A Phase 1b/2 Study to Evaluate Safety and Clinical Activity of Avelumab in Combination with Bempegaldesleukin (NKTR-214) with or without Talazoparib or Enzalutamide in Participants with Locally Advanced or Metastatic Solid Tumors

STATISTICAL ANALYSIS PLAN – B9991040

Compounds:	MSB0010718C NKTR-214 PF-04998299 PF-06944076
Compound Name:	Avelumab Bempegaldesleukin (NKTR-214) Talazoparib Enzalutamide
Version:	1.0
Date:	03-Sep-2019

TABLE OF CONTENTS

LIST OF TABLES 6
LIST OF FIGURES 8
1. VERSION HISTORY 9
2. OBJECTIVES, ENDPOINTS AND STUDY DESIGN 9
2.1. Study Objectives, Endpoints, and Estimands 9
2.2. Study Design 13
3. BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS 14
3.1. Baseline Variables 14
3.1.1. Study drug, study treatment and baseline definitions 14
3.1.2. Baseline characteristics 17
3.2. Safety Endpoints 17
3.2.1. Adverse events 17
4. ANALYSIS SETS 17
4.1. Full Analysis Set 17
4.2. Safety Analysis Set 17
4.3. Other Analysis Set 18
4.3.1. DLT-evaluable set 18
4.3.2. PK analysis sets 18
4.3.3. Biomarker analysis set 18
4.3.4. Immunogenicity analysis set 18
5. GENERAL METHODOLOGY AND CONVENTIONS 19
5.1. Hypotheses and Decision Rules 19
5.1.1. Hypotheses and sample size determination 19
5.1.2. Decision rules 20
5.2. General Methods 22
5.2.1. Data handling after the cut-off date 24
5.2.2. Pooling of centers 24
5.2.3. Presentation of continuous and qualitative variables 24
5.2.4. Definition of study day 24
5.2.5. Definition of start of new anti-cancer drug therapy 25
5.2.6. Definition of start of new anti-cancer therapy 25
5.2.7. Definition of on-treatment period 25

5.2.8. Standard derivations and reporting conventions 25
5.2.9. Unscheduled visits 26
5.2.10. Adequate baseline tumor assessment 26
5.2.11. Adequate post-baseline tumor assessment 26
5.3. Methods to Manage Missing Data 26
5.3.1. Missing data 26
5.3.1.1. Pharmacokinetic concentrations 27
5.3.1.2. Pharmacokinetic parameters 27
5.3.2. Handling of incomplete dates 28
5.3.2.1. Disease history 28
5.3.2.2. Adverse events 28
5.3.2.3. Prior and concomitant medications 28
5.3.2.4. Exposure 29
5.3.3. Imputation rules for date of last contact and efficacy assessments 29
5.3.3.1. Date of last contact 29
5.3.3.2. Death date 30
5.3.3.3. Tumor assessments 30
5.3.3.4. Date of start of new anti-cancer therapy 30
6. ANALYSES AND SUMMARIES 32
6.1. Primary Endpoints 32
6.1.1. DLT for Phase 1b 32
6.1.1.1. Primary analysis 32
6.1.2. Objective response as assessed by the Investigator per RECIST v1.1 in participants with SCCHN 34
6.1.2.1. Primary analysis 34
6.1.3. Soft tissue objective response as assessed by the Investigator per RECIST v1.1 and PCWG3 criteria in participants with mCRPC 35
6.1.3.1. Primary analysis 35
6.1.4. PSA response for participants with mCRPC 37
6.1.4.1. Primary analysis 37
6.2. Secondary Endpoint(s) 38
6.2.1. Safety endpoints 38
6.2.2. Efficacy endpoints 38

