STATISTICAL ANALYSIS PLAN (SAP)
RN5609C00/PRO-MERIT

Version: Final v 2.0 **Date:** 27 APR 2023
Sponsor: BioNTech SE

Protocol number:	RN5609C00
Protocol title:	First-in-human, dose titration and expansion trial to evaluate safety, immunogenicity and preliminary efficacy of W_pro1 (BNT112) monotherapy and in combination with cemiplimab in patients with prostate cancer
Short Title / Acronym	PRO-MERIT (**Pro**state Cancer **Me**ssenger **R**NA **I**mmuno**t**herapy)
Trial Phase	1/2A
Protocol version:	6.0 (including Amendments 1 to 5)
Protocol date:	23 FEB 2022
Compounds:	W_pro1, cemiplimab
SAP version:	Final v 2.0
SAP date:	27 Apr 2023
CRO name:	Syneos Health
SAP author:	PPD

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 SAP APPROVAL

This SAP has been prepared, reviewed, and approved in accordance with the sponsor's and Syneos Health standard operating procedures (SOP). Documentation of this process is filed in the trial master file (TMF).

I confirm that I have reviewed this document and agree with the content.

Approvals		
Syneos Health Approval		
PPD Senior Principal Biostatistician	PPD	*Electronically signed by:* PPD *Reason: I am the author* *Date: Apr 27, 2023 13:27 GMT+2*
Name, Title Lead Biostatistician	Signature	Date (DD-Mmm-YYYY)
PPD	PPD	*Electronically signed by* PPD *Reason: I am the review* *Date: Apr 27, 2023 14:35 GMT+2*
Name, Title Senior Reviewing Biostatistician	Signature	Date (DD-Mmm-YYYY)
BioNTech SE Approval		
Dr PPD PPD	PPD	*Electronically signed by:* PPD *Reason: I am the approve* *Date: Apr 27, 2023 10:00 EDT*
Name, Title Sponsor Contact	Signature	Date (DD-Mmm-YYYY)
PPD	PPD	*Electronically signed by:* PPD *Reason: I am the approver* *Date: May 8, 2023 11:28 GMT+2*
Name, Title Sponsor Contact	Signature	Date (DD-Mmm-YYYY)

2 VERSION HISTORY

Table 1: SAP Version History Summary

SAP version	Approval date	Document Owner	Change
Version 1.0	18 OCT 2021	PPD	Initial Release Version
Version 2.0	27 APR 2023		Implementation of relevant changes for analyses based on new Protocol version V6.0: Change of the immunogenicity secondary endpoint to an exploratory immunogenicity endpoint (see Section 8.7.4). The schedule of assessment was adapted to allow for additional blood draws at C1D8, C1D15, C2D8, and C2D15 for prostate-specific antigen level assessment. Final analysis for mCRPC patients and the final analysis of the LPC patients are planned to be performed separately (see modifications in Section 5). Further changes: Analysis set for all analyses related to PSA data changed. MITT set will be used instead of Pharmacodynamic set.

3 INTRODUCTION

This is a first-in-human, open-label, multicenter, dose titration and expansion four-arm Phase I/IIa trial to evaluate the safety, tolerability, immunogenicity, and preliminary efficacy of W_pro1 cancer vaccine (W_pro1 or BNT112, which the company product name has been changed to in protocol RN5609C00, dated 23 FEB 2022 (v6.0)) monotherapy or in combination with cemiplimab in patients with metastatic castration-resistant prostate cancer (mCRPC: Part 1 and Part 2 Arms 1A and 1B) and in patients with high-risk, localized prostate cancer (LPC) eligible for treatment with androgen-deprivation therapy (ADT) followed by radical prostatectomy (LPC: Part 2 Arms 2 and 3).

The trial consists of two parts: Part 1 (dose titration) and Part 2 (dose expansion).

The results might be included in a regulatory submission.

This statistical analysis plan (SAP) describes the detailed procedures for the planned statistical analysis for protocol mentioned aboveto support the completion of the Clinical Trial Report (CTR). However, although the company product name has been changed to BNT112 in the current protocol, W_pro1 will remain unchanged in this SAP and other trial-related documentation.

The purpose of this SAP is to define and describe the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the trial objectives.

Syneos Health will perform the statistical analyses (using SAS® software version 9.4 or higher, and/or other statistical software as required) and is responsible for the production and quality control of all tables, figures and listings (TFLs).

Templates for each unique table, figure and patients listing are provided in a separate document “Mock Tables, Listings and Figures”.

3.1 Objectives and endpoints

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

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

OBJECTIVES	ENDPOINTS
PRIMARY OBJECTIVE	**PRIMARY ENDPOINTS**
• (Part 1 and Part 2) Assess safety and tolerability profile of W_pro1 monotherapy or in combination with cemiplimab	• Occurrence of dose-limiting toxicities (DLTs). • Occurrence of treatment-emergent adverse events (TEAEs) reported by relationship, grade, and seriousness according to NCI CTCAE v5.0.

OBJECTIVES	ENDPOINTS
• (Part 2 Arms 1a and 1b) Evaluate preliminary anti-tumor activity of W_pro1 monotherapy and in combination with cemiplimab in patients with mCRPC based on ORR	• Objective response rate (ORR), defined as the number of patients with a complete response (CR) or partial response (PR) per Prostate Cancer Working Group 3 (PCWG3) [3] as determined by the investigator as best objective response divided by the number of patients in the analysis set.
SECONDARY OBJECTIVES	**SECONDARY ENDPOINTS**
• Evaluate anti-tumor activity based on levels of prostate-specific antigen (PSA)	• Prostate-specific antigen (PSA) decline of 0 to 25%, >25% to 50%, and >50% compared to baseline. • PSA doubling time (PSADT) post-treatment on C4D1 and D1 of every fourth subsequent cycle (e.g., Cycle 8 Day 1 [C8D1], C12D1, etc.) in Part 1 and Part 2 Arms 1A and 1B, or on C4D1, C8D1, and end of treatment (EoT) in Part 2 Arms 2 and 3 compared to baseline. • PSA decline of ≥50% (according to the PCWG3).
• (Part 1) Evaluate preliminary anti-tumor activity of W_pro1 monotherapy in patients with mCRPC based on ORR	• ORR, defined as the number of patients with a CR or PR per PCWG3 as determined by the investigator as best objective response divided by the number of patients in the analysis set.
• Evaluate preliminary anti-tumor activity of W_pro1 monotherapy or in combination with cemiplimab in patients with newly diagnosed LPC	• Tumor response post-treatment compared to baseline.
EXPLORATORY OBJECTIVES	**EXPLORATORY ENDPOINTS**
• Determine systemic induction/expansion of W_pro1 antigen-specific T cells for W_pro1 monotherapy or in	• Occurrence of *de novo* induction or increase of W_pro1 antigen-specific T cells in peripheral blood under treatment on C3D15, and/or C8D15, EoT, or safety follow-up compared to baseline.

OBJECTIVES	ENDPOINTS
combination with cemiplimab	
• Evaluate preliminary anti-tumor activity of W_pro1 monotherapy and in combination with cemiplimab in patients with mCRPC	• Duration of response (DoR), defined as the time from the first occurrence of a documented objective response (OR) to the time of the first disease progression per PCWG3 [3], as determined by the investigator, or death from any cause, whichever occurs first. • ORR and DoR, defined as above, using immune-modified Response Evaluation Criteria in Solid Tumors (iRECIST) [4]. • Progression-free survival (PFS), defined as the time from the first trial treatment to the first disease progression per PCWG3 as determined by the investigator, and per iRECIST determined by central reading, or death from any cause, whichever occurs first. • Overall survival (OS), defined as the time from first trial treatment until death from any cause. • Number of cycles received and relative dose intensity (RDI).
• Evaluate preliminary anti-tumor activity of cemiplimab in patients with mCRPC who have been previously treated with, and who have progressed after W_pro1 monotherapy.	• ORR, defined as the number of patients with a CR or PR per PCWG3 as determined by the investigator as best objective response (OR) divided by the number of patients in the analysis set. • DoR, defined as the time from the first occurrence of a documented OR to the time of the first disease progression per PCWG3, as determined by the investigator, or death from any cause, whichever occurs first. • ORR and DoR, defined as above, using iRECIST. • PFS, defined as the time from the first cemiplimab treatment to the first disease progression per PCWG3 as determined by the investigator, and per iRECIST

OBJECTIVES	ENDPOINTS
	determined by central reading, or death from any cause, whichever occurs first. • PFS2, defined as the time from the first trial treatment to the first disease progression after start of cemiplimab per PCWG3 as determined by the investigator, or death from any cause, whichever occurs first. • OS, defined as the time from first trial treatment until death from any cause. • Number of cycles received and RDI.
• Assess safety and tolerability profile of cemiplimab monotherapy in patients following progression after W_pro1 monotherapy.	• Occurrence of TEAEs reported by relationship, grade, and seriousness according to NCI CTCAE v5.0.
• Evaluate preliminary anti-tumor activity of W_pro1 monotherapy or in combination with cemiplimab in patients with newly diagnosed LPC	• PFS, defined as the time from the first trial treatment to the first disease progression per PCWG3 [3] as determined by the investigator, or death from any cause, whichever occurs first. • OS, defined as the time from first trial treatment until death from any cause.
• Preliminary assessment of biomarkers that might act as potential predictive, pharmacodynamics, anti-tumor, and safety indicators of activity of W_pro1 monotherapy or in combination with cemiplimab	• Status of tumor mutational burden and immune-related gene expression (at the RNA level) in tumor tissue prior to treatment. • Change in protein expression pattern/levels of tumor microenvironment markers (e.g., CD3, CD8, MHC-I, PD-L1, etc.) and prostate tumor markers (e.g., PSA, PSAP, NKX3-1, etc.) in tumor tissue post-treatment compared to baseline. • Baseline status or change in RNA target expression of W_pro1–encoded antigens in the post-treatment tissue compared to baseline. • Change in T cell clonality/diversity post-treatment compared to baseline.

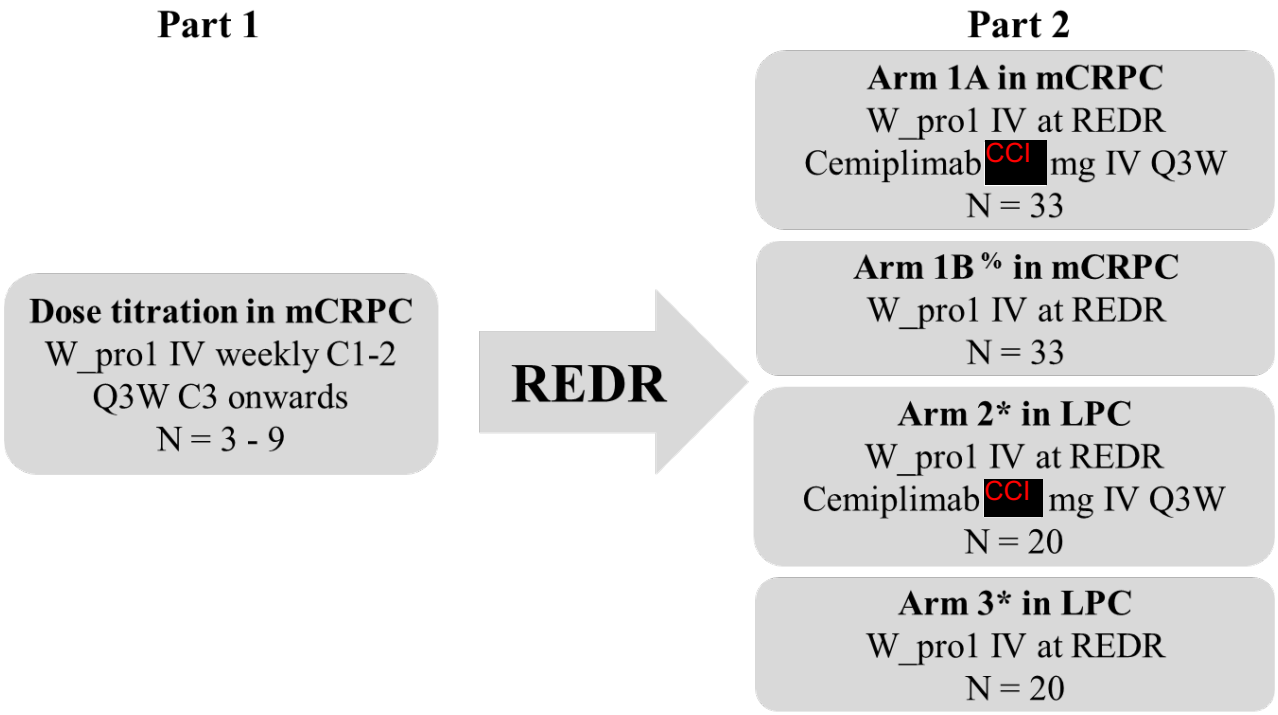
OBJECTIVES	ENDPOINTS
	• Changes in blood biomarkers prior to and during trial treatment.

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

3.2 Trial design

Trial design	This is an open-label, multicenter, dose titration and expansion four-arm trial to evaluate the safety, tolerability, immunogenicity, and preliminary efficacy of W_pro1 monotherapy or in combination with cemiplimab in patients with mCRPC (mCRPC: Part 1 and Part 2 Arms 1A and 1B) and in patients with LPC eligible for treatment with ADT followed by radical prostatectomy (LPC: Part 2 Arms 2 and 3). The trial consists of 2 parts: Part 1 (dose titration) and Part 2 (dose expansion). Part 2 consists of 4 arms: Arms 1A and 1B (mCRPC patients) and Arms 2 and 3 (LPC patients). Part 1 contains a dose titration for initial safety assessment and identification of the recommended expansion dose range (REDR). It will enroll mCRPC patients to receive W_pro1 monotherapy at 3 predefined dose levels (DLs) until a discontinuation-of-treatment criterion is met (see Section 7 of the protocol). Part 1 of the trial will employ a modified 3+3+3 design (adapted from Hamberg et al. 2010 [1]) with up to 9 evaluable patients. Once the REDR is defined, the trial will commence with Part 2 and enroll approximately 106 patients in 4 arms (see the expansion part, Section 4.2 of the protocol). Part 2 Arms 1A and 1B will enroll patients with mCRPC to receive W_pro1 monotherapy or W_pro1 in combination with cemiplimab, and Part 2 Arms 2 and 3 will enroll patients with newly diagnosed LPC eligible for treatment with ADT (e.g., goserelin acetate) to receive W_pro1 monotherapy or W_pro1 in combination with cemiplimab.

Figure 3-1: Trial Design



Abbreviations and Footnotes:
C = Cycle; IV = intravenous; LPC = localized prostate cancer; mCRPC = metastatic castration-resistant prostate cancer; Q3W = every 3 weeks; REDR = recommended expansion dose range.
* In combination with ADT (e.g., Goserelin).
% Following progression after W_pro1 monotherapy, patients in Arm 1b have the option to be treated with cemiplimab monotherapy CCI mg IV Q3W.

Trial population	Part 1 (mCRPC) Dose titration for initial safety assessment and identification of the REDR. In this part patients with histologically confirmed mCRPC who progressed after at least 2 but no more than 3 lines of life-prolonging systemic therapy (e.g., abiraterone or enzalutamide, docetaxel, cabazitaxel) or who cannot tolerate or have refused any of these therapies will be enrolled. Patients in Part 1 will receive W_pro1 monotherapy at 3 predefined dose levels (DLs) until a discontinuation-of-treatment criterion is met (see Section 7 of the protocol). Up to 9 evaluable patients will be enrolled in Part 1. Part 2 Arms 1A and 1B (mCRPC) Approximately 66 (33 per arm) patients with histologically confirmed mCRPC who progressed after at least 2 but no more

	than 3 lines of life-prolonging systemic therapy (e.g., abiraterone or enzalutamide, docetaxel, cabazitaxel) or who cannot tolerate or have refused any of these therapies will be enrolled in Part 2 Arms 1A and 1B. Following progression after W_pro1 monotherapy, patients in Arm 1B will have the option to be treated with cemiplimab monotherapy. <u>Part 2 Arm 2 and Arm 3 (LPC)</u> Treatment-naive patients with LPC (i.e., N0, M0) defined according to European Association of Urology Guidelines on Prostate Cancer (2018) [2] and in line with the U.S. National Comprehensive Cancer Network (NCCN 2020) [7], who are eligible for treatment with ADT (e.g., goserelin acetate) followed by radical prostatectomy will be enrolled in Part 2 Arms 2 and 3. A list of all inclusion and exclusion criteria can be found in Section 5 of the protocol.
Trial centers and geographic regions	Approximately 30 investigational sites in up to 5 countries including US, UK, Hungary and Germany.
Investigational medicinal products (IMPs):	
IMP 1:	W_pro1
Composition:	The W_pro1 consists of messenger ribonucleic acid (mRNA [or RNA]) targeting 5 antigens expressed in *de novo* and metastatic prostate cancer that are separately complexed with liposomes to form serum-stable RNA lipoplexes.
Administration:	Five slow intravenous (IV) bolus injections per administration (i.e., one injection per each antigen followed by a saline flush and separated from the next injection by at least 5 minutes)
Dosage regimen:	One cycle (C) is defined as 21 days. The patients will receive the following treatments in the following dose and schedule: <u>Part 1 and Part 2 Arms 1A and 1B (mCRPC)</u> • IV administration of W_pro1 on Day (D)1/8/15 of C1 (intra-patient dose titration) and C2, thereafter starting with D1 of C3 every 3 weeks (Q3W) until end of treatment criterion is met. • Part 1/Dose Titration

	- Three doses of W_pro1 will be used for an intra-patient dose titration during C1: CCI µg, CCI µg, and CCI µg of total RNA, comprising CCI µg, CCI µg, and CCI µg of RNA of each of the 5 antigens encoded by the W_pro1, respectively. • Part 2/Expansion - REDR was selected after the review of individual and cumulative safety data, and preliminary pharmacodynamic data of Part 1 by the Safety Review Committee (SRC). The selected dose range consists of a starting first dose of W_pro1 of CCI µg, with an intra-patient dose titration to CCI µg in the second dose, and CCI µg of total RNA in the next doses. Total RNA of CCI µg, CCI µg and CCI µg comprise CCI µg, CCI µg, and CCI µg of RNA of each of the 5 antigens encoded by the W_pro1, respectively. - Part 2 Arm 1A: Cemiplimab CCI mg IV Q3W. - Part 2 Arm 1B: Following progression after W_pro1 monotherapy, patients have the option to be treated with cemiplimab CCI mg IV Q3W monotherapy. <u>Part 2 Arms 2 and 3 (LPC) – Part 2/Expansion ONLY</u> • IV administration of W_pro1 on D1/8/15 of C1 (intra-patient dose titration) and C2, thereafter starting with D1 of C3 in a Q3W schedule until C8 followed by radical prostatectomy. • Part 2 Arm 2: Cemiplimab CCI mg IV Q3W.
Duration of treatment:	• <u>Part 1 and Part 2 Arms 1A and 1B (mCRPC):</u> The treatment with W_pro1 will last until unacceptable toxicity or disease progression. • <u>Part 2 Arms 2 and 3 (LPC):</u> The treatment with W_pro1, cemiplimab will last until unacceptable toxicity or disease progression, or up to C8. • If either W_pro1 or cemiplimab needs to be discontinued, treatment with either cemiplimab or W_pro1 can continue upon investigator's and sponsor's agreement. • If treatment with ADT (e.g., goserelin acetate) needs to be discontinued, cemiplimab and/or W_pro1 also need(s) to be discontinued.

