer in long-term remission is allowed (refer to exclusion criterion 7).

Other comorbidities:

10. Current evidence of ongoing NCI-CTCAE (v5.0) Grade > 1 toxicity of prior therapies before the start of treatment, with the exception of hair loss, hearing loss, Grade 2 peripheral neuropathy, or laboratory abnormalities not considered clinical significant per investigator's discretion, and those Grade 2 toxicities listed as permitted in other eligibility criteria.
11. Patients who have a local infection (e.g., cellulitis, abscess) or systemic infection (e.g., pneumonia, septicemia) which requires systemic antibiotic treatment within 2 wks prior to the first dose of trial treatment.
12. Patients who have had a splenectomy.
13. Patients who have had major surgery (e.g., requiring general anesthesia) within 4 wks before screening, have not fully recovered from surgery, or have a surgery planned during the time of trial participation.
14. Current evidence of new or growing brain or spinal metastases during screening. Patients with leptomeningeal disease are excluded. Patients with known brain or spinal metastases may be eligible if they:
    a. had radiotherapy or another appropriate therapy for the brain or spinal bone metastases,
    b. have no neurological symptoms that can be attributed to the current brain lesions,
    c. have stable brain or spinal disease on the CT or MRI scan within 4 wks before randomization (confirmed by stable lesions on two scans at least 4 wks apart, the second scan can be carried out during screening),
    d. do not require steroid therapy within 14 days before the first dose of trial treatment,
    e. spinal bone metastases are allowed, unless imminent fracture or cord compression is anticipated.
15. History or current evidence of significant cardiovascular disease including, but not limited to:
    a. angina pectoris requiring anti-anginal medication, uncontrolled cardiac arrhythmia(s), severe conduction abnormality, or clinically significant valvular disease,
    b. QTc (F) prolongation > 480 ms,
    c. arterial thrombosis or pulmonary embolism within ≤ 6 months before the start of treatment,
    d. myocardial infarction within ≤ 6 months before the start of treatment,
    e. pericarditis (any NCI-CTCAE grade), pericardial effusion (NCI-CTCAE Grade ≥ 2), non-malignant pleural effusion (NCI-CTCAE Grade ≥ 2) or malignant pleural effusion (NCI-CTCAE Grade ≥ 3) within ≤ 6 months before the start of treatment,
    f. Grade ≥ 3 symptomatic congestive heart failure (CHF) or New York Heart Association (NYHA) criteria Class ≥ II within ≤ 6 months before the start of treatment.
16. Patients who have received a live vaccine within 28 days of planned start of trial therapy.

Other exclusions:

17. Known hypersensitivity to the active substances or to any of the excipients.
18. Presence of a severe concurrent illness or other condition (e.g., psychological, family, sociological, or geographical circumstances) that does not permit adequate follow-up and compliance with the protocol.
19. Prior treatment with BNT111 and/or with cemiplimab.

5.1.3 Inclusion criteria for entering add-on therapy

1. Patients must have confirmed disease progression on monotherapy in Arm 2 or 3 of the trial.
   a. An initial radiological progression needs to be verified by BICR.
   b. Radiological progression to be confirmed by two scans 4 to 12 wks apart unless initial progression is accompanied by new symptoms, or deterioration of PS not attributed to toxicity, in which case one scan is sufficient.
2. Patients must sign a new ICF to continue with add-on therapy. Informed consent must be documented before any add-on-specific procedure is performed.
3. WOCBP must have a negative serum (beta-hCG) at baseline. Patients that are post-menopausal or permanently sterilized can be considered as not having reproductive potential. For a definition of WOCBP, see Section 10.4.
4. Female patients of reproductive potential must agree to use adequate contraception during and for 6 months after the last trial drug administration (Section 10.4).
5. WOCBP must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during trial starting at screening, during the trial and for 6 months after receiving the last trial treatment.
6. A man who is sexually active with a WOCBP and has not had a vasectomy must agree to use a barrier method of birth control, e.g., either condom with spermicidal foam/gel/film/cream/suppository or partner with occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository, and all men must also not donate sperm during the trial and for 6 months after receiving the last trial treatment. For a definition of adequate contraception, see Section 10.4.

5.1.4 Exclusion criteria for entering add-on therapy

1. Prior toxicity related to trial medication should have resolved to NCI-CTCAE v5.0 Grade ≤ 1 before the start of add-on treatment and may not have led to permanent discontinuation.
2. The time between confirmed PD on monotherapy and start of add-on therapy shall not exceed 6 wks.
3. Current evidence of new or growing brain or spinal metastases at baseline (lesions that remained stable during initial treatment are allowed).
4. Systemic immune suppression:

a. use of chronic systemic steroid medication (up to 5 mg/day prednisolone equivalent is allowed); patients using physiological replacement doses of prednisone for adrenal or pituitary insufficiency are eligible,
b. other clinically relevant systemic immune suppression.

5. Presence of cardiovascular, renal, hepatic or any other disease that in the investigator's opinion, may increase the risks associated with trial participation or require treatments that may interfere with the conduct of the trial or the interpretation of trial results.

5.2 Screen failures

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

Individuals who do not meet the criteria for participation in this trial (screen failure) may be rescreened once. Rescreened patients should be assigned a new patient number.

6 TRIAL TREATMENTS

Trial treatment is defined as any investigational treatments, or marketed products intended to be administered to a trial patient according to the trial protocol.

6.1 Trial treatments administered

In all countries participating in the trial, BNT111 and cemiplimab are considered as investigational medicinal products (IMPs). An overview of the trial treatments and dosage information is shown in Table 2.

Detailed information on how BNT111 and cemiplimab should be administered is described in the current Pharmacy Manual (Appendices 1 and 2).

Table 2: Trial treatments administered

IMP name	BNT111	Cemiplimab
Type	Biologic	Biologic
Dosage form	Vial	Vial
Unit dose strengths	Each drug product CCI in a single-dose vial for dilution with 0.9% sodium chloride	Each vial contains CCI mg cemiplimab in 7 mL of solution
Dosage levels	CCI ug total RNA for the first dose, and CCI ug total RNA subsequently per schedule in the SoAs. Lowest possible dose is CCI ug total RNA	CCI mg
Administration route	IV injection	IV infusion
Use	Experimental	Experimental
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and labeling	IMP will be provided in a folding box. Each folding box and each vial will be labeled as per country requirement	IMP will be provided in a folding box. Each folding box and each vial will be labeled as per country requirement

Abbreviations: IMP = investigational medicinal product; IV = intravenous; RNA = ribonucleic acid; SoA = schedule of activities.

6.2 Schedule of trial treatments

Patients will receive BNT111 and cemiplimab as outlined in the respective SoA in Section 1.3.

Delayed doses of BNT111 are to be managed as following:

In patients receiving weekly BNT111 doses, if a given dose is delayed for >2 d outside the visit window this BNT111 dose is to be skipped, and the patient should receive the next planned BNT111 dose as per the respective SoA. Exception is to be made in cases where the first day of the subsequent treatment cycle is delayed (i.e., C2D1, C3D1, add-on C2D1, add-on C3D1). In such cases, the delayed dosing visit is not skipped but performed as soon as possible to minimize the delay of the second trial treatment administration (cemiplimab). This rule/exception is also applicable to a delay of the first day of the subsequent cycle treatment in Arm 2 patients (receiving BNT111 as monotherapy) and Arm 3 add-on treatment.

In patients receiving BNT111 as 3-weekly doses (from Cycles 3 or 4 onwards), if a given dose is delayed, the next trial treatment should be administered as soon as possible to minimize the delay of the second trial treatment administration (cemiplimab).

The schedule of BNT111 should be maintained throughout the treatment period, and when feasible, the investigator should try to harmonize with the administration of cemiplimab, especially if it is delayed at any time point.

Patients from Arm 2 who continue to add-on therapy should maintain the same dose of BNT111 as given during monotherapy treatment, if dose was reduced, this reduction should be maintained during combination therapy.

6.3 Duration of treatments

The duration of treatment with BNT111 + cemiplimab (Arm 1) or BNT111 or cemiplimab as single agents is up to 24 months and will continue until unacceptable toxicity, withdrawal of consent, discontinuation due to investigator's decision or (confirmed) disease progression. Treatment with cemiplimab and/or BNT111 may be continued through initial radiological disease progression if the patient derives clinical benefit, e.g., until symptomatic disease, confirmation of progression, or unacceptable toxicity (whatever comes first).

Patients in Arm 2 (BNT111 monotherapy) or Arm 3 (cemiplimab monotherapy) may enter add-on therapy (addition of the other compound). The start of the add-on therapy should be scheduled with as little therapy interruption as possible and at latest start within 6 wks after confirmed disease progression. The duration of therapy for patients entering into add-on therapy is a total of 24 months for both the monotherapy and add-on therapy part.

If one of the compounds needs to be discontinued, single-agent treatment with the other can continue upon investigator's and sponsor's agreement.

6.4 Preparation/handling/storage/accountability

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

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

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

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

6.5 Measures to minimize bias: randomization and blinding

This is an open-label trial, potential bias in assigning patients to treatment groups will be reduced by automated randomization. Information on trial treatment will be inaccessible for the radiologists that assess the CT scans by central review (primary analysis, BICR).

6.6 Trial treatment compliance

Patients will receive trial treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered must be recorded in the source documents and recorded in the electronic case report form (eCRF). The dose of both trial treatments and trial patient identification will be confirmed by a member of the trial site staff other than the person administering the trial treatment.

6.7 Concomitant therapy

6.7.1 Permitted concomitant therapy

Any operation, treatment, medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) or other specific categories of interest that the patient is receiving at the time of enrollment or receives during the trial must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care except for those medications identified as “prohibited” (Section 6.7.2).

- Palliative radiotherapy during the trial will be allowed for local symptom control (e.g., pain) 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.
- G-CSF 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 or platelet transfusion is allowed during the trial if clinically indicated. No transfusion is allowed within 1 wk prior to trial treatment initiation.
- Steroid treatment is permitted to modulate symptoms of an irAE 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 orally [PO] or IV, or equivalent) should be avoided as it counteracts with the mechanism of action of the vaccine.

6.7.2 Prohibited concomitant therapy

The following concomitant therapies and medications are not allowed during the treatment phase:

- Any concomitant systemic anti-cancer therapy defined as any agent or combination of agents with clinically proven anti-neoplastic 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.
- Any immunosuppressive therapy including immunosuppressive or maintenance therapy with systemic corticosteroids (PO or IV prednisone > 5 mg per day, or its equivalent), **unless required per investigator's decision** for treatment of an AE (maintenance therapy of prednisone > 5 mg should be discussed with the medical monitor).

  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 28 days prior to the first dose of BNT111 and 3 months after the last dose of BNT111.
- Concomitant treatment with interferon is prohibited for all patients included into the trial.

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.

6.8 Dose modifications and interruptions

6.8.1 Interruption of the intravenous infusion of cemiplimab

The infusion of cemiplimab should be interrupted if any of the following AEs are observed:

- sustained/severe cough
- rigors/chills
- rash, pruritus (itching)
- urticaria (hives, welts, wheals)
- diaphoresis (sweating)
- hypotension
- dyspnea (shortness of breath)

- vomiting
- flushing

The reaction(s) should be treated symptomatically. The restart of the infusion at an infusion rate of 50% on the same day is at the discretion of the investigator if the NCI-CTCAE grade of the AE is Grade ≤ 1. For any AE with a NCI-CTCAE Grade ≥ 2, no restart of the infusion on the same day is permitted yet continuation of trial therapy may be allowed depending of the evolution of the AE.

6.8.2 Dose modification for BNT111

Treatment ***must*** be discontinued if any of the following applies:

- First occurrence of anaphylaxis or a Grade 4 injection-related reaction (IRR).
- Second occurrence of Grade ≥ 3 IRR regardless of pre-medication prior to the next administration of BNT111.
- Re-treatment at a lower dose leads to a further identical ADR of Grade ≥ 3.
- ADR of Grade ≥ 3 which fails to resolve to Grade ≤ 1 within 21 days after the planned dosing date.

Note: Asymptomatic Grade 3 to 4 elevations of non-hematological laboratory values that resolve to NCI-CTCAE Grade ≤ 2 within 14 days (with or without medical intervention) do not require treatment discontinuation.

- Dose delay of more than 21 days (longer delays may be permitted after consultation with the medical monitor).

The dose should be reduced or withdrawn if at least one of the following ADRs occurred in a given patient receiving BNT111 vaccinations, regardless of pre-medication:

- Grade 4 fever.
- Grade 3 fever and Grade 3 hypotension.
- Grade 4 hypotension.
- No dose reduction of BNT111 below CCI µg total RNA is allowed.

Further dose modification is outlined in Figure 2. Following dose reduction of BNT111, no dose re-escalation is permitted. If the BNT111 dose is not increased from the initial CCI µg to CCI µg total RNA due to an AE on C1D8 (or AOC1D8), dose-escalation may be considered at C1D15 or during Cycle 2. This should only be carried out following consultation with a medical monitor and if the AE has abated and can be controlled through supportive medication in the future.

If the investigator is not able to attribute the toxicity to either cemiplimab or BNT111, cemiplimab should be interrupted or discontinued and BNT111 doses to be modified per

Figure 2. Further dose modifications should be based on clinical judgment by the investigator and after discussion with the sponsor's medical monitor.