6.2.2.1. Tumor shrinkage from baseline 38
6.2.2.2. PSA reduction from baseline 38
6.2.2.3. Disease control 39
6.2.2.4. Duration of tumor response 39
6.2.2.5. Duration of PSA response 42
6.2.2.6. Time to tumor response 44
6.2.2.7. Time to PSA response 44
6.2.2.8. Progression-free survival 45
6.2.2.9. Time to PSA progression for participants with mCRPC 47
6.2.2.10. Overall Survival 49
6.2.2.11. CTC count conversion and CTC0 for participants with mCRPC 50
6.2.3. Pharmacokinetic endpoints 51
6.2.4. Population pharmacokinetic endpoints 53
6.2.5. Biomarker endpoints 53
6.2.6. Endpoints for immunogenicity data of avelumab, bempegaldesleukin (NKTR-214), and IL-2 54
6.2.6.1. Time to and Duration of ADA and nAb response 56
6.2.6.2. ADA titer 57
6.2.6.3. Analysis of PK and safety by immunogenicity status 57
CCI
6.4. Subset Analyses 59
6.5. Baseline and Other Summaries and Analyses 60
6.5.1. Baseline summaries 60
6.5.1.1. Demographic characteristics 60
6.5.1.2. Medical history 61
6.5.1.3. Disease characteristics 61
6.5.1.4. Prior anti-cancer therapies 62
6.5.2. Study conduct and participant disposition 63
6.5.2.1. Patient disposition 63
6.5.2.2. Protocol deviations 63

6.5.3. Study treatment compliance and exposure 64
6.5.3.1. Exposure to avelumab 65
6.5.3.2. Exposure to NKTR-214 65
6.5.3.3. Exposure to talazoparib 66
6.5.3.4. Exposure to enzalutamide 66
6.5.3.5. Dose reductions 67
6.5.3.6. Dose interruptions 67
6.5.3.7. Dose delays 68
6.5.3.8. Infusion rate reductions 68
6.5.3.9. Infusion interruptions 68
6.5.4. Concomitant medications and non-drug treatments 69
6.5.5. Subsequent anti-cancer therapies 69
6.6. Safety Summaries and Analyses 70
6.6.1. Adverse events 70
6.6.1.1. All adverse events 71
6.6.1.2. Adverse events leading to dose reduction 72
6.6.1.3. Adverse events leading to interruption of study treatment 73
6.6.1.4. Adverse events leading to discontinuation of study treatment 74
6.6.2. Deaths 74
6.6.3. Serious adverse events 75
6.6.4. Other significant adverse events 75
6.6.5. Laboratory data 76
6.6.5.1. Hematology and chemistry parameters 76
6.6.5.2. Other laboratory parameters 79
6.6.6. Vital signs 79
6.6.7. Electrocardiogram 79
6.6.8. ECOG performance status 81
7. INTERIM ANALYSES 81
8. REFERENCES 82
9. APPENDICES 83

LIST OF TABLES

Table 1. Summary of Major Changes in SAP Amendments 9
Table 2. Treatment Groups 15
Table 3. Study Summaries 23
Table 4. Outcome and Event Dates for DR Analyses 40
Table 5. Criteria for Evidence of Radiographic Progression for Participants with mCRPC 41
Table 6. DR Censoring Reasons and Hierarchy 42
Table 7. Outcome and Event Dates for Duration of PSA Response Analysis 43
Table 8. Duration of PSA Response Censoring Reasons and Hierarchy 44
Table 9. Outcome and Event Dates for PFS Analyses 46
Table 10. PFS Censoring Reasons and Hierarchy 47
Table 11. Outcome and Event Dates for Time to PSA Progression Analysis 48
Table 12. PSA Progression Censoring Reasons and Hierarchy 49
Table 13. OS Censoring Reasons and Hierarchy 50
Table 14. PK Parameters to be Determined for Avelumab, Bempegaldesleukin (NKTR-214), IL-2, Talazoparib and Enzalutamide 52
Table 15. Biomarker Definition and Determination 54
Table 16. Participants Characterized Based on Anti-Drug Antibody Results (ADA Status) 55
Table 17. Participants Characterized Based on Neutralizing Antibody Results (nAb Status) 56
Table 18. Case Definition for irAEs 83
Table 19. Case Definition for IRRs – IV Study Drugs Administered Alone Or In Combination With Non-IV Study Drugs 85
Table 20. Case Definition for IRRs – IV Study Drugs Administered in Combination (eg, Doublets or Triplets) 86
Table 21. Historical Dose Limiting Toxicity Data From Study EXCEL 89
Table 22. Prior Distributions for the Parameters of the MAP Model Used to Derive the Prior for the Single-Agent Bempegaldesleukin (NKTR-214) Model Parameters 90
Table 23. Historical Dose Limiting Toxicity Data from Study EMR100070-001 90
Table 24. Prior Distributions for the Parameters of the MAP Model Used to Derive the Prior for the Single-Agent Avelumab Model Parameters 91
Table 25. Prior Distribution for the Model Parameters 91