IMP 2:	Cemiplimab (LIBTAYO)
Composition:	Programmed death receptor-1 (PD-1) blocking antibody
Dosage regimen and duration of treatment:	Refer to above description of IMP1 for dosage regimen and duration of treatment
Non-investigational medicinal product (NIMP):	
Part 2 Arms 2 and 3 (LPC) ADT, e.g., Goserelin acetate subcutaneous (SC) injection at a dose of 10.8 mg every 12 weeks (Q12W) or other ADT according the current prescribing information valid in a given country.	
Product:	Goserelin acetate (Zoladex® LA 10.8 mg implant)
Composition:	Goserelin acetate (equivalent to 10.8 mg goserelin)
Administration:	SC
Dosage regimen:	One 10.8 mg depot injection given into the anterior abdominal wall Q12W
Duration of treatment:	Two injections (≤7 days C1D1 and 12 weeks after the first injection); treatment will last until unacceptable toxicity or disease progression, or up to C8
Treatment and trial duration	**Treatment and follow–up duration:** **Part 1 and Part 2 Arms 1A and 1B (mCRPC):** mCRPC patients will be treated until a discontinuation-of-treatment criterion is met. One cycle is defined as 21 days. End of treatment (EoT) assessment will be performed up to 21 days after administration of last dose of IMP for patients who discontinued trial treatment, except if patient was lost to follow-up or died. All patients (Part 1 and Part 2 Arms 1A and 1B) will be actively followed up 30 days for safety (D30 Safety FU) after last intake of W_pro1. Patients in Part 2 Arm 1A will be followed up 90 days for safety (D90 Safety FU) after last intake of cemiplimab, or 30 days for safety (D30 Safety FU) after last intake of W_pro1, whichever is later. All patients will be followed up 6 and 12 months after last IMP administration for efficacy. Within 28 days after confirmation of disease progression, patients of Arm 1B can optionally start cemiplimab monotherapy and will follow the Schedule of Activities (SoA) shown in Section 13.6 after performing the EoT for W_pro1 treatment. **Part 2 Arm 2 and Arm 3 (LPC):**

	LPC patients will be treated with up to 8 cycles or until unacceptable toxicity or disease progression. One cycle is defined as 21 days. EoT assessment will be performed up to 21 days after administration of last dose of IMP for patients who discontinued trial treatment, except if patient was lost to follow-up or died. After EoT assessment a Safety follow-up (FU) after 30 days for Arm 2 and Arm 3 and an additional Safety FU after 90 days for Arm 2 patients are performed. Both Arms 2 and 3 will be followed up 6 and 12 months after last IMP administration for efficacy. **Trial duration:** First patient was included on 19 December 2019. The end of the trial is defined as the date of last patient contact, whether in-person or by phone, for the last patient in the trial globally, including the efficacy follow-up for 12 months after the last dose of trial treatment.
Planned number of patients	There will be 3 to 9 patients in Part 1 (dose titration part, single arm) and up to 106 patients in Part 2 (expansion part, 4 arms: up to 33 patients in Arm 1A and Arm 1B, respectively, and approximately 20 patients in Arm 2 and Arm 3, respectively). Drop-outs may be replaced. In total, there will be approximately 115 patients. Re-screening of patients is allowed.
Randomization and blinding	At screening, patients will be assigned a unique number (patient identification code), regardless of whether they actually receive trial treatment. In Part 2, patients with mCRPC treated in Arm 1A or Arm 1B, and patients with LPC treated in Arm 2 or Arm 3, will be randomized in 1:1 ratio. Central randomization will be used. No stratification factors will be used for the randomization. The site will contact the central randomization service prior to the start of trial treatment administration for each patient. The treatment assignment will be recorded on the applicable electronic case report form (eCRF), as required. This is an open-label trial.
Tumor assessment schedule	**Part 1 and Part 2 Arms 1A and 1B (mCRPC):** Bone scintigraphy (bone scans) and CT/MRI of the chest, abdomen, and pelvis should be performed at the following time points: - during screening period (within 28 days before C1D1) - at C3D15 (±7 days)

	- every 8 weeks (±7 days) for 24 weeks (i.e. between C6D1 and C8D15) - and every 3 months (±7 days) thereafter, i.e., from C11D15 until disease progression is assessed by the investigator or the start of a new anti-cancer therapy or withdrawal of consent, or death, whichever occurs first - At EoT visit (only if clinically indicated); not required if previous imaging was performed within ≤ 9 weeks before the EoT visit Patients in Arm 1B who moved to treatment with cemiplimab monotherapy following progression after W_pro1 monotherapy, should have radiographic assessments performed every 3 months (±7 days) thereafter, until disease progression is assessed by the investigator or the start of new anti-cancer therapy or withdrawal of consent, or death, whichever occurs first. **Part 2 Arms 2 and 3 (LPC):** Tumor measurement using multi-parametric MRI (mpMRI) or MRI will be used consistently throughout the trial. The same imaging modality should be used at screening and at all subsequent assessments. Tumor measurements should be performed at the following time points: - during screening period (within 28 days before C1D1) - prior to surgery (i.e. at the end of C8/EoT visit)

Treatment overview:	

Treatment sequence: (if applicable) NIMP ADT is to be administered first, thereafter W_pro1, and then cemiplimab.

Part 1

Dose Titration[&]

	C1			C2			C3 →		
Day	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**
W_pro1[$]									
CCI µg IV	X								
CCI µg IV		X							
CCI µg IV			X						
Highest tolerable dose*				X	X	X	X	→	Q3W

Part 2

Arm 1a (W_pro1 + cemiplimab in mCRPC)
Arm 2[#] (W_pro1 + cemiplimab in LPC)

	C1			C2			C3 →		
Day	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**
W_pro1[$]									
CCI µg IV	X								
CCI µg IV		X							
CCI µg IV			X	X	X	X	X	→	Q3W
Cemiplimab									
CCI mg IV Q3W	X			X			X	→	Q3W

Part 2

Arm 1b[%] (W_pro1 monotherapy in mCRPC)
Arm 3[#] (W_pro1 monotherapy in LPC)

	C1			C2			C3 →		
Day	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**
W_pro1[$]									
CCI µg IV	X								
CCI µg IV		X							
CCI µg IV			X	X	X	X	X	→	Q3W

Abbreviations and Footnotes:

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

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

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

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

[$] From Day 1 of C1 onward, each patient will receive the individual standard dose (or the highest tolerated dose from Cycle 1) at each W_pro1 administration.

[%] Following progression after W_pro1 monotherapy, patients in Arm 1b will have the option to be treated with cemiplimab monotherapy CCI mg IV Q3W.

3.3 Schedule of activities

See Section 13.6 for the SoA.

4 STATISTICAL HYPOTHESES

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

Apart from this hypothesis, no formal statistical comparison between treatment groups will be performed for any of the other endpoints. All other p-values will be considered as supportive or explorative. The results of all other endpoints will be described with nominal p-values without any statement on statistical significance.

5 INTERIM ANALYSES AND ANALYSIS SEQUENCE

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

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

However, after the interim analysis, the enrollment of Part 2 Arms 1A and 1B (mCRPC) was stopped prior to the complete enrollment of the planned LPC patients. Therefore, the final analysis for mCRPC and the final analysis for LPC are planned to be performed separately.

The final analysis for mCRPC will be performed based on all available data from a clinical data cut-off that will occur after all the enrolled patients in Part 2 Arms 1A and 1B (mCRPC) have completed 8 cycles of treatment or discontinued.

The final analysis for patients with LPC will be performed based on all available data from a clinical data cut-off that will occur after all the planned patients in the Part 2 Arms 2 and 3 (LPC) have completed 8 cycles of treatment or discontinued.

Note: for both final analyses, the data from both LPC and mCRPC will be analyzed.

- At the final analysis for mCRPC, all the data for LPC up to the data cutoff for this analysis will also be analyzed.
- At the final analysis for LPC, all the data for mCRPC up to the data cutoff for this analysis will also be analyzed.

A further analysis, termed Follow-up analysis, will be performed when the last patient discontinues from the trial. For the Follow-up analysis only a subset of TFLs generated for the main analysis may be produced again, this analysis will include all new data collected in the database. All TFLs to be generated for the Follow-up analysis will be defined after the final analysis has be performed.

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

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

The SRC will review all DLTs and suspected unexpected serious adverse reactions, make the REDR recommendation at the end of the Dose Titration Part (Part 1) and periodically review safety and efficacy in Part 2. The SRC will make a recommendation to the sponsor after each meeting and how to proceed with the trial and whether to activate the respective expansion arms of the trial. The SCR will meet at least every 3 months throughout the trial.

The materials provided for review to the SRC, the SRC role and responsibilities and the general procedures (including communications) are defined and documented in the SRC charter (v4.0, dated 02 NOV 2020). The preparation of the review material for the SRC is not part of the SAP for this trial.

6 SAMPLE SIZE DETERMINATION

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

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

A patient will be considered as evaluable if included in the primary analysis set (mITT set, see Section 7.1) which is defined as all patients who are randomized to the IMP and have a baseline and at least one post-baseline (i.e., one on-treatment or post-treatment) tumor assessment (clinical or imaging assessment).

No formal sample size calculation is performed for the LPC setting in Part 2 (Arms 2 and 3) due to its exploratory nature. However, 20 patients are planned to be enrolled into Arm 2 and Arm 3. Based on this sample size (N=20) the one-sided 95% CI of binary

endpoints will have a width of up to +/-0.19 in each group depending on the observed effect size.

7 ANALYSIS SETS AND SUBGROUPS

7.1 Analysis sets

The following analysis sets are defined:

Population	Description
Screened	The screened analysis set is defined as all patients who sign the informed consent form (ICF).
Intent-to-Treat (ITT)	**Part 1:** The ITT set is defined as all patients to whom IMP is assigned. **Part 2:** The ITT set is defined as all patients who are randomized to the IMP.
Modified Intent-to-Treat (mITT)	**Part 1:** The mITT set is defined as all patients to whom IMP is assigned and have a baseline and at least one post-baseline (i.e., one on-treatment or post-treatment) tumor assessment (clinical or imaging assessment). **Part 2:** The mITT set is defined as all patients who are randomized to the IMP and have a baseline and at least one post-baseline (i.e., one on-treatment or post-treatment) tumor assessment (clinical or imaging assessment).
Safety (SAF)	The safety set is defined as all patients who have received IMP (i.e., at least 1 dose of W_pro1 and/or cemiplimab).
DLT Evaluation	**Only applicable for Part 1:** The DLT evaluation set includes all patients from the safety set who either have completed the DLT evaluation period and meet the minimum exposure criterion or have experienced a DLT during C1. Patients who do not experience any DLTs during C1 are considered to be evaluable if they have been observed for a minimum of 21 days following the first dose and are considered to have sufficient safety data to conclude that a DLT did not occur. A patient is considered to have met the minimum exposure criterion if the relative dose intensity of W_pro1 in C1 is at least 90%.
Per Protocol (PP)	The per protocol (PP) set is defined as all patients who have received IMP 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 1 cycle • Availability of baseline and at least one on-treatment / post-treatment tumor assessment Important deviations will lead to an exclusion of patients from the PP set and will be agreed at the data review meeting (DRM) prior to database snapshot for the final analysis. Protocol deviations that may be considered important will be specified in the SAP (see Section 7.2)
Pharmacodynamic	The pharmacodynamic set is defined as all patients who have received IMP (i.e., at least 1 dose of W_pro1 and/or cemiplimab) and with a baseline and at least 1 on-treatment/post-treatment follow-up

Population	Description
	pharmacodynamic assessment as specified in Section 8.8.1 (i.e. Hormones (Testosterone), Cytokines).
Subsequent Cemiplimab Monotherapy on Progression (Cemi Mono on PD)	**Only applicable for Part 2 Arm 1B:** The subsequent cemiplimab monotherapy on progression set (Cemi Mono on PD) is defined as all mCRPC patients in Arm 1B (W_pro1 monotherapy) who switch to cemiplimab monotherapy after disease progression and who received at least one dose of cemiplimab.

The DLT evaluation set will be used for the evaluation of DLTs in order to assess the REDR in Part 1 of the trial.

The safety set will be used for all other safety analyses, while the mITT set will be used as primary analysis set for efficacy analyses.

The subsequent cemiplimab monotherapy on progression set will be used for all exploratory safety and efficacy analyses for the Arm 1B patients who received cemiplimab (i.e., at least 1 dose of cemiplimab) after progression to W_pro1 monotherapy.

The ITT analysis set will be used for disposition analyses.

Further, the ITT and PP sets will be used for sensitivity analyses of some predefined efficacy endpoints depending on the number of patients excluded. If none of the patients are excluded from the mITT set, compared to the ITT set, or if the number of patients excluded from the PP set is small (exclusion rate ≤10%), no additional sensitivity analyses for the ITT or the PP set will be generated. The final decision to perform sensitivity analyses for the ITT set or for the PP set will be made during the DRM meeting for the final analysis.

All safety analyses and analyses based on the Pharmacodynamic set will be based on the treatment actually taken by the patient (“as treated”).

All other analyses will be based on the treatment the patient was assigned/randomized to (“as randomized”), unless stated otherwise.

7.2 Protocol deviations

Protocol deviation management for this trial is detailed in the trial specific Protocol Deviation and Non-compliance Management Plan. According to this plan, protocol deviations or site non-compliance are documented concisely in the Clinical Trail Management System (CTMS) and periodically reviewed as part of the project oversight by a wider study team.

Protocol deviations are failures to adhere to the inclusion/exclusion criteria and protocol requirements and will be classified into important protocol deviations and not important protocol deviations.

- Important protocol deviations are a subset of protocol deviations that may significantly affect the completeness, accuracy, and/or reliability of the trial data or that may significantly affect a patient’s rights, safety, or well-being. For example, important

protocol deviations may include enrolling patients in violation of key eligibility criteria designed to ensure a specific patient population or failing to collect data necessary to interpret primary endpoints, as this may comprise the scientific value of the trial

- Non-important protocol deviations are those that are not considered to significantly affect the efficacy evaluation and hence do not warrant patients' exclusion from the PP set
- Important protocol deviations will be identified by study team review during the DRM prior to database snapshot for main analysis

Additional important protocol deviations may be defined at the DRM prior to data base lock for the main analysis. During the DRM, protocol deviations as specified in this section of the SAP and all protocol deviations as reported in the CTMS system will be evaluated and decided which important protocol deviation will results in an exclusion of a patient from the PP set.

Important and non-important protocol deviations will be presented in a listing. The number and percentage of patients excluded from the PP set will be summarized in total and by protocol deviation type for the ITT set.

7.2.1 Protocol deviations due to COVID-19

Protocol deviations related to COVID-19 are documented in the CTMS with the preface "COVID-19" in the deviation description.

COVID-19 related protocol deviations are, for example:

- COVID-19, Visit xx on date xx of patient not conducted due to site facility re-organization related to COVID-19 disruption
- COVID-19, missing Visit xx due to patient affected by COVID-19

A separate table will be generated summarizing the number and percentage of patients with a COVID-19 protocol deviation. Respective data will be listed.

Protocol deviation due to COVID-19 will be summarized using the ITT set.

7.3 Subgroups

The following subgroups are defined for statistical analysis:

- Age categories (< 50 years, >= 50 - < 65 years , >= 65 years)
- mCRPC patients: Visceral metastasis at study entry (Yes, No)
- mCRPC patients: Prior treatment with Docetaxel or other Taxanes (Yes, No)
  (use ATC Level 4 Code = L01CD for the derivation)

- LPC patients: PSA level at baseline
  (<= 20 ng/mL, > 20 ng/mL)
- LPC patients: NCCN Risk Group at diagnosis
  (Very low risk, Low risk, Intermediate risk, High risk, Very high risk, Unkown)

The definition of subgroups and the respective cut points could be modified for the analysis depending on the enrolled patients. Further subgroups may be defined during the DRM meeting for the final analysis.

Subgroup analyses will be provided for the mITT set (for ORR and PFS per PCWG3), unless otherwise specified.

8 STATISTICAL ANALYSES

8.1 General considerations

In general, the statistical analysis will be performed by trial part (i.e., Part 1 and Part 2) and by treatment group in the Part 2 (i.e., Part 1 mCRPC W_pro1, Part 2 mCRPC W_pro1 + Cemiplimab, Part 2 mCRPC W_pro1, Part 2 LPC W_pro1 + Cemiplimab, Part 2 LPC W_pro1). A detailed description of treatment labels to be used for the analysis is provided in Section 13.4.

For Part 2 of the trial all analyses (disposition, baseline characteristics, efficacy and safety (except adverse event (AE) analysis)) will be analyzed by treatment group and in addition for 3 combined treatment groups “Part 2 Total mCRPC”, “Part 2 Total LPC” and “Part 2 Total”. “Part 2 Total” is an optional treatment group only for some predefined tables.

AE analyses will be analyzed for 6 additional combined treatment groups i.e. “Part 2 Total Monotherapy”, “Part 2 Total Combination Therapy”, “Part 2 Total”, “Parts 1 and 2 Total mCRPC”, “Parts 1 and 2 Total Monotherapy” and “Parts 1 and 2 Total”. A detailed description of all combined treatment groups is available in Section 13.4.

Continuous variables will be summarized by treatment group using the following descriptive statistics: number of patients with non-missing data (n), mean, standard deviation, median, minimum, maximum, lower quartile (Q1) and upper quartile (Q3) where appropriate.

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

Shift tables from baseline will summarize only cases, where both time points are available, to avoid a “missing” category. The percentages are calculated with respect to the available patients.

Generally, only measurements at scheduled visits will be summarized and included in the tables by visit. Unscheduled measurements will be included in the listings, only.

Time-to-event-endpoints (DoR, PFS, and OS) will be analyzed using Kaplan-Meier methodology and censored in accordance with the US FDA Guidance: “Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics” [6].

The median survival time (including two-sided 95% confidence limits according to Brookmeyer and Crowley) and the first and third quartiles will be presented for each treatment group. Survival rates (including 95% confidence interval (CI) based on Greenwood's formula) as well as the number and percentage of patients with events,

censored and under risk will be displayed for selected time points (e.g. after 3 months, after 6 months and after 12 months).

The survival distributions for two treatment groups will be compared using the log-rank test, and the p-value will be provided. The associated hazard ratio (HR) and two-sided 95% confidence interval will be estimated by using Cox proportional hazard model with treatment as model covariate.

All treatment comparisons, except the analysis defined for the primary efficacy endpoint see Section 4, are purely exploratory. Exploratory treatment comparisons will be performed separately for patients with mCRPC (comparison of Arm 1A versus Arm 1B) and for patients with LPC (comparison of Arm 2 versus Arm 3).

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

Efficacy data collected for patients in Arm 1B after the switch from W_pro1 monotherapy to cemiplimab monotherapy will not be considered in the efficacy analyses. These measurements will only be considered in the exploratory efficacy analyses comprising ORR, DoR, PFS (per PCWG3 and iRECIST (central reading)) and PFS2 on cemiplimab monotherapy based on last tumor assessment prior to start of cemiplimab treatment. These exploratory endpoints to analyze the preliminary anti-tumor activity of cemiplimab monotherapy will be generated using the subsequent cemiplimab monotherapy on progression set. More details regarding these analyses can be found in Section 8.7.4.2.

The safety and tolerability profile of cemiplimab monotherapy will be analyzed using the subsequent cemiplimab monotherapy on progression set. The definition of cemiplimab TEAEs will be provide in detail in Section 8.9.3. All other safety data (e.g. laboratory, electrocardiogram (ECG), vital signs) reported for patients in Arm 1B after the switch to cemiplimab monotherapy will be included in the respective listings.

All relevant data will be listed. The listing will be sorted by treatment group, patient number and date/time of assessment (if applicable). Unscheduled measurements will be included in the listings.

See Section 11 for the definition of planned summary tables, figures and listings. Templates for each unique table and patient listing are provided in a separate document “Mock Tables, Listings and Figures”.

8.2 Key definitions

Date/time of first administration of IMP (W_pro1 or Cemiplimab):

Is defined as first administration date/time of IMP (W_pro1 or cemiplimab), whichever was administered first.

Baseline Definition:

Baseline is defined as last available value prior to or on the date/time of first administration of IMP (W_pro1 or cemiplimab, whichever was administered first). Unscheduled measurements prior to first administration of IMP will be considered in the calculation of the baseline values. In the case that date/time of first administration of IMP is missing (i.e.,

for randomized not treated patients) the date/time of randomization will be used for the definition of baseline values.

Cemiplimab Baseline – Baseline definition for Arm 1B patients who switch to cemiplimab monotherapy:

Cemiplimab Baseline is defined as last available value prior to or on the date/time of first administration of cemiplimab.

In case no time of the assessment is reported, measurements at the same date as first administration of cemiplimab will be considered as baseline.

Change and percent change from baseline:

Change from baseline will be calculated as follows:

- Change from baseline = post-baseline assessment value – baseline assessment value.
- Percent change from baseline = (post-baseline assessment value – baseline assessment value) / baseline assessment value * 100.

Age (in years) at date of informed consent:

Age is derived in the database based on the collected Year of birth as follows:

Age = ICF Date – (01July + Year of birth) / 365.25.

Age as derived in the database will be used for all analyses.

Body mass index (BMI):

BMI will be calculated as follows:

$$\text{BMI}\left(\frac{\text{kg}}{\text{m}^2}\right) = \frac{\text{Weight (kg)}}{\text{Height(m)}^2}$$

Duration:

Duration will be calculated as follows:

- Duration (days) = last observation date – first observation date + 1

For conversion of days to months or years the following rules will be applied:

- 1 month = 30.4375 days
- 1 year = 365.25 days

Time from first diagnosis to enrollment (in months):

Date of initial diagnosis is collected in Month/Year. Missing day will be replaced with the first day of the month. In case month is not reported, missing month will be replaced with July.

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

(ICF date – imputed date of initial diagnosis) / 30.4375

Time from treatment start to post treatment prostatectomy for LPC patients (in days):

For date of prostatectomy or radical prostatectomy, missing day will be replaced with the first day of the month. In case month is not reported, missing month will be replaced with July.

Time from treatment start to prostatectomy (days) will be calculated as:

(Date of prostatectomy – date of first IMP administration (W_pro1 or cemiplimab) + 1

Study day:

Study day is defined as follows:

If date of assessment is on or after the date of first IMP administration (W_pro1 or cemiplimab):

- Date of assessment – date of first IMP administration + 1

If date of assessment is before date of first IMP administration (W_pro1 or cemiplimab):

- Date of assessment – date of first IMP administration

Laboratory values with "< xx" or "> xx":

Any laboratory values given as "< xx" or "> xx" in the database will be imputed with the numeric value of xx without the sign for the descriptive statistics and the calculation of changes from baseline (e.g., a value of < 1 will be imputed as 1 for the calculations).

Last date known to be alive:

Last date known to be alive is defined as last documented date in the database for the patient, including all visit dates, assessment dates (if different from visit dates), trial treatment administration dates, tumor assessment dates, end of treatment dates, date of trial completion or early trial withdrawal date, start/stop dates of AEs, PSA response date, survival follow-up date (where patients survival status is alive), whichever comes last.

Start of Follow-up Period:

Part 1 and Part 2 mCRPC patients: Follow-up period starts at the administration of the last dose of IMP.

Part 2 LPC patients: Follow-up period starts at the last administration of IMP at Cycle 8 or at administration of the last IMP in case of discontinuation of trial treatment.

Pooling of centers:

No pooling of centers is planned for this trial.

Conventions for imputing missing/partially missing dates:

When computations on dates are to be performed, incomplete/missing dates will be imputed using the following rules.

- Missing day, month/year present: If the month/year is the same as the month/year of the first IMP administration date, then impute missing start dates with first IMP administration date. Otherwise, for dates corresponding to a start date, impute with the first day of the month and, for dates corresponding to a stop date, impute with the last day of the month.
- Missing month/day, year present: If the year is the same as the year of the first IMP administration date, then impute missing start dates with first IMP administration date. Otherwise, for dates corresponding to a start date, impute with the first day of the year and, for dates corresponding to a stop date, impute with the last day of the year.
- Missing month/day/year: no imputation.
- In case imputed start date is after available stop date, the imputed start date will be replaced with the stop date to avoid negative durations.