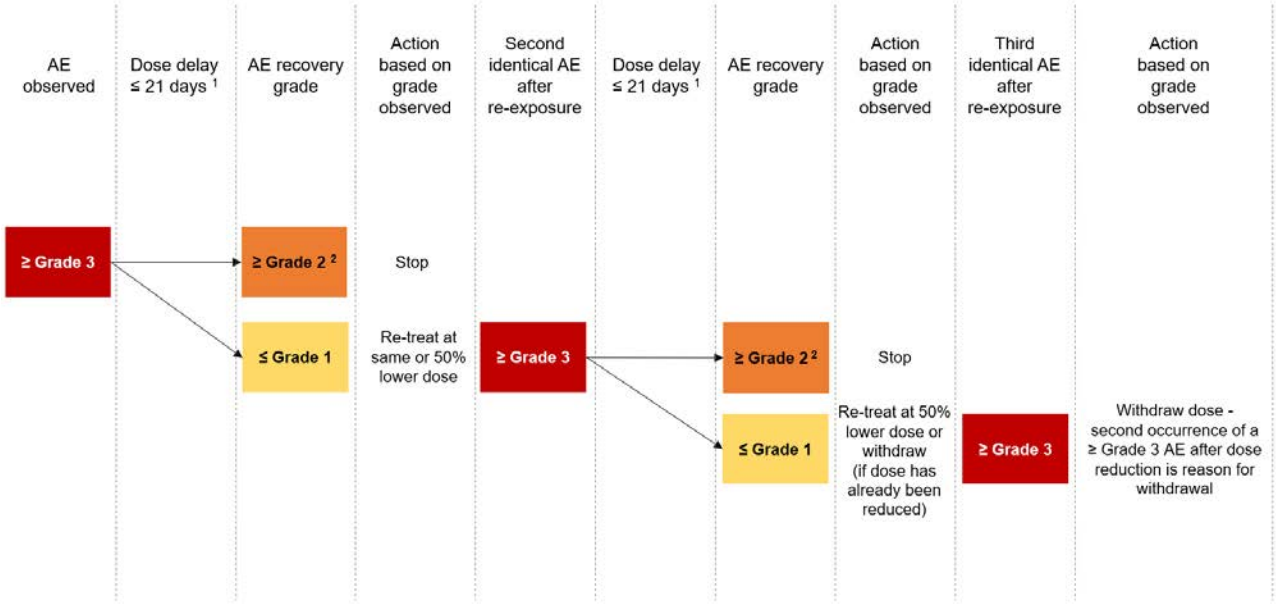

Figure 2: Dose modification for BNT111

Note: Exceptions can be made for recurrent Grade 3 AEs that do not impact the safety of the patient (e.g., short-lasting Grade 3 fever) after discussion with the medical monitor.
1 Dose delay: Next dose of BNT111 can be delayed by a maximum of 21 days, unless approved otherwise by the sponsor's medical monitor.
2 No further delay for recovery allowed, unless baseline NCI-CTCAE grade was Grade ≥ 2 and TEAE has resolved to baseline grade.
Abbreviations: G = grade; grading according to NCI-CTCAE v5.0.

6.8.3 Dose modification for cemiplimab

No dose reductions are recommended. Dosing delay or treatment discontinuation may be required based on individual safety and tolerability. Recommended modifications to manage adverse reactions are provided in Table 3 and in the cemiplimab (LIBTAYO®) locally approved label.

Table 3: Dose modification for cemiplimab

Adverse reaction	Severity [a]	Dose modification	Additional intervention
Pneumonitis	Grade 2	Withhold cemiplimab	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
		Resume cemiplimab if pneumonitis improves and remains at Grade 0 to 1 after corticosteroid taper to ≤ 5 mg/day prednisone or equivalent	
	Grade 3 or 4 or recurrent Grade 2	Permanently discontinue	Initial dose of 2 to 4 mg/kg/day prednisone or equivalent followed by a taper
Colitis	Grade 2 or 3	Withhold cemiplimab	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
		Resume cemiplimab if colitis or diarrhea improves and remains at Grade 0 to 1 after corticosteroid taper to ≤ 5 mg/day prednisone or equivalent	
	Grade 4 or recurrent Grade 3	Permanently discontinue	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
Hepatitis	Grade 2 with AST or ALT > 3 and ≤5 × ULN or total bilirubin > 1.5 and ≤ 3 × ULN	Withhold cemiplimab	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
		Resume cemiplimab if hepatitis improves and remains at Grade 0 to 1 after corticosteroid taper to ≤ 5 mg/day prednisone or equivalent or returns to baseline AST or ALT after completion of corticosteroid taper	
	Grade ≥ 3 with AST or ALT > 5 × ULN or total bilirubin > 3 × ULN	Permanently discontinue	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
Hypothyroidism	Grade 3 or 4	Withhold cemiplimab	Initiate thyroid hormone replacement as clinically indicated
		Resume cemiplimab when hypothyroidism returns to Grade 0 to 1 or is otherwise clinically stable	
Hyperthyroidism	Grade 3 or 4	Withhold cemiplimab	Initiate symptomatic management
		Resume cemiplimab when hyperthyroidism returns to Grade 0 to 1 or is otherwise clinically stable	
Hypophysitis	Grade 2 to 4	Withhold cemiplimab	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper and hormone replacement as clinically indicated

Adverse reaction	Severity [a]	Dose modification	Additional intervention
		Resume cemiplimab if hypophysitis improves and remains at Grade 0 to 1 after corticosteroid taper to ≤ 5 mg/day prednisone or equivalent or is otherwise clinically stable	
Adrenal insufficiency	Grade 2 to 4	Withhold cemiplimab	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
		Resume cemiplimab if adrenal insufficiency improves and remains at Grade 0 to 1 after corticosteroid taper to ≤ 5 mg/day prednisone or equivalent or is otherwise clinically stable	
Type 1 diabetes mellitus	Grade 3 or 4 (hyperglycaemia)	Withhold cemiplimab	Initiate treatment with anti-hyperglycaemics as clinically indicated
		Resume cemiplimab when diabetes mellitus returns to Grade 0 to 1 or is otherwise clinically stable	
Skin adverse reactions	Grade 2 lasting longer than 1 wk, Grade 3 or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold cemiplimab	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
		Resume cemiplimab if skin reaction improves and remains at Grade 0 to 1 after corticosteroid taper to ≤ 5 mg/day prednisone or equivalent	
	Grade 4 or confirmed SJS or TEN	Permanently discontinue	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
Immune-related skin reaction or other immune-related adverse reactions in patients with prior treatment with idelalisib	Grade 2	Withhold cemiplimab	Initiate symptomatic management immediately, including initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
		Resume cemiplimab if skin reaction or other immune-related adverse reaction improves and remains at Grade 0 to 1 after corticosteroid taper to ≤ 5 mg/day prednisone or equivalent	
	Grade 3 or 4 (excluding endocrinopathies) or recurrent Grade 2	Permanently discontinue	Initiate symptomatic management immediately, including initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
Nephritis	Grade 2	Withhold cemiplimab	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper

Adverse reaction	Severity [a]	Dose modification	Additional intervention
		Resume cemiplimab if nephritis improves and remains at Grade 0 to 1 after corticosteroid taper to ≤ 5 mg/day prednisone or equivalent	
	Grade 3 or 4	Permanently discontinue	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
Other immune-related adverse reactions (including, but not limited to, paraneoplastic encephalomyelitis, meningitis, myositis, solid organ transplant rejection, graft-vs-host disease, Guillain-Barré syndrome, central nervous system, inflammation, chronic inflammatory demyelinating poly-radiculoneuropathy, encephalitis, myasthenia gravis, neuropathy peripheral, myocarditis, pericarditis, immune thrombocytopenic purpura, vasculitis, arthralgia, arthritis, muscular weakness, myalgia, polymyalgia rheumatica, Sjogren's syndrome, keratitis, stomatitis, thyroiditis[b]	Grade 2 or 3 based on type of reaction with clinical signs or symptoms of an immune-related adverse reaction not described elsewhere	Withhold cemiplimab	Initiate symptomatic management
		Resume cemiplimab if other immune-related adverse reaction improves and remains at Grade 0 to 1 after corticosteroid taper to ≤ 5 mg/day prednisone or equivalent	
	• Grade 3 based on type of reaction or Grade 4 adverse reaction (excluding endocrinopathies) • Grade 3 or 4 neurologic adverse reaction • Grade 3 or 4 myocarditis or pericarditis • Recurrent Grade 3 immune-related adverse reaction • Persistent Grade 2 or 3 immune-related adverse reactions lasting 12 wks or longer (excluding endocrinopathies) • Inability to reduce corticosteroid dose to 5 mg or less of prednisone or equivalent per day within 12 wks	Permanently discontinue	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
Infusion-related reaction	Grade 1 or 2	Interrupt or slow rate of infusion	Initiate symptomatic management
	Grade 3 or 4	Permanently discontinue	

a. Toxicity should be graded with the current version of NCI-CTCAE.
b. Observed with cemiplimab or with other anti-PD-1/PD-L1 monoclonal antibodies.
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PD-1 = programmed cell death protein 1; PD-L1 = programmed death ligand 1; ULN = upper limit of normal.

6.8.4 Mitigation plans for specific AEs

6.8.4.1 BNT111

It is anticipated that patients may experience AEs of flu-like symptoms following the administration of BNT111 due to its mechanism of action. This may include, but is not limited to fever, tachycardia, arthralgia, myalgia, headache, nausea, chills and rigors. Sporadically patients also experienced moderate to severe hypotension that is potentially related to the pharmacodynamic effect of BNT111. Treatment of these events is dependent on the discretion of the investigators; however, guidance for monitoring and suggestions for management are provided below.

Safety monitoring, prophylaxis, and treatment of fever and associated symptoms

- Vital signs must be monitored prior, during and after injection:
  - Within 60 min prior to first injection.
  - At 30 min, 60 min, 4 h and 6 h after last injection of BNT111 vaccine. If no Grade ≥ 2 in the first cycle (3 vaccinations), 4 h and 6 h post dose may be skipped as per investigator's discretion and as per local clinical standard practice in subsequent cycles.
  - Optional at 24 h, based on symptomatology, clinical necessity and/or local clinical standard practice.
  - Observation period should be prolonged in case of Grade ≥ 2 fever and Grade ≥ 2 hypotension in the first 6 h until resolution of fever to Grade ≤ 1 and full resolution of hypotension.
  - Additional time points to be added at investigator's discretion.
- If a patient develops fever of ≥ 38°C after the administration of the BNT111 vaccine (during the observation period), secondary prophylactic pre-treatment with paracetamol and/or NSAIDs prior to all further vaccination cycles is recommended, at least 60 min before BNT111 vaccine administration followed by a second dose 2 to 8 h after BNT111 vaccine.
- Corticosteroid should be avoided as either prophylaxis or treatment as it counteracts the pharmacodynamic effects of BNT111 vaccine.

Table 4: Recommendations for dose modifications in case of fever

NCI-CTCAE v5.0	Guidance
Grade 1 (38 to 39˚C)	Consider usage of physical/clinical methods to reduce fever (e.g., ice packs, blankets and fluids). Treat with antipyretics and pretreat with antipyretics at next vaccinations. No change in dose. If AE occurs before C1D8 or for the add-on therapy before AOC1D8, the dose may be increased to CCI µg total RNA.
Grade 2 (39 to 40˚C)	Consider usage of physical/clinical methods to reduce fever (e.g., ice packs, blankets and fluids). Treat with antipyretics and pretreat with antipyretics at next vaccinations. No change in dose. If an AE occurs before C1D8 or for the add-on therapy before AOC1D8, the dose may be increased to CCI µg total RNA.
Grade 3 (> 40˚C, < 24 h)	Consider usage of physical/clinical methods to reduce fever (e.g., ice packs, blankets and fluids). Treat with antipyretics and pretreat with antipyretics at next vaccinations. No change in dose. If an AE occurs before C1D8 or for the add-on therapy before AOC1D8, consider to maintain the dose at CCI µg. Dose increase may be considered at the discretion of the investigator. If already pre-treated with antipyretics, consider to reduce dose. If accompanied by Grade 3 hypotension, reduce dose. If the lowest dose is already reached, withdraw treatment.
Grade 4 (> 40˚C, > 24 h)	Consider usage of physical/clinical methods to reduce fever (e.g., ice packs, blankets and fluids). Treat with antipyretics and pretreat with antipyretics at next vaccinations. Reduce or withdraw dose.

Abbreviations: AE = adverse event; AOCnDn = add-on, cycle "n", day "n"; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0.

Management of flu-like symptoms (other than fever)

Patients should be assessed for potential cytokine release syndrome in the presence of severe flu-like symptoms.

Management of these symptoms should follow local standard clinical practice; however, corticosteroids should be avoided as either prophylaxis or treatment as it counteracts the pharmacodynamic effects of the BNT111 vaccine.

Table 5: Recommendations for management of flu-like symptoms/influenza-like illness related to BNT111

NCI-CTCAE v5.0	Guidance
Grade 1 to 3	Treat symptomatically as indicated, including antipyretics, antihistamines, and/or analgesics as needed. Treat fever and neutropenia if present. Monitor fluid balance; administer IV fluids as clinically indicated. Observe patients as specified in the protocol. Continue same dose level. For subsequent events a dose reduction may be considered depending on severity of the event and recovering with concomitant medication, as per investigator judgment. For subsequent dosing and dose reduction, please refer to relevant section of protocol.

Abbreviations: IV = intravenous; NCI-CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0.

Safety monitoring, prophylaxis and treatment of hypotension

- Vital signs are monitored prior, during and after injection:
  - Within 60 min prior to first injection.
  - At 30 min, 60 min, 4 h, and 6 h after last injection of BNT111 vaccine. If no hypotension in the first cycle (3 vaccinations), 4 h and 6 h post dose may be skipped at investigator's discretion and as per local clinical standard practice.
  - Observation period should be prolonged in case of Grade ≥ 2 hypotension in the first 6 h until full resolution.
  - Optional at 24 h, based on symptomatology, clinical necessity and/or local clinical standard practice.
  - Additional time points to be added at investigator's discretion.
- Ensure adequate hydration of patients on the day of trial drug administration.
- For patients taking more than one anti-hypertensive, the shorter-acting one(s) may be omitted on the day of injection.
- For patients taking one anti-hypertensive, consider omitting the dose on day of injection or during trial duration if prior event of hypotension has occurred.
- For any patient who experienced Grade ≥ 2 hypotension with prior dose of trial drug:
  - Administer IV isotonic fluid (e.g., normal saline, 500 to 1000 mL) approximately 2 h following trial drug injections per institutional standards.
- For any patient who experienced Grade ≥ 3 hypotension with prior dose of trial drug:

- Consider holding or modifying anti-hypertensive medication as per investigator discretion on the day of trial drug injection and consider seeking recommendations from a cardiologist regarding anti-hypertensive medication.
- Administer IV isotonic fluid (e.g., normal saline, 500 to 1000 mL) and/or balanced crystalloid fluids approximately 2 h following trial drug injections per institutional standards.