Table 26. Summary of Prior Distribution of Dose Limiting Toxicity Rates for the Doublet Combination of Avelumab in Combination with Bempegaldesleukin (NKTR-214) 92
Table 27. Combination A: Data Scenarios, Next Dose Recommendation, and the Interval Probability of Target Toxicity and Overdosing at Next Dose. 93
Table 28. Combination A: Dose Limiting Toxicity Rate Scenarios (Fixed Avelumab Dose 10 mg/kg every 2 Weeks) 93
Table 29. Combination A: Operating Characteristics 95
Table 30. Historical Dose Limiting Toxicity data from Study PRP-001 98
Table 31. Prior Distributions for the Parameters of the MAP Model Used to Derive the Prior for the Single-Agent Talazoparib Model Parameters 99
Table 32. Prior Distribution for the Model Parameters 100
Table 33. Summary of Prior Distribution of DLT Rates for the Triplet Combination of Avelumab in Combination with Bempegaldesleukin (NKTR-214) and Talazoparib 101
Table 34. Combination B: Clinically Meaningful Starting Dose Given Hypothetical Data from the Combination A, and the Interval Probability of Target Toxicity and Overdosing at Starting Dose. 102
Table 35. Combination B: Data Scenarios (Given Hypothetical Combination A Data), Next Dose Recommendation, and the Interval Probability of Target Toxicity and Overdosing at Next Dose. 103
Table 36. Combination B: Dose Limiting Toxicity Rate Scenarios (Fixed Avelumab Dose 10 mg/kg Every 2 Weeks) 104
Table 37. Combination B: Operating Characteristics 105
Table 38. Historical Dose Limiting Toxicity data from Study S-3100-1-01 108
Table 39. Prior Distributions for the Parameters of the MAP Model Used to Derive the Prior for the Single-Agent Enzalutamide Model Parameters 108
Table 40. Prior Distribution for the Model Parameters 109
Table 41. Summary of Prior Distribution of DLT Rates for the Triplet Combination of Enzalutamide in Combination with Bempegaldesleukin (NKTR-214) and Avelumab (Combination C) 110
Table 42. Combination C: Clinically Meaningful Starting Dose Given Hypothetical Data from the Doublet Combination, and the Interval Probability of Target Toxicity and Overdosing at Starting Dose. 111
Table 43. Combination C: Data Scenarios (Given Hypothetical Doublet Data), Next Dose Recommendation, and the Interval Probability of Target Toxicity and Overdosing at Next Dose. 111
Table 44. Combination C: Dose Limiting Toxicity Rate Scenarios (Fixed Avelumab Dose 10 mg/kg Every 2 Weeks) 112

Table 45. Combination C: Operating Characteristics 113

LIST OF FIGURES

Figure 1. Study Design Schema 13

1. VERSION HISTORY

This Statistical Analysis Plan (SAP) for study B9991040 is based on the protocol amendment 1 dated 27JUN2019.

Table 1. Summary of Major Changes in SAP Amendments

Version	Version Date	Summary of Changes
1	03-Sep-2019	Not applicable (N/A)

2. OBJECTIVES, ENDPOINTS AND STUDY DESIGN

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in study B9991040. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

Statistical analyses will be performed using cleaned eCRF data as well as non-CRF data (ie, pharmacokinetics, immunogenicity, and biomarker data). The primary analysis will include all data up to a cut-off date corresponding to 24 months after the last participant receives the first dose of study treatment. The final analysis of the data will be performed after last participant last visit (LPLV).

Additional analyses of the data may be performed for publication or regulatory reporting purposes.

2.1. Study Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary	
Phase 1b: • To assess the dose-limiting toxicity (DLT) rate of avelumab in combination with bempegaldesleukin (NKTR-214) (**Combination A)** and talazoparib (**Combination B)** or enzalutamide (**Combination C)** in order to determine the recommended Phase 2 dose (RP2D) for the combinations.	**Phase 1b:** • DLT during the DLT evaluation period (Cycle 1)
Phase 2: • **Combination A**: To assess objective response rate (ORR) of avelumab in combination with bempegaldesleukin (NKTR-214) in participants with locally recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN). • **Combination B:** To assess soft tissue ORR of avelumab in combination with bempegaldesleukin (NKTR-214) and talazoparib in participants with DDR defect positive metastatic castration-resistant prostate cancer (mCRPC).	**Phase 2:** • **Combination A**: Confirmed objective response (OR) as determined by the investigator using RECIST v1.1. • **Combination B**: Confirmed soft tissue OR as determined by the investigator using RECIST v 1.1 with no evidence of confirmed bone disease progression on repeat bone scan at least 6 weeks later per prostate cancer working group 3 (PCWG3) criteria.