This imputation method will be applied to the following dates:

- Onset date of AEs (for treatment-emergent purpose), incomplete AE end dates
- Medical history start date to define prior medical history and concomitant diseases
- Date of prior/concomitant medication (start dates) to define prior and concomitant medication, incomplete stop dates of prior/concomitant medications

Conventions for imputing missing/partial start dates of the subsequent anti-cancer therapy:

- If the start date of the first subsequent anti-cancer therapy is missing, it will be imputed with the date of the End of Treatment (EoT) visit.
- Missing day, month/year present: If the month/year is the same as the month/year of the EoT visit date, then impute missing start dates with EoT visit date. Otherwise, for dates corresponding to a start date, impute with the first day of the month and, for dates corresponding to a stop date, impute with the last day of the month.
- Missing month/day, year present: If the year is the same as the year of the EoT visit date, then impute missing start dates with the EoT visit date. Otherwise, for dates corresponding to a start date, impute with the first day of the year and, for dates corresponding to a stop date, impute with the last day of the year.
- If the EoT visit date is missing, the date of the last study treatment administration + 14 days to be used for the imputation.
- In case imputed start date is after available stop date, the imputed start date will be replaced with the stop date to avoid negative durations.

Clinical progression:

Clinical progression reported more than 14 days after start of the first subsequent anti-cancer therapy will not be considered in the analysis of clinical progression.

Best Overall Response (BOR) based on Radiological Soft Tissue Evaluation:

The BOR is defined as a single best response status at any tumor response assessment after first administration of IMP and prior to or at the start date of the first subsequent anti-cancer therapy. Overall response of PD within 14 days after the start date of the first subsequent anti-cancer therapy will be considered.

Only responses up to and including the date of the first progressive disease will be considered in the derivation of the BOR.

The following order of tumor response categories will be used, with “Complete Response” is the best category:

Complete Response (CR) – Partial Response (PR) – Stable Disease (SD) – Progressive Disease (PD) – Not Evaluable (NE) – Not Applicable (NA).

Best Overall Response (BOR) based on iRECIST (central reading):

The following order of tumor response categories will be used to define the BOR category based on iRECIST (central reading), with “Complete Response” is the best category:

Complete Response (iCR) – Partial Response (iPR) – Stable Disease (iSD) - Unconfirmed Progressive Disease (iUPD) – Confirmed Progressive Disease (iCPD) – Not Evaluable (NE) – Not Applicable (NA).

Only central reading assessments after first administration of IMP and prior to or at the start date of the first subsequent anti-cancer therapy will be considered in the derivation. Overall response of iUPD or iCPD within 14 days after the start date of the first subsequent anti-cancer therapy will be considered.

Only responses up to and including the date of the first progressive disease will be considered in the derivation of the BOR.

Further information on the definition of the BOR based on iRECIST is available in Section 13.3.

PSA Response definition based on PCWG3:

PSA response definition based on PCWG3 will be derived based on the PSA response data reported by the investigator.

If a PSA PD occurred >= 12 weeks after first administration of IMP. This PSA PD needs no confirmation.

For the derivation of best overall PSA Response based on PCWG3, the PSA responses have to be c**onfirmed**. The following rules have to be implemented for PSA response confirmation:

- **PSA PR Response Confirmation**
  - PSA PR needs to be confirmed by:
    - Subsequent [Radiological Soft Tissue PR or CR response] or Subsequent [PSA PR response]

        - Which occurs within >= 20 days and <= start date of first subsequent anti-cancer therapy, immediately after initial PSA PR response
        - With no worse response (SD, PD) between initial PR and confirmation response
        - Worse responses are defined as [Radiological Soft Tissue SD or PD response] or [Clinical Progression Event] or [Progressive Bone Disease] or [PSA SD or PD response]

- **PSA SD Response Confirmation**
    - PSA SD needs to be confirmed by:
        - Subsequent [Radiological Soft Tissue SD, PR or CR response] or Subsequent [PSA SD or PR response]
        - Which occurs within >= 20 days and <= start date of first subsequent anti-cancer therapy, immediately after initial PSA SD response
        - With no worse response (PD) between initial SD and confirmation response
        - Worse responses are defined as [Radiological Soft Tissue PD response] or [Clinical Progression Event] or [Progressive Bone Disease] or [PSA PD response]

- **PSA PD Response Confirmation**
    - If a PSA PD occurred < 12 weeks after first administration of IMP, this PSA PD needs to be confirmed by:
        - Another PSA PD that occurred immediately after the initial PSA PD and >= 12 weeks after first administration of IMP and <= start date of first subsequent anti-cancer therapy + 14, immediately after the initial PSA PD response.
        - Subsequent [Radiological Soft Tissue PD] or [Clinical Progression] or [Progressive Bone Disease] immediately after the initial PSA PD and <= start date of first subsequent anti-cancer therapy + 14.
        - PSA PD confirmation can only occur if there are no better responses (CR, PR, SD) between the initial PSA PD and confirmation assessment.
        - Better responses are defined as [Radiological Soft Tissue CR, PR or SD response] or [PSA PR, SD response]

Best Overall PSA Response definition based on PCWG3:

The best overall PSA response based on PCWG3 is defined as a single best PSA **confirmed** response status at any response assessment after first administration of IMP and prior to or at the start date of the first subsequent anti-cancer therapy. Overall response of PD within 14 days after the start of the first subsequent anti-cancer therapy will be considered.

Only responses up to and including the date of the first progressive disease will be considered in the derivation of the best overall PSA Response.

The following order of response categories will be used, with “Partial Response” is the best category:

Partial Response (PR) – Stable Disease (SD) – Progressive Disease (PD) – Unknown – Not Applicable (NA).

Best Overall Response (BOR) based on PCWG3:

The rules for the definition of BOR based on PCWG3 are referring to the following data reported in the CRF:

- Confirmed PSA response reported by the investigator (see Section 8.2 for more details regarding PSA response confirmation)
- Radiological Soft Tissue Evaluation (response data collected in the CRF on the “RECIST 1.1” page)
- Clinical Progression (data collected in the CRF on the “Clinical Progression” page)
- Bone Disease Progression (data collected in the CRF on the “Bone Lesion” pages with Clinical Impression = Progression)

Only assessments after first administration of IMP and prior to or at the start date of the first subsequent anti-cancer therapy will be considered in the derivation. Overall response of PD within 14 days after start date of the first subsequent anti-cancer therapy will be considered.
Only responses up to and including the date of the first progressive disease will be considered in the derivation of the BOR.

Overall Response of CR, PR, SD per PCWG3 is based on radiological soft tissue response or confirmed PSA response.

Progression of Disease per PCWG3 is based on the earliest radiological soft tissue progression, Bone disease progression, confirmed PSA progression or clinical progression.

The following order of tumor response categories will be used, with “Complete Response” is the best category:

Complete Response (CR) – Partial Response (PR) – Stable Disease (SD) – Progressive Disease (PD) – Not Evaluable (NE) – Not Applicable (NA).

Derivation of PSADT:

PSADT will be derived based on the PSA measurements provided by the investigator in the database and collected during the trial at screening visit and during each cycle.

PSADT will be calculated post-treatment on C4D1 and D1 of every fourth subsequent cycle (e.g. C8D1, C12D1, etc.) in Part 1 and Part 2 Arms 1A and 1B, or on C4D1, C8D1, and EoT in Part 2 Arms 2 and 3.

PSA measurements reported after EoT visit or after start of the first subsequent anti-cancer therapy will not be considered in the derivation of PSADT.

PSADT will be calculated using a linear regression model of the natural logarithm of PSA values and time ([3] and [https://drhaddad.com.au/wp-content/uploads/2022/07/13.pdf], [8].

Derivation of PSADT post-treatment at every fourth subsequent cycle:

1. Compute the slope of the regression line of natural logarithm of PSA vs. time (which is the number of doublings per unit time) where PSA is the PSA level in ng/mL at each time point
2. Compute PSADT (days) = natural log (2) / slope,
   natural log (2) = 0.693.
3. Multiply PSADT (days) by 12/365.25 to get PSADT (months)

The calculation of post-treatment PSADT should be based on (1) at least 3 consecutive PSA values with each value >= 0.2 ng/dL (or >= 0.002 ng/mL), (2) inclusion of the most recent PSA values during androgen deprivation therapy, and (3) interval between first and last PSA value of >= 8 weeks but <= 12 months.

8.3 Missing Data

All reasonable efforts will be made to obtain complete data for all patients. However, missing observations may occur due to patients lost to follow-up or to noncompliance with required trial visits and / or assessments. Missing data will not be imputed and data analysis will be performed based on the observed values, unless otherwise specified.

8.4 Visit Windows

Every attempt should be made to perform evaluations at the designated time point / visit. Visit windows for visits per cycles, for Safety FU visits, and for Efficacy FU visits are defined in the SoA (see Section 13.6). All visits will be summarized according to the nominal visit.

8.5 Patient disposition

Patient disposition will be summarized by presenting the number and percentage of patients screened, re-screened, number of screening failures, along with a summary of the primary reason for screening failure for the screened set.

The number and percentage of patients eligible to participate in the trial, number of randomized patients (for Part 2), and the number and percentage of patients in each analysis set will be summarized by treatment group for the patients in the screened set.

For each analysis set (e.g., ITT set, mITT set, Safety set, PP set and Pharmacodynamic set) the number and percentage of patients being excluded from the analysis set will be presented by treatment group along with a summary of the reasons for exclusion based on

the ITT set. In addition, the number of patients in the subsequent cemiplimab monotherapy on progression set will be reported.

The number and percentage of screened / randomized / treated patients will be presented by country and site including the number and percentage of patients with important protocol deviations (by treatment group) for the screened set.

For the ITT set the treatment status will be reported, including the number and percentage of patients having prematurely discontinued treatment by treatment group along with a summary of the primary reason for premature treatment discontinuation of W_pro1 treatment, of cemiplimab treatment and of ADT treatment (e.g., completed per protocol, AEs, disease progression, death, withdrawal of consent, lost to follow-up), as applicable.

Further, the number and percentage of patients started follow- up period, and end of trial disposition will be reported including the number and percentage of patients having completed or discontinued the trial with a summary of the primary reason for trial discontinuation including the number of deaths.

Important protocol deviations will be summarized for the ITT set by treatment group. In addition, a table will be generated summarizing the number and percentage of patients with a protocol deviation due to COVID-19 for the ITT set.

All data will be listed (patient disposition listing, protocol deviation listing, protocol deviation due to COVID-19 listing), and a listing of all patients excluded from any of the analysis sets including the primary reason for exclusion from the analysis sets.

In addition, a listing of all inclusion and exclusion criteria which were not met, based on the screened set will be generated.

Further, the following listings will be generated for the ITT set to report the impact of COVID-19 to patients enrolled in this trial:

- Patients impacted by COVID-19 related trial disruption
- Missing Visits due to COVID-19

8.6 Baseline characteristics

8.6.1 Demographics

Demographic and baseline variables will be summarized for patients in the mITT set. Age (years), weight (kg), height (cm), body mass index (kg/m2) and Glomerular filtration rate (mL/min/1.73 m2) will be summarized as continuous data. Age (< 50 years, >= 50 - <65 years, >= 65 years), Gender (must be male), Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reportable), race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Not Reportable, Unknown, Other) and BMI categories (<18 kg/m2, >=18 kg/m2 - <25 kg/m2, >=25 kg/m2 - <30 kg/m2, >=30 kg/m2) will be summarized as categorical data.

Demographic tables for the ITT set, Safety set and the PP set will be generated, depending on the number of patients excluded from the respective analysis set.

A listing of demography will be provided for the ITT set.

8.6.2 Disease characteristics

Disease characteristics will be summarized for patients in the mITT set. Time from initial diagnosis to enrollment will be summarized as continuous data. Tumor stage at diagnosis, tumor grade (Gleason Score) at diagnosis, National Comprehensive Cancer Network (NCCN) Risk Group at diagnosis, PSA level at diagnosis (ng/mL), prostate cancer diagnosis at screening (mCRPC, LPC), tumor stage at screening, ECOG performance status at baseline, tetanus vaccination status, histology will be summarized as categorical data.

Further, on the basis of the initial tumor response assessment (based on PCWG3) reported at the Screening visit, the following variables will be reported:

- Disease Characteristics – Imaging: Target Lesions (Absent / Present), Non-Target Lesions (Absent / Present), Locations of Target Lesions (Anus, Abdominal Cavity, Other - as collected in the database) and Sum of target lesion diameters.

Further information regarding bone lesions at screening to be reported:
Bone-only disease (patients with no target and no non-target lesion at screening evaluation, only bone lesions reported), Bone lesions (Yes, No), in case of “Yes” the total number of lesions related to metastatic disease (1, 2-4, 5-9, 10-20, >20).

Visceral metastasis (Yes, No) defined based on the location of target or non-target lesions at screening evaluation. For more details see Section 13.5.

Further the number of patients with at least one visceral metastasis (target or non-target lesions) in liver and lung separately, will be reported.

Lymph node metastasis (Yes, No) defined based on the location of target or non-target lesions at screening evaluation with location = Lymph Node.

Disease characteristics data will be listed for the ITT set.

8.6.3 Prior anti-cancer treatments

The following prior anti-cancer therapies will be summarized using frequency tables for the mITT set.

- Prior cancer surgery
- Prior cancer radiotherapy
- Prior systemic cancer therapy

Prior cancer surgeries will be coded using Medical Dictionary for Regulatory Activities (MedDRA version 22.1 or later version).

Prior systemic cancer therapies will be coded using the World Health Organization Drug Dictionary (WHO-DD) drug codes of the most recent version (WHO-DD Global B3 Sep

2019, or later version) resulting in Anatomical-Therapeutic-Chemical (ATC) codes indicating therapeutic classification.

The number and percentages of patients with any prior cancer surgery will be summarized by System Organ Class (SOC) and Preferred Term (PT) for each treatment group.

All prior cancer therapy types as specified below:

A table “Prior Therapy Lines” will be generated including:

- Number of prior systemic cancer therapies per patient, setting of last systemic cancer therapy (adjuvant, neoadjuvant, palliative, other, unknown), disease status at the end of the last prior systemic cancer therapy (CR, PR, PD, SD, NE, Unknown, Non-Progressive disease), Reasons for termination of the last prior systemic cancer therapy (AE, Disease Progression, Other, Unknown, Completion of therapy)

A table “Prior Therapy Types” will be generated including the number of patients and percentages of

- Any prior cancer surgery including information of treatment intent (palliative, curative, diagnostic, unknown)
- Any prior cancer radiotherapy including information of site and setting (adjuvant, neoadjuvant, palliative, curative, unknown)
- Any prior systemic cancer therapy including information of setting (adjuvant, neoadjuvant, palliative, other, unknown)
- Number of patients with any prior systemic cancer therapy with Docetaxel or other Taxanes. (Use ATC Level 4 Code = L01CD (Taxanes) for the derivation)
- Number of patients with any prior systemic cancer therapy with ADT or Degarelix. (Use ATC Level 4 Code = L02AE (Gonadotropin releasing hormone analogues), to identify all ADTs,
  L02BX (Other hormone antagonists and related agents) and standardized medication name = Degarelix or Degarelix acetate for the selection of Degarelix.)
  Including details of Adjuvant or Neo-adjuvant ADT or Degarelix therapy
- Number of patients with any prior systemic cancer therapy: Novel hormone therapies (Use ATC Level 4 Code = L02BB (Anti-Androgens) and L02BX (Other hormone antagonists and related agents), except medication name = Degarelix or Degarelix acetate)

Prior cancer surgery, prior cancer radiotherapy and prior systemic cancer therapy will be listed for the ITT set.

8.6.4 Prior and concomitant medication

All medications will be coded using the WHO-DD drug codes of the most recent version (WHO-DD Global B3 Sep 2019, or later version) resulting in ATC codes indicating therapeutic classification.

Prior and concomitant medications will be defined using start and stop dates recorded, relative to the first and last IMP administration dates.

A **prior medication** will be defined as any therapy taken prior up to (but not including) the start date of first IMP administration.

A **concomitant medication** will be defined as any medication either ongoing at the start date of first IMP administration or with a start date on or after the first IMP administration date up to (but not including) the Safety FU-D30 or Safety FU-D90 visit as appropriate.

The number and percentage of patients taking prior medication or concomitant medications will be summarized by ATC therapeutic class (ATC level 2), ATC pharmacological class (ATC level 3), and chemical substance (ATC level 4) for each treatment group based on the mITT set.

A listing of prior and concomitant medications will be provided for the ITT set.

In addition, a listing of further antineoplastic therapies after discontinuation of IMPs, as collected in the eCRF, will be generated.

8.6.5 Other Procedures

Concomitant cancer radiotherapy:

During the course of the trial concomitant new cancer radiotherapies within 28 days prior to start of first IMP administration up to (but not including) the Safety FU-D30 or Safety FU-D90 Visit as appropriate will be reported.

A summary table presenting the number and percentage of patients with any concomitant cancer radiotherapy, including information of site will be summarized by treatment group for the mITT set. All data will be listed for the ITT set.

Concomitant Procedures and Non-Drug Therapies:

During the course of the trial concomitant procedures/non-drug therapies, e.g. invasive procedures / surgery, may take place and will be documented on the eCRF page “Procedures / Non-Drug Therapies”. Data will be reported within 28 days prior to start of the first administration of IMP up to (but not including) the Safety FU-D30 or Safety FU-D90 Visit as appropriate will be reported. Procedures and Non-Drug Therapies will be coded using MedDRA (version 22.1 or later version).

The number and percentages of patients with any concomitant procedures/non-drug therapies will be summarized by SOC and PT for each treatment group for the mITT set.

All data will be listed for the ITT set.

8.6.6 Medical history

Medical history data will be coded using MedDRA (version 22.1 or later version). The number and percentage of patients with a medical history (prior medical history and concomitant diseases) will be summarized by SOC and PT. This summary will be done by treatment group for patients in the mITT set.

Medical history terms with ongoing ticked “No” will be considered as prior medical history, with ongoing ticked “Yes” as concomitant diseases.

A listing of medical history data will be provided for the ITT set.

8.7 Efficacy analyses

8.7.1 Primary analysis

8.7.1.1 Primary Efficacy Endpoint

Objective Response Rate

For Part 2, Arms 1A and 1B, ORR is defined as primary efficacy endpoint. The primary analysis will be performed using the mITT set.

The ORR is defined as the number of patients with CR or PR as best objective response per PCWG3 divided by the number of patients in the mITT set. Patients not meeting the criteria for CR or PR, including those without any post-baseline response assessments, will be considered as non-responders. The ORR will be summarized with absolute and relative frequencies along with two-sided 95% Clopper-Pearson CIs by treatment group.

For each Part 2 Arm 1A and 1B the null hypothesis (see Section 4) that the true response rate is 5% will be tested against a one-sided alternative (i.e. H_0: ORR=5% versus H_1: ORR >5%). There will be no formal comparison between treatment groups.

BOR (all categories) based on PCWG3 will be summarized with absolute and relative frequencies.

Further, the BOR (all categories) based on Radiological Soft Tissue Evaluation will be summarized with absolute and relative frequencies.

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

Tumor response assessment including overall response, BOR and clinical progression as documented in the eCRF will be listed. In addition, listings including all tumor assessments per PCWG3 (target lesion, non-target lesion, new lesion) will be generated.

Subgroup analyses of the primary efficacy endpoint will be performed for the mITT set.

Sensitivity analysis

For the primary endpoint ORR, sensitivity analyses will be performed using the ITT set and the PP set.

8.7.2 Supplementary analyses

Not applicable.

8.7.3 Secondary analyses

8.7.3.1 Secondary efficacy endpoints

Prostate-specific antigen decline

PSA will be collected for all patients in Part 1 and Part 2 at several visits during the course of the trial (see SoA in Section 13.6 for more details). PSA values will be provided by a central laboratory and reported by the investigator in the database. For the analyses, it

was agreed to use the PSA measurements as provided by the investigator together with the PSA response per PCWG3 criteria as reported in the database.

PSA decline calculated as percentage change compared to baseline will be summarized using descriptive summary statistics for each visit by treatment group.

PSA decline of 0 to 25%, > 25% to 50%, and > 50% compared with baseline and PSA decline of <50% versus >=50% compared to baseline will be summarized with absolute and relative frequencies (n and %) of patients by visit and treatment group for the mITT set.

Bar charts for PSA decline compared to baseline in the above defined categories by visit will be generated for the mITT set.

Waterfall plots for maximum PSA decline from baseline per patient will be generated.

For the derivation of maximum decline from baseline only measurements which were reported >= 4 weeks after treatment start and prior to or at the EoT visit and prior to or at the start date of the subsequent anti-cancer therapy to be considered. Only PSA measurements corresponding to a confirmed PSA response (see Section 8.2 for the definition of confirmed PSA response) or reported after a confirmed PSA response have to be considered in the derivation of maximum PSA decline (an initial PSA response will confirm all subsequent PSA responses of the same response value, as long as there is not a better or worse response between them).

PSA response per PCWG3 criteria (as reported by the investigator) will be summarized with absolute and relative frequencies (n and %) of patients by visit and treatment group for the mITT set.

Best overall PSA response, ORR and Clinical Benefit Rate (CBR) per PCWG3 criteria will be summarized for the mITT set.

Sensitivity analyses for PSA decline will be performed using the ITT set and the PP set depending on the number of patients excluded.

Prostate-specific antigen doubling time

The number and percentage of patients per PSADT under-treatment on C4D1 and D1 of every fourth subsequent cycle (e.g., C8D1, C12D1, etc.) in Part 1 and Part 2 Arm 1A and 1B, or on C4D1, C8D1, and EoT in Part 2 Arms 2 and 3 compared with baseline. For more details for the calculation of PSADT, see Section 8.2.

The following categorization of PSADT should be reported: 0 - 3 months, >3 – 6 months, >6 – 9 months, >9 – 12 months , >12 – 18 months, >18 – 24 months, >24 months.

Sensitivity analyses will be performed using the ITT set and the PP set depending on the number of patients excluded.

Objective Response Rate for Part 1

For Part 1, ORR is defined as secondary efficacy endpoint as best objective response per PCWG3 and will be analyzed descriptively for the mITT set. For more details, see Section 8.7.1.1.