Table 6: Recommendations for dose modifications in case of hypotension

NCI-CTCAE v5.0	Guidance
Grade 1 Asymptomatic, intervention not indicated	No intervention.
Grade 2 Non-urgent medical intervention indicated	• Treat with IV fluids and consider administering IV isotonic fluid (e.g., normal saline 500 to 1000 mL) and/or balanced crystalloid fluids within approximately 2 h following the next dose of trial drug per institutional standard. • If AE occurs before C1D8 or for the add-on therapy before AOC1D8, the dose may be increased to CCI ug total RNA at the discretion of the investigator. Maintaining the dose is also an option.
Grade 3 Medical intervention indicated; hospitalization indicated	• Treat with IV fluids and/or vasopressor(s) and consider administering IV isotonic fluid (e.g., normal saline 500 to 1000 mL) and/or balanced crystalloid fluids within approximately 2 h following the next dose of trial drug per institutional standard. • If AE occurs before C1D8 or for the add-on therapy before AOC1D8, consider to maintain the dose at CCI ug. Dose increase may be considered at the discretion of the investigator. • Consider to reduce dose. • If accompanied by Grade ≥ 3 fever, reduce dose. If the lowest dose is already reached, withdraw treatment.
Grade 4 Life-threatening consequences and urgent intervention indicated	• Treat with IV fluids and/or vasopressor(s) and consider administering IV isotonic fluid (e.g., normal saline 500 to 1000 mL) and/or balanced crystalloid fluids within approximately 2 h following the dose of trial drug per institutional standard. • Reduce or withdraw dose.

Abbreviations: AE = adverse event; IV = intravenous; NCI-CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0.

Management of infusion-related reactions

Reactions that occur since the beginning of the dose, during the dose and up to 60 min after the end of the dose, may be considered as infusion-related reactions as per investigator discretion.

Vital signs are monitored prior, during and after infusion:

- Within 60 min prior to first infusion.
- At 30 min, 60 min, 4 h and 6 h after the trial treatment. If no IRR in the first cycle, 4 h and 6 h post dose may be skipped at investigator's discretion and as per local clinical standard practice.
- Optional at 24 h, based on symptomatology, clinical necessity and/or local clinical standard practice.
- Additional time points to be added at investigators discretion.

The key principles of these recommendations are to maintain the comfort of the patient by management of infusion-related AEs experienced by other patients through:

- Effective prophylaxis and management of nausea and vomiting to support the patient's hydration status.
- Rapid administration of an appropriate amount of fluids.
- Keep the patient warm.
- Maintain organ function such as blood pressure, cognitive function and urinary output.
- Close monitoring of cardiac and other organ function as guided by comorbidities.
- Clinical pictures may vary, and recommendations do not replace medical reason.
- Keep other causes for symptoms in mind.

Table 7: Recommendations for management of infusion-related reactions related to trial drug

NCI-CTCAE v5.0	Guidance
Grade 1 or 2	• Treat symptomatically as indicated, including antipyretics, antihistamines, and/or analgesics as needed. • Treat fever and neutropenia if present. • Monitor fluid balance; administer IV fluids as clinically indicated. • Observe patients for at least 4 h. • Continue next dose at the same dose level. • For subsequent dosing, consider to use pre-medication as prophylaxis as per local clinical practice. Corticosteroids should be avoided if possible as they may counteract the pharmacodynamic effects of BNT111.
Grade 3	• Withhold further treatment with trial drugs that day. • Strongly consider cardiopulmonary and organ function monitoring in an Intensive Care Unit. • Closely monitor and maintain fluid balance; administer IV fluids as clinically indicated. • Oxygen for hypoxia. • Vasopressor support for hypotension refractory to IV fluids.

NCI-CTCAE v5.0	Guidance
	• Other supportive care as clinically indicated (e.g., fever and neutropenia, infection). • Consider administration of corticosteroids (e.g., methylprednisolone or dexamethasone), in addition to antihistamines, antipyretics. • May receive the next dose of trial treatment if symptoms resolve to Grade ≤ 1 for three consecutive days with approval of the medical monitor. • For subsequent dosing consider to resume treatment with reduced dose. • For subsequent dosing, use pre-medication as prophylaxis as per local clinical practice. Corticosteroids should be avoided if possible as they may counteract the pharmacodynamic effects of BNT111 vaccine.
Grade 4	• Cardiopulmonary and organ function monitoring in Intensive Care Unit. • Aggressive supportive treatment as described for Grade 3 IRRs (e.g., monitor/maintain fluid balance, treatment of fever and neutropenia). • Mechanical ventilator support for respiratory failure. • Aggressive vasopressor support for hypotension. • Other supportive care as clinically indicated (e.g., fever and neutropenia, infection). • Administer corticosteroids (e.g., methylprednisolone or dexamethasone), in addition to antihistamines, antipyretics, and/or analgesics; consider other immunosuppressive agents. • Permanently discontinue trial drug.

Abbreviations: IRRs = infusion-related reactions; IV = intravenous; NCI-CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0.

6.8.4.2 Cemiplimab

Special warnings and precautions for use of cemiplimab are:

Immune-related adverse reactions

Severe and fatal immune-related adverse reactions have been observed with cemiplimab (see locally approved label). These immune-related reactions may involve any organ system. Most immune-related reactions initially manifest during treatment with cemiplimab; however, immune-related adverse reactions can occur after discontinuation of cemiplimab.

Immune-related adverse reactions should be managed with cemiplimab treatment modifications, hormone replacement therapy (if clinically indicated), and corticosteroids. For suspected immune-related adverse reactions, patients should be evaluated to confirm an immune-related adverse reaction and to exclude other possible causes. Depending upon the severity of the adverse reaction, cemiplimab should be withheld or permanently discontinued (see Table 3).

Immune-related pneumonitis

Immune-related pneumonitis, defined as requiring use of corticosteroids with no clear alternate etiology, including fatal cases, has been observed in patients receiving cemiplimab (see locally approved label). Patients should be monitored for signs and symptoms of pneumonitis. Patients with suspected pneumonitis should be evaluated with

radiographic imaging as indicated based on clinical evaluation and managed with cemiplimab treatment modifications and corticosteroids (see Table 3).

Immune-related colitis

Immune-related diarrhea or colitis, defined as requiring use of corticosteroids with no clear alternate etiology, has been observed in patients receiving cemiplimab (see locally approved label). Patients should be monitored for signs and symptoms of diarrhea or colitis and managed with cemiplimab treatment modifications, anti-diarrheal agents, and corticosteroids (see Table 3).

Immune-related hepatitis

Immune-related hepatitis, defined as requiring use of corticosteroids with no clear alternate etiology, including fatal cases, has been observed in patients receiving cemiplimab (see locally approved label). Patients should be monitored for abnormal liver tests prior to and periodically during treatment as indicated based on clinical evaluation and managed with cemiplimab treatment modifications and corticosteroids (see Table 3).

Immune-related endocrinopathies

Immune-related endocrinopathies, defined as treatment-emergent endocrinopathies with no clear alternate etiology, have been observed in patients receiving cemiplimab (see locally approved label).

Thyroid disorders (hypothyroidism/hyperthyroidism)

Immune-related thyroid disorders have been observed in patients receiving cemiplimab. Thyroid disorders can occur at any time during the treatment. Patients should be monitored for changes in thyroid function at the start of treatment and periodically during the treatment as indicated based on clinical evaluation (see locally approved label). Patients should be managed with hormone replacement therapy (if indicated) and cemiplimab treatment modifications. Hyperthyroidism should be managed according to standard medical practice (see Table 3).

Hypophysitis

Immune-related hypophysitis has been observed in patients receiving cemiplimab (see locally approved label). Patients should be monitored for signs and symptoms of hypophysitis and managed with cemiplimab treatment modifications and corticosteroids (see Table 3).

Adrenal insufficiency

Adrenal insufficiency has been observed in patients receiving cemiplimab (see locally approved label). Patients should be monitored for signs and symptoms of adrenal insufficiency during and after treatment and managed with cemiplimab treatment modifications and corticosteroids (see Table 3).

Type 1 Diabetes mellitus

Immune-related type 1 diabetes mellitus, including diabetic ketoacidosis, has been observed in patients receiving cemiplimab (see locally approved label). Patients should be monitored for hyperglycaemia and signs and symptoms of diabetes as indicated based on clinical evaluation and managed with oral anti-hyperglycaemics or insulin and cemiplimab treatment modifications (see Table 3). Cemiplimab should be withheld and anti-hyperglycemics or insulin should be administered in patients with severe or life-threatening (Grade ≥ 3) hyperglycaemia. Cemiplimab should be resumed when metabolic control is achieved on insulin replacement or anti-hyperglycemics (see Table 3).

Immune-related skin adverse reactions

Immune-related skin adverse reactions, defined as requiring use of systemic corticosteroids with no clear alternate etiology, including severe cutaneous adverse reactions (SCARs), such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) (some cases with fatal outcome), and other skin reactions such as rash, erythema multiforme, pemphigoid, have been reported in association with cemiplimab treatment (see locally approved label).

Patients should be monitored for evidence of suspected severe skin reactions and exclude other causes. Patients should be managed with cemiplimab treatment modifications and corticosteroids (see Table 3).

Cases of SJS, fatal TEN and stomatitis occurred following one dose of cemiplimab in patients with prior exposure to idelalisib, who were participating in a clinical trial evaluating cemiplimab in Non-Hodgkin Lymphoma (NHL), and who had recent exposure to sulfa containing antibiotics (see locally approved label). Patients should be managed with cemiplimab treatment modifications and corticosteroids as described above (see Table 3).

Immune-related nephritis

Immune-related nephritis, defined as requiring use of corticosteroids with no clear alternate etiology, has been observed in patients receiving cemiplimab (see locally approved label). Patients should be managed with cemiplimab treatment modifications and corticosteroids (see Table 3).

Other immune-related adverse reactions

Other fatal and life-threatening immune-related adverse reactions have been observed in patients receiving cemiplimab including paraneoplastic encephalomyelitis and meningitis (see locally approved label for other immune-related adverse reactions).

Patients should be monitored for signs and symptoms of immune-related adverse reactions and managed with cemiplimab treatment modifications and corticosteroids (see Table 3).

Infusion-related reactions

Cemiplimab can cause severe or life-threatening infusion-related reactions (see locally approved label). Patients should be monitored for signs and symptoms of infusion-related

reactions and managed with cemiplimab treatment modifications and corticosteroids. Cemiplimab should be interrupted or the rate of infusion slowed for mild or moderate infusion-related reactions. The infusion should be stopped and cemiplimab should be permanently discontinued for severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions (see Table 3).

Patients previously treated with idelalisib

Any patient receiving cemiplimab who was previously treated with a PI3K inhibitor and who develops stomatitis or mucositis should suspend trial treatment. If this or any other irAE occurs among these patients, the sponsor should be informed about it as soon as possible as an AE of special interest (AESI) to discuss further management of the patient.

6.9 Treatment after the end of the trial

Not applicable.

7 DISCONTINUATION OF TRIAL TREATMENT AND PATIENT DISCONTINUATION / WITHDRAWAL

7.1 Discontinuation of trial treatment

Patients must permanently discontinue trial treatment if any of the following applies:

- Patient withdraws his consent to trial participation.
- Any medical condition that the investigator or sponsor determines may jeopardize the patient's safety if he or she continues to receive trial treatment.
- Investigator or sponsor determination that treatment discontinuation is in the best interest of the patient.
- Pregnancy.
- Confirmed disease progression, as determined by the investigator after an integrated assessment of radiographic data, biopsy sample results (if available), and clinical status (patients in Arms 2 and 3 may continue to combination therapy).
- Occurrence of new primary tumor, as assessed by the investigator.
- Intolerable toxicity related to trial treatment, determined by the investigator to be unacceptable given the individual patient's potential response to therapy and the severity of the event.
- Substantial non-compliance with trial procedures.
- Use of illicit drugs, prohibited concomitant medications, 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.

The primary reason for trial treatment discontinuation should be documented in the appropriate eCRF. Patients who discontinue trial treatment will not be replaced.

Patients who discontinue from treatment will return to the trial site for an end of treatment (EoT) Visit within 0 to 21 days after the final dose of trial treatment.

After treatment discontinuation, patients will be followed-up for safety, efficacy (if applicable) and survival (unless the patient withdraws consent, is lost to follow-up or the sponsor terminates the trial) for up to 48 months.

See the SoA (Section 1.3) for data to be collected at the time of discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.1 Temporary discontinuation

- Delay of dosing of BNT111 and/or cemiplimab of up to 21 days is allowed (longer delays may be permitted after consultation with the medical monitor).
- If one of the compounds needs to be temporarily discontinued, single-agent treatment with the other can continue upon investigator's and sponsor's agreement.

7.1.2 Rechallenge

Once the dose of BNT111 is reduced, it may not be re-escalated.

Cemiplimab may either be fully dosed, withheld or permanently discontinued as described in Section 6.8.3. No cemiplimab dose reductions are allowed.

7.2 Patient discontinuation/withdrawal from the trial

- A patient may withdraw from the trial at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, or behavioral, compliance. This is expected to be uncommon.
- At the time of discontinuing from the trial, if possible, an EoT visit should be conducted, as shown in the SoA (Section 1.3).
- In case of consent withdrawal, the patient will be permanently discontinued both from the trial treatment and from the trial at that time.
- 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/she may request destruction of any samples taken and not tested, and the investigator must document this in the trial source data.

7.3 Lost to follow-up

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

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

- The trial site staff 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 considered lost to follow-up, the investigator or designee must make every effort to regain contact with the patient (where possible, three phone 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, they will be considered to have withdrawn from the trial.

7.4 Discontinuation of trial by the sponsor

The sponsor may temporarily pause the trial or discontinue the trial in case new safety information becomes available.

In order to protect the safety and integrity of trial participants, the sponsor will engage in continuous medical monitoring of eligibility before the start of trial therapy as well as of all AEs including SAEs, suspected unexpected serious adverse reactions (SUSARs) and irAEs as well as deaths and laboratory values for all patients in the trial through a dedicated Medical Monitoring Plan and a Safety Management Plan. In addition, an IDMC will receive full safety information for each of the scheduled meetings (three-monthly during the first 12 months following the start of treatment of the first patient, six-monthly thereafter). *Ad hoc* meetings of the IDMC are foreseen by the IDMC charter in case circumstances like unexpected findings or safety signals would require so.