• **Combination C:** To assess the prostate specific antigen (PSA) response rate of avelumab in combination with bempegaldesleukin (NKTR-214) and enzalutamide in participants with mCRPC after progression on abiraterone.	• **Combination C:** Confirmed PSA response decrease ≥ 50% from baseline confirmed by a second consecutive assessment at least 3 weeks later.
Secondary	
• To assess the overall safety and tolerability of the combinations (**A, B and C).**	• Adverse events (AEs) as characterized by type, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v4.03), timing, seriousness, and relationship to study therapy. • Laboratory abnormalities as characterized by type, severity (as graded by NCI CTCAE v4.03) and timing.
• To assess other measures of anti-tumor activity.	• Time-to-event endpoints as determined by the investigator, using RECIST v1.1 (**Combination A**) and in participants with mCRPC **(Combinations B and C**), RECIST v1.1 (soft tissue disease) and PCWG3 (bone disease), including time to tumor response (TTR), duration of response (DR), progression free survival (PFS), and Overall Survival (OS). • **Combination B**: Confirmed PSA response ≥50% decrease from baseline confirmed by a second consecutive assessment at least 3 weeks later. • **Combination C**: Confirmed soft tissue OR as determined by the investigator using RECIST v 1.1 with no evidence of confirmed bone disease progression on repeat bone scan at least 6 weeks later per PCWG3 criteria. • **Combination C:** Circulating tumor cells CTC count conversion (decrease in CTC count from ≥ 5 CTC per 7.5 mL of blood at baseline to < 5 CTC per 7.5 mL of blood) at any assessment on treatment), and CTC0 (CTC0 is defined as a CTC count of ≥1 CTC per 7.5 mL of blood at baseline and 0 CTC per 7.5 mL of blood at any assessment on treatment). • **Combinations B and C:** Time to PSA progression (TTPSAP) defined according to the consensus guidelines of the Prostate Cancer Clinical Trials Working Group 3 (PCWG3) criteria.
• To characterize the pharmacokinetic (PK) of avelumab, bempegaldesleukin (NKTR-214), and talazoparib or enzalutamide when given in combination.	• PK parameters including trough concentrations (C_{trough}) for avelumab, bempegaldesleukin (NKTR-214), IL-2 (active form of NKTR-214), talazoparib, enzalutamide, and N-desmethyl-enzalutamide and maximum concentrations (C_{max}) for avelumab and bempegaldesleukin (NKTR-214) and IL-2 (active form of NKTR-214).
• To assess the immunogenicity of avelumab and bempegaldesleukin (NKTR-214) when combined together and with talazoparib or enzalutamide.	• Anti-drug antibody (ADA) and neutralizing antibodies (NAb) against avelumab, bempegaldesleukin (NKTR-214) and IL-2 (active

	form of NKTR-214) when combined together and with talazoparib or enzalutamide.
• To assess the correlation of anti-tumor activity with PD-L1 expression level in baseline tumor tissue.	• PD-L1 expression level in baseline tumor tissue.
• **Combination A:** To assess the correlation of anti-tumor activity with PD-L1 expression level in on-treatment tumor tissue.	• **Combination A:** PD-L1 expression level in on-treatment tumor tissue.

CCI

Estimands

The estimands associated with the primary endpoints and the secondary efficacy endpoints of the study are described below.

The populations associated with estimands for each combination are as follows:

- Combination A - participants with 1L SCCHN.
- Combination B Phase 1b - participants with mCRPC after progression on taxane-based chemotherapy.

- Combination B Phase 2 - participants with DNA Damage Repair (DDR) defect positive (DDR+) mCRPC after progression on taxane-based chemotherapy.
- Combination C - participants with mCRPC after progression on abiraterone therapy.

The endpoint definitions, the observations that will be considered in the derivation of the endpoint and the associated analyses are described or referenced below.