Tumor assessment post-treatment compared to baseline for Part 2, Arm 2 and Arm 3

Tumor measurements using mpMRI or, if tumor measurement is not feasible with a mpMRI, imaging according to local practice (e.g. CT or MRI), should be performed at the following time points:

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

Tumor response will be assessed based on Radiological Soft Tissue Evaluation at both time points. Number of patients in each category and ORR will be summarized with absolute and relative frequencies along with two-sided 95% Clopper-Person CIs by treatment group for the mITT set.

Tumor response assessment including overall response, best overall response and clinical progression as documented in the eCRF will be listed. In addition, listings including all tumor assessments per PCWG3 (target lesion, non-target lesion, new lesion) will be generated.

Sensitivity analyses will be performed using the ITT set and the PP set depending on the number of patients excluded.

8.7.4 Exploratory analyses

Exploratory efficacy analyses will be performed using the mITT set.

Exploratory efficacy endpoints comprise ORR (in the mCRPC arms and only per iRECIST), DoR, PFS, and OS. Tumor assessments will be performed using PCWG3 for all patient in Part 1 and Part 2 of the trial. For mCRPC patients enrolled in Part 1 and Part 2, tumor assessment using iRECIST (central reading) will be performed in addition.

For mCRPC patients enrolled in Part 1 and Part 2, ORR, DoR, and PFS will be analyzed separately for PCWG3 and iRECIST (central reading).

ORR, and DoR will be analyzed for Part 1 and Part 2 Arms 1A and 1B only.

Sensitivity analyses for exploratory endpoints will be performed using the ITT set and the PP set depending on the number of patients excluded.

In addition, subgroup analyses for some of the exploratory endpoints (i.e. DoR and PFS) will be performed based on the mITT set. The final decision will be made during the DRM.

Exploratory efficacy analyses will also be performed on patients in Arm 1B who are treated with cemiplimab monotherapy following progression after W_pro1 monotherapy. These exploratory analyses will comprise ORR, DoR, PFS (per PCWG3 and iRECIST (central reading)) on cemiplimab monotherapy based on last tumor assessment prior to start of cemiplimab treatment and OS. PFS2 will be analyzed as well. These exploratory efficacy

analyses will be performed using the subsequent cemiplimab monotherapy on progression set.

Exploratory immunogenicity analyses of W_pro1 antigen-specific T-cells based on ELISPOT and further immune monitoring data are not part of this SAP. Respective data will be provided by a central laboratory.

8.7.4.1 Exploratory efficacy endpoints

Objective Response Rate based on iRECIST (central reading)

ORR based on iRECIST will be analyzed for mCRPC patients in Part 1 and Part 2 only.

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

BOR (all categories) will be summarized with absolute and relative frequencies.

Tumor response assessment including overall response and BOR will be listed. In addition, listings including all tumor assessments per iRECIST (central reading) (target lesion, non-target lesion, new lesion) will be generated.

Duration of Response

DoR will be analyzed for Part 1 and Part 2 Arms 1A and 1B only. DoR will be analyzed separately for PCWG3 and iRECIST (central reading).

The DoR is defined as the time from the date of first radiographic documented OR to the date of first disease progression or death from any cause, whichever occurs first. Only patients who experience a confirmed OR will be analyzed for DoR.

In case death date is reported after trial discontinuation date, these death details will not be considered in the DoR analysis. The patient will be censored at the day of the last response assessment.

DoR will be analyzed using the Kaplan-Meier method. Kaplan-Meier plots will be generated.

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 response assessment.

Only response assessments prior to or at the start date of the first subsequent anti-cancer therapy will be considered for DoR analysis. PD within 14 days after the start date of the first subsequent anti-cancer therapy will be considered.

DoR based on PCWG3:

OR is defined as CR or PR. Disease progression is defined as tumor response = Progressive Disease (PD)

DoR expressed in months for patients whose objective response was confirmed CR or PR = (MIN [Date of first documented disease progression (PD), date of death from any cause] – Date of first documented overall response (CR or PR) + 1) / 30.4375 for events

or

(Date of the last evaluable response assessment – Date of first documented overall response (CR or PR) + 1) / 30.4375 in case of censoring.

DoR based on iRECIST (central reading):

OR is defined as iCR or iPR. Disease progression is defined as tumor response = Confirmed progressive disease (iCPD)

DoR expressed in months for patients whose objective response was confirmed iCR or iPR = (MIN [Date of first documented disease progression (iCPD), date of death from any cause] – Date of first documented overall response (iCR or iPR) + 1) / 30.4375 for events

or

(Date of the last evaluable response assessment – Date of first documented overall response (iCR or iPR) + 1) / 30.4375 in case of censoring.

Progression-free survival

PFS will be analyzed for Part 1 and Part 2 Arms 1A and 1B, Arm 2 and Arm 3.

PFS is defined as the time from the date of the first dose of IMP to the date of the first disease progression, or death from any cause, whichever occurs first.

Only death dates reported prior to or at the date of trial discontinuation will be considered in the PFS analysis.

PFS will be analyzed using the Kaplan-Meier method. Kaplan-Meier plots will be generated.

Patients alive and without disease progression at the data cut-off date or patients lost to follow-up will be censored at the day of their last response assessment.

Only response assessments prior to or at the start date of the first subsequent anti-cancer therapy will be considered for PFS analysis. PD within 14 days after the start date of the first subsequent anti-cancer therapy will be considered.

If no post-baseline tumor response is available, the patient will be censored at the date of the first dose of IMP.

PFS expressed in months = (MIN [Date of first disease progression, date of death from any cause] – date of first dose of IMP + 1) / 30.4375 if the patient has a PFS event

or

(Date of last evaluable response assessment – date of first dose of IMP + 1) / 30.4375 in case of censoring.

In the case that date of the first dose of IMP is missing, randomization date will be used for the calculation of PFS.

For Part 1 and Part 2 Arms 1A and 1B, PFS will be analyzed separately based on PCWG3 and iRECIST (central reading).

Sensitivity analyses of PFS will be performed using the ITT set and the PP set depending on the number of patients excluded.

Overall survival

OS will be analyzed for Part 1 and Part 2 Arms 1A and 1B, Arm 2 and Arm 3.

OS is defined as the time from the date of the first dose of IMP to the date of death from any cause. OS will be analyzed using the Kaplan-Meier method. Kaplan-Meier plots will be generated.

In case date of death is reported after trial discontinuation date, this data will not be considered in the OS and the patient will be censored at the day of their last date known to be alive.

Patients alive or patients lost to follow-up at the date of analysis cut-off will be censored at the day of their last date known to be alive.

OS expressed in months = (Date of death from any cause – date of first dose of IMP + 1) / 30.4375 for patients with available death date

or

(Last date of known to be alive – date of first dose of IMP + 1) / 30.4375 in case of censoring.

In the case that date of the first dose of IMP is missing, randomization date will be used for the calculation of OS.

8.7.4.2 Exploratory efficacy endpoints for patients in Arm 1B who are treated with cemiplimab monotherapy following progression on W_pro1

Patients in Arm 1B will be given the option to be treated with cemiplimab monotherapy following progression on W_pro1 monotherapy treatment and will be assessed for some exploratory efficacy endpoints, where the last measurement prior to start of cemiplimab treatment will serve as baseline measurement and the time-to-event endpoints (DoR, and PFS) will start from first dose of cemiplimab treatment. In particular, the last radiographic tumor assessment prior to cemiplimab treatment will re-define target and non-target lesions as basis for tumor response assessment on cemiplimab treatment. Additionally, PFS2 will be evaluated based on initial start of IMP.

These exploratory efficacy analyses will be performed using the subsequent cemiplimab monotherapy on progression set.

Objective Response Rate based on PCWG3 and iRECIST (central reading)

ORR will be analyzed separately for PCWG3 and iRECIST (central reading).

The ORR is defined as the number of patients with CR or PR as best objective response per PCWG3 (or number of patients with iCR or iPR as best objective response per iRECIST (central reading)) after start of cemiplimab treatment, divided by the number of patients in the subsequent cemiplimab monotherapy on progression set.

Patients not meeting the criteria for CR or PR (iCR or iPR per iRECIST (central reading)), including those without any post-baseline response assessments, will be considered as non-responders. The ORR will be summarized with absolute and relative frequencies along with two-sided 95% Clopper-Pearson CIs.

BOR (all categories) will be summarized with absolute and relative frequencies.

Duration of Response based on PCWG3 or iRECIST (central reading)

DoR will be analyzed separately for PCWG3 and iRECIST (central reading).

The DoR is defined as the time from the date of first radiographic documented OR to the date of first disease progression or death from any cause, whichever occurs first. Only patients who experience a confirmed OR after start of cemiplimab treatment will be analyzed for DoR.

Only death dates reported prior to or at the date of trial discontinuation will be considered in the DoR analysis.

DoR will be analyzed using the Kaplan-Meier method. Kaplan-Meier plots will be generated.

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 response assessment.

Only response assessments prior to or at the start date of the first subsequent anti-cancer therapy will be considered for DoR analysis. PD within 14 days after the start date of the first subsequent anti-cancer therapy will be considered.

DoR based on PCWG3:

OR is defined as CR or PR. Disease progression is defined as tumor response = Progressive Disease (PD)

DoR expressed in months for patients whose objective response was confirmed CR or PR after start of cemiplimab treatment =

(MIN [Date of first documented disease progression (PD) after start of cemiplimab treatment, date of death from any cause] – Date of first documented overall response (CR or PR) + 1) / 30.4375 for events

or

(Date of the last evaluable response assessment after start of cemiplimab treatment – Date of first documented overall response (CR or PR) + 1) / 30.4375 in case of censoring.

DoR based on iRECIST (central reading):

OR is defined as iCR or iPR. Disease progression is defined as tumor response = Confirmed progressive disease (iCPD)

DoR expressed in months for patients whose objective response was confirmed iCR or iPR after start of cemiplimab treatment =

(MIN [Date of first documented disease progression (iCPD) after start of cemiplimab treatment, date of death from any cause] – Date of first documented overall response (iCR or iPR) + 1) / 30.4375 for events

or

(Date of the last evaluable response assessment after start of cemiplimab treatment – Date of first documented overall response (iCR or iPR) + 1) / 30.4375 in case of censoring.

Progression-free survival based on PCWG3 or iRECIST (central reading)

PFS will be analyzed separately for PCWG3 and iRECIST (central reading).

PFS is defined as the time from the date of the first dose of cemiplimab treatment to the date of the first disease progression, or death from any cause, whichever occurs first.

Only death dates reported prior to or at the date of trial discontinuation will be considered in the PFS analysis.

PFS will be analyzed using the Kaplan-Meier method. Kaplan-Meier plots will be generated.

Patients alive and without disease progression after start of cemiplimab treatment at the data cut-off date or patients lost to follow-up will be censored at the day of their last response assessment.

Only response assessments prior to or at the start date of the first subsequent anti-cancer therapy will be considered for PFS analysis. PD within 14 days after the start date of the first subsequent anti-cancer therapy will be considered.

If no post-baseline response assessment after start of cemiplimab treatment is available, the patient will be censored at the date of the first dose of cemiplimab treatment.

PFS expressed in months = (MIN [Date of first disease progression after start of cemiplimab treatment, Date of death from any cause] – date of first dose of cemiplimab treatment + 1) / 30.4375 if the patient has a PFS event

or

(Date of last evaluable response assessment after start of cemiplimab treatment – date of first dose of cemiplimab treatment + 1) / 30.375 in case of censoring.

Progression-free survival 2 (PFS2) based on PCWG3

PFS2 is defined as the time from the date of the first IMP to the date of the first disease progression after start of cemiplimab per PCWG3, or death from any cause, whichever occurs first.

Only death dates reported prior to or at the date of trial discontinuation will be considered in the PFS2 analysis.

PFS2 will be analyzed using the Kaplan-Meier method. Kaplan-Meier plots will be generated.

Patients alive and without disease progression after start of the first IMP at the data cut-off date or patients lost to follow-up will be censored at the day of their last response assessment. Only response assessments prior to or at the start date of the first subsequent anti-cancer therapy will be considered for PFS2 analysis. PD within 14 days after the start date of the first subsequent anti-cancer therapy will be considered.

If no post-baseline response assessment after start of cemiplimab treatment is available, the patient will be censored at the date of the first dose of cemiplimab treatment.

PFS2 expressed in months = (MIN [Date of first disease progression after start of cemiplimab treatment, Date of death from any cause] – date of first dose IMP + 1) / 30.4375 if the patient has a PFS2 event

or

(Date of last evaluable response assessment after start of cemiplimab treatment – date of first dose of IMP + 1) / 30.375 in case of censoring.

Overall survival for the subset of patients in Arm 1B who are treated with cemiplimab monotherapy

OS is defined as the time from the date of first dose of IMP to the date of death from any cause. OS will be analyzed using the Kaplan-Meier method. Kaplan-Meier plots will be generated. OS expressed in months will be derived as defined in Section 8.7.4.1.

8.7.5 Further efficacy analyses

Survival status and biochemical recurrence

Survival status will be assessed at month 6 and month 12, beginning from the day of the last IMP dose and continues until the patient dies or withdrawal from the trial.

Disease status (CR, PR, SD, PD, Unknown) will be collected for all patients in Part 1 and Part 2 on the survival follow-up CRF page and will be summarized with absolute and relative frequencies at time points as collected during the survival follow-up reporting period.

Biochemical recurrence after radical prostatectomy based on the post-treatment PSA levels at Efficacy FU Month 6 and FU Month 12 will be summarized for patients in Arms 2 and 3.

For LPC patients (Arm 2 and Arm 3) the time (in days) from treatment start to post treatment prostatectomy will be reported.

8.7.6 Interim analysis for futility

An interim statistical analysis for futility is planned for Part 2, Arm 1A and Arm 1B based on the Simon's two-stage design (Simon, 1989 [5], see Section 6).

Simon's two-stage design based on the Minimax approach will be used for Arm 1A and Arm 1B separately. The null hypothesis that the true response rate is 5% will be tested against a one-sided alternative.

In the first stage, 20 patients will be enrolled. Enrollment will continue until the SRC decision and 13 additional patients may be accrued for a total of 33.

The interim analysis will be performed based on all available data from a clinical data cut-off that will occur when the required number of patients in the respective arm (Arm 1A and 1B) have performed the first post-baseline tumor assessment based on PCWG3 or discontinued before; tumor assessment scheduled every 8 weeks for the first 24 weeks and every 3 months thereafter.

One interim analysis is planned, where the decision for both treatment Arms 1A and 1B will be made.

If there are 1 or fewer responses in the first 20 patients in Part 2, Arm 1A or Arm 1B, the enrollment for that arm may be stopped. In case there are no responses reported in the first 19 patients in the respective treatment arms, the sponsor will check and decide if enrollment should stop for futility and no 20th patient to be included.

A patient will be considered as a responder if the best objective response per PCWG3 is CR or PR. All other patients or patients without any post-baseline tumor assessments will be considered as non-responders. Interim analysis will be performed on the mITT set.

A predefined set of TFLs to be generated for the interim analysis is defined in Section 11.

After the interim analysis performed in August 2022 (using a data cut-off date = 01 JUN 2022), the sponsor decided to stop enrollment of mCRPC patients in Part 2 Arms 1A and 1B.

8.8 Pharmacodynamic analyses

Blood samples and tumor samples for biomarker analysis are collected from patients with mCRPC (Part 1 and Part 2 Arms 1A and 1B) and LPC (Part 2 Arms 2 and 3) at time points shown in the SoA (see Section 13.6). Biomarker and pharmacodynamics parameters are analyzed by different laboratories (central laboratory and speciality laboratories).

8.8.1 Pharmacodynamic parameters

Clinical and immunological parameters assessed by qualified assays will be measured as part of Pharmacodynamic set and correlated with clinical response and outcome. As part of this SAP, the following listings will be provided for the Pharmacodynamic set:

Blood	Hormones (Testosterone):
	Cytokines: Interferon Alpha, Interleukin 6, Interleukin 10, Interferon Gamma, Interferon Gamma-induced Protein 10, Tumor Necrosis Factor alpha
	Tumor response and extension

Tissue (only available for LPC patients)	Immune cell infiltration in tumor bed

8.8.2 Exploratory Biomarker Analyses

Cellular immune responses and further immunological parameters will be analyzed as part of exploratory objective to identify potential predictive, pharmacodynamic, anti-tumor and safety biomarkers indicating activity of W_pro1 monotherapy or in combination with cemiplimab. The analyses except those for cytokines are not part of this SAP.

Table 8-1 provides an overview of the biomarker parameters:

Table 8-1: Biomarker Assessment - Overview

Rationale	Test
Safety	**Cytokines:** Interferon Alpha, Interleukin 6, Interleukin 10, Interferon Gamma, Interferon Gamma-induced Protein 10, Tumor Necrosis Factor alpha
MoA/PD	**Cellular immune response (Immunogenicity by Post IVS ELISpot)**
MoA/PD	**HLA typing:** HLA DP Beta1 Antigen, HLA DQ Beta1 Antigen, HLA DR Beta1 Antigen, HLA Class IA Antigen, HLA Class IB Antigen, HLA Class IC Antigen. Tumor associated antigen profile (PSA, ACPP, HOXB13, KLK2, NKX3-1)
MoA/PD	T cell profiling, TCR discovery & profiling, Reverse Immune Monitoring,
MoA/PD	Tumor composition, mutation burden & transcriptome (RNA)

HLA = human leukocyte antigen; ICS = intracellular cytokine staining; MoA/PD = mechanism (mode) of action/pharmacodynamics; TCR = T cell receptor.

The following exploratory endpoints based on biomarkers and pharmacodynamics parameters will be analyzed:

- Status of tumor mutational burden and immune-related gene expression (at the RNA level) in tumor tissue prior to treatment.
- Change in protein expression pattern/levels of tumor microenvironment markers (e.g., CD3, CD8, MHC-I, PD-L1, etc.) and prostate tumor markers (e.g., PSA, PSAP, NKX3-1, etc.) in tumor tissue post-treatment compared to baseline.
- Baseline status or change in RNA target expression of W_pro1–encoded antigens in the post-treatment tissue compared to baseline.
- Change in T cell clonality/diversity post-treatment compared to baseline.
- Changes in blood biomarkers prior to and during trial treatment.

These exploratory biomarker and pharmacodynamics analyses are not part of this SAP.

The respective analysis will be specified and performed in the context of the exploratory BioNTech biomarker report.

8.9 Safety analyses

Safety data that will be summarized include extent of exposure, AEs, occurrence of DLTs during Part 1, clinical laboratory assessments, vital signs and body weight, ECGs, physical examination and ECOG performance status (ECOG PS). All safety analyses will be based on the safety set and will be summarized by treatment groups, and for several combined treatment groups as defined in Section 13.4, unless otherwise stated.

Patients will be assigned to the treatment groups according to the actual treatment they have received (“as treated”).

All safety data will be listed for the safety set.

8.9.1 Primary safety endpoints dose-limiting toxicities and treatment-emergent adverse events

The primary endpoint is the occurrence of DLTs and TEAEs reported by relationship, grade, and seriousness according to NCI CTCAE v5.0. The number and percentage of patients with any DLT only for Part 1, and/or TEAEs in Part 1 and Part 2 will be presented.

Moreover, a patient listing will be provided with all relevant dose exposure data of all patients enrolled into Part 1 and Part 2, and a listing of all recorded DLTs and/or AEs will be presented including the reported term and SOC and PT terms coded usingMedDRA®, its time of onset, relationship, NCI CTCAE grade, and seriousness including dose exposure data (e.g., W_pro1 DL).

The respective analyses are specified in Section 8.9.3.

8.9.2 Extent of exposure

The following dose-exposure variables will be derived and analyzed for each IMP compound (W_pro1 and cemiplimab). The respective analyses for ADT are depending on the different kinds of ADT administered during the trial and will be defined at a later stage:

- Number of cycles (Total)
- Number of cycles with W_pro1, Number of cycles with cemiplimab, Number of ADT administrations
- Number of patients who stopped Part 2 mCRPC W_pro1 and switch to cemiplimab monotherapy
- Actual Treatment duration (weeks) for each compound defined as follows:

  (Date of last administration - date of first administration +1 + planned duration)/7, whereas the planned duration (days) is defined as the planned time between two consecutive administrations.
  Planned duration for cemiplimab is 21 days (to be used for the calculation of actual treatment duration).
  Planned duration for W_pro1 in the first 2 cycles is 7 days because there are 3 treatment administration planned (one every 7 days). Starting from Cycle 3 onwards,

the planned duration of W_pro1 is 21 days (only one treatment administration per cycle). To be used for the for the calculation of actual treatment duration.

ADT: Treatment duration (weeks): (Date of last administration - date of first administration + 1) / 7.

- Actual Cumulative Dose (µg) is defined as sum of all administered doses separate for W_pro1 (µg), cemiplimab (mg) and ADT (mg).

Dose Intensity (DI), Relative Dose Intensity (RDI), planned cumulative dose and planned treatment duration for W_pro1 and cemiplimab are defined as follows:

- DI is defined as Cumulative Dose (µg)/Treatment Duration (weeks)
- RDI is defined as follows:

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

whereas

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

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

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

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

Planned cumulative dose for W_pro1 and cemiplimab compounds is defined as follows:

- The planned dose of W_pro1 is CCI µg (CCI µg + CCI µg + CCI µg) for Cycle 1, CCI µg CCI µg + CCI µg + CCI µg) for Cycle 2, and CCI µg for all following cycles. In the case a patient has attended 5 cycles, the planned cumulative dose for W_pro1 is CCI µg, irrespectively if the patient has been treated at each cycle or not.
- The planned dose of cemiplimab is CCI mg per cycle. In the case a patient has attended 5 cycles, the planned cumulative dose of cemiplimab is CCI mg, irrespectively if the patient has been treated at each cycle or not.

Planned treatment duration (weeks) for W_pro1 and cemiplimab is defined as follows:

- W_pro1 and cemiplimab:
  Planned duration per cycle is 21 days.
  Planned treatment duration (weeks) = (number of cycles * 21)/7, irrespectively if the patient has been treated at each cycle or not.