After each IDMC meeting, the IDMC will provide a recommendation to the sponsor concerning the continuation of the trial.

In addition to the scheduled IDMC meetings described above, another IDMC meeting will occur after the first ten patients in Arm 1 have been treated for at least two cycles (6 wks) or discontinued treatment for any reason during the first two cycles.

Specific stopping criteria will be based on the cumulative incidence of TEs. TEs include all related SAEs, related Grade 3 to 5 TEAEs/irAEs except for transient Grade 3 flu-like symptoms, clinically insignificant laboratory abnormalities and Grade 3 hypotension lasting for less than 6 h.

An accumulation of TEs occurring in ≥ 40% of the first ten patients in Arm 1, who have been treated for at least two cycles (6 wks) or discontinued treatment for any reason during the first two cycles, is deemed excessive and will result in an enrollment pause and an *ad hoc* IDMC meeting. This is based on the safety profile observed in the ongoing Lipo-MERIT trial (NCT02410733; Sahin et al. 2020), the expected benefit/risk and the safety profile of a CPI + CPI combination observed in the CheckMate 511 trial, where the FDA-approved combination of ipilimumab and nivolumab caused treatment-related AEs of NCI-CTCAE Grade 3 to 5 in 48% of participants (Lebbé et al. 2019).

Therefore, if four or more patients out of the first ten patients in Arm 1 (40%) experience one or multiple TEs during the first two cycles of trial treatment, enrollment will be paused, an *ad hoc* IDMC meeting will be scheduled within 10 business days, and a formal safety review by both companies providing the trial treatment (BioNTech and Regeneron) will be performed. Of note, the occurrence of one single Grade 5 TEAE (unless clearly unrelated to study drug, e.g., due to underlying disease) in the first ten patients in Arm 1 during the first two cycles will trigger an enrollment pause and IDMC *ad hoc* meeting.

The decision to restart enrollment will be the responsibility of the sponsor, and will be based on the results of the safety review of both companies (BioNTech and Regeneron) providing trial treatment, the recommendation of the IDMC and the principal investigators of the trial provided that the reviews of the totality of data confirm that resuming enrollment does not present an undue risk to patients.

8 TRIAL ASSESSMENTS AND PROCEDURES

See the respective SoAs (Section 1.3) for all planned time points for assessments.

Protocol waivers or exemptions are not allowed.

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

24/7 coverage for urgent protocol-related medical questions:

For discussion of urgent protocol-related medical questions in a trial-related health emergency in cases where assigned medical monitors for a trial cannot be reached by a caller, an on-call physician can be reached 24 h per day, 7 d per week via a Bexon Call Center. Use the country-specific numbers as shown below:

Country	Prefix	Number	Full number
Spain	+34	CCI	
USA	+1		
Australia	+61		
Poland	+48		
Italy	+39		
France	+33		

Country	Prefix	Number	Full number
UK	+44	CCI	
Germany	+49		

There may be restrictions when dialing a country-specific number from a mobile phone.

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 (i.e., radiology and histopathology tests) 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 (Section 1.3).

8.1 Efficacy assessments

Planned time points for efficacy assessments are provided in SoAs (Section 1.3).

8.1.1 Confirmation of anti-PD-1/PD-L1-refractory/relapsed patients

Patients should be resistant to prior anti-PD-1/PD-L1 therapy as specified by:

a. Previous exposure to approved anti-PD-1/PD-L1 containing regimen for melanoma for at least 12 consecutive weeks **and**

b. Current radiological progression to be confirmed by two scans 4 to 12 wks apart. If progression is accompanied by new symptoms, or deterioration of PS not attributed to toxicity, one scan is sufficient **and**

c. Inclusion into this trial must be within 6 months of confirmation of disease progression on anti-PD-1/PD-L1 treatment, regardless of any intervening therapy.

The anti-PD-1/PD-L1 therapy may have been given in the (neo)-adjuvant or metastatic setting as long as resistance to anti-PD-1/PD-L1 therapy was confirmed. Patients should have received at least one line and not more than five lines of prior therapy. A line of therapy is defined as an anti-cancer regimen given until (confirmed) disease progression. The subsequent therapy given will be considered a new line of therapy. Interruption and reinitiation of a therapy due to toxicity will not be considered a new line.

8.1.2 Tumor evaluations

At screening and during treatment

Patients will undergo regular CT or MRI imaging (include chest, abdomen and pelvis and other locations with tumor involvement) assessments of tumors from screening and

throughout the trial. Skin lesions can be followed by photography. At screening, preferably an MRI scan should be done to assess presence of brain metastasis (for patients with a contra-indication for MRI, a contrast-enhanced CT scan is allowed). If a patient has brain metastasis, stability of the lesions should be confirmed and lesions should be followed at each tumor assessment.

All measurable and evaluable lesions should be assessed at screening and target as well as non-target lesions identified and documented following RECIST 1.1 criteria. Tumor assessments, including brain imaging, performed as standard of care prior to obtaining informed consent and within 28 days prior to randomization do not have to be repeated at screening.

Tumor response will be assessed every 6 (±1) wks for the first 3 months, then every 9 (±1) wks for the next 9 months and every 12 (±2) wks thereafter, regardless of dose delays, until (confirmed) disease progression, death, withdrawal of consent, or until the start of next-line anti-cancer therapy, whichever occurs earlier (Section 1.3).

Lesion photography should be performed for cutaneous or palpable lesions at the required tumor assessment time points. When possible, the same individual should photograph and measure the lesions for a given patient to decrease intra-patient variability.

Radiological progression should be confirmed by two scans 4 to 12 wks apart. If progression is accompanied by new symptoms or deterioration of PS not attributed to toxicity one scan is sufficient.

Tumor responses will be measured by RECIST 1.1 / iRECIST and are to continue according to the schedule in patients who undergo complete trial treatment and in patients who discontinue treatment for reasons other than disease progression, consent withdrawal, or patient's withdrawal from the trial.

The same radiographic procedure used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same protocol for CT scan). An extra scan should be scheduled if clinically indicated.

The investigator will determine the tumor response based on the radiologist's measurement of all anatomic regions involved according to the RECIST 1.1 and iRECIST criteria and make treatment decisions.

After start of add-on therapy

Patients in Arms 2 and 3, who experience (centrally verified) disease progression under single-agent treatment, may be offered addition of the respective other compound to the ongoing treatment. In such cases, tumor assessments are to continue, and additional images should be collected in accordance with the imaging schedule and modalities outlined in Section 1.3.2.

The CT or MRI scan or photographs that confirmed disease progression after monotherapy can be used as baseline scan for the add-on therapy. The scan/photo should not be older than 21 days prior to start of the add-on therapy. At baseline, for patients

without brain metastasis during initial therapy, a brain MRI – or CT scan should be repeated to assess presence of new brain metastasis.

For the add-on baseline target lesions and non-target lesions can be redefined. These lesions should be re-assessed at each subsequent tumor evaluation.

Tumor response during add-on therapy will be assessed every 6 (±1) wks for the first 3 months, then every 9 (±1) wks for the next 9 months and every 12 (±2) wks thereafter, regardless of dose delays, until (confirmed) disease progression, death, withdrawal of consent, or until the start of next-line anti-cancer therapy, whichever occurs earlier (Section 1.3).

Radiological progression during add-on therapy should be confirmed by a second scan 4 to 12 wks apart. If progression is accompanied by new symptoms or deterioration of PS not attributed to toxicity one scan is sufficient.

Tumor responses will be measured by RECIST 1.1 / iRECIST and are to continue according to the schedule in patients who undergo complete trial treatment and in patients who discontinue treatment for reasons other than disease progression, consent withdrawal, or patient's withdrawal from the trial.

The same radiographic procedure used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same protocol for CT scan). An extra scan should be scheduled if clinically indicated.

The investigator will determine the tumor response based on the radiologist's measurement of all anatomic regions involved according to the RECIST 1.1 and iRECIST criteria and will make treatment decisions.

8.1.3 Blinded independent central review

Digital images from all tumor response assessments, including the screening scan(s), must be sent to the independent central review service as outlined in the imaging manual. Blinded centralized review and response assessment according to RECIST 1.1/iRECIST will take place on a continuous basis. The blinded tumor response evaluation will not be shared with the trial sites or have an influence on treatment decisions made by the investigator. Where patients have central PD verification in Arm 2 or Arm 3 prior to switching to add-on therapy, blinded tumor response evaluation will be permitted to be shared with trial sites.

8.1.4 Survival follow-up

After the last trial assessment (i.e., safety or efficacy whichever occurs last) information on survival status and new anti-cancer therapy (including but not limited to targeted therapy and immunotherapy) will be collected via phone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent for survival follow-up or the sponsor terminates the trial).

If a patient asks to be withdrawn from survival follow-up, this request must be documented in the source documents and signed by the investigator.

8.1.5 Patient-reported outcomes/quality of life

Patient-reported outcome (PRO)/quality of life (QoL) assessment questionnaire EORTC QLQ-C30, Patient Global Impression of Severity (PGIS) and Patient Global Impression of Change (PGIC) must be completed before any assessments are done, before the visit with the clinician and before any treatment is given.

All questionnaires will be filled out at selected time points during the trial as described in the respective schedule of events.

8.1.6 ECOG performance status

The ECOG PS of patients will be assessed by the investigator. ECOG PS should be assessed at screening, no later than 10 days prior to treatment start, and at each treatment visit or when there are apparent changes in PS.

ECOG PS will be assessed using scale shown in Table 8.

Table 8: Description of ECOG PS assessments

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

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group Performance Status.

8.2 Safety assessments

Planned time points for all safety assessments are provided in the respective SoAs (Section 1.3).

8.2.1 Physical examinations

Complete physical examinations will be performed at screening, at add-on baseline, and at EoT. Brief physical examinations will be performed at other time points (see the SoAs in Section 1.3).

Any abnormality identified at screening/baseline should be recorded in the General Medical History and Baseline Conditions eCRF. Changes from screening/baseline

abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as AEs in the AE eCRF.

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal and neurological systems.
- A brief (symptom-directed) physical examination includes an overall health judgment. In-depth physical examinations are required if obvious pathological signs are visible or in the case the patient states any signs or symptoms.

8.2.2 Height and body weight

Height will be measured at screening only and weight will be measured and recorded according to the SoA (Section 1.3).

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.3 Vital signs

Body temperature, pulse rate, respiratory rate, and blood pressure will be assessed at the times given in the SoA (Section 1.3).

All patients will be observed for at least 6 h after the first three administrations of BNT111 and the first administration of cemiplimab. A decision on a possible extension of the observation time to 24 h will be made at the discretion of the investigator at time of discharge.

In case a given patient tolerated the administration of the trial treatment without occurrence of significant inflammatory ADRs during the first three vaccinations (or during the next treatment cycle) of BNT111, an observation period of 2 to 4 h is acceptable at the discretion of the investigator. Prior to the dismissal of the patient, vital signs should be measured. From the second administration of cemiplimab, no observation time is stipulated with reference to cemiplimab (local protocol should be followed).

Blood pressure (systolic/diastolic, in mmHg) and pulse (in bpm) measurements will be assessed while the trial patient is in a supine position/at rest. If available, a completely automated device should be used, otherwise manual techniques can be used. The same method of measurement should be used for the trial patient during the course of the trial.

Blood pressure and pulse measurements should be preceded by at least 5 min of rest for the trial patient in a quiet setting without distractions (e.g., television, cell phones).

Vital signs to be taken before blood collection for laboratory tests.

Abnormalities observed at screening/baseline should be reported in the General Medical History. New or worsened clinically significant abnormalities observed at subsequent visits should be recorded in the AE eCRF.

8.2.4 Electrocardiograms

Single 12-lead electrocardiograms (ECG) will be obtained as outlined in the respective SoAs using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc (F) (QT interval corrected for heart rate according to the Fridericia formula) intervals.

The investigator must review the ECG, document this review, and record any clinically relevant changes occurring during the trial in the AE section of the eCRF.

8.2.5 Safety laboratory assessments

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

All clinical laboratory assessments will be analyzed centrally at the time points outlined in the respective SoAs. Local assessments will be carried out in order to make a decision on the dosing and as otherwise specified in the SoAs (Section 1.3). Centrally analyzed screening laboratory results must be obtained within 10 d prior to initiation of trial treatment, if not otherwise specified.

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

All laboratory tests with values considered clinically significantly abnormal during participation in the trial or within 90 days after the last dose of trial intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or the sponsor’s medical monitor. Unscheduled laboratory tests can be done locally, or sent to the central laboratory.

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

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

If local laboratory assessments require a change in patient management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the eCRF. If both central and local laboratory assessments are done at the same time, the highest grade of clinically significant abnormal findings will be reported and collected in the eCRF.

8.2.6 Viral serology

Viral serology screening will be performed using a commercially available kit at the times given in the SoA (Section 1.3).

The screen will test for hepatitis B core antibodies (anti-HBc), hepatitis B surface antigens (HBsAg), hepatitis surface antibodies (anti-HBs), HCV antibodies (anti-HCV). Additionally, HIV (1/2) testing is required if the patient has never been tested for HIV, or if testing was done prior to primary cancer diagnosis or performed ≥ 12 months prior to trial start.

8.2.7 Safety follow-up (SFU1 and SFU2)

Patients will be followed-up for safety assessments at two safety follow-up visits (SFU1 and SFU2) after last treatment, where all AEs and concomitant medications must be reported. If the patient is not able to attend the clinic due to his/her clinical condition, a phone call should be done to assess possible AEs.

The first safety follow-up visit (SFU1) takes place 30 (+ 5) days after last treatment and the second safety follow-up visit (SFU2) takes place 90 (±7) days after last treatment.

8.3 Adverse events and serious adverse events

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs and SAEs.