- Phase 1b: The primary endpoint (Combinations A, B and C) will be the occurrence of DLT during the primary DLT evaluation period (Cycle 1). DLTs are defined in Section 6.1.1. DLTs will only be collected during Cycle 1 of Phase 1b and the DLT rate will be estimated for participants who are evaluable for DLTs. DLT-evaluable participants are those enrolled in Phase 1b who receive at least one dose of the combination treatment, and either experience DLT during the first cycle (28 days) of treatment, or complete the DLT observation period for the first cycle of treatment without DLT. Participants without DLTs who withdraw from study treatment before receiving at least 2 doses of avelumab and bempegaldesleukin (NKTR-214; all Combinations) or 75% of the planned dose of talazoparib (Combination B) or enzalutamide (Combination C), in Cycle 1 for reasons other than treatment-related toxicity are not evaluable for DLT. All participants deemed non-evaluable for DLT may be replaced.

- Phase 2 Objective Response (Combination A) or soft tissue Objective Response (Combination B): The primary estimand is the treatment effect of OR (Combination A) or soft tissue OR (Combination B) from the time of first dose until progression is met or subsequent anticancer therapy is administered. Point estimates and confidence intervals (following the methodology outlined in Sections 6.1.2.1 and 6.1.3.1) will be calculated.

- Phase 2 PSA Response (Combination C): The primary estimand is the treatment effect of PSA response from the time of first dose until progression is met or subsequent anticancer therapy is administered. Point estimates and confidence intervals (following the methodology outlined in Section 6.1.4.1) will be calculated.

- Phase 2 Tumor related endpoints: (TTR[Combinations A, B, and C], DR [Combinations A, B, and C], time to PSA progression [TTPSAP, Combinations B and C only], CTC count conversion [Combination C only]) and CTC0 [Combination C only]) are defined in Section 6.2.2. This is a non-randomized study and there will be no statistical comparisons between treatment groups; to address the objectives associated with tumor-related endpoints, point estimates and confidence intervals (following the methodology outlined in Section 6.2.2) will be calculated for each tumor-related endpoint including only assessments on or before start of new anti-cancer therapy and on or before progression.

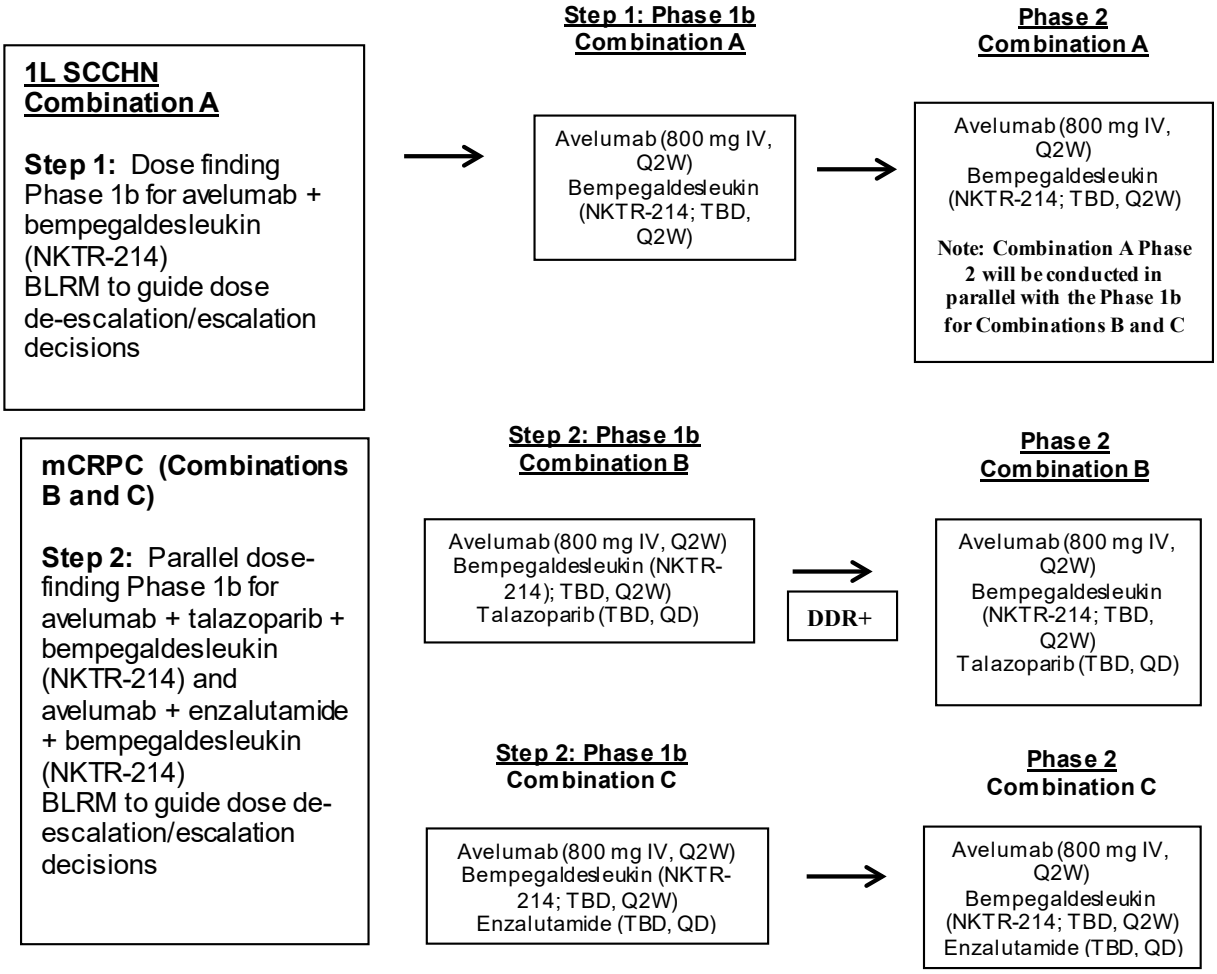
- Phase 2: OS is defined as the time from the first dose of study treatment to the date of death due to any cause. This is a non-randomized study and there will be no statistical comparisons between treatment groups; to address the OS objective, point estimates and confidence intervals (following the methodology outlined in