For patients who did not receive any amount of a compound, the dose exposure parameters for that treatment (number of cycles, duration of treatment, cumulative dose, dose intensity, and relative dose intensity) will be set to 0.

Additionally, the relative dose intensity will be presented categorically (i.e., number and percentage of patients with relative dose intensity of < 60%, 60 - < 80%, 80 - < 90%, 90 - < 110%, ≥ 110%). Moreover, the number and percentage of patients with any dose delay, with any dose modification, and any dose interruption by compound will be presented.

All data will be listed.

8.9.3 Adverse events

AEs will be coded using the MedDRA® (version 22.1 or later version) coding system to get a SOC and PT for each AE and will be graded for severity using NCI CTCAE v5.0.

A **TEAE** is defined as any AE with an onset date on or after the first administration of IMP (if the AE was absent before the first administration of IMP (W_pro1 or cemiplimab, whichever comes first)) or worsened after the first administration of IMP (if the AE was present before the first administration of IMP).

AEs with an onset date more than 30 days (after the last administration of W_pro1) or 90 days (90 days after last administration of cemiplimab for Part 2, Arm 1A and Arm 2), respectively, after the last administration of W_pro1 or cemiplimab will be considered as treatment-emergent only if assessed as related to IMP by the investigator. TEAEs will be summarized overall and by treatment group for patients in the safety set.

For patients from Arm 1B who switch to cemiplimab monotherapy, the analysis of AEs will be additionally performed for each IMP separately, (i.e. only TEAEs from the first dose of W_pro1 until last dose of W_pro1 +30 days will be reported as TEAEs for Arm 1B).

In addition, **cemiplimab TEAEs** will be reported in separate AE tables using the subsequent cemiplimab monotherapy on progression set. Cemiplimab TEAEs are defined as TEAEs with an onset date on or after the first dose of cemiplimab until the last dose of cemiplimab +90 days. TEAEs with an onset within the 30 days after last dose of W_pro1 but after start of first cemiplimab treatment will be counted twice, as TEAE for Arm 1B and as cemiplimab TEAE in the respective tables and listings.

AEs started prior to first administration of IMP or AEs after last administration of IMP (follow-up AEs) will be included only in the AE listings.

<u>AEs related to W_pro1</u>

AEs related to W_pro1 are AEs with the item “Causality (relationship to W_pro1)” ticked “*Related*” in “*Adverse Events*” form of the eCRF. If the item is missing, the AE will be considered as related to W_pro1.

<u>AEs related to cemiplimab</u>

AEs related to cemiplimab are AEs with the item “Causality (relationship to cemiplimab)” ticked “*Related*” in “*Adverse Events*” form of the eCRF. If the item is missing, the AE will be considered as related to cemiplimab.

AEs related to IMP (W_pro1 + cemiplimab)

AEs related to IMP are AEs related to either W_pro1 or cemiplimab (or both).

AE leading to permanent study treatment discontinuation (any compound)

AE leading to discontinuation are the AEs with the items "*Action taken with W_pro1*" or "*Action taken with Cemiplimab*" ticked "Trial treatment permanently withdrawn".

AE leading to dose reduction (any compound)

AE leading to dose reduction are the AEs with the items "*Action taken with W_pro1*" or "*Action taken with Cemiplimab*" ticked "Dose reduced".

AE leading to dose delay (any compound)

AE leading to dose delay are the AEs with the items "*Action taken with W_pro1*" or "*Action taken with Cemiplimab"* ticked "Trial treatment withdrawn temporarily".

AE leading to dose modification (any compound)

AE leading to dose modification are the AEs with the items "*Action taken with W_pro1*" or "*Action taken with Cemiplimab*" ticked "Dose reduced" or "Trial treatment withdrawn temporarily".

Overall summary of treatment-emergent adverse events (TEAEs)

The number and percentage of patients reporting at least one TEAE will be summarized for each of the following AE types:

- Any TEAEs
- TEAEs related to IMP
- TEAEs related to W_pro1
- TEAEs related to Cemiplimab
- Grade ≥3 (Maximum intensity) TEAEs
- Grade ≥3 TEAEs related to IMP
- Grade ≥3 TEAEs related to W_pro1
- Grade ≥3 TEAEs related to Cemiplimab
- TEAEs related to trial procedure
- TEAEs related to prostate cancer surgery (Part 2 Arm 2 / Arm 3)
- Any Serious TEAEs
- Serious TEAEs related to IMP

- Serious TEAEs related to W_pro1
- Serious TEAEs related to Cemiplimab
- Serious TEAEs leading to death
- Serious TEAEs leading to death related to IMP
- Serious TEAEs leading to death related to W_pro1
- Serious TEAEs leading to death related to Cemiplimab
- TEAEs leading to IMP dose modification
- TEAEs leading to W_pro1 dose modification
- TEAEs leading to Cemiplimab dose modification
- TEAEs leading to IMP dose reduction
- TEAEs leading to W_pro1 dose reduction
- TEAEs leading to Cemiplimab dose reduction
- TEAEs leading to IMP dose delay
- TEAEs leading to W_pro1 dose delay
- TEAEs leading to Cemiplimab dose delay
- TEAEs leading to permanent discontinuation of IMP
- TEAEs leading to permanent discontinuation of W_pro1
- TEAEs leading to permanent discontinuation of Cemiplimab

For the analysis of Part 1 of the trial, the following AE types will be added in the overall summary of TEAEs:

- DLTs

Analyses of adverse events

The number and percentage of patients for each category above will be summarized by SOC and PT as per MedDRA. If a SOC / PT is reported more than once for a patient, the patient will only be counted once for this SOC / PT. All AE summary tables will be sorted by descending frequency (%) by SOC and by PT within SOC with respect to the Parts 1 and 2 Total column. The number of events will be summarized in the same table.

The following AE tables by SOC and PT will be generated:

- TEAEs by System Organ Class and Preferred Term
- TEAEs related to IMP by System Organ Class and Preferred Term
- TEAEs related to W_pro1 by System Organ Class and Preferred Term

- TEAEs related to Cemiplimab by System Organ Class and Preferred Term
- Grade ≥3 (Maximum intensity) TEAEs by System Organ Class and Preferred Term
- Grade ≥3 TEAEs related to IMP by System Organ Class and Preferred Term
- Grade ≥3 TEAEs related to W_pro1 by System Organ Class and Preferred Term
- Grade ≥3 TEAEs related to Cemiplimab by System Organ Class and Preferred Term
- TEAEs related to trial procedure by System Organ Class and Preferred Term
- TEAEs related to prostate cancer surgery (Part 2 Arm 2 / Arm 3) by System Organ Class and Preferred Term
- Any Serious TEAEs by System Organ Class and Preferred Term
- Serious TEAEs related to IMP by System Organ Class and Preferred Term
- Serious TEAEs related to W_pro1 by System Organ Class and Preferred Term
- Serious TEAEs related to Cemiplimab by System Organ Class and Preferred Term
- Serious TEAEs leading to death by System Organ Class and Preferred Term
- Serious TEAEs leading to death related to IMP by System Organ Class and Preferred Term
- Serious TEAEs leading to death related to W_pro1 by System Organ Class and Preferred Term
- Serious TEAEs leading to death related to Cemiplimab by System Organ Class and Preferred Term
- TEAEs leading to IMP dose reduction by System Organ Class and Preferred Term
- TEAEs leading to W_pro1 dose reduction by System Organ Class and Preferred Term
- TEAEs leading to Cemiplimab dose reduction by System Organ Class and Preferred Term
- TEAEs leading to IMP dose delay by System Organ Class and Preferred Term
- TEAEs leading to W_pro1 dose delay by System Organ Class and Preferred Term
- TEAEs leading to Cemiplimab dose delay by System Organ Class and Preferred Term
- TEAEs leading to IMP dose modification by System Organ Class and Preferred Term
- TEAEs leading to W_pro1 dose modification by System Organ Class and Preferred Term
- TEAEs leading to Cemiplimab dose modification by System Organ Class and Preferred Term
- TEAEs leading to permanent discontinuation of IMP by System Organ Class and Preferred Term
- TEAEs leading to permanent discontinuation of W_pro1 by System Organ Class and Preferred Term

- TEAEs leading to permanent discontinuation of Cemiplimab by System Organ Class and Preferred Term

For the analysis of Part 1 of the trial, the following AE tables by SOC and PT will be generated:

- DLTs by System Organ Class and Preferred Term

In addition, the number and percentages of patients reporting the most frequent TEAEs (PT >= 5% in any treatment group) will be summarized by PT only.

Similar tables to be generated for

- Most frequent TEAEs (>= 5%) related to IMP by Preferred Term
- Most frequent TEAEs (>= 5%) related to W_pro1 by Preferred Term
- Most frequent TEAEs (>= 5%) related to Cemiplimab by Preferred Term

TEAEs by IMP relationship:

The number and percentages of patients with TEAEs will be summarized by relationship to IMP (IMP related and not IMP related) by PT nested within SOC. The worst relationship to IMP will be counted if a TEAE is reported more than once by the same patients for this SOC / PT. Same tables will be generated for TEAEs by relationship to W_pro1 (related to W_pro1 and not related to W_pro1) and by relationship to Cemiplimab (related to Cemiplimab and not related to Cemiplimab).

TEAEs by worst NCI-CTCAE grade:

Moreover, the number and percentage of patients with any TEAE will be summarized by worst NCI CTCAE grade by PT nested within SOC. Only the worst grade will be counted if a TEAE is reported more than once by the same patients for the SOC / PT. The same tables will be generated for TEAEs related to IMP by worst NCI CTCAE grade, TEAEs related to W_pro1 by worst NCI CTCAE grade and TEAEs related to Cemiplimab by worst NCI CTCAE grade.

TEAE table per CT.gov.req:

Moreover, the number and percentage of patients with any non-serious TEAE will be summarized by SOC and PT. A table for non-serious TEAE (> 3% of patients in any treatment arm at the PT level) will be generated .

For patients from Arm 1B who switch to cemiplimab monotherapy, separate AE tables summarizing cemiplimab TEAEs using the safety subsequent cemiplimab monotherapy on progression set will be generated.

Overall summary of cemiplimab TEAEs

The number and percentage of patients reporting at least one cemiplimab TEAE will be summarized for each of the following AE types:

- Any TEAEs
- TEAEs related to Cemiplimab
- Grade ≥3 (Maximum intensity) TEAEs
- Grade ≥3 TEAEs related to Cemiplimab
- Any serious TEAEs
- Serious TEAEs related to Cemiplimab
- Serious TEAEs leading to death
- Serious TEAEs leading to death related to Cemiplimab
- TEAEs leading to Cemiplimab dose modification
- TEAEs leading to Cemiplimab dose reduction
- TEAEs leading to Cemiplimab dose delay
- TEAEs leading to permanent discontinuation of Cemiplimab

The following AE tables by SOC and PT will be generated for cemiplimab TEAEs:

- TEAEs by System Organ Class and Preferred Term
- TEAEs related to Cemiplimab by System Organ Class and Preferred Term
- Grade ≥ 3 (Maximum intensity) TEAEs
- Grade ≥ 3 TEAEs related to Cemiplimab by System Organ Class and Preferred Term
- Any serious TEAEs by System Organ Class and Preferred Term
- Serious TEAEs related to Cemiplimab by System Organ Class and Preferred Term
- Serious TEAEs leading to death by System Organ Class and Preferred Term
- Serious TEAEs leading to death related to Cemiplimab by System Organ Class and Preferred Term
- TEAEs leading to Cemiplimab dose reduction by System Organ Class and Preferred Term
- TEAEs leading to Cemiplimab dose delay by System Organ Class and Preferred Term
- TEAEs leading to Cemiplimab dose modification by System Organ Class and Preferred Term
- TEAEs leading to permanent discontinuation of Cemiplimab by System Organ Class and Preferred Term

AE listings

All AEs will be listed. Further, all deaths, SAEs, all AEs leading to death, and AEs leading to permanent discontinuation of IMP (W_pro1 and/or cemiplimab) will be listed. Cemiplimab TEAEs in Arm 1B will be flagged in the AE listings.

For Part 1 a listing of DLTs will be generated.

8.9.4 Laboratory assessments

Clinical laboratory data to be summarized include hematology, blood chemistry, coagulation, thyroid hormones and urinalysis. The clinical laboratory parameters to be assessed are listed in Table 8-2 and the scheduled time points for assessment are presented in the SoA (see Section 13.6).

All laboratory parameters, except serology assessments, are reported in the clinical database using local safety laboratories. Measurements and corresponding Low and High ranges will be converted into Standard International (SI) units. Values outside the normal ranges are classified as “Not clinically significant” or “Clinically significant” by the investigator.

Serology parameters are analyzed by a central laboratory.

For the derivation of the minimum post-baseline measurement / maximum post-baseline measurement / or worst post-baseline toxicity CTC grades, measurements collected at unscheduled visits will be considered.

The End of Study measurement is defined as last available safety assessment, either at Safety FU D30 or Safety FU D90 Visit (whichever occurs later) or last available safety assessment in case of early trial discontinuation or death. Measurements after switch to cemiplimab monotherapy will not be considered in the derivation of the End of Study measurement.

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

The number and percentage of patients reporting markedly abnormal clinical laboratory values as reported by the investigator at any point on the trial will be summarized for each parameter by visit and treatment group using the following categories: Clinically significant low, Low, Normal, High, Clinically significant high.

Shift tables from baseline to Minimum Post-baseline / Maximum Post-baseline and to End of Study measurement with respect to reference range values (Clinically significant low, Low, Normal, High, Clinically significant high) will be generated for each parameter by treatment group.

Clinical laboratory results will be classified according to of NCI CTCAE v5.0. Laboratory results not corresponding to a NCI CTCAE term will not be graded. CTC grades for the respective parameters will be reported using the following categories: Grade 0, Grade 1, Grade 2, Grade 3, Grade 4 by visit and treatment group. Shift tables from baseline to worst post-baseline toxicity grade and to End of Study measurement will be provided for each laboratory parameter by treatment group.

A list or laboratory parameters to be analyzed by CTC grades is available in Section 13.6.

Urinalysis, dipstick results will be reported only by number of patients and percentage for each parameter by visit and treatment group.

Microscopic urinalysis parameters (where available), serology parameters and circulating tumor cells will be listed only.

All clinical laboratory data will also be presented in the data listings. Abnormal clinical laboratory values and clinically significant values as reported by the investigator will be flagged in the listing.

Table 8-2: Local Safety Laboratory Tests (Blood and Urine) - Overview

Parameters (by group)
Hematology: hemoglobin, hematocrit, red blood cell count (RBC), white blood cell count (WBC) and differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), platelet count
Coagulation*:* international normalized ratio (INR), activated partial thromboplastin time, fibrinogen
Blood chemistry: alkaline phosphatase (ALP), creatinine, ferritin, C-reactive protein (CRP), albumin, alanine aminotransferase (ALT), amylase, aspartate aminotransferase (AST), gamma glutamyl transpeptidase (GGT), total bilirubin, blood urea nitrogen (BUN), glucose, lipase, sodium, potassium, calcium
Thyroid Hormones (only collected for Arm 1A and Arm 2) thyroid function (thyroid stimulating hormone [TSH], free thyroxine [fT4], free triiodothyronine [fT3] and total triiodothyronine [T3])
Urinalysis: **Dipstick**: specific gravity, pH, glucose, protein, ketones, blood **Microscopic urinalysis:** If warranted by dipstick results, urine sediment will be microscopically examined for presence of red blood cells, white blood cells, casts, crystals, epithelial cells, and bacteria
Circulating tumor cells (optional)
Serology (provided by a central laboratory): Hepatitis B Virus Core Antibody, Hepatitis B Virus Core IgM Antibody, Hepatitis B Virus Surface Antigen, Hepatitis B Virus Surface Antibody, Hepatitis C Virus Antibody, HIV-1/2 Antibody + HIV-1 p24 Antigen The following serology parameters will be provided only in case of positive findings in the normal serology tests above: Hepatitis C Virus RNA, Hepatitis B Virus Surface Antibody (quantitative), Hepatitis B Virus e Antigen, Hepatitis B Virus DNA, HIV-1 p24 Antigen, HIV-1/2 Antibody, HIV 1 (Blot), HIV 2 (Blot), HIV-1 RNA

8.9.5 Vital signs

Vital sign parameters (blood pressure, pulse rate, and body temperature) and the scheduled visits and time points (pre-treatment or post-treatment) for assessments are presented in the SoA (see Section 13.6).

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. In addition, weight and BMI reported at Screening, C4 D1, EoT, Safety FU D30 and Safety FU D90 Visit (where applicable) will be summarized in the same way.

The End of Study measurement is defined as last available safety assessment, either at Safety FU D30 or Safety FU D90 Visit (whichever occurs later) or last available safety assessment in case of early trial discontinuation or death. Measurements after switch to cemiplimab monotherapy will not be considered in the derivation of the End of Study measurement.

Vital sign values for each parameter will be assigned an LNH classification according to whether the value is lower (L), within (N), or higher (H) the reference range for that parameter. The values will be summarized using shift tables from baseline to End of Study measurement with respect to reference range values (low, normal, high) for each parameter by treatment group.

Table 8-3: Normal Ranges for Vital Signs

Parameter	Range
Systolic blood pressure	90-140 mmHg
Diastolic blood pressure	40-90 mmHg
Pulse rate	40-100 bpm
Temperature (where applicable)	≤ 38 °C

Scatter plots will be produced for each vital signs parameter comparing baseline and End of Study measurement.

All vital sign data will also be presented in the data listings, abnormal values will be flagged.

8.9.6 ECG

ECGs parameters and the scheduled visits for assessment are presented in the SoA (see Section 13.6).

ECGs will be judged by the investigator as normal, abnormal not clinically significant (NCS) or abnormal clinically significant (CS). The number and percentage of patients with clinically significant ECG findings will be summarized by treatment group for visit.

Ventricular heart rate (bpm) at each visit and change from baseline to each post-baseline time point will be summarized using descriptive summary statistics by treatment group.

All ECG parameters will also be presented in the data listings.

8.9.7 Physical examination

Comprehensive physical examinations will be performed at screening. During the treatment, the investigators should make an overall health judgement and make only in-depth examinations if clinically indicated.

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

The complete physical examination at screening including the following body systems: General Appearance, Head and Neck, Skin, Eyes, Ears, Nose & Throat, Lungs, Heart, Abdomen, Lymph Nodes, Musculoskeletal System (including Extremities and Spine), Neurological Findings, Genito-Urinary System, Anus/Rectum, and Other.

At all visits after screening, an abbreviated physical examination will be performed.

The abbreviated physical examination includes an overall health judgement (any new or worsened abnormalities since previous assessment [Y/N]) and brief interim history (change of symptoms). In-depth physical examinations are required if obvious pathological signs are visible or in the case the patient states any signs or symptoms.

The number and percentage of patients with assessments of normal, abnormal NCS, abnormal CS at screening visit will be displayed in a summary table for each body system. For visits after Screening, the number of percentages of patients with any new or worsened abnormalities since previous assessment will be presented. Details regarding the new or worsened abnormalities will be reported in the physical examination listing.

All physical examination data will be listed.

8.9.8 ECOG PS

ECOG PS will be assessed according to the SoA (see Section 13.6).

The following ECOG PS categories will be reported:

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair

GRADE	ECOG PERFORMANCE STATUS
5	Dead

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

The number and percentage of patients in each ECOG PS category will be summarized by visit and treatment group.

Shift tables from baseline to the D1 post baseline visits for each cycle with respect to ECOG PS categories by treatment group will be generated. All ECOG PS data will be listed.

9 QUALITY CONTROL

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. An overview of the development of programs is detailed in Syneos Health Developing Statistical Programs SOP (3907).

Syneos Health Developing Statistical Programs SOP (3907), Conducting the Transfer of Biostatistical Deliverables SOP (3908) and the SAS Programming and Validation Plan (version 2.0, dated 23 APR 2021) describes the quality control procedures that are performed for all SAS programs and output. Quality control (QC) is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

10 PROGRAMMING CONSIDERATIONS

All tables, data listings, figures, and statistical analyses will be generated using SAS® for Windows, Release 9.4 or higher (SAS® Institute Inc., Cary, NC, USA). Computer-generated table, listing, and figure output will adhere to the following specifications.

10.1 General Considerations

- A separate SAS program will be created for each output.
- Each output will be stored in a separate file.
- Output files will be delivered in rtf format. In addition, 3 combined pdf files for tables, figures and listings will be delivered (combined pdf file including bookmarks).
- Numbering of TFLs will follow ICH E3 guidance.

10.2 Table, Listing, and Figure Format

10.2.1 General

- All TFLs will be produced in A4 landscape format, unless otherwise specified.
- All TFLs will be produced using the Arial font, size 9 for Header and Body. Arial font, size 8 in Footer.
- The data displays for all TFLs will have a Top / Left / Bottom / Right:1 inch (2.54 cm), 1 inch (2.54 cm), 0.5 inch (1.27 cm), 0.5 inch (1.27 cm) blank margin on all sides.
- Headers for figures will be in Arial font, size 9, footers for figures will be in Arial font, size 8.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TFLs will be in black and white (no color).
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TFLs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used.
- Only standard keyboard characters will be used in the TFLs. Special characters, such as nonprintable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., µ). Certain subscripts and superscripts (e.g., cm2, Cmax) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer supplied formats, as appropriate.

10.2.2 Headers

- All output should have the following header at the top left of each page:
- BioNTech SE Protocol: RN5609C00

- Draft/Final Run <*date*>

- All output should have Page n of N at the top or bottom right corner of each page. TFLs are internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).

- The date output was generated should appear along with the program name as a footer on each page.

10.2.3 Display Titles

- Each TFL are identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering will be applied for the current trial. A decimal system (x.y and x.y.z) are used to identify TFLs with related contents. The title is centered. The analysis set are identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the Column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z: First Line of Title
Second Line of Title if Needed - ITT Set

10.2.4 Column Headers

- Column headings are displayed immediately below the solid line described above in initial upper-case characters.

- For numeric variables, include “unit” in column or row heading when appropriate.

- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings, if applicable). This is distinct from the “n” used for the descriptive statistics representing the number of patients in the analysis set.