8.3.1 Time period and frequency for collecting adverse event and serious adverse event information

All AEs and SAEs will be collected from the first signing of the ICF until the SFU2 visit (90 days after last trial dose or until a new anti-cancer therapy is started) at the time points specified in the SoA (Section 1.3). Additionally, in case a new anti-cancer therapy is started within 90 days after last treatment, the safety follow-up visit should be performed just prior to starting the new anti-cancer therapy. Adverse events after start of new anti-cancer therapy do not need to be reported unless a causal relationship to BNT111-01 or cemiplimab is suspected.

All SAEs (initial and follow-up reports) will be recorded and reported to the sponsor or designee within the appropriate time frame and under no circumstance should this exceed 24 h after knowledge of the event, as indicated in Section 10.3.1.10. AESIs should also be reported within an appropriate time frame (i.e., no more than 24 h after knowledge of the event).

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

8.3.2 Method of detecting adverse events and serious adverse events

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

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

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each patient at subsequent visits/contacts. All 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 10.3.1.7.

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 the 90-day safety 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.

All ongoing AEs/SAEs will be followed until resolution, considered by the investigator to be stable or chronic (resolved with sequelae), the patient is lost to follow-up or the patient withdraws consent. If no final status is reached at SFU2 (90 days after last trial treatment), the investigator must confirm the unavailability of a final status.

8.3.4 Regulatory reporting requirements for SAEs

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

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a trial treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review boards (IRBs)/independent ethics committees (IECs), and investigators. The execution of expedited reporting to the different entities may be delegated as detailed in the trial-specific Safety Management Plan.

Safety reports will be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

For events related to IMPs, it is the sponsor’s or delegate’s responsibility to perform SUSAR reporting to the regulatory authority, the IRB/IEC and the other investigators as required by national law and applicable guidelines.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor should review it and then file it together with the IB. If required by local requirements, the investigator will notify the relevant IRB/IEC.

8.3.5 Pregnancy

Pregnant and breastfeeding women are excluded from participation in the trial. Any WOCBP must have a negative pregnancy test (beta-HCG) at baseline and be willing to use highly effective methods of contraception (less than 1% of unintended pregnancies per year, according to ICH M3) for the duration of trial treatment until 6 months after the last administration of the trial drug. Male patients must use an accepted contraceptive method for the duration of trial treatment and at least 6 months after the last administration of the trial drug.

If a pregnancy occurs during the trial and within 90 days after the last trial treatment, the investigator should inform the sponsor within 24 h of knowledge of the pregnancy and should follow the procedures outlined in Section 10.4.

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

8.3.6 Death events

Any death that occurs within the observation period (from the first signing of the ICF until 90 d after the last trial dose) will be reported as an SAE. A copy of an autopsy report should be submitted if available upon request. Date and cause of death will be recorded.

In case of a fatal event, the event term should not be “death” but the underlying event which led to death (death = outcome). If there is more than 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, the most likely reason for death should be documented as event term.

Deaths due to disease progression occurring **within 90 days** of the last trial treatment **must** be reported as a Grade 5 SAE. The AE term on the SAE form should be reported as “disease progression” of the disease under trial treatment, i.e., “progression of advanced/metastatic melanoma”. All deaths due to disease progression occurring after 90 days from the end of trial treatment will be reported on the trial-specific death page of the eCRF.

8.3.7 Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs

Non-fatal events that are clearly consistent with the expected pattern of progression of the underlying disease (e.g., new metastases) should **not** be recorded as AEs. These data will be captured as efficacy assessment data only and will be recorded on the tumor response evaluation pages in the eCRF. In most cases, the expected pattern of progression will be based on RECIST 1.1. In rare cases, the determination of clinical progression will be

based on symptomatic deterioration; however, every effort should be made to document progression using objective criteria.

If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an AE.

Note: Symptoms resulting from the progression and clearly stated as related to the PD will not be documented as AEs nor reported as SAEs. However, specific symptoms at time of progression that may be caused by other reason and death due to disease progression, will have to be documented as AEs and reported as SAEs if applicable.

8.3.8 Immune-related adverse events

irAEs are defined in Appendix 12.1. The investigators are asked to pay special attention to the detection and reporting of irAEs and their relationship to either of the treatments.

8.4 Adverse events of special interest

An AESI, serious or non-serious, is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor are appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (e.g., regulators) might also be warranted.

The following AEs should be reported if related to cemiplimab:

- Grade ≥ 2 infusion-related reactions are considered AESIs and must be reported within 24 h of identification by the investigator.
- Grade ≥ 3 irAEs are considered AESIs and should be reported within 24 h of identification by the investigator.

Note: An irAE can occur shortly after the first dose or several months after the last dose of treatment. All AEs of unknown etiology associated with drug exposure should be evaluated to determine possible immune etiology. If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an AE as an irAE.

AESI including non-serious AESI should be reported via the SAE Report Form according to the timelines and contact details given in Section 10.3.1.10 of this protocol. For non-serious AESI, the seriousness criterion should not be reported/selected as these non-serious AESIs are to be reported according to the timelines of SAEs, but mostly do not have the seriousness of an SAE.

8.5 Treatment of overdose

For this trial, accidental or intentional overdose is defined as at least two times the intended dose of trial treatment within the intended therapeutic window, if associated with an AE.

In the event of an overdose, the investigator should:

- Contact the medical monitor immediately (within 24 h).
- Closely monitor the patient for any AE/SAE and laboratory abnormalities.
- 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 medical monitor based on the clinical evaluation of the patient.

8.6 Pharmacokinetics

Not applicable.

8.7 Pharmacodynamic

Blood samples will be collected from all trial patients at time points shown in the respective SoAs (Section 1.3) to characterize pharmacodynamic markers (e.g., IFN-α, IFN-γ, IL-6, IL-10, IP-10, TNF-α, and IL12p70 cytokine levels) under treatment with BNT111 and cemiplimab in combination or as single agents.

Detailed information about the handling, labeling, and shipment of samples for pharmacodynamic analysis will be provided in a separate document (i.e., Laboratory Manual).

8.8 Genetics

Tumor tissue will be collected from all trial patients in order to retrospectively evaluate tumor mutational burden as potential outcome-predictive biomarker. Mutational analysis will be performed by use of predefined gene panels addressing only somatic mutations.

An optional whole blood sample will be collected in order to perform pharmacogenomics analyses if the patient has consented to this using the ICF. Respective analyses will be performed by use of whole exome sequencing, whole genome sequencing and/or genotyping analyses of genomic DNA (including germline variants). Detailed information about the handling, labeling, and shipment of samples for genetic analysis will be provided in a separate document (i.e., Laboratory Manual).

8.9 Biomarkers

Participation in the biomarker sub-study is possible even if no paired biopsies are feasible. Tumor tissue will be collected from all trial patients in order to retrospectively test BNT111

target antigen expression, and potential outcome-predictive biomarkers and immune signature molecules (e.g., PD-L1 expression) at screening.

For patients in Arms 1 or 2, or add-on treatment at selected trial sites:
Blood samples will be collected from trial patients after randomization to Arm 1, 2, or add-on treatment, at subsequent time points shown in the respective SoAs (Section 1.3) in order to isolate PBMCs for analysis of cellular immune responses.

In addition, when feasible and consented, paired biopsies will be performed at screening and approximately 6 to 8 wks after treatment start (and optionally at progression) to collect fresh tumor tissue. The fresh tumor tissue (non-FFPE material) will be collected in order to investigate anti-tumor specific activity within the tumor under treatment compared to before treatment by e.g., functional T cell tests (e.g., enzyme-linked immunospot [ELISpot], cytotoxicity assays with autologous tumor cell lines), phenotypic characterization of TILs and analysis of TCR repertoire (by e.g., RNA sequencing). The tumor sample can be from a core biopsy or from resected tumor tissue. Fine needle aspirates and cytological specimens are not acceptable. In patients who have had biopsies taken during BNT111 monotherapy, the number of biopsies during add-on is to be adjusted as appropriate (up to three in total during the duration of the trial). For patients who are part of the biomarker sub-study (Arms 1 or 2, or add-on treatment), if a biopsy is not taken at baseline prior to the first dose of BNT111, no subsequent biopsies are to be taken during the trial as part of the biomarker sub-study procedures. It is recommended to perform the biopsy on progression only if 4 wks or more have elapsed since the last biopsy (on-treatment biopsy). If the time is shorter, no biopsy on progression should be taken.

For all trial sites, if any biopsies or resections are to be performed as part of standard clinical care, tissue samples from such procedures should be provided (if feasible) for the sponsor for biomarker testing.

The biomarker parameters will be analyzed by different laboratories (central laboratory and specialty laboratories). Detailed information about the handling, labeling, and shipment of samples and biomarker analysis will be provided in separate documents (i.e., Laboratory Manual). Samples for future research purposes will be retained for use for up to 5 years after the end of this clinical trial.

8.10 Immunogenicity assessments

Analysis of cellular immune responses in peripheral blood under treatment compared to the response at screening will be performed by functional T cells tests (e.g., ELISpot) and phenotypic characterization of tumor-antigen-specific T cells (e.g., flow cytometry). For the latter, an additional blood sample will be collected for characterization of the respective HLA types. For detailed information about the handling, labeling, and shipment of samples and biomarker analysis will be provided in separate documents (i.e., Laboratory Manual).

8.11 Blood collection

The blood volumes taken per patient are described below:

Central safety laboratory

Table 9: Overview of blood collection for safety assessments (Central Safety Laboratory)

Material/time point	Screening	Baseline (C1D1)	C1D8 to C2D15	C3D1	Every cycle CnD1 (3 wks)	At progression or EoT	SFU1
Blood volumes	25 mL	12 mL	12 mL per visit (6 visits in total)	12 mL	12 mL	25 mL	25 mL

Abbreviations: CnDn = cycle "n", day "n"; EoT = end of treatment; SFU = safety follow-up; wks = weeks.

Blood volumes taken from patients at selected trial sites (Arm 1, 2 or add-on therapy only) for PBMC preparation (cellular immune response analyses) are shown in Table 10 and Table 11. All blood volumes are given in mL.

Table 10: Overview of blood collection for cellular immune response analysis in Arm 1 and Arm 2 (including patients entering Arm 2 add on therapy, selected trial sites only)

Treatment arm/ time points	Screening	C3D1	C5D1	C8D1	C14D1	C20D1	C26D1	C32D1	At progression or EoT
Arm 1	120 mL	60 mL	120 mL or LP [b]	60 mL	60 mL	60 mL	60 mL	60 mL	80 to 120 mL [c,d]
Arm 2 [a]	120 mL	60 mL	120 mL or LP [b]	60 mL	60 mL	60 mL	60 mL	60 mL	80 to 120 mL [c,d]

a For patients in Arm 2 entering add-on treatment, the blood collection should be continued as outlined above.
b Preferred option is leukapheresis (LP).
c 120 mL if EoT is prior to C5D1, if after C5D1 then only 80 mL blood to be drawn.
d After C5D1 no EoT blood draw if EoT is within two cycles (=6 wks) of any previous cellular immune response blood draw.

Abbreviations: CnDn = cycle "n", day "n"; EoT = end of treatment; wks = weeks.

Table 11: Overview of blood collection for cellular immune response analysis in Arm 3 add-on therapy (selected trial sites only)

Treatment arm/time points	Baseline add-on therapy	Add-on C3D1	Add-on C5D1	Add-on C8D1	Add-on C14D1	Add-on C20D1	Add-on C26D1	Add-on C32D1	EoT
Arm 3 Add-on therapy	120 mL	60 mL	120 mL or LP [a]	60 mL	60 mL	60 mL	60 mL	60 mL	100 mL [b]

a Preferred option is leukapheresis (LP).
b No EoT blood draw if EoT is within two cycles (=6 wks) of any previous cellular immune response blood draw.

Abbreviations: CnDn = cycle "n", day "n"; EoT = end of treatment; wks = weeks.

This trial will investigate an experimental medicine; therefore, the sponsor may decide to draw up to five additional blood samples for explorative biomarker/immunogenicity research purposes. Blood draw volumes may vary, but the total blood volume drawn at any single time point will not exceed 200 mL.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical hypotheses

The primary endpoint is ORR and the primary statistical objective is to demonstrate that the ORR of BNT111 + cemiplimab is greater than CCI using an overall significance level of CCI

CCI

Regarding Arms 2 and 3, i.e., single-agent BNT111 and cemiplimab, respectively, the primary endpoint ORR will be analyzed descriptively in a non-confirmatory sense in order to obtain an estimate for the single-agent anti-cancer activity. No formal statistical comparisons between treatment groups will be performed and no statistical hypothesis is defined. Hence, no further adjustments are required to control the overall type I error.

9.2 Sample size determination

The original sample size calculation for the BNT111 + cemiplimab group (Arm 1) is based on the following specifications and assumptions:

CCI

Based on these specifications, at least CCI

CCI

CCI patients are planned to be randomized into the BNT111 + cemiplimab group. The assumed true effect size for ORR is based on preliminary data of the ongoing Phase I Lipo-MERIT trial with a selected population of patients with melanoma.

After the originally planned interim analysis (IA1), where there were CCI patients in the BNT111 + cemiplimab group, one additional interim analysis (IA2) will be performed. IA2 will assess efficacy after CCI of the planned number of CCI patients are response evaluable (i.e., having at least two post-screening tumor assessments or

discontinued before) in the BNT111 + cemiplimab group. Given [redacted]

The sample size calculation for the calibrator groups (i.e., single-agent BNT111 and cemiplimab, respectively) [redacted]

This sample size is based on both practical and clinical considerations, rather than statistical justification.

9.3 Analysis sets

The following analyses sets are defined in Table 12.

Table 12: Analysis sets

Analysis Set	Description
Screened set	The screened set is defined as all patients who signed the ICF.
ITT	The ITT set is defined as all patients who are randomized.
mITT	The mITT set is defined as all patients who are randomized, had at least one dose of trial treatment and have a baseline and at least one post-randomization tumor response assessment.
Safety set	The safety set is defined as all patients who received trial treatment (i.e., at least one dose of BNT111 or cemiplimab).
PPS	The PPS is defined as all patients who received trial treatment and fulfil the following criteria: • The absence of any important protocol deviations that could affect the primary efficacy analysis. • The completion of a minimal exposure to the treatment of one cycle. • Availability of baseline and at least one on-treatment / post-randomization tumor assessment. Important deviations will lead to an exclusion of patients from the PPS and will be agreed at the data review meeting prior to database snapshot for the primary analysis. Protocol deviations that may be considered important will be specified in the SAP.