Section 6.2.2) will be calculated for OS including survival status for each participant at the time of the analysis; survival status is expected to be collected irrespective of study treatment discontinuation or participant's request to discontinue study procedures. All participants who have not withdrawn consent for further participation in the study should be followed for survival until at least 2 years after enrollment of the last participant in the study.

2.2. Study Design

This is a Phase 1b/2, open-label, multi-center study of avelumab in combination with bempegaldesleukin (NKTR-214) with or without talazoparib or enzalutamide in adult participants with 1L SCCHN (Combination A) or with mCRPC (Combinations B and C) (Figure 1).

Figure 1. Study Design Schema



Abbreviations: 1L SCCHN== locally recurrent (not amendable for treatment with curative intent) or metastatic squamous cell carcinoma of the head and neck; BLRM= Bayesian Logistic Regression Model; DDR=DNA damage repair; DDR+=positive for DNA damage repair defects; IV=intravenous; mCRPC=metastatic castration-resistant prostate cancer; Q2W=every two weeks; QD=once daily; TBD=to be determined.

Phase 1b Design

Phase 1b will include 2 sequential dose-finding steps:

Step 1. Combination A will be evaluated in participants with 1L SCCHN to determine RP2D. There are two possible levels for this combination (Table 2).

Step 2. Upon the determination of the RP2D for Combination A, the Phase 1b dose-finding for Combinations B and C in participants with mCRPC will commence to determine the RP2D for Combinations B and C separately. Combinations B and C each have 6 possible dose levels (Table 2).

Phase 2 Design

Once Phase 1b is completed for each combination and the RP2Ds have been determined, Phase 2 will be initiated to further evaluate the safety and anti-tumor activity in Combinations A, B, and C.

- Combination A will enroll up to approximately 31 participants with 1L SCCHN.
- Combination B will enroll up to approximately 20 participants with DDR+ mCRPC post taxane-based chemotherapy.
- Combination C will enroll up to approximately 40 participants with mCRPC post-abiraterone therapy.

Combination A will proceed into Phase 2 once RP2D for Combination A has been determined in the Phase 1b dose finding component, in parallel with dose-finding for Phase 1b for Combinations B and C.

3. BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Baseline Variables

3.1.1. Study drug, study treatment and baseline definitions

In this study, '**study drug**' refers to avelumab, bempegaldesleukin (NKTR-214), talazoparib, or enzalutamide and '**study treatment**' (or '**treatment group**') refers to one of the treatment groups in Table 2.