- The order of treatments in the tables and listings will Active comparators first, followed by a total column (if applicable).

10.2.5 Body of the Data Display

10.2.5.1 General Conventions

Data in columns of a table or listing are formatted as follows:

- Alphanumeric values are left-justified;

- Whole numbers (e.g., counts) are center-justified; and
- Numbers containing fractional portions are center-justified.

10.2.5.2 Table Conventions

- Units will be included where available
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category are presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	n
Mild	0
Moderate	8
Severe	3

- Where percentages are presented in these tables, zero percentages will not be presented and so counts of 0 will be presented as 0 and not as 0 (0%).
- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Trial, etc.), then only those categories for which there is at least 1 patient represented in 1 or more groups are included.
- Unless otherwise specified, the estimated mean and median for a set of values are printed out to 1 more significant digit than the original values, and standard deviations are printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

n	XX
Mean	XXX.X
Std Dev	X.XX
Median	XXX.X
Minimum	XXX
Maximum	XXX

- P-values are output in the format: “0.xxx”, where xxx is the value rounded to 3 decimal places. Every p-value less than 0.001 will be presented as <0.001. If the p-value is returned as >0.999, then present as >0.999.
- Percentage values are printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Unless otherwise noted, for all percentages, the number of patients in the analysis set for the treatment group who have an observation will be the denominator. Percentages after zero counts should not be displayed and percentages equating to 100% are presented as 100%, without decimal places.
- The percentage of patients is normally calculated as a proportion of the number of patients assessed in the relevant treatment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of patients exposed. Describe details of this in footnotes or programming notes.
- For categorical summaries (number and percentage of patients) where a patient can be included in more than one category, describe in a footnote or programming note if the patient are included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.

10.2.5.3 Listing Conventions

- Listings will be sorted for presentation in order of treatment groups as above, patient number, visit/collection day, and visit/collection time.
- Dates are printed in SAS DATE9.format (“ddMMMyyyy”: 01JUL2000). Missing portions of dates are represented on patient listings as dashes (--JUL2000).
- All observed time values are to be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the trial.
- Units will be included where available

10.2.5.4 Figure Conventions

- Unless otherwise specified, for all figures, trial visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis.

10.2.6 Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Patient specific footnotes are avoided, where possible.
- Footnotes will be used sparingly and add value to the table, figure, or listing. If more than six lines of footnotes are planned, then a cover page is strongly recommended to be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, date the program was run, (i.e., Program name: myprogram; Run Date/time: ddmmmyyyy hh:mm).

11 TABLE OF CONTENTS FOR TABLES, FIGURES AND LISTINGS

This section contains lists of the summary table, figures and listings tentatively planned for this trial. Changes in the number or content of planned TFLs are not considered deviations from this SAP.

The TFLs to be generated for the Interim Analysis are flagged with a “Yes” in the corresponding columns in the sections below.

The decision which TFLs to be generated for the Follow-up Analysis will be specified after the main analysis is available.

11.1.1 Tables

Header	Table Number	Name	Analysis Set	Interim Analysis
14.		TABLES		
14.1		Demographic Data		
14.1.1		Patient Disposition		
	14.1.1.1	Screening failures	Screened set	
	14.1.1.2	Analysis sets	Screened set	Yes
	14.1.1.3	Enrollment by site	Screened set	
	14.1.1.4	Patient disposition	ITT set	Yes
14.1.2		Protocol Deviations		
	14.1.2.1	Important protocol deviations	ITT set	
	14.1.2.2	Important protocol deviations due to COVID-19	ITT set	
14.1.3		Demographic and Baseline Characteristics		
14.1.3.1		Patient Demographic and Baseline Characteristics		
	14.1.3.1.1	Demographic and baseline characteristics	mITT set	Yes
	14.1.3.1.2	Demographic and baseline characteristics (optional)	Safety set	
	14.1.3.1.3	Demographic and baseline characteristics (optional)	ITT set	
	14.1.3.1.4	Demographic and baseline characteristics (optional)	PP set	
14.1.3.2		Baseline Disease Characteristics		
	14.1.3.2.1	Disease characteristics	mITT set	Yes
	14.1.3.2.2	Disease characteristics – TNM Stage	mITT set	Yes
	14.1.3.2.3	Disease characteristics – Imaging (PCWG3)	mITT set	Yes
	14.1.3.2.4	Prior therapy lines	mITT set	Yes
	14.1.3.2.5	Prior therapy types	mITT set	
	14.1.3.2.6	Prior cancer surgeries	mITT set	
	14.1.3.2.7	Prior systemic cancer therapies	mITT set	
14.1.4		Medications		
	14.1.4.1.1	Prior medications	mITT set	
	14.1.4.1.2	Concomitant medications	mITT set	
		Medical History		

Header	Table Number	Name	Analysis Set	Interim Analysis
	14.1.4.2.1	Prior medical history	mITT set	
	14.1.4.2.2	Concomitant diseases	mITT set	
14.1.5		Other Procedures		
	14.1.5.1	Cancer radiotherapies	mITT set	
	14.1.5.2	Procedures and non-drug therapies	mITT set	
14.1.6		Exposure		
	14.1.6.1	Exposure to IMP/NIMP: Number of cycles	Safety set	Yes
	14.1.6.2	Exposure to IMP/NIMP: Dose intensities	Safety set	Yes
	14.1.6.3	Exposure to IMP/NIMP: Dose delays, reductions and interruptions	Safety set	Yes
14.2		Efficacy Data		
14.2.1		Primary Efficacy Parameter Objective Response Rate		
	14.2.1.1.1	Objective Response Rate (ORR) based on PCWG3	mITT set	Yes
	14.2.1.1.1a	Objective Response Rate (ORR) based on PCWG3, SAS output	mITT set	
	14.2.1.1.2	Objective Response Rate (ORR) based on PCWG3	ITT set	Yes
	14.2.1.1.2a	Objective Response Rate (ORR) based on PCWG3, SAS output	ITT set	
	14.2.1.1.3	Objective Response Rate (ORR) based on PCWG3	PP set	
	14.2.1.1.3a	Objective Response Rate (ORR) based on PCWG3, SAS output	PP set	
		Subgroup Analyses		
	14.2.1.1.1.1	Objective Response Rate (ORR) based on PCWG3 by age category	mITT set	
	14.2.1.1.1.1a	Objective Response Rate (ORR) based on PCWG3 by age category, SAS output	mITT set	
	14.2.1.1.1.2	Objective Response Rate (ORR) based on PCWG3 by subgroup 2	mITT set	
	14.2.1.1.1.2a	Objective Response Rate (ORR) based on PCWG3 by subgroup 2, SAS output	mITT set	
	14.2.1.1.4	Objective Response Rate (ORR) based on Radiological Soft Tissue Evaluation per Investigator	mITT set	Yes
	14.2.1.1.5	Clinical Progression	mITT set	Yes
14.2.2		Secondary Efficacy Parameters		
14.2.2.1		Secondary Efficacy Parameter 1: PSA decline		
	14.2.2.1.1	PSA decline for each visit compared to baseline (including all PSA data as reported)	mITT set	
	14.2.2.1.2	PSA decline for each visit compared to baseline (including all PSA data as reported) (optional)	ITT set	

Header	Table Number	Name	Analysis Set	Interim Analysis
	14.2.2.1.3	PSA decline for each visit compared to baseline (including all PSA data as reported) (optional)	PP set	
	14.2.2.2	Best PSA decline compared to baseline	mITT set	Yes
Figure	14.2.2.2.1	PSA decline (Categorization 1): Bar Chart for each visit compared to baseline (including all PSA data as reported)– mITT set – mCRPC patients	mITT set	
Figure	14.2.2.2.2	PSA decline (Categorization 1): Bar Chart for each visit compared to baseline (including all PSA data as reported)– mITT set – LPC patients	mITT set	
Figure	14.2.2.2.3	PSA decline (Categorization 2): Bar Chart for each visit compared to baseline (including all PSA data as reported)– mITT set – mCRPC patients	mITT set	
Figure	14.2.2.2.4	PSA decline (Categorization 2): Bar Chart for each visit compared to baseline (including all PSA data as reported)– mITT set – LPC patients	mITT set	
	14.2.2.3.1	PSA decline: Summary by visit and percentage change from baseline (including all PSA data as reported)	mITT set	
	14.2.2.3.2	PSA decline: Summary by visit and percentage change from baseline (including all PSA data as reported) (optional)	ITT set	
	14.2.2.3.3	PSA decline: Summary by visit and percentage change from baseline (including all PSA data as reported) (optional)	PP set	
Figure	14.2.2.4.1	PSA decline: Waterfall plot of maximum decline from baseline – mITT set – mCRPC patients	mITT set	
Figure	14.2.2.4.2	PSA decline: Waterfall plot of maximum decline from baseline – mITT set – LPC patients	mITT set	
Figure	14.2.2.4.3	PSA decline: Waterfall plot of maximum decline from baseline – ITT set – mCRPC patients (optional)	ITT set	
Figure	14.2.2.4.4	PSA decline: Waterfall plot of maximum decline from baseline – ITT set – LPC patients (optional)	ITT set	
Figure	14.2.2.4.5	PSA decline: Waterfall plot of maximum decline from baseline – PP set – mCRPC patients (optional)	PP set	
Figure	14.2.2.4.6	PSA decline: Waterfall plot of maximum decline from baseline – PP set set – LPC patients (optional)	PP set	
	14.2.2.5.1	PSA response per PCWG3 criteria (including all PSA data as reported)	mITT set	

Header	Table Number	Name	Analysis Set	Interim Analysis
	14.2.2.5.2	PSA response per PCWG3 criteria (including all PSA data as reported) (optional)	ITT set	
	14.2.2.5.3	PSA response per PCWG3 criteria (including all PSA data as reported) (optional)	PP set	
	14.2.2.5.4	Objective Response Rate (ORR) based on PSA per PCWG3 Criteria	mITT set	Yes
		Secondary Efficacy Parameter 2: PSA doubling time		
	14.2.2.6.1	PSA doubling time (PSADT)	mITT set	
	14.2.2.6.2	PSA doubling time (PSADT) (optional)	ITT set	
	14.2.2.6.3	PSA doubling time (PSADT) (optional)	PP set	
		Secondary Efficacy Parameter 3: Tumor response post-treatment compared to baseline		
	14.2.2.7.1	Tumor assessment post-treatment compared to baseline based on Radiological Soft Tissue Evaluation per Investigator	mITT set	
	14.2.2.7.2	Tumor assessment post-treatment compared to baseline based on Radiological Soft Tissue Evaluation per Investigator (optional)	ITT set	
	14.2.2.7.3	Tumor assessmente post-treatment compared to baseline based on Radiological Soft Tissue Evaluation per Investigator (optional)	PP set	
14.2.3		Exploratory Efficacy Parameters		
	14.2.3.1.1	Objective Response Rate (ORR) based on iRECIST (central reading)	mITT set	
	14.2.3.1.2	Objective Response Rate (ORR) based on iRECIST (central reading) (optional)	ITT set	
	14.2.3.1.3	Objective Response Rate (ORR) based on iRECIST (central reading) (optional)	PP set	
	14.2.3.2.1	Duration of Response (DoR) based on PCWG3	mITT set	Yes
	14.2.3.2.1a	Duration of Response (DoR) based on PCWG3, SAS output	mITT set	Yes
Figure	14.2.3.2.2	Kaplan-Meier curve of Duration of Response (DoR) based on PCWG3 - mCRPC patients	mITT set	Yes
	14.2.3.2.3	Duration of Response (DoR) based on PCWG3 (optional)	ITT set	Yes
	14.2.3.2.3a	Duration of Response (DoR) based on PCWG3, SAS output (optional)	ITT set	Yes
Figure	14.2.3.2.4	Kaplan-Meier curve of Duration of Response (DoR) based on PCWG3 - mCRPC patients (optional)	ITT set	Yes
	14.2.3.2.5	Duration of Response (DoR) based on PCWG3 (optional)	PP set	
	14.2.3.2.5a	Duration of Response (DoR) based on PCWG3, SAS output (optional)	PP set	

Header	Table Number	Name	Analysis Set	Interim Analysis
Figure	14.2.3.2.6	Kaplan-Meier curve of Duration of Response (DoR) based on PCWG3 - mCRPC patients (optional)	PP set	
		Subgroup Analyses		
	14.2.3.2.2.1	Duration of Response (DoR) based on PCWG3 by age category	mITT set	
	14.2.3.2.2.1a	Duration of Response (DoR) based on PCWG3 by age category, SAS output	mITT set	
Figure	14.2.3.2.2.2	Kaplan-Meier curve of Duration of Response (DoR) based on PCWG3 - mCRPC patients by age category	mITT set	
	14.2.3.2.2.3	Duration of Response (DoR) based on PCWG3 by subgroup 2	mITT set	
	14.2.3.2.2.3a	Duration of Response (DoR) based on PCWG3 by subgroup 2, SAS output	mITT set	
Figure	14.2.3.2.2.4	Kaplan-Meier curve of Duration of Response (DoR) based on PCWG3 - mCRPC patients by subgroup 2	mITT set	
	14.2.3.3.1	Duration of Response (DoR) based on iRECIST (central reading)	mITT set	
	14.2.3.3.1a	Duration of Response (DoR) based on iRECIST (central reading), SAS output	mITT set	
Figure	14.2.3.3.2	Kaplan-Meier curve of Duration of Response (DoR) based on iRECIST (central reading) - mCRPC patients	mITT set	
	14.2.3.3.3	Duration of Response (DoR) based on iRECIST (central reading) (optional)	ITT set	
	14.2.3.3.3a	Duration of Response (DoR) based on iRECIST (central reading), SAS output (optional)	ITT set	
Figure	14.2.3.3.4	Kaplan-Meier curve of Duration of Response (DoR) based on iRECIST (central reading) - mCRPC patients (optional)	ITT set	
	14.2.3.3.5	Duration of Response (DoR) based on iRECIST (central reading) (optional)	PP set	
	14.2.3.3.5a	Duration of Response (DoR) based on iRECIST (central reading), SAS output (optional)	PP set	
Figure	14.2.3.3.6	Kaplan-Meier curve of Duration of Response (DoR) based on iRECIST (central reading) - mCRPC patients (optional)	PP set	
	14.2.3.4.1	Progression-free Survival (PFS) based on PCWG3	mITT set	Yes
	14.2.3.4.1a	Progression-free Survival (PFS) based on PCWG3, SAS output	mITT set	Yes
Figure	14.2.3.4.2	Kaplan-Meier curve for Progression-free Survival (PFS) based on PCWG3 - mCRPC patients	mITT set	Yes
Figure	14.2.3.4.3	Kaplan-Meier curve for Progression-free Survival (PFS) based on PCWG3 - LPC patients	mITT set	

Header	Table Number	Name	Analysis Set	Interim Analysis
	14.2.3.4.4	Progression-free Survival (PFS) based on PCWG3 (optional)	ITT set	Yes
	14.2.3.4.4a	Progression-free Survival (PFS) based on PCWG3, SAS output (optional)	ITT set	Yes
Figure	14.2.3.4.5	Kaplan-Meier curve for Progression-free Survival (PFS) based on PCWG3 - mCRPC patients (optional)	ITT set	Yes
Figure	14.2.3.4.6	Kaplan-Meier curve for Progression-free Survival (PFS) based on PCWG3 - LPC patients (optional)	ITT set	
	14.2.3.4.7	Progression-free Survival (PFS) based on PCWG3 (optional)	PP set	
	14.2.3.4.7a	Progression-free Survival (PFS) based on PCWG3, SAS output (optional)	PP set	
Figure	14.2.3.4.8	Kaplan-Meier curve for Progression-free Survival (PFS) based on PCWG3 – mCRPC patients (optional)	PP set	
Figure	14.2.3.4.9	Kaplan-Meier curve for Progression-free Survival (PFS) based on PCWG3 – LPC patients (optional)	PP set	
		Subgroup Analyses		
	14.2.3.4.3.1	Progression-free Survival (PFS) based on PCWG3 by age category	mITT set	
	14.2.3.4.3.1a	Progression-free Survival (PFS) based on PCWG3 by age category, SAS output	mITT set	
Figure	14.2.3.4.3.2	Kaplan-Meier curve for Progression-free Survival (PFS) based on PCWG3 by age category - mCRPC patients	mITT set	
Figure	14.2.3.4.3.3	Kaplan-Meier curve for Progression-free Survival (PFS) based on PCWG3 by age category - LPC patients	mITT set	
	14.2.3.4.3.4	Progression-free Survival (PFS) based on PCWG3 by subgroup 2	mITT set	
	14.2.3.4.3.4a	Progression-free Survival (PFS) based on PCWG3 by subgroup 2, SAS output	mITT set	
Figure	14.2.3.4.3.5	Kaplan-Meier curve for Progression-free Survival (PFS) based on PCWG3 by subgroup 2 - mCRPC patients	mITT set	
Figure	14.2.3.4.3.6	Kaplan-Meier curve for Progression-free Survival (PFS) based on PCWG3 by subgroup 2 - LPC patients	mITT set	
	14.2.3.5.1	Progression-free Survival (PFS) based on iRECIST (central reading)	mITT set	
	14.2.3.5.1a	Progression-free Survival (PFS) based on iRECIST (central reading), SAS output	mITT set	
Figure	14.2.3.5.2	Kaplan-Meier curve for Progression-free Survival (PFS) based on iRECIST (central reading) – mCRPC patients	mITT set	
	14.2.3.5.3	Progression-free Survival (PFS) based on iRECIST (central reading) (optional)	ITT set	

Header	Table Number	Name	Analysis Set	Interim Analysis
	14.2.3.5.3a	Progression-free Survival (PFS) based on iRECIST (central reading), SAS output (optional)	ITT set	
Figure	14.2.3.5.4	Kaplan-Meier curve for Progression-free Survival (PFS) based on iRECIST (central reading) – mCRPC patients (optional)	ITT set	
	14.2.3.5.5	Progression-free Survival (PFS) based on iRECIST (central reading) (optional)	PP set	
	14.2.3.5.5a	Progression-free Survival (PFS) based on iRECIST (central reading), SAS output (optional)	PP set	
Figure	14.2.3.5.6	Kaplan-Meier curve for Progression-free Survival (PFS) based on iRECIST (central reading) – mCRPC patients (optional)	PP set	
	14.2.3.6.1	Overall Survival (OS)	mITT set	
	14.2.3.6.1a	Overall Survival (OS) SAS output	mITT set	
Figure	14.2.3.6.2	Kaplan-Meier curve for Overall Survival (OS) – mCRPC patients	mITT set	
Figure	14.2.3.6.3	Kaplan-Meier curve for Overall Survival (OS) – LPC patients	mITT set	
	14.2.3.6.4	Overall Survival (OS) (optional)	ITT set	
	14.2.3.6.4a	Overall Survival (OS) SAS output (optional)	ITT set	
Figure	14.2.3.6.5	Kaplan-Meier curve for Overall Survival (OS) – mCRPC patients (optional)	ITT set	
Figure	14.2.3.6.6	Kaplan-Meier curve for Overall Survival (OS) – LPC patients (optional)	ITT set	
	14.2.3.6.7	Overall Survival (OS) (optional)	PP set	
	14.2.3.6.7a	Overall Survival (OS) SAS output (optional)	PP set	
Figure	14.2.3.6.8	Kaplan-Meier curve for Overall Survival (OS) mCRPC patients (optional)	PP set	
Figure	14.2.3.6.9	Kaplan-Meier curve for Overall Survival (OS) LPC patients (optional)	PP set	
14.2.4		Exploratory Efficacy Parameters for patients in Arm 1B who are treated with cemiplimab Monotherapy		
	14.2.4.1.1	Objective Response Rate (ORR) based on PCWG3	Cemi Mono on PD set	
	14.2.4.1.2	Objective Response Rate (ORR) based on iRECIST (central reading)	Cemi Mono on PD set	
	14.2.4.1.3	Duration of Response (DoR) based on PCWG3	Cemi Mono on PD set	
	14.2.4.1.3a	Duration of Response (DoR) based on PCWG3, SAS output	Cemi Mono on PD set	
Figure	14.2.4.1.4	Kaplan-Meier curve of Duration of Response (DoR) based on PCWG3	Cemi Mono on PD set	
	14.2.4.1.5	Duration of Response (DoR) based on iRECIST (central reading)	Cemi Mono on PD set	

Header	Table Number	Name	Analysis Set	Interim Analysis
	14.2.4.1.5a	Duration of Response (DoR) based on iRECIST (central reading), SAS output	Cemi Mono on PD set	
Figure	14.2.4.1.6	Kaplan-Meier curve of Duration of Response (DoR) based on iRECIST (central reading)	Cemi Mono on PD set	
	14.2.4.1.7	Progression-free Survival (PFS) based on PCWG3	Cemi Mono on PD set	
	14.2.4.1.7a	Progression-free Survival (PFS) based on PCWG3, SAS output	Cemi Mono on PD set	
Figure	14.2.4.1.8	Kaplan-Meier curve for Progression-free Survival (PFS) based on PCWG3	Cemi Mono on PD set	
	14.2.4.1.9	Progression-free Survival (PFS) based on iRECIST (central reading)	Cemi Mono on PD set	
	14.2.4.1.9a	Progression-free Survival (PFS) based on iRECIST (central reading), SAS output	Cemi Mono on PD set	
Figure	14.2.4.1.10	Kaplan-Meier curve for Progression-free Survival (PFS) based on iRECIST (central reading)	Cemi Mono on PD set	
	14.2.4.1.11	Progression-free Survival 2 (PFS2) based on PCWG3	Cemi Mono on PD set	
	14.2.4.1.11a	Progression-free Survival 2 (PFS2) based on PCWG3, SAS output	Cemi Mono on PD set	
Figure	14.2.4.1.12	Kaplan-Meier curve for Progression-free Survival 2 (PFS2) based on PCWG3	Cemi Mono on PD set	
	14.2.4.1.13	Overall Survival (OS)	Cemi Mono on PD set	
	14.2.4.1.13a	Overall Survival (OS) SAS output	Cemi Mono on PD set	
Figure	14.2.4.1.14	Kaplan-Meier curve for Overall Survival (OS)	Cemi Mono on PD set	
14.2.5		Further Efficacy Analyses		
	14.2.5.1.1	Disease status during Survival Follow-up Period	mITT set	
	14.2.5.1.2	Biochemical recurrence after radical prostatectomy – post-treatment PSA values	mITT set	
	14.2.5.1.3	Time from treatment start to post-treatment prostatectomy – LPC patients	mITT set	
14.3		Safety Data		
14.3.1		Displays of Adverse Events		
	14.3.1.1	Summary of adverse events	Safety set	Yes
	14.3.1.2	Number (%) of patients with TEAEs by system organ class and preferred term	Safety set	Yes
	14.3.1.3	Number (%) of patients with TEAEs related to IMP by system organ class and preferred term	Safety set	Yes
	14.3.1.4	Number (%) of patients with TEAEs related to W_pro1 by system organ class and preferred term	Safety set	