Abbreviations: ICF = informed consent form; ITT = intent-to-treat; mITT = modified intent-to-treat; PPS = per protocol set; SAP = statistical analysis plan.

The primary and secondary efficacy analyses will be performed [redacted]

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 randomized to ('as randomized'), unless stated otherwise.

9.4 Statistical analyses

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

The SAP will be finalized prior to database snapshot for the primary analysis and before a substantial amount of data have been collected (within approximately 3 months after first patient in). The SAP will include a more technical and detailed description of the statistical analyses described in this section. Any deviations from the planned analyses described in the final SAP will be described and justified in the clinical trial report. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1 General considerations

In general, the statistical analysis will be performed by treatment group. Additionally, for each calibrator arm the secondary analyses will be performed based on subsequent single-agent treatment following progression.

Continuous variables will be summarized by treatment group using the following descriptive statistics: number of patients (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 will be analyzed using Kaplan-Meier methodology by treatment group and censored in accordance with the FDA Guidance: "Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics" and the EMA guidance "Guideline on the evaluation of anticancer medicinal products in man". Censoring rules will be defined in the SAP.

The median survival time including two-sided 95% confidence limits according to (Brookmeyer and Crowley 1982) and the first and third quartile will be presented for each treatment group. Survival rates including two-sided 95% confidence interval based on Greenwood's formula (Greenwood 1926) as well as the number and percentage of patients with events, censored and under risk will be displayed for selected time points (e.g., at 3, 6, 12 months).

The time-to-event analysis will be illustrated using Kaplan-Meier plots by treatment group and strata.

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

Tumor response assessments will be performed every 6(±1) wks for the first 3 months following the randomization, every 9(±1) wks for the next 9 months, and every 12(±2) wks thereafter. Tumor response will be assessed by investigator as well as by BICR of radiographic images and will be measured using RECIST 1.1 and iRECIST. The primary analysis will be based on BICR using RECIST 1.1, while investigators assessment and assessments based on iRECIST will be considered as secondary/exploratory analysis.

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

9.4.2 Primary endpoints

CCI [redacted]

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

The primary endpoint ORR is based on independent read using RECIST 1.1 criteria. The ORR based on iRECIST criteria will be evaluated as exploratory analysis. The ORR based on investigator's criteria will be evaluated as exploratory analysis.

ORR will be summarized with absolute and relative frequencies along with two-sided 95% Clopper-Pearson confidence intervals by treatment group. The statistical hypotheses defined in Section 9.1 will be tested using CCI [redacted]
CCI [redacted]

CCI [redacted]

CCI [redacted] The IA1 for efficacy has been performed after there were CCI [redacted] of the planned number of CCI [redacted] patients. IA1, which was based on CCI [redacted] patients in the BNT111 + cemiplimab group, has been performed at a one-sided CCI [redacted] significance level and required an ORR of at least CCI [redacted] to show statistical significance. IA2 will be performed after approximately CCI [redacted] of the planned number of CCI [redacted] patients are response evaluable (i.e., having at least two post-screening tumor assessments or discontinued before). The minimal statistically significant ORR at IA2 will be CCI [redacted] i.e., the smallest ORR that will result in a statistically significant p value of CCI [redacted] The final analysis will be performed once all the planned CCI [redacted] patients in Arm 1 are response evaluable (i.e., having at least three post-screening tumor assessments or discontinued before). The minimal statistically significant ORR at final analysis would be CCI [redacted] i.e., the smallest ORR that will result in a statistically significant p value of CCI [redacted] is [redacted]

The operational characteristics of IA1, IA2, and the final analysis of ORR are summarized in Table 13.

Regarding the calibrator arms (i.e., single-agent BNT111 and cemiplimab, respectively) the primary endpoint ORR will be analyzed descriptively in a non-confirmatory sense in order to obtain an estimate for the single-agent anti-cancer activity. No formal statistical comparisons between treatment groups will be performed. Hence, no further adjustments are required to control the overall type I error.

9.4.3 Secondary endpoints

The secondary analyses will be performed using the CCI set.

The secondary endpoints related to tumor assessments (e.g., DCR, DOR, PFS) are based on independent read using RECIST 1.1 criteria. The endpoints based on iRECIST criteria will be evaluated as exploratory analysis. The endpoints based on investigator's criteria will be evaluated as exploratory analysis.

Disease control rate

DCR is defined as the proportion of patients in whom a CR or PR or SD (SD assessed at least 6 wks [+/- 1 wk] after first dose) is observed as best overall response. Patients not meeting the criteria for CR or PR or SD, including those without any post-randomization tumor assessments, will be considered as non-responders.

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

Time to response

TTR is defined as the time from randomization to first objective response (CR or PR). Only patients in whom a CR or PR is observed will be analyzed for TTR.

TTR will be analyzed using summary statistics by treatment group.

Duration of response

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

DOR will be analyzed using Kaplan-Meier methodology by treatment group. 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 randomization to first objective tumor progression (PD according to RECIST 1.1), or death from any cause, whichever occurs first.

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

Overall survival

OS is defined as the time from randomization to death from any cause.

OS will be analyzed using Kaplan-Meier methodology by treatment group. Patients alive or patients lost to follow-up at 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.

Health-related quality of life

HRQoL will be measured by EORTC QLQ-C30 using PGIS and PGIC for calibration

HRQoL will be assessed through changes from baseline in the global health status score and individual scores of the EORTC QLQ-C30 as well as first clinically meaningful deterioration in global health status score and individual scores of the EORTC QLQ-C30.

9.4.4 Exploratory endpoints

The exploratory analyses will be detailed in the SAP.

9.4.5 Safety analyses

Safety data that will be summarized includes AEs, safety laboratory parameters, vital signs and ECGs. All safety analyses will be based on the safety set and will be summarized descriptively by treatment group unless otherwise stated.

Adverse events

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

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 reduction
- AE leading to permanent discontinuation of treatment
- any irAE (listed in Appendix 12.1)

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

Laboratory parameters

Safety laboratory assessments to be summarized include hematology, blood chemistry, and urinalysis. The safety laboratory parameters to be assessed are listed in Section 10.2 and the scheduled time points for assessment are outlined in the SoAs (Section 1.3).

Safety 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.

Safety laboratory results will be classified according to the most recent version of NCI-CTCAE. Shift tables from baseline to worst grade on treatment will be provided for each laboratory parameter by treatment group.

Additionally, the occurrence of clinically significant abnormal laboratory results within a patient will be analyzed using descriptive summary statistics for each parameter and visit by treatment group.

Laboratory results will be listed along with the normal ranges and NCI-CTCAE grade. Laboratory values that are below or above the normal ranges will be flagged.

Vital signs

Vital sign parameters and the scheduled time points for assessment are presented Section 8.2.3 and Section 1.3.

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.

Additionally, the occurrence of abnormal vital sign results within a patient will be analyzed using descriptive summary statistics for each parameter and visit by treatment group.

ECG

ECG parameters and the scheduled time points for assessment are presented in Section 8.2.4 and Section 1.3.

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 visit.

9.4.6 Other analyses

Other analyses including treatment exposure will be detailed in the SAP.

9.5 Interim analyses and analysis sequence

The IA1 for efficacy has been performed after there were CCI of the planned number of CCI patients in Arm 1.

The IA2 for efficacy will be performed after CCI of the planned number of CCI patients in Arm 1 are response evaluable (i.e., having at least two post-baseline tumor assessments or discontinued before).

The primary analysis of the trial will be performed based on all available data from a clinical data cut-off that will occur when all the planned CCI patients in Arm 1 are response evaluable (i.e., having at least three post-baseline tumor assessments or discontinued before).

An analysis update will be performed when the last patient discontinued from the trial and once all patients have been randomized and have been followed-up for at least 24 months. An analysis update may be subsequently performed.

Further details will be specified in a separate IDMC Charter.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Regulatory, ethical, and trial oversight considerations

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

10.1.1 Regulatory and ethical considerations

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

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

The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) will be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the trial is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate hazard to trial patients.

The investigator will be responsible for the following:

- Providing written summaries of the status of the trial to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the trial at the trial site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 (if applicable), and all other applicable local regulations.

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

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

10.1.2 Financial disclosure

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

10.1.3 Informed consent process

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

Patients must be informed that their participation is voluntary.

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

The ICF must be signed prior to performance of any trial-related activity. The ICF that is used must be approved both by the sponsor and by the reviewing IRB/IEC.

The medical record must include a statement that written informed consent was obtained using the ICF before the patient was enrolled in the trial and the date the written consent

was obtained. The authorized person obtaining the informed consent must also sign the ICF.

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

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

Patients who are rescreened must sign a new ICF.

Patients will be informed in their native language, comprehensive, concise, clear, relevant, and understandable to a layperson, that their participation is voluntary and that they are free not to participate in the trial and may withdraw consent to participate at any time. They will be told which alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that their records may be examined by competent authorities and authorized persons but that their personal data will be treated as strictly confidential and will not be publicly available. Patients must be given the opportunity to ask questions.

10.1.4 Data protection

Patients will be assigned a unique identifier by the investigator according to the sponsor specifications on unique identifier assignment. Any patient records or datasets that are transferred to the sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.

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

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

10.1.5 Committee's structure (IDMC)

An IDMC will be established to review the interim efficacy and safety results. The frequency will be based on the number of enrolled patients and will occur at least once every 3 months for the first year and every 6 months thereafter. In addition, an ad hoc IDMC meeting will be performed once the first ten patients in Arm 1 have been treated for at least two cycles or discontinued treatment for any reason during the first two cycles.

The board will act according to its own written rules described in a charter and will prepare written minutes of its meetings including the recommendations of the IDMC, that will be provided to the sponsor for evaluation.

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

10.1.7 Data quality assurance

All patient data relating to the trial will be recorded on the 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., CRO).

Trial monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized trial site staff 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 15 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. At a minimum, source documentation must be available to substantiate proper informed consent procedures, adherence to protocol procedures, adequate reporting and follow-up of AEs, administration of concomitant medications, drug receipt/dispensing/return records, and trial drug administration information.

Source data are all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

Source documents are original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, patient diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, patient files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

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 starts recruitment of patients.

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

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

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

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

If the trial is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any CROs 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 multi-site trials 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.

10.1.11 Protocol preparation and approval

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

10.2 Safety laboratory tests

The planned safety laboratory tests are outlined in Table 14.

Table 14: Safety laboratory tests

Laboratory assessment	Parameter	
Hematology	WBC count with differential	Neutrophils
		Lymphocytes
		Monocytes
		Eosinophils
		Basophils
	RBC count	Platelets
		Hemoglobin
		Hematocrit
	RBC indices	MCV
		MCH
		MCHC
Clinical chemistry	Electrolytes	Sodium
		Calcium
		Chloride
		Phosphate
		Potassium
		Magnesium
	Alkaline phosphatase	
	Total protein	
	Albumin	

Laboratory assessment	Parameter	
	Lipase	
	CK	
	LDH	
	Amylase	
	CRP	
	Bicarbonate or carbon dioxide	
	Glucose	
	Renal function tests	BUN or urea, creatine, uric acid, calculated eGFR
	Liver function test	Total bilirubin
		AST
		ALT
Coagulation factors	PT, aPTT, INR	
Endocrine tests	TSH, T4	
Serology	Hepatitis B: HBsAg, anti-HBc, anti-HBs	
	Hepatitis C: anti-HCV	
	HIV: anti-HIV 1/2	
Other tests	Highly sensitive serum or urine hCG pregnancy test in WOCBP	
Urinalysis	pH, specific gravity, glucose, protein, ketones, blood, bilirubin, urobilinogen, nitrite, leukocyte esterase	

Abbreviations: anti-HBc = hepatitis B core antibodies; anti-HBs = hepatitis surface antibodies; aPTT = activated partial thromboplastin time; ALAT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CRP = C-reactive protein; CK = creatine kinase; eGFR = estimated glomerular filtration rate; HBsAg = hepatitis surface antigen; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; HIV = human immunodeficiency virus; INR = international normalized ratio; LDH = lactate dehydrogenase; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PT = prothrombin time; RBC = red blood cell; T4 = free thyroxine; TSH = thyroid-stimulating hormone; WBC = white blood cell; WOCBP = women of childbearing potential.

10.3 Adverse events: Definitions and procedures for recording, evaluating, follow-up, and reporting

10.3.1 Definition of AE

AE definition

An AE is any untoward medical occurrence in a patient or clinical trial patient, administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the 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 trial treatment (if the AE was absent before the first administration of trial treatment) or worsened after the first administration of trial treatment (if the AE was present before the first administration of trial treatment). AEs with an onset date more than 90 days after the last administration of trial treatment will be considered as treatment-emergent only if assessed as related to IMP by the investigator.

10.3.1.1 Events meeting the AE definition

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

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

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

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

Signs, symptoms, or the clinical sequelae of a suspected overdose of either trial treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE.

10.3.1.2 Events not meeting the AE definition

Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient's condition.

The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient's condition.

Exceptions: All deaths due to disease progression occurring within 90 days of the last trial treatment **must** be reported as SAEs. Specific symptoms at time of progression that may be caused by other reason (unrelated to progression) 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.

10.3.1.3 Suspected adverse reaction (suspected AR)

All untoward and unintended responses related to any of the IMPs or their administered dose solutions.

The definition covers also medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product.

The definition implies a reasonable possibility of a causal relationship between the event and the IMP. This means that there are facts (evidence) or arguments to suggest a causal relationship.

10.3.1.4 Definition of a serious adverse event

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under trial).

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

- Results in death
- Is life-threatening

  The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization
  - In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether “hospitalization” occurred or was necessary, the AE should be considered serious.
  - Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- Results in persistent disability/incapacity
  - The term disability means a substantial disruption of a person’s ability to conduct normal life functions.
  - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect.

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

10.3.1.5 Suspected unexpected serious adverse reactions

All suspected ARs related to an IMP that occur in this trial, and that are both unexpected and serious are 'suspected unexpected serious adverse reactions' or SUSARs. SUSARs are subject to expedited reporting.