Table 2. Treatment Groups

Phase	Treatment groups (Dose Level)	Tumor Type	Avelumab (mg IV Q2W)	Bempegaldesleukin (NKTR-214) (mg/kg IV Q2W)	Talazoparib (mg QD PO)	Enzalutamide (mg QD PO)
1b	A1 (D0)	SCCHN	800	0.006	-	-
1b	A2 (D-1)	SCCHN	800	0.003	-	-
1b	B1 (D0-A*)	mCRPC post PD on chemo therapy	800	0.006	1.0	-
1b	B2 (D-1A)	mCRPC post PD on chemo therapy	800	0.006	0.75	-
1b	B3 (D-2A)	mCRPC post PD on chemo therapy	800	0.006	0.5	-
1b	B4 (D0-B*)	mCRPC post PD on chemo therapy	800	0.003	1.0	-
1b	B5 (D-1B)	mCRPC post PD on chemo therapy	800	0.003	0.75	-
1b	B6 (D-2B)	mCRPC post PD on chemo therapy	800	0.003	0.5	-
1b	C1 (D0-A*)	mCRPC post PD on abiraterone	800	0.006	-	160
1b	C2 (D-1A)	mCRPC post PD on abiraterone	800	0.006	-	120
1b	C3 (D-2A)	mCRPC post PD on abiraterone	800	0.006	-	80
1b	C4 (D0-B*)	mCRPC post PD on abiraterone	800	0.003	-	160
1b	C5 (D-1B)	mCRPC post PD on abiraterone	800	0.003	-	120
1b	C6 (D-2B)	mCRPC post PD on abiraterone	800	0.003	-	80
2	Cohort A	SCCHN	800	RP2D for Combination A	-	-
2	Cohort B	DDR+ mCRPC post PD on chemotherapy	800	RP2D for Combination B	RP2D for Combination B	-
2	Cohort C	mCRPC post PD on abiraterone	800	RP2D for Combination C	-	RP2D for Combination C

1L SCCHN= locally recurrent squamous cell carcinoma of the head and neck; mCRPC=metastatic castration-resistant prostate cancer; mg=milligram; Q2W= every 2 weeks; IV= intravenous; QD=once daily; PD = progressive disease; PO=orally; RP2D=recommended phase 2 dose.
D0= starting dose; D-1=reduced dose; D-2=second reduced dose.
*Dose levels for Combinations B and C designated with 'A' are applicable if the bempegaldesleukin (NKTR-214) dose is 0.006 mg/kg Q2W; dose levels for Combinations B and C designated with 'B' are applicable if the bempegaldesleukin (NKTR-214) dose is 0.003 mg/kg Q2W.

Start and end dates of study treatment:

The date/time of first dose of study treatment in a combination group is the earliest date/time of the first non-zero dose date/time for the study drugs in the combination.

The date/time of last dose of study treatment in a combination group is the latest date/time of the last non-zero dose date/time for the study drugs in the combination.

Definition of baseline:

Definition of baseline for safety and efficacy analyses

The last available assessment prior to the start of study treatment is defined as 'baseline' value or 'baseline' assessment for safety and efficacy analyses. If an assessment is planned to be performed prior to the first dose of study treatment in the protocol and the assessment is performed on the same day as the first dose of study treatment, it will be assumed that it was performed prior to study treatment administration, if assessment time point is not collected or is missing. If assessment time points are collected, the observed time point will be used to determine pre-dose on study day 1 for baseline calculation. Unscheduled assessments will be used in the determination of baseline. However, if time is missing, an unscheduled assessment on study day 1 will be considered to have been obtained after study treatment administration.

Participants who start treatment and discontinue from the study on the same day may have two different sets of data collected on study day 1 (one during study and one in the End of Treatment (EOT) visit). Data reported at the EOT visit are not eligible for baseline selection.

If a scheduled pre-dose measurement actually occurred post-dose, then the corresponding measurement will be treated and analyzed similar to an unscheduled post-dose measurement.

Baseline for RR and QT/QTc interval assessments will be derived from the visit where both RR and QT are not missing. Triplicate ECGs are collected in Phase 1b of the study and the baseline for each ECG parameter is the average of the pre-dose replicate measurements on the baseline day. Unscheduled assessments will not be included in the calculation of the average. QTcB and QTcF will be derived based on RR and QT. The average of the replicate measurements will be determined after the derivation of the individual parameter at each time point.

Definition of baseline for immunogenicity analyses

The last available assessment prior to the start of treatment with avelumab and bempegaldesleukin (NKTR-214) is defined as 'baseline' result or 'baseline' assessment. If an assessment is planned to be performed prior to the first dose of avelumab and bempegaldesleukin (NKTR-214) in the protocol and the assessment is performed on the same day as the first dose of avelumab and bempegaldesleukin (NKTR-214), it will be assumed

that it was performed prior to administration of avelumab and bempegaldesleukin (NKTR-214), if assessment time point is not collected or is missing.