Header	Table Number	Name	Analysis Set	Interim Analysis
	14.3.1.5	Number (%) of patients with TEAEs related to Cemiplimab by system organ class and preferred term	Safety set	
	14.3.1.6	Number (%) of patients with maximum intensity grade >= 3 TEAEs by system organ class and preferred term	Safety set	Yes
	14.3.1.7	Number (%) of patients with maximum intensity grade >= 3 TEAEs related to IMP by system organ class and preferred term	Safety set	Yes
	14.3.1.8	Number (%) of patients with maximum intensity grade >= 3 TEAEs related to W_pro1 by system organ class and preferred term	Safety set	Yes
	14.3.1.9	Number (%) of patients with maximum intensity grade >= 3 TEAEs related to Cemiplimab by system organ class and preferred term	Safety set	Yes
	14.3.1.10	Number (%) of patients with TEAEs related to trial procedure by system organ class and preferred term	Safety set	
	14.3.1.11	Number (%) of patients with TEAEs related to prostate cancer surgery by system organ class and preferred term	Safety set	
	14.3.1.12	Number (%) of patients with serious TEAEs by system organ class and preferred term	Safety set	Yes
	14.3.1.13	Number (%) of patients with serious TEAEs related to IMP by system organ class and preferred term	Safety set	Yes
	14.3.1.14	Number (%) of patients with serious TEAEs related to W_pro1 by system organ class and preferred term	Safety set	Yes
	14.3.1.15	Number (%) of patients with serious TEAEs related to Cemiplimab by system organ class and preferred term	Safety set	Yes
	14.3.1.16	Number (%) of patients with serious TEAEs leading to death by system organ class and preferred term	Safety set	Yes
	14.3.1.17	Number (%) of patients with serious TEAEs leading to death related to IMP by system organ class and preferred term	Safety set	
	14.3.1.18	Number (%) of patients with serious TEAEs leading to death related to W_pro1 by system organ class and preferred term	Safety set	
	14.3.1.19	Number (%) of patients with serious TEAEs leading to death related to Cemiplimab by system organ class and preferred term	Safety set	
	14.3.1.20	Number (%) of patients with TEAEs leading to IMP dose reduction by system organ class and preferred term	Safety set	
	14.3.1.21	Number (%) of patients with TEAEs leading to W_pro1 dose reduction by system organ class and preferred term	Safety set	
	14.3.1.22	Number (%) of patients with TEAEs leading to Cemiplimab dose reduction by system organ class and preferred term	Safety set	

Header	Table Number	Name	Analysis Set	Interim Analysis
	14.3.1.23	Number (%) of patients with TEAEs leading to IMP dose delay by system organ class and preferred term	Safety set	
	14.3.1.24	Number (%) of patients with TEAEs leading to W_pro1 dose delay by system organ class and preferred term	Safety set	
	14.3.1.25	Number (%) of patients with TEAEs leading to Cemiplimab dose delay by system organ class and preferred term	Safety set	
	14.3.1.26	Number (%) of patients with TEAEs leading to permanent discontinuation of IMP by system organ class and preferred term	Safety set	Yes
	14.3.1.27	Number (%) of patients with TEAEs leading to permanent discontinuation of W_pro1 by system organ class and preferred term	Safety set	Yes
	14.3.1.28	Number (%) of patients with TEAEs leading to permanent discontinuation of Cemiplimab by system organ class and preferred term	Safety set	Yes
	14.3.1.29	Number (%) of patients with DLTs by system organ class and preferred term	Safety set	Yes
	14.3.1.30	Number (%) of patients with most frequent TEAEs (>= 5%) by preferred term	Safety set	Yes
	14.3.1.30.1	Number (%) of patients with most frequent TEAEs (>= 5%) related to IMP by preferred term	Safety set	
	14.3.1.30.2	Number (%) of patients with most frequent TEAEs (>= 5%) related to W_pro1 by preferred term	Safety set	
	14.3.1.30.3	Number (%) of patients with most frequent TEAEs (>= 5%) related to Cemiplimab by preferred term	Safety set	
	14.3.1.31	Number (%) of patients with TEAEs by system organ class, preferred term and worst IMP relationship	Safety set	
	14.3.1.32	Number (%) of patients with TEAEs by system organ class, preferred term and worst relationship to W_pro1	Safety set	
	14.3.1.33	Number (%) of patients with TEAEs by system organ class, preferred term and worst relationship to Cemiplimab	Safety set	
	14.3.1.34	Number (%) of patients with TEAEs by system organ class, preferred term and worst NCI CTAE grade	Safety set	
	14.3.1.35	Number (%) of patients with TEAEs related to IMP by system organ class, preferred term and worst NCI CTAE grade	Safety set	
	14.3.1.36	Number (%) of patients with TEAEs related to W_pro1 by system organ class, preferred term and worst NCI CTAE grade	Safety set	
	14.3.1.37	Number (%) of patients with TEAEs related to Cemiplimab by system organ class, preferred term and worst NCI CTAE grade	Safety set	

Header	Table Number	Name	Analysis Set	Interim Analysis
	14.3.1.38	Number (%) of patients with non-serious TEAEs (>3% at preferred term level) by system organ class and preferred term	Safety set	
	14.3.1.39	Number (%) of patients with TEAEs leading to IMP dose modification by system organ class and preferred term	Safety set	
	14.3.1.40	Number (%) of patients with TEAEs leading to W_pro1 dose modification by system organ class and preferred term	Safety set	
	14.3.1.41	Number (%) of patients with TEAEs leading to Cemiplimab dose modification by system organ class and preferred term	Safety set	
		Cemiplimab TEAEs		
	14.3.1.42	Summary of cemiplimab TEAEs	Cemi Mono on PD set	
	14.3.1.43	Number (%) of patients with cemiplimab TEAEs by system organ class and preferred term	Cemi Mono on PD set	
	14.3.1.44	Number (%) of patients with cemiplimab TEAEs related to Cemiplimab by system organ class and preferred term	Cemi Mono on PD set	
	14.3.1.45	Number (%) of patients with grade >= 3 cemiplimab TEAEs by system organ class and preferred term	Cemi Mono on PD set	
	14.3.1.46	Number (%) of patients with grade >= 3 cemiplimab TEAEs related to Cemiplimab by system organ class and preferred term	Cemi Mono on PD set	
	14.3.1.47	Number (%) of patients with serious cemiplimab TEAEs by system organ class and preferred term	Cemi Mono on PD set	
	14.3.1.48	Number (%) of patients with serious cemiplimab TEAEs related to Cemiplimab by system organ class and preferred term	Cemi Mono on PD set	
	14.3.1.49	Number (%) of patients with serious cemiplimab TEAEs leading to death by system organ class and preferred term	Cemi Mono on PD set	
	14.3.1.50	Number (%) of patients with serious cemiplimab TEAEs leading to death related to Cemiplimab by system organ class and preferred term	Cemi Mono on PD set	
	14.3.1.51	Number (%) of patients with cemiplimab TEAEs leading to Cemiplimab dose reduction by system organ class and preferred term	Cemi Mono on PD set	
	14.3.1.52	Number (%) of patients with cemiplimab TEAEs leading to Cemiplimab dose delay by system organ class and preferred term	Cemi Mono on PD set	
	14.3.1.53	Number (%) of patients with cemiplimab TEAEs leading to Cemiplimab dose modification by system organ class and preferred term	Cemi Mono on PD set	

Header	Table Number	Name	Analysis Set	Interim Analysis
	14.3.1.54	Number (%) of patients with cemiplimab TEAEs leading to permanent discontinuation of cemiplimab by system organ class and preferred term	Cemi Mono on PD set	
14.3.2		Listings of Deaths, Other Serious and Certain Other Significant Adverse Events	Safety set	
	14.3.2.1	Deaths, Listing	Safety set	Yes
	14.3.2.2	Serious Adverse Events, Listing	Safety set	Yes
	14.3.2.3	Treatment emergent Adverse Events leading to permanent discontinuation of IMP, Listing	Safety set	Yes
	14.3.2.4	Dose-limiting toxicities (Part 1), Listing	Safety set	
14.3.3	Not to be used for any Tables	Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events *(NOTE: this section is for Medical Writing narratives only, normally not completed by Syneos Health Biostatistics. No tables should go here. Nevertheless, the section is kept and a note should indicate the responsible party).*		
14.3.4		Laboratory, Vital Signs, and Physical Examination Changes		
14.3.4.1		Clinical Laboratory Data		
14.3.4.1.1		Hematology Data		
	14.3.4.1.1.1	Hematology: Summary by visit and change from baseline	Safety set	
	14.3.4.1.1.2	Hematology: Abnormal and clinically significant values per visit	Safety set	
	14.3.4.1.1.3	Hematology: Shift from baseline	Safety set	
	14.3.4.1.1.4	Hematology: CTC Grade per visit	Safety set	
	14.3.4.1.1.5	Hematology: CTC Grade shift from baseline	Safety set	
14.3.4.1.2		Blood Chemistry Data		
	14.3.4.1.2.1	Blood Chemistry: Summary by visit and change from baseline	Safety set	
	14.3.4.1.2.2	Blood Chemistry: Abnormal and clinically significant values per visit	Safety set	
	14.3.4.1.2.3	Blood Chemistry: Shift from baseline	Safety set	
	14.3.4.1.2.4	Blood Chemistry: CTC Grade per visit	Safety set	
	14.3.4.1.2.5	Blood Chemistry: CTC Grade shift from baseline	Safety set	
14.3.4.1.3		Coagulation Data		
	14.3.4.1.3.1	Coagulation: Summary by visit and change from baseline	Safety set	
	14.3.4.1.3.2	Coagulation: Abnormal and clinically significant values per visit	Safety set	
	14.3.4.1.3.3	Coagulation: Shift from baseline	Safety set	
	14.3.4.1.3.4	Coagulation: CTC Grade per visit	Safety set	
	14.3.4.1.3.5	Coagulation: CTC Grade shift from baseline	Safety set	
14.3.4.1.4		Urinalysis Data		

Header	Table Number	Name	Analysis Set	Interim Analysis
	14.3.4.1.4.1	Urinalysis dipstick: Summary by visit	Safety set	
14.3.4.1.5		Thyroid Hormones		
	14.3.4.1.5.1	Thyroid Hormones: Summary by visit and change from baseline	Safety set	
	14.3.4.1.5.2	Thyroid Hormones: Abnormal and clinically significant values per visit	Safety set	
	14.3.4.1.5.3	Thyroid Hormones: Shift from baseline	Safety set	
14.3.4.2		Vital Signs		
	14.3.4.2.1	Vital signs: Summary by visit and change from baseline	Safety set	
	14.3.4.2.2	Vital signs: Shift from baseline	Safety set	
Figure	14.3.4.2.3	Vital signs: Scatter plot per parameter	Safety set	
14.3.4.3		Electrocardiogram (ECG) Data		
	14.3.4.3.1	12-lead ECG assessment by visit	Safety set	
	14.3.4.3.2	Ventricular Heart Rate (bmp): Summary by visit and change from baseline	Safety set	
14.3.4.4		Physical Examination		
	14.3.4.4.1	Physical examination by visit	Safety set	
14.3.4.5		ECOG data		
	14.3.4.5.1	ECOG performance status by visit	Safety set	
	14.3.4.5.2	ECOG performance status: Shift from baseline	Safety set	

***Note**: no table number should go beyond 14.3.4.x (i.e. 14.3.5.x or 14.4.x)*

11.1.2 Listings

Header	Listing Number	Name	Analysis Set	Interim Analysis
16.2		Patient Data Listings		
16.2.1		Patient Disposition		
	16.2.1.1	Patient disposition	Screened set	Yes
	16.2.1.2	Informed consent	Screened set	
	16.2.1.3	Patients impacted by COVID-19 related study disruption	ITT set	
	16.2.1.4	Missing visits due to COVID-19	ITT set	
16.2.2		Protocol Deviations		
	16.2.2.1	Protocol Deviations	ITT set	
	16.2.2.2	Protocol Deviation due to COVID-19	ITT set	
16.2.3		Patients Excluded from the Efficacy Analysis		
	16.2.3.1	Inclusion/exclusion criteria not met	Screened set	
	16.2.3.2	Exclusion from analysis set	Screened set	Yes
16.2.4		Demographic Data		
	16.2.4.1	Demographics	ITT set	Yes
	16.2.4.2	Disease characteristics	ITT set	Yes
	16.2.4.3	Medical History	ITT set	
	16.2.4.4	Prior systemic cancer therapies	ITT set	Yes
	16.2.4.5	Prior cancer radiotherapies	ITT set	
	16.2.4.6	Prior cancer surgeries	ITT set	
	16.2.4.7	Prior and concomitant medications	ITT set	
	16.2.4.8	Further antineoplastic therapies	ITT set	
	16.2.4.9	Cancer radiotherapies	ITT set	
	16.2.4.10	Procedures and non-drug therapies	ITT set	
16.2.5		Compliance and/or Drug Concentration Data (if available) *(Note; exposure information will be included in this section)*		
	16.2.5.1	Trial treatment – W_pro1	Safety set	
	16.2.5.2	Trial treatment – Cemiplimab	Safety set	
	16.2.5.3	Trial treatment – ADT	Safety set	
	16.2.5.4	Drug exposure	Safety set	Yes
16.2.6		Individual Efficacy Response Data		
		Primary and Secondary Efficacy Endpoint		
	16.2.6.1.1	Overall PCWG3 and LPC tumor response assessment based on Radiological Soft Tissue Evaluation per Investigator	ITT set	Yes
	16.2.6.1.2	PCWG3 and LPC tumor assessment based on Radiological Soft Tissue Evaluation per Investigator – target lesions	ITT set	Yes
	16.2.6.1.3	PCWG3 and LPC tumor assessment based on Radiological Soft Tissue Evaluation per Investigator – non-target lesions	ITT set	Yes

Header	Listing Number	Name	Analysis Set	Interim Analysis
	16.2.6.1.4	PCWG3 and LPC tumor assessment based on Radiological Soft Tissue Evaluation per Investigator – new lesions	ITT set	Yes
	16.2.6.1.5	PCWG3 Bone lesions based on Radiological Soft Tissue Evaluation per Investigator – new lesions	ITT set	Yes
	16.2.6.1.6	Clinical progression	ITT set	Yes
	16.2.6.1.7	Overall tumor response assessment based on PCWG3	ITT set	
	16.2.6.2	Prostate-specific antigen (PSA)	ITT set	Yes
		Exploratory Efficacy Endpoints		
	16.2.6.3.1	Overall iRECIST (central reading)tumor response assessment	ITT set	
	16.2.6.3.2	iRECIST (central reading) assessment – target lesions	ITT set	
	16.2.6.3.3	iRECIST (central reading) assessment – non-target lesions	ITT set	
	16.2.6.3.4	iRECIST (central reading) assessment – new lesions	ITT set	
	16.2.6.4.1	Duration of response based on PCWG3	ITT set	Yes
	16.2.6.4.2	Duration of response based iRECIST (central reading)	ITT set	
	16.2.6.4.3	Progression-free survival based on PCWG3	ITT set	Yes
	16.2.6.4.4	Progression-free survival based on iRECIST (central reading)	ITT set	
	16.2.6.4.5	Overall survival time	ITT set	
	16.2.6.4.6	Duration of response based on PCWG3	Cemi Mono on PD set	
	16.2.6.4.7	Duration of response based on iRECIST (central reading)	Cemi Mono on PD set	
	16.2.6.4.8	Progression-free survival based on PCWG3	Cemi Mono on PD set	
	16.2.6.4.9	Progression-free survival based on iRECIST (central reading)	Cemi Mono on PD set	
	16.2.6.4.10	Progression-free survival 2 based on PCWG3	Cemi Mono on PD set	
	16.2.6.5.1	Disease status reported during Survival Follow-up	ITT set	
		Pharacodynamic and Biomarker Listings		
	16.2.6.6.1	Hormones (Testosterones [nmol/L])	Pharmacodynamic set	
	16.2.6.6.2	Cytokines	Pharmacodynamic set	
	16.2.6.6.3	HLA typing (optional)	Pharmacodynamic set	
	16.2.6.6.4	Tumor tissue sample (optional)	ITT set	
	16.2.6.6.5	TCR profiling (optional)	Pharmacodynamic set	

Header	Listing Number	Name	Analysis Set	Interim Analysis
	16.2.6.6.6	Genetics (optional)	Pharmacodynamic set	
16.2.7		Adverse Event Listings		
	16.2.7.1	Adverse Events	Safety set	Yes
	16.2.7.2	Cemiplimab treatment-emergent adverse events	Cemi Mono on PD set	
16.2.8		Listing of individual laboratory measurements by patient		
	16.2.8.1.1	Hematology	Safety set	
	16.2.8.1.2	Blood Chemistry	Safety set	
	16.2.8.1.3	Coagulation	Safety set	
	16.2.8.1.4	Urinalysis dipstick	Safety set	
	16.2.8.1.5	Urinalysis microscopic	Safety set	
	16.2.8.1.6	Thyroid hormones	Safety set	
	16.2.8.1.7	Serology	Safety set	
	16.2.8.1.8	Circulating tumor cells	Safety set	
	16.2.8.2	Other Safety Data	Safety set	
	16.2.8.2.1	Vital Signs	Safety set	
	16.2.8.2.2	12-lead ECG assessment	Safety set	
	16.2.8.2.3	Physical examination	Safety set	
	16.2.8.2.4	ECOG performance status	Safety set	

***Note**: no listing number should go beyond 16.2.8.x (i.e. 16.2.9)*

12 REFERENCES

1. Hamberg P, Ratain MJ, Lesaffre E, Verweij J. Dose-escalation models for combination phase I trials in oncology. Eur. J. Cancer 2010; 46(16):2870–8.
2. Mottet N, Bellmunt J, Bolla M, Briers E, Cumberbatch MG, Santis M de, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. Eur Urol 2017 Apr; 71(4):618–629.
3. Scher HI, Morris MJ, Stadler WM, Higano C, Basch E, Fizazi K, et al. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations from the Prostate Cancer Clinical Trials Working Group 3. J. Clin. Oncol. 2016 Apr 20; 34(12):1402–18. DOI: 10.1200/JCO.2015.64.2702.
4. Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol 2017; 18(3):e143-e152.
5. Simon R. Optimal two-stage designs for Phase II clinical trials. Control Clin. Trials. 1989 Mar; 10(1):1-10.
6. U.S. Department of Health and Human Services, Food and Drug Administration, Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (available at https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/).
7. U.S. National Comprehensive Cancer Network (NCCN 2020; available at https//www.nccn.org/professionals/physician_gls/pdf/prostate.pdf).
8. Pound CR, Partin AW, Eisenberger MA, et al: Natural History of Progression after PSA Elevation Following Radical Prostatectomy. JAMA 281: 1591-1597.

13 SUPPORTING DOCUMENTATION

Not applicable

13.1 Appendix 1: Changes to protocol-planned analyses

Definition of PP set added in Section 7.1 and supporting analyses of some efficacy endpoints using the PP set and ITT set defined.

Definition of the subsequent cemiplimab monotherapy on progression set added in Section 7.1. This analysis set has to be used for all exploratory safety and efficacy analyses for the Arm 1B patients who are treated with cemiplimab monotherapy following progression after W_pro1 monotherapy.