10.3.1.6 Use of the terms "severe" and "serious"

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (e.g., rated as mild, moderate, or severe, or according to NCI-CTCAE); see Section 10.3.1.7 for guidance on the assessment of intensity; the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

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

SAEs must be reported by the investigator to the sponsor within 24 h after knowledge of the event; see Section 10.3.1.10 for reporting instructions).

10.3.1.7 Recording and follow-up of adverse events and/or serious adverse events

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 (refer to Section 8.3.1).

- 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 NCI-CTCAE v5.0
  - Seriousness
  - Outcome
  - Causal relationship of the AE to the trial treatment/trial procedure
  - Any trial treatment action and/or any other action taken
- All assessments as well as AE term (diagnosis/description), start date and time of onset, end date and time need to be documented in the eCRF.
- There may be instances when copies of medical records for certain cases are requested by the sponsor. In this case, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before submission to the sponsor.
- To avoid colloquial expressions, the AE should be reported in standard medical terminology. The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE. If a definitive diagnosis is not possible, the individual signs and symptoms should be recorded.

Assessment of intensity

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

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
- Grade 2 – Moderate
- Grade 3 – Severe
- Grade 4 – Life-threatening consequences; urgent intervention indicated
- Grade 5 – Death related to AE

With regards to the intensity of an AE the following needs to be documented in the patient's notes and recorded in the eCRF:

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

A change of intensity only needs to be documented if there is a clearly definable change in grading of the AE (e.g., a laboratory result changes from severe to moderate according to NCI-CTCAE v5.0 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 (prepared from IMPs) by the investigator:

- Dose not changed (= continuation of trial treatment administration according to the trial protocol)
- Dose reduced
- Drug interrupted:
  - Delayed administration of trial treatment within one cycle
  - Delayed start of the next treatment cycle
  - Cancellation of administration at a given visit
  - Interruption of trial treatment administration during a given visit
- Drug 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)

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

- None
- Initiation of a concomitant medication for the treatment of the AE

- Termination of a concomitant medication (please specify; e.g., if this might be the cause of the AE)
- Change of the dose of a concomitant medication
- Hospitalization or prolongation of hospitalization (please complete the SAE Form)
- Initiation/termination of a non-drug therapy

Outcome

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

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

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

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

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

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

Assessment of causality

The investigator is obligated to assess the relationship between trial treatment/trial procedure and each occurrence of each AE/SAE.

The investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to trial treatment administration will be considered and investigated.

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

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

Relationship to trial treatment

The relationship or association of an AE or SAE should be assessed separately for each of the trial drugs by the investigator after having evaluated all accessible data and, if necessary, he/she will re-evaluate the case as new information becomes available.

If the investigator feels that the event cannot be firmly attributed to one of the trial drugs, then the same assessment should be documented for each trial drug.

Events caused by the procedure of trial treatment administration should be differentiated from events caused by the trial treatment itself. Only events suspected to be caused by the trial treatment itself should be documented as suspected ARs but not events caused by procedure of trial treatment administration.

Relationship to trial procedures

In this trial, it cannot be excluded that during the course of the trial some procedures give rise to AEs which are related to the trial procedure and not to the trial treatment. Procedure related AE can occur on the site of injection of the trial treatment e.g., redness, swelling, hematoma or itching or during or after trial-specific procedure, e.g., discomfort after blood drawing. These events have to be reported in the eCRF on AE 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.

Applicable for all categories

There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.

The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

10.3.1.8 Serious adverse event exemptions

In general, SAEs are defined according to ICH Topic E2A (CPMP/ICH/377/95), EU Directive 2001/20/EC and ENTR/CT-3 (see Section 10.3.1.4). In the present trial, some events are excluded from the SAE definition. The following events do not need to be reported as SAEs:

- SAEs occurring later than the SFU2 visit (see Section 1.3) 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.
- 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 an SAE (but needs to be documented as AE).
- 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 (unless the intervention/procedure is not caused by an acute worsening of the pre-existing condition during the time trial participation).
  - if it was planned and documented in patient record before the trial-specific patient informed consent was signed (ICF for trial participation, see Section 10.1.3, or
  - if it was scheduled during the trial when elective surgery became necessary and the patient has not experienced an AE.

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

- The progression of underlying disease (e.g., new metastases) during trial participation is not considered as AE. However, specific symptoms at time of progression that may be caused by other reason, and fatal cases where other reason rather than the PD may not be discarded, have to be documented as AEs and reported as SAEs if applicable.
- Routine treatment or monitoring of the underlying disease not associated with any deterioration in the patient’s condition.

10.3.1.9 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.

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 medications). 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.

10.3.1.10 Reporting of serious adverse events

All SAEs which occur in a patient during the observation period, whether considered to be associated with trial treatment or not, must be reported by the investigator to the sponsor 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 within the appropriate time frame if the investigator suspects a relationship to trial treatment or the trial procedure.

SAE reporting to the sponsor using a paper (SAE report) form

For the period of observation please refer to Section 8.3.1.

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

- Safety report fax no.:
- 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 site identification)
- An event or outcome that can be identified as serious

SAE follow-up information should be sent to the sponsor (indicating that this is a “follow-up” report using the SAE Form or the Additional Information and Follow-Up Form) without delay as described above and accompanied by appropriate anonymous supporting documentation (e.g., discharge letters, medical reports or death certificates), until a final outcome and date are available. All confidential information (name, address, full day of birth) needs to be blackened before sending. In addition to a medical record, the investigator should complete an Additional Information and Follow-Up Form, which contains the SAE term and patient number.

A copy of the submitted SAE report must be retained on file by the investigator. If explicitly required according to national legislation, the investigator must submit copies of the SAEs to the IRB/IEC or authority and retain documentation of these submissions in the Site Trial File.

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

- E-mail:

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

10.4 Contraceptive guidance and collection of pregnancy information

10.4.1 Definitions

Definition of reproductive potential and measures of contraception for BNT111 are detailed below. Further guidance for other trial treatments should be according to the authorized product information (for approved concomitant medications).

Female patients

In this trial, female patients are considered to be WOCBP, **unless** they are post-menopausal or permanently sterile:

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

All female patients must agree not to donate eggs (ova, oocytes) for the purpose of assisted reproduction during the trial and for 6 months after receiving the last dose of BNT111.

Female patients of reproductive potential must agree to use adequate contraception during and for 6 months after the last BNT111 administration. Adequate contraception is defined as highly effective methods of contraception (Table 15). Birth control methods are considered highly effective if they have a failure rate of less than 1% per year, when used consistently and correctly.

The investigator or delegate should advise the patient how to achieve effective contraception as outlined in Table 15.

Table 15: 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 Clinical Trial Facilitation Group (CTFG)-meeting in Rome 2014 (CTFG 2014).

Male patients

Recommendations for male patients with pregnant partner:

Male contraception (condom) is recommended in order to avoid exposure of an existing embryo/fetus. Contraception should be continued for 6 months after receiving the last dose of BNT111.

Recommendations for male patients with non-pregnant WOCBP partner:

The male patient should use condom during treatment and for 6 months after receiving the last dose of BNT111. For a non-pregnant WOCBP partner, contraception recommendations should also be considered.

Male patients must also not donate sperm during the trial and for 6 months after receiving the last dose of BNT111.

10.4.2 Collection of pregnancy information

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

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

The initial and follow-up information must be documented on the paper-based Pregnancy Reporting Form and submitted to the sponsor within 24 h of knowledge of a patient's pregnancy/partner's pregnancy. The completed form needs to be sent to the Safety Report Fax number or E-mail given in Section 10.3.1.10. Completed pregnancy forms must be signed by an investigator before faxing/mailing them to the sponsor. Blank reporting forms are provided to the investigator during the site initiation visit and are filed in the investigator's site file (ISF).

The investigator will collect follow-up information on the patient/patient's partner and the neonate and the information will be forwarded to the sponsor. Pregnancy follow-up should describe the outcome of the pregnancy, including any voluntary or spontaneous

termination, details of the birth, the presence or absence of any congenital abnormalities, birth defects, maternal or newborn complications and their presumed relation to the IMPs. Generally, the follow-up will be of a duration determined in consultation with the pediatrician.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.

A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-trial pregnancy related SAE considered reasonably related to the trial intervention by the investigator will be reported to the sponsor within the appropriate time frame. While the investigator is not obligated to actively seek this information in former trial patients, he or she may learn of an SAE through spontaneous reporting.

10.5 Genetics

Genetic analyses will be performed as outlined in Section 8.8.

10.6 Liver safety: suggested actions and follow-up assessments

Based upon data from other studies using RNA-LPX formulations (refer to the BNT111 IB), the sponsor does not expect to encounter any liver safety issues.

For cemiplimab, please refer to the locally approved label.

10.7 Investigators and trial administrative structure

10.7.1 Investigators and trial site personnel

There must be an investigator at each trial site.

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

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

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

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

10.7.2 Trial site personnel assigned trial-related duties

The principal investigator may define appropriately qualified personnel at a trial site to perform significant trial-related procedures and/or to make trial-related decisions under

his/her supervision. In this case, the principal investigator must maintain a signed list of the persons to whom they delegate significant trial-related duties/responsibilities; the delegated trial-related duties/responsibilities must be specified in the list.

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

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

10.7.3 Contract research organizations

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

10.7.4 The sponsor and sponsor’s personnel

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

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

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

10.8 Country-specific requirements

Country-specific requirements will be met; specific information is not available as the sites have not yet been defined.

10.9 Other standard abbreviations and definitions

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

For definitions related to safety, see Section 10.3.

Abbreviation	Explanation
AE	Adverse event
CFR	(US) Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CRO	Contract research organization
d	Day(s)
eCRF	Electronic case report form
GCP	Good Clinical Practice
h	Hour(s)
ICF	Informed consent form
ICH	International Conference on Harmonisation (of technical requirements for registration of pharmaceuticals for human use)
IDMC	Independent data monitoring committee
IEC	Independent ethics committee
IMP	Investigational medicinal product
IRB	Institutional review board
(ir)RECIST	(Immune-related) Response Evaluation Criteria in Solid Tumors
ISF	Investigator's site file
min	Minute(s)
NCI-CTCAE	US National Cancer Institute Common Terminology Criteria for Adverse Events
PRO	Patient-reported outcomes
QoL	Quality of life
SAE	Serious adverse event
SoA	Schedule of activities
SOP	Standard operating procedure (used as synonym for all procedural documents)
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TMF	Trial master file
US	United States (of America)
Wks	Week(s)
WOCBP	Women of childbearing potential

10.10 Protocol amendments

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 TMF.

10.10.1 Protocol amendment no. 01

Amendment rationale

The trial protocol was amended on 03 NOV 2020. The key changes were:

- Clarification of secondary endpoint on PRO/QoL measurements
- Clarification on the add-on therapy (requirement for central verification of radiological progression prior to inclusion to add-on treatment)
- Addition and clarification of inclusion and exclusion criteria: exclusion criterion on prior malignancy added and criteria for add-on treatment further specified
- Specific TEs and an additional IDMC review after 10 patients (after two treatment cycles) in Arm 1 added to Section 7.4

This amendment was issued before any trial subjects were enrolled into the trial.

10.10.2 Protocol amendment no. 02

Amendment rationale

This amendment implements changes that were required based on comments from the Medicines and Healthcare products Regulatory Agency (MHRA). The key changes were:

- Wording in Sections 4.1.1 and 4.1.3 regarding sponsor involvement in determination of trial eligibility in removed
- Amendment of inclusion criterion 10 in regard to patients with BRAF-V600-positive tumor(s)
- Amendment of exclusion criterion 10 in regard to Grade 2 neuropathy
- Table 3 in Section 6.8.3 updated to align with current version of the cemiplimab SmPC

This amendment was issued before any trial subjects were enrolled into the trial.

10.10.3 Protocol amendment no. 03

Amendment rationale

The trial protocol was amended on 03 MAR 2021. This amendment implements changes that were required based on comments from the Paul-Ehrlich-Institute (PEI) on 16 FEB 2021. The key changes were:

- Amendment of key exclusion criterion in Section 1.1 and exclusion criterion #8 in Section 5.1.2 to define the time-span of prior/concomitant therapy
- Amendment of Sections 1.3.1 and 1.3.2 which now requires for WOCBP to have a pregnancy test at each cycle (every three weeks) before the application of trial treatment

This amendment was issued before any trial subjects were enrolled into the trial.

10.10.4 Protocol amendment no. 04

Amendment rationale

This amendment was generated in order to incorporate changes made in the country-specific clinical trial protocols (as described above) to a global protocol amendment. Additional changes also included:

- Patient randomization number increased and statistics amended (Sections 1.1 and 9)
- Benefits/risk section added in relation to COVID-19 vaccination
- Amendment of inconsistencies

10.10.5 Protocol amendment no. 05

Amendment rationale

This amendment was generated in order to incorporate the following substantial changes:

- Change in inclusion criterion 5 and removal of inclusion criterion 6 to make patients eligible if they have confirmed disease progression with an approved anti-PD-L1 regimen as an alternative to anti-PD-1
- Change in inclusion criterion 17 to make biopsies no longer mandatory for patients who are part of the biomarker sub-study
- Addition of a new row to SoA 1 to clarify that pharmacogenomic analyses should be carried out at screening
- Correction of some inconsistencies/additions of clarification to some sections

10.10.6 Protocol amendment no. 06

Amendment rationale

This amendment was generated in order to incorporate the following substantial changes:

- Sections 4.1.4, 8.3.1, SoA 1 footnote c, and SoA 2 footnote b was revised to include information on the safety follow-up in case a new anti-cancer therapy is started within 90 days after last treatment.

- Text was added to Section 8.9 to indicate optional biopsies in biomarker substudy.

10.10.7 Protocol amendment no. 07

This amendment was generated in order to incorporate the following substantial changes:

- A second interim analysis (IA2) which will be performed after approximately CCI of the planned number of CCI patients are response evaluable.
- Updates to allow that patients in Arm 3 who have entered add-on treatment are eligible to take part in the biomarker sub-study.
- Additional exclusion criterion (criterion 19).
- Dose modification schema for BNT111 was changed.
- Non-substantial updates throughout the CTP for clarity / further information or correction of inconsistencies were also implemented.

10.11 Data collection and management

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

10.11.1 Case report forms

eCRFs will be completed through use of an electronic data capture (EDC) system. Trial site personnel will receive training and have access to a manual for appropriate eCRF completion. The eCRFs will be submitted electronically to the sponsor via the system and should be handled in accordance with instructions from the sponsor.

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

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

10.11.2 Patient-reported outcomes

PROs will be collected after randomization as outlined in the SoAs (see Section 1.3). PROs will be provided to the trial site as printed copies as part of the ISF or electronically. At the given time points each patient has to complete all PROs by him/herself. PROs completed by the patient are considered as source documents. The investigator or designee must transfer the PROs data to the eCRF if provided on paper.

10.11.3 Data management

The data management activities of this trial, including quality checking of the data will be performed by the CRO (see the title page).

Data entered manually will be submitted to the sponsor through use of an EDC system, data extracts and reports. Trial sites will be responsible for data entry into the EDC system. In the event of discrepant data, the data management service provider will request data clarification from the trial sites, which the trial sites will resolve electronically in the EDC system.

The data management service provider will produce a Trial Data Validation Specification document that describes the quality checking to be performed on the data. eCRF entries and corrections will be documented and maintained in the EDC system's audit trail.

Central laboratory data will be sent directly to the data management service provider.

System backups for data stored by the sponsor and records retention for the trial data will be in accordance with regulatory requirements.

10.11.4 Investigator's Site File and the Trial Master File

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

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

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

10.12 Other data

10.12.1 Demographic data

At screening, the following demographic data will be recorded for all trial patients:

- Age (in years/months)
- Sex (male/female)
- Ethnic group

10.12.2 Medical history and underlying disease history

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

Medical history includes clinically significant diseases, surgeries, previous medical procedures, smoking history, use of alcohol and/or drugs of abuse, reproductive status, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or

homeopathic remedies, and nutritional supplements) used by the patient within 7 d prior to treatment start.

Underlying disease history should include histology, tumor, node, metastasis at diagnosis, prior anti-neoplastic therapies/procedures.

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12 APPENDICES

12.1 Appendix 1 Definition of irAEs

Table 16: List of irAEs definitions by MedDRA and composite terms

MedDRA Preferred Term	Composite Term
Addison's disease	Adrenal insufficiency
Adrenal androgen deficiency	Adrenal insufficiency
Adrenal atrophy	Adrenal insufficiency
Adrenal insufficiency	Adrenal insufficiency
Adrenal suppression	Adrenal insufficiency
Adrenocortical insufficiency acute	Adrenal insufficiency
Glucocorticoid deficiency	Adrenal insufficiency
Hypoaldosteronism	Adrenal insufficiency
Mineralocorticoid deficiency	Adrenal insufficiency
Primary adrenal insufficiency	Adrenal insufficiency
Secondary adrenocortical insufficiency	Adrenal insufficiency
Arthralgia	Arthralgia
Arthritis	Arthritis
Autoimmune arthritis	Arthritis
Immune-mediated arthritis	Arthritis
Polyarthritis	Arthritis
Rheumatoid arthritis	Arthritis
Autoimmune demyelinating disease	Autoimmune demyelinating disease
Demyelination	Autoimmune demyelinating disease
Autoimmune disorder	Autoimmune disorder
Autoimmune eye disorder	Autoimmune eye disorder
Blood alkaline phosphatase increased	Blood alkaline phosphatase increased
Blood creatine phosphokinase increased	Blood creatine phosphokinase increased
Blood thyroid-stimulating hormone decreased	Blood thyroid-stimulating hormone decreased
Blood thyroid-stimulating hormone increased	Blood thyroid-stimulating hormone increased
Central nervous system inflammation	Central nervous system inflammation
Chronic inflammatory demyelinating polyradiculoneuropathy	Chronic inflammatory demyelinating polyradiculoneuropathy
Cutaneous vasculitis	Cutaneous vasculitis
Duodenitis	Duodenitis
Encephalitis	Encephalitis

MedDRA Preferred Term	Composite Term
Autoimmune encephalopathy	Encephalitis
Encephalitis autoimmune	Encephalitis
Immune-mediated encephalitis	Encephalitis
Noninfective encephalitis	Encephalitis
Immune-mediated endocrinopathy	Endocrine disorder
Autoimmune endocrine disorder	Endocrine disorder
Episcleritis	Episcleritis
Gastrointestinal perforation	Gastrointestinal perforation
Guillain-Barre syndrome	Guillain-Barre syndrome
Basedow's disease	Hyperthyroidism
Hyperthyroidism	Hyperthyroidism
Marine Lenhart syndrome	Hyperthyroidism
Primary hyperthyroidism	Hyperthyroidism
Secondary hyperthyroidism	Hyperthyroidism
Thyrotoxic crisis	Hyperthyroidism
Thyrotoxic periodic paralysis	Hyperthyroidism
Toxic goitre	Hyperthyroidism
Toxic nodular goitre	Hyperthyroidism
Hypophysitis	Hypophysitis
Hypopituitarism	Hypopituitarism
Autoimmune hypothyroidism	Hypothyroidism
Hypothyroidic goitre	Hypothyroidism
Hypothyroidism	Hypothyroidism
Immune-mediated hypothyroidism	Hypothyroidism
Myxoedema	Hypothyroidism
Primary hypothyroidism	Hypothyroidism
Secondary hypothyroidism	Hypothyroidism
Tertiary hypothyroidism	Hypothyroidism
Immune-mediated adverse reaction	Immune-related adverse reaction
Autoimmune anaemia	Immune-related anaemia
Autoimmune aplastic anaemia	Immune-related anaemia
Autoimmune haemolytic anaemia	Immune-related anaemia
Acute haemorrhagic ulcerative colitis	Immune-related colitis
Allergic colitis	Immune-related colitis
Autoimmune colitis	Immune-related colitis

MedDRA Preferred Term	Composite Term
Autoimmune enteropathy	Immune-related colitis
Colitis	Immune-related colitis
Colitis erosive	Immune-related colitis
Colitis ischemic	Immune-related colitis
Colitis microscopic	Immune-related colitis
Colitis ulcerative	Immune-related colitis
Crohn's disease	Immune-related colitis
Diarrhea	Immune-related colitis
Diarrhea hemorrhagic	Immune-related colitis
Enterocolitis	Immune-related colitis
Enterocolitis hemorrhagic	Immune-related colitis
Eosinophilic colitis	Immune-related colitis
Immune-mediated enterocolitis	Immune-related colitis
Inflammatory bowel disease	Immune-related colitis
Necrotising colitis	Immune-related colitis
Neutropenic colitis	Immune-related colitis
Acute hepatic failure	Immune-related hepatitis
Autoimmune hepatitis	Immune-related hepatitis
Hepatic failure	Immune-related hepatitis
Hepatic function abnormal	Immune-related hepatitis
Hepatitis	Immune-related hepatitis
Hepatitis acute	Immune-related hepatitis
Hepatotoxicity	Immune-related hepatitis
Hyperbilirubinaemia	Immune-related hepatitis
Immune-mediated hepatitis	Immune-related hepatitis
Jaundice	Immune-related hepatitis
Liver injury	Immune-related hepatitis
Alanine aminotransferase increased	Immune-related hepatitis
Aspartate aminotransferase increased	Immune-related hepatitis
Blood bilirubin increased	Immune-related hepatitis
Gamma-glutamyltransferase increased	Immune-related hepatitis
Hepatic enzyme increased	Immune-related hepatitis
Liver function test abnormal	Immune-related hepatitis
Transaminases increased	Immune-related hepatitis
Autoimmune hyperlipidaemia	Immune-related hyperlipidaemia

MedDRA Preferred Term	Composite Term
Autoimmune inner ear disease	Immune-related inner ear disease
Blood creatinine increased	Immune-related nephritis
Glomerular filtration rate decreased	Immune-related nephritis
Acute kidney injury	Immune-related nephritis
Autoimmune nephritis	Immune-related nephritis
Chronic autoimmune glomerulonephritis	Immune-related nephritis
Immune-mediated nephritis	Immune-related nephritis
Lupus nephritis	Immune-related nephritis
Nephritis	Immune-related nephritis
Nephritis haemorrhagic	Immune-related nephritis
Perinephritis	Immune-related nephritis
Renal failure	Immune-related nephritis
Renal impairment	Immune-related nephritis
Tubulointerstitial nephritis	Immune-related nephritis
Tubulointerstitial nephritis and uveitis syndrome	Immune-related nephritis
Autoimmune neutropenia	Immune-related neutropenia
Autoimmune pancytopenia	Immune-related pancytopenia
Immune-mediated pancytopenia	Immune-related pancytopenia
Acute interstitial pneumonitis	Immune-related Pneumonitis
Autoimmune lung disease	Immune-related Pneumonitis
Immune-mediated pneumonitis	Immune-related Pneumonitis
Interstitial lung disease	Immune-related Pneumonitis
Pneumonitis	Immune-related Pneumonitis
Autoimmune retinopathy	Immune-related retinopathy
Rash pustular	Immune-related skin adverse reaction
Perineal rash	Immune-related skin adverse reaction
Acute generalised exanthematous pustulosis	Immune-related skin adverse reaction
Autoimmune dermatitis	Immune-related skin adverse reaction
Dermatitis	Immune-related skin adverse reaction
Dermatitis acneiform	Immune-related skin adverse reaction
Dermatitis bullous	Immune-related skin adverse reaction
Dermatitis exfoliative	Immune-related skin adverse reaction
Dermatitis exfoliative generalised	Immune-related skin adverse reaction
Drug eruption	Immune-related skin adverse reaction

MedDRA Preferred Term	Composite Term
Drug reaction with eosinophilia and systemic symptoms	Immune-related skin adverse reaction
Dyshidrotic eczema	Immune-related skin adverse reaction
Erythema	Immune-related skin adverse reaction
Erythema multiforme	Immune-related skin adverse reaction
Exfoliative rash	Immune-related skin adverse reaction
Immune-mediated dermatitis	Immune-related skin adverse reaction
Oculomucocutaneous syndrome	Immune-related skin adverse reaction
Parapsoriasis	Immune-related skin adverse reaction
Pemphigoid	Immune-related skin adverse reaction
Psoriasis	Immune-related skin adverse reaction
Rash	Immune-related skin adverse reaction
Rash erythematous	Immune-related skin adverse reaction
Rash generalised	Immune-related skin adverse reaction
Rash macular	Immune-related skin adverse reaction
Rash maculo-papular	Immune-related skin adverse reaction
Rash maculovesicular	Immune-related skin adverse reaction
Rash morbilliform	Immune-related skin adverse reaction
Rash papular	Immune-related skin adverse reaction
Rash pruritic	Immune-related skin adverse reaction
Rash rubelliform	Immune-related skin adverse reaction
Rash scarlatiniform	Immune-related skin adverse reaction
Rash vesicular	Immune-related skin adverse reaction
Skin reaction	Immune-related skin adverse reaction
Stevens-Johnson syndrome	Immune-related skin adverse reaction
Toxic epidermal necrolysis	Immune-related skin adverse reaction
Toxic skin eruption	Immune-related skin adverse reaction
Immune thrombocytopenic purpura	Immune thrombocytopenic purpura
Insulin autoimmune syndrome	Insulin autoimmune syndrome
Iridocyclitis	Iridocyclitis
Iritis	Iritis
Keratitis	Keratitis
Meningitis	Meningitis
Meningitis aseptic	Meningitis
Motor dysfunction	Motor dysfunction

MedDRA Preferred Term	Composite Term
Mucosal inflammation	Mucosal inflammation
Muscular weakness	Muscular weakness
Myalgia	Myalgia
Myasthenia gravis	Myasthenia gravis
Myasthenic syndrome	Myasthenia gravis
Myelitis transverse	Myelitis transverse
Autoimmune myocarditis	Myocarditis
Immune-mediated myocarditis	Myocarditis
Myocarditis	Myocarditis
Blood creatine phosphokinase MB increased	Myocarditis
Troponin increased	Myocarditis
Autoimmune myositis	Myositis
Immune-mediated myositis	Myositis
Myositis	Myositis
Polymyositis	Myositis
Autoimmune neuropathy	Neuropathy peripheral
Immune-mediated neuropathy	Neuropathy peripheral
Neuritis	Neuropathy peripheral
Neuropathy peripheral	Neuropathy peripheral
Peripheral sensory neuropathy	Neuropathy peripheral
Polyneuropathy	Neuropathy peripheral
Autoimmune pancreatitis	Pancreatitis
Immune-mediated pancreatitis	Pancreatitis
Pancreatitis	Pancreatitis
Pancreatitis acute	Pancreatitis
Paraneoplastic encephalomyelitis	Paraneoplastic encephalomyelitis
Autoimmune pericarditis	Pericarditis
Pericarditis	Pericarditis
Polymyalgia rheumatica	Polymyalgia rheumatica
Pruritus	Pruritus
Pruritus allergic	Pruritus
Pruritus generalised	Pruritus
Pseudopolyposis	Pseudopolyposis
Sarcoidosis	Sarcoidosis
Sjogren's syndrome	Sjogren's syndrome

MedDRA Preferred Term	Composite Term
Epidermal necrosis	Skin necrosis
Skin necrosis	Skin necrosis
Stomatitis	Stomatitis
Systemic inflammatory response syndrome	Systemic inflammatory response syndrome
Thyroid dermatopathy	Thyroid dermatopathy
Autoimmune thyroid disorder	Thyroid disorder
Thyroid disorder	Thyroid disorder
Autoimmune thyroiditis	Thyroiditis
Immune-mediated thyroiditis	Thyroiditis
Thyroiditis	Thyroiditis
Thyroiditis acute	Thyroiditis
Thyroiditis chronic	Thyroiditis
Thyroiditis fibrous chronic	Thyroiditis
Thyroiditis subacute	Thyroiditis
Diabetes mellitus	Type 1 diabetes mellitus
Diabetic ketoacidosis	Type 1 diabetes mellitus
Latent autoimmune diabetes in adults	Type 1 diabetes mellitus
Type 1 diabetes mellitus	Type 1 diabetes mellitus
Autoimmune uveitis	Uveitis
Immune-mediated uveitis	Uveitis
Uveitis	Uveitis
Vasculitis	Vasculitis
Vitiligo	Vitiligo