13.2 Appendix 2: List of abbreviations

Abbreviation	Definition
ADT	Androgen-deprivation therapy
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
AST	Aspartate Transaminase
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BOR	Best Overall Response
bpm	beats per minute
C	Cycle
CI	Confidence Interval
CMI	Cell-mediated immune
CR	Complete Response
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-Reactive Protein
CS	Clinically Significant
CT	Computer tomography
CTC	Common Toxicity Criteria
CTCAE v5.0	Common Terminology Criteria for Adverse Events, version 5.0
CTMS	Clinical Trail Management System
CTR	Clinical Trial Report
D	Day of cycle
DI	Dose intensity
DL	Dose level
DLT	Dose-limiting toxicity
DoR	Duration of response
DRM	Data Review Meeting
eCRF	Electronic Case Report Form
ELISpot	Enzyme-Linked Immuno-Spot
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EoT	End of Treatment
FDA	Food and Drug Administration

FU	Follow-up
GGT	Gamma-Glutamyl-Transpeptidase
h	Hour
HR	Hazard Ratio
ICF	Informed consent form
ICH	International Conference on Harmonization
IMM	Immunogenicity
IMP	Investigational Medicinal Product
iRECIST	Immune-modified Response Evaluation Criteria in Solid Tumors
ITT	Intent-To-Treat
IV	Intravenous
LNH	Low, Normal, High
LPC	Localized prostate cancer
Max	Maximum
mCRPC	Metastatic castration-resistant prostate cancer
MedDRA™	Medical Dictionary for Regulatory Activities
Mg	Milligram
Min	Minimum
mITT	Modified Intent-To-Treat
mmHg	millimeter of mercury
mpMRI	Multi-parametric MRI
MRI	Magnetic resonance imaging
mRNA (or RNA)	Messenger ribonucleic acid
N	Number of Patients
n	Number of Observations
NA	Not Applicable
NCI	National Cancer Institute
NCS	Not Clinically Significant
NE	Not Evaluable
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
NIMP	Non-investigational medicinal product
OR	Objective Response
ORR	Objective Response Rate
OS	Overall Survival
PCWG3	Prostate Cancer Working Group 3
PD	Progressive Disease

PFS	Progression-Free Survival
PP	Per Protocol
PR	Partial Response
PSA	Prostate-specific antigen
PSADT	Prostate specific antigen doubling time
PT	Preferred Term
Q1	Lower quartile
Q12W	Every 12 weeks
Q3	Upper quartile
Q3W	Every 3 weeks
QC	Quality Control
RBC	Red Blood Cell
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumors
REDR	Recommended expansion dose range
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SC	Subcutaneous(ly)
SD	Stable Disease
SI	International System of Units
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedures
SRC	Safety Review Committee
TEAE	Treatment-Emergent Adverse Event
TFL	Tables, Figures and Listings
TMF	Trial Master File
TSH	Thyroid Stimulating Hormones
ULN	Upper Limit of Normal
US FDA	United States Food and Drug Administration
V	Visit
W_pro1	W_pro1 cancer vaccine (BioNTech IMP)
WBC	White Blood Cell
WHO DD	World Health Organization Drug Dictionary

13.3 Appendix 3: Best Overall Response derivation for iRECIST

Scenarios of assignments of best overall response (iBOR) using iRECIST, based on Seymour at all (2017) [4]

	Time point response 1	**Time point response 2**	**Time point response 3**	**Time point response 4**	**Time point response 5**	**iBOR**
Example 1	iCR	iCR, iPR, iUPD, or NE	iCR, iPR, iUPD, or NE	iUPD	iCPD	iCR
Example 2	iUPD	iPR, iSD, or NE	iCR	iCR, iUPD, or NE	iCR, iPR, iSD, iUPD, iCPD, or NE	iCR
Example 3	iUPD	iPR	iPR, iSD, iUPD, or NE	iPR, iSD, iUPD, NE, or iCPD	iPR, iSD, iUPD, NE, or iCPD	iPR
Example 4	iUPD	iSD or NE	iPR	iPR, iSD, iUPD, or NE	iPR, iSD, iUPD, iCPD, or NE	iPR
Example 5	iUPD	iSD	iSD, iUPD, or NE	iSD, iUPD, iCPD, or NE	iSD, iUPD, iCPD, or NE	iSD
Example 6	iUPD	iCPD	Any	Any	Any	iCPD
Example 7	iUPD	iUPD (no iCPD)	iCPD	Any	Any	iCPD
Example 8	iUPD	NE	NE	NE	NE	iUPD

Eight examples are presented for patients with target disease at baseline, but many more scenarios exist following the same principles. Table assumes a randomised study in which confirmation of complete response or partial response is not required. For patients with non-target disease only at baseline, only iCR or non-complete response or non-progression of disease can be assigned at each time point (not shown in the table for ease of presentation). "i" indicates immune responses assigned using iRECIST. iBOR=best overall response. iCR=complete response. iPR=partial response. NE=not evaluable. iUPD=unconfirmed progression. iCPD=confirmed progression. iSD=stable disease. RECIST=Response Evaluation Criteria in Solid Tumours.

See iRECIST guidelines and wording about Best Objective response. See tables 1 and 2 as well from this paper:

"Although the principles of the assignment of the time point response and best overall response closely follow RECIST 1.1, and reflect assessment of target and non-target lesions as well as the presence of new lesions, the possibility of pseudoprogression adds complexity (tables 1–3, panel 2, appendix pp 2–4). The time point response is calculated using the response assigned for each category of lesion (as for RECIST 1.1), but takes into account the last time point response.

The algorithm for patients with no previous iUPD is identical to RECIST 1.1. For patients with iUPD at the last time point response, the next time point response is dependent on the status of all lesions, including target, non-target, new lesion target, and new lesion non-target; on whether any increase in size has occurred (either a further increase in size or a sufficient increase to assign a new iUPD if the criteria were not previously met); or the appearance of additional new lesions.

For iRECIST, the best overall response (iBOR) is the best time point response recorded from the start of the study treatment until the end of treatment, taking into account any requirement for confirmation. iUPD will not override a subsequent best overall response of iSD, iPR, or iCR (tables 1–3, appendix pp 2–4), meaning that iPR or iSD can be assigned (time point response or iBOR) even if new lesions have not regressed, or if unequivocal progression (non-target lesions) remains unchanged, providing that the criteria for iCPD are not met."

13.4 Appendix 4: Reporting conventions

The following treatment labels will be used in the analysis:

Treatment Group	Treatment Label	Treat-ment Code	Analysis
Part 1:	Part 1 mCRPC W_pro1	1	Disposition, Demog, Efficacy, AE, Safety
Part 2: Arm 1A	Part 2 mCRPC W_pro1 + Cemiplimab	2	Disposition, Demog, Efficacy, AE, Safety
Part 2: Arm 1B	Part 2 mCRPC W_pro1	3	Disposition, Demog, Efficacy, AE, Safety
Part 2: Arm 2	Part 2 LPC W_pro1 + Cemiplimab	4	Disposition, Demog, Efficacy, AE, Safety
Part 2: Arm 3	Part 2 LPC W_pro1	5	Disposition, Demog, Efficacy, AE, Safety
Combined Treatment Groups			
Part 2: Arm 1A and Arm 1B	Part 2 Total mCRPC	6	Disposition, Demog, Efficacy, AE, Safety
Part 2: Arm 2 and Arm 3	Part 2 Total LPC	7	Disposition, Demog, Efficacy, AE, Safety
Part 2: Arm 1B and Arm 3	Part 2 Total Monotherapy	8	AE
Part 2: Arm 1A and Arm 2	Part 2 Total Combination Therapy	9	AE
Part 1 and Part 2: Arm 1A and Arm 1B	Parts 1 and 2 Total mCRPC	10	AE
Part 1 and Part 2: Arm 1B and Arm 3	Parts 1 and 2 Total Monotherapy	11	AE
Part 2: all 4 Arms Combined	Part 2 Total	12	Disposition, Demog (optional), AE
All 5 Arms Combined	Parts 1 and 2 Total	13	AE (optional)

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

The column “Analysis” specify which treatment labels / treatment columns to be used for which kind of analysis. More details are provided in the separate document “Mock Tables, Listings and Figures”.

13.5 Appendix 5: Definition of visceral metastasis

Definition of visceral metastasis based on location of target or non-target lesions at study entry:

Location as collected in Database	Visceral metastasis (Yes or No)
Prostate	No
Lymph node	No
Anus	Yes
Abdominal Cavity	Yes
Adrenal Gland or Adrenal	Yes
Biliary Tract	Yes
Bladder	Yes
Bone	No
Brain	No
Breast, Bilateral	No
Breast, Left	No
Breast, Right	No
Bronchus	No
Chest Wall	No
Colon	Yes
Esophagus	Yes
Gastroesophageal Junction	Yes
Head and Neck	No
Hypopharynx	No
Kidney bilateral	Yes
Kidney, Left	Yes
Kidney, Right	Yes
Large Intestine	Yes
Liver	Yes
Lung bilateral	Yes
Lung, Left	Yes
Lung, Right	Yes
Oesophagus	Yes
Oral Cavity	No
Pancreas	Yes
Pericardial Effusion	No
Peritoneum wall	Yes
Pleura wall	Yes
Pleural Effusion	No
Rectosigmoid Junction	Yes
Rectum	Yes
Renal	Yes
Skin	No
Small Intestine	Yes
Soft Tissue	No
Spinal Cord	No
Spleen	Yes
Stomach	Yes

Testicle right	Yes
Testicle left	Yes
Thyroid	No

13.6 Appendix 5: Schedule of activities

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

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

	Screening		Treatment																Follow-up (FU)			UV
1 cycle = 21 days			**C1[4]**			**C2**			**C3#**		**C4**	**C5**	**C6**	**C7**	**C8**		**≥C9#**	**EoT ***	**Safety FU ****	**Efficacy FU ****		
Visit	**≤28d**	**≤7d**	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**D1**	**D15**	**D1**	**D1**	**D1**	**D1**	**D1**	**D15**	**D1**		**D30 / D90**	**M6**	**M12**	
Visit window				**±1d**	**±1d**	**±1d**	**±1 d**	**±1d**	**±1d**	**±3d**	**±1d**	**±1d**	**±1d**	**±1d**	**±1d**	**±3d**	**±3d**		**+7d**	**±14 d**	**±14 d**	
Inclusion/Exclusion criteria	X	X	X[&]																			
Randomization[22]			X[&]																			
IMP Administration																						
Part 1 (monotherapy dose titration)																						
W_pro1 (IMP)			X	X	X	X	X	X	X		X	X	X	X	X		X					
Part 2 Arm 1A (with cemiplimab)																						
W_pro1 (IMP)			X	X	X	X	X	X	X		X	X	X	X	X		X					
Cemiplimab (IMP)			X			X			X		X	X	X	X	X		X					
Part 2 Arm 1B (monotherapy)																						
IMP 1 admin. Arm: W_pro1			X	X	X	X	X	X	X		X	X	X	X	X		X					
Safety laboratory tests [11]																						
Serology	X																					
Hematology		X		X[&]	X[&]	X[&]	X[&]	X[&]	X[&]		X[&]	X[&]	X[&]	X[&]	X[&]		X[&]	X	X			X[5]
Coagulation		X				X[&]					X[&]		X[&]		X[&]		X[&]	X	X			X[5]
Blood chemistry		X		X[&]	X[&]	X[&]	X[&]	X[&]	X[&]		X[&]	X[&]	X[&]	X[&]	X[&]		X[&]	X	X			(X)[5]
Thyroid hormones [18, 20]		X				X					X		X		X		X[20]		X			(X)[5]
Urinalysis		X		X[&]	X[&]	X[&]	X[&]	X[&]	X[&]		X[&]	X[&]	X[&]	X[&]	X[&]		X[&]	X	X			(X)[5]
AE/TEAE [12, 13]	X	X	X[&$]	X[&$]	X[&$]	X[&$]	X[&$]	X[&$]	X[&$]	X	X[&$]	X[&$]	X[&$]	X[&$]	X[&$]	X	X[&$]	X	X			X
Survival/disease status [14]																				X	X	
Blood Biomarkers																						
Cytokines			X[15]	X[15]	X[15]	X[15]	X[15]	X[15]	X[15]		X[17]	X[17]	X[17]	X[17]	X[17]		X[17]	X	X			(X)

	Screening		Treatment															Follow-up (FU)			UV
1 cycle = 21 days			**C1[4]**			**C2**			**C3#**		**C4**	**C5**	**C6**	**C7**	**C8**		**≥C9#**	**EoT ***	**Safety FU ****	**Efficacy FU ****	
Visit	**≤28d**	**≤7d**	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**D1**	**D15**	**D1**	**D1**	**D1**	**D1**	**D1**	**D15**	**D1**		**D30 / D90**	**M6**	**M12**	
Visit window				**±1d**	**±1d**	**±1d**	**±1 d**	**±1d**	**±1d**	**±3d**	**±1d**	**±1d**	**±1d**	**±1d**	**±1d**	**±3d**	**±3d**		**+7d**	**±14 d**	**±14 d**	
PSA		X	X[16]	X[16]	X[16]	X[16]	X [16]	X[16]	X[16]		X[16]	X[16]	X[16]	X[16]	X[16]		X[16]	X	X			(X)
Testosterone		X																				(X)
ELISpot and further immune monitoring		X[18]								X						X		X[19]	X[19]			(X)
HLA typing		X[18]																				
TCR profiling		X[18]														X		X[19]	X[19]			(X)
Circulating tumor cells [9]	(X)	(X)																				

Abbreviations and Footnotes:

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

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

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

** All patients (Part 1 and 2) will be actively followed up for safety (FU-D30) after last intake of W_pro1. Patients in Part 2 Arm 1A will be followed up for safety (FU-D90) after last intake of cemiplimab or (FU-D30) after last intake of W_pro1, whichever is later. All patients will be followed up for efficacy (FU-M6 after the last intake of IMP, FU-M12 after the last intake of IMP). Within 28 days after confirmation of disease progression, patients of Arm 1B can optionally start cemiplimab monotherapy and will follow the Schedule of Activities shown in Section 1.5 in the protocol after performing the EoT for W_pro1 treatment.

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

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

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

[4] Vital signs (blood pressure, pulse rate, body temperature) should be assessed pre-treatment and 1 h (±15 min), 4 h (±1 h) and 6 h (±1 h) post-treatment and as clinically indicated during C1. Patients must be observed for at least 4 to 6 h after administration of W_pro1 and vital signs collected pre-treatment, 4 to 6 h (±1 h) post-treatment and as clinically indicated.

[5] Only if clinically indicated.

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

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

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

[9] Only if routinely performed locally.

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

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

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

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

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

[15] Blood collection before and 4 h (±30 min) after administration of W_pro1.

[16] Blood collection before administration of W_pro1.

[17] Blood collection 4 h (±30 min) after administration of W_pro1.

[18] Variable time point; either during screening ≤7 d or at C1D1 before administration of W_pro1.

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

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

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

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

Schedule of Activities: Part 2 Arms 2 and 3

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

	Screening		Treatment															Follow-up (FU)			UV	Surgery
1 cycle = 21 days			**C1**			**C2**			**C3**		**C4**	**C5**	**C6**	**C7**	**C8**		**EoT***	**Safety FU ** **	**Efficacy FU ** **			
Visit	**≤28 d**	**≤7d**	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**D1**	**D15**	**D1**	**D1**	**D1**	**D1**	**D1**	**D15**		**D30/ D90**	**M6**	**M12**		
Visit window				**±1d**	**±1d**	**±1d**	**±1d**	**±1d**	**±1d**	**±3d**	**±1d**	**±1d**	**±1d**	**±1d**	**±1d**	**±3d**		**+7d**	**±14d**	**±14d**		
Part 2 Arm 2 (with cemiplimab)																						
W_pro1 (IMP)			X	X	X	X	X	X	X		X	X	X	X	X							
Cemiplimab (IMP)			X			X			X		X	X	X	X	X							
ADT (NIMP) [11]		X										X										

	Screening		Treatment															Follow-up (FU)			UV	Surgery
1 cycle = 21 days			C1			C2			C3		C4	C5	C6	C7	C8		EoT*	Safety FU **	Efficacy FU **			
Visit	**≤28 d**	**≤7d**	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**D1**	**D15**	**D1**	**D1**	**D1**	**D1**	**D1**	**D15**		**D30/ D90**	**M6**	**M12**		
Visit window				**±1d**	**±1d**	**±1d**	**±1d**	**±1d**	**±1d**	**±3d**	**±1d**	**±1d**	**±1d**	**±1d**	**±1d**	**±3d**		**+7d**	**±14d**	**±14d**		
Part 2 Arm 3 (monotherapy)																						
W_pro1 (IMP)			X	X	X	X	X	X	X		X	X	X	X	X							
ADT (NIMP) [11]		X										X										
Safety laboratory tests [12]																						
Serology	X																					
Hematology		X		X[&]	X[&]	X[&]	X[&]	X[&]	X[&]		X[&]	X[&]	X[&]	X[&]	X[&]		X	X			X[5]	
Coagulation		X				X[&]					X[&]		X[&]		X[&]		X	X			X[5]	
Blood chemistry		X		X[&]	X[&]	X[&]	X[&]	X[&]	X[&]		X[&]	X[&]	X[&]	X[&]	X[&]		X	X			X[5]	
Thyroid hormones [19, 21]		X				X					X		X		X			X			(X)[5]	
Urinalysis		X		X[&]	X[&]	X[&]	X[&]	X[&]	X[&]		X[&]	X[&]	X[&]	X[&]	X[&]		X	X			X	
AE/TEAE[14]	X	X	X[&$]	X[&$]	X[&$]	X[&$]	X[&$]	X[&$]	X[&$]	X	X[&$]	X[&$]	X[&$]	X[&$]	X[&$]	X	X	X			X	
Survival/disease status[15]																			X	X		
Blood Biomarkers																						
Cytokines			X[16]	X[16]	X[16]	X[16]	X[16]		X[16]		X[18]	X[18]	X[18]	X[18]	X[18]		X	X			(X)	
PSA		X	X[17]	X[17]	X[17]	X[17]	X[17]	X[17]	X[17]		X[17]	X[17]	X[17]	X[17]	X[17]		X	X	X	X	(X)	X [20]
ELISpot and further immune monitoring		X[19]								X						X	X[10]	X[10]			(X)	
HLA typing		X[19]																				
TCR profiling		X[19]														X	X[10]	X[10]			(X)	

Abbreviations and Footnotes

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

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

** All patients (Part 1 and 2) will be actively followed up for safety (FU-D30) after last intake of W_pro1. Patients in Part 2 Arm 2 will be followed up for safety (FU-D90) after last intake of cemiplimab or (FU-D30) after last intake of W_pro1, whichever is later. Efficacy FU-M6 and M12 are performed for Part 2 Arms 2 and 3 after last IMP administration

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

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

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

[4] For all patients, vital signs (blood pressure, pulse rate, body temperature) should be assessed pre-treatment and 1 h (±15 min), 4 h (±1 h) and 6 h (±1 h) post-treatment and as clinically indicated during C1. Patients must be observed for at least 4 to 6 h after administration of W_pro1 and vital signs collected pre-treatment, 4 to 6 h (±1 h) post-treatment and as clinically indicated.

[5] Only if clinically indicated.

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

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

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

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

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

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

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

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

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

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

[16] Blood collection before and 4 h after administration of W_pro1.

[17] Blood collection before administration of W_pro1.

[18] Blood collection 4 h (±30 min) after administration of W_pro1.

[19] Variable time point; either during screening ≤7 d or at C1D1 before administration of W_pro1.

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

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

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

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

Schedule of Activities: Part 2 Arms 1B – Optional Cemiplimab Treatment Following Progression after W_pro1 monotherapy

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

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

Abbreviations and Footnotes:

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

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

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

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

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

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

[3] Only if clinically indicated.

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

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

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

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

[8] For details on safety laboratory tests, see Section 10.2 in the protocol. If warranted by dipstick results, urine sediment will be microscopically examined.

[9] Thyroid hormones (thyroid stimulating hormone [TSH], free thyroxine [fT4] and triiodothyronine [T3]) will be performed every 6 weeks, at Safety FU D90, or as clinically indicated at the investigator's discretion.

[10] At treatment visits, patients will also be monitored for TEAEs at site, according to local prescribing guidelines for cemiplimab.

[11] For details on patient's survival status and disease status, see Sections 8.1 and 10.9 in the protocol.

[12] Sampling at CemC3 or at EoT, whichever occurs first.

[13] Only if routinely performed locally.

[14] Assessments will be performed at CemC1, CemC4, CemC7 and when considered as clinically indicated by the investigator.

13.7 Appendix 6: Laboratory parameters to be categorized by Toxicity Grades (NCI CTCAE v5.0)

Parameters (by group)

Hematology:

- Hemoglobin decrease / Hemoglobin increase
- WBC decrease
- Neutrophils decrease
- Lymphocytes decrease
- Eosinophils increase
- Platelet count decrease

Coagulation:

- Activated partial thromboplasting time (APTT) increase
- International normalized ratio (INR) increase
- Fibrinogen decrease

Blood Chemistry:

- Amylase increase
- Alkaline phosphatase (ALP) increase
- Alanine aminotransferase (ALT) increase

- Asparate aminotransferase (AST) increase
- Gamma glutamyl transpeptidase (GGT) increase
- Total bilirubin increase
- Glucose decrease / Glucose increase
- Sodium decrease / Sodium increase
- Potassium decrease / Potassium increase
- Calcium decrease / Calicum increase

BioNTech RN5609C00_SAP_V2.0_27Apr2023

Final Audit Report 2023-05-08

Created:	2023-04-27
By:	PPD
Status:	Signed
Transaction ID:	PPD

"BioNTech RN5609C00_SAP_V2.0_27Apr2023" History

Document created by PPD
2023-04-27 - 11:24:38 AM GMT- IP address: PPD

Signer PPD entered name at signing as PPD
2023-04-27 - 11:27:39 AM GMT- IP address: PPD

PPD authenticated with Adobe Acrobat Sign.
2023-04-27 - 11:27:41 AM GMT

Document e-signed by PPD
Signing reason: I am the author
Signature Date: 2023-04-27 - 11:27:41 AM GMT - Time Source: server- IP address: PPD

Document emailed to PPD for signature
2023-04-27 - 11:27:43 AM GMT

Email viewed by PPD
2023-04-27 - 12:34:25 PM GMT- IP address: PPD

Signer PPD entered name at signing as PPD
2023-04-27 - 12:35:45 PM GMT- IP address: PPD

PPD authenticated with Adobe Acrobat Sign.
2023-04-27 - 12:35:47 PM GMT

Document e-signed by PPD
Signing reason: I am the reviewer
Signature Date: 2023-04-27 - 12:35:47 PM GMT - Time Source: server- IP address: PPD

Document emailed to PPD for signature
2023-04-27 - 12:35:49 PM GMT

Email viewed by PPD

2023-04-27 - 1:56:12 PM GMT- IP address: PPD

PPD authenticated with Adobe Acrobat Sign.

2023-04-27 - 2:00:31 PM GMT

Document e-signed by PPD

Signing reason: I am the approver

Signature Date: 2023-04-27 - 2:00:31 PM GMT - Time Source: server- IP address: PPD

Document emailed to PPD for signature

2023-04-27 - 2:00:35 PM GMT

Email viewed by PPD

2023-05-08 - 9:22:26 AM GMT- IP address: PPD

New document URL requested by PPD

2023-05-08 - 9:22:35 AM GMT- IP address: PPD

PPD authenticated with Adobe Acrobat Sign.

2023-05-08 - 9:28:34 AM GMT

Document e-signed by PPD

Signing reason: I am the approver

Signature Date: 2023-05-08 - 9:28:34 AM GMT - Time Source: server- IP address: PPD

Agreement completed.

2023-05-08 - 9:28:34 AM GMT