3.1.2. Baseline characteristics

Baseline characteristics (including demographics, physical measurements, disease history and prior anti-cancer therapies) are described in Section 6.5.1. These baseline characteristics are not planned to be included as stratification variables or covariates in statistical models unless otherwise specified in Section 6.

3.2. Safety Endpoints

3.2.1. Adverse events

Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are those events with onset dates occurring during the on-treatment period.

On-treatment period is defined as the time from the first dose of study treatment through minimum (30 days + last dose of study treatment, start day of new anti-cancer drug therapy – 1 day). The start day of new anti-cancer drug therapy after the first dose of study treatment is derived as outlined in Section 5.2.5.

Adverse Events of Special Interest (AESIs)

AESIs are immune-related adverse events (irAE) and infusion-related reactions (IRRs). The criteria for classification of an AE as an irAE or IRR are described in Appendix 1 and Appendix 2, respectively.

4. ANALYSIS SETS

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to releasing the database and classifications will be documented per Pfizer's standard operating procedures.

Only participants who signed informed consent will be included in the analysis sets below.

4.1. Full Analysis Set

The FAS will include all participants who receive at least one dose of study drug. Participants will be classified according to the study treatment actually received. If a participant receives more than one treatment the participant will be classified according to the first study treatment received.

4.2. Safety Analysis Set

The safety analysis set will include all participants who receive at least one dose of study drug. Participants will be classified according to the study treatment actually received. If a participant receives more than one study treatment, the participant will be classified

according to the first study treatment received. In this non-randomized study, the FAS and the safety analysis set are identical.

4.3. Other Analysis Set

4.3.1. DLT-evaluable set

The DLT-evaluable analysis set is a subset of the safety analysis set and includes all enrolled participants in Phase 1b who receive at least one dose of the combination treatment and either experience DLT during the first cycle (28 days) of treatment, or complete the DLT observation period for the first cycle of treatment without a DLT.

Participants without DLTs who withdraw from study treatment before receiving at least 2 doses of avelumab and bempegaldesleukin (NKTR-214; all Combinations) or 75% of the planned dose of talazoparib (Combination B) or enzalutamide (Combination C) in Cycle 1 for reasons other than treatment-related toxicity are not evaluable for DLT. All participants deemed non-evaluable for DLT may be replaced.

4.3.2. PK analysis sets

The PK concentration analysis set is a subset of the safety analysis set and will include participants who have at least one post-dose concentration measurement above the lower limit of quantitation (LLQ) for avelumab, bempegaldesleukin (NKTR-214), IL-2, talazoparib, enzalutamide, or N-desmethyl-enzalutamide.

The PK parameter analysis set is a subset of the safety analysis set and will include participants who have at least one of the PK parameters of interest for avelumab, bempegaldesleukin (NKTR-214), IL-2, talazoparib, enzalutamide, or N-desmethyl-enzalutamide.

4.3.3. Biomarker analysis set

The biomarker analysis set for biomarkers that are only measured at screening is a subset of the safety analysis set and will include participants who have at least one baseline biomarker assessment.

The biomarker analysis set for biomarkers that are measured sequentially is a subset of the safety analysis set and will include participants who have at least one baseline and one on-treatment biomarker assessment for the same marker.

The biomarker analysis set is defined separately for each biomarker of interest.

Analysis sets will be defined separately for blood-based and tumor tissue-based biomarkers.

4.3.4. Immunogenicity analysis set

The immunogenicity analysis set is a subset of the safety analysis set and will include participants who have at least one ADA/nAb sample collected for avelumab, bempegaldesleukin (NKTR-214), or IL-2.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

5.1.1. Hypotheses and sample size determination

There is no formal hypothesis testing in this study.

Approximately 160 participants will be screened to achieve approximately 127 participants assigned to study intervention, with 27-36 participants in Phase 1b and up to approximately 91 participants in Phase 2. A given combination size may be expanded in Phase 2 only by a limited number of additional participants (approximately 10) per sponsor's discretion subsequent to the identification of any early signal of clinical activity that may emerge from the generated data in a biomarker-defined population.

During the Phase 1b dose finding, it is estimated that approximately up to 12 and 15 participants will be enrolled and assigned to treatment in each of the three combinations (one doublet combination, two triplet combinations). Each combination will include at least 6 participants treated at the Maximum Tolerated Dose (MTD) level and at least 9 participants at the RP2D. The actual number of participants for the Phase 1b dose finding will depend on the number of DLT events and dose levels/combinations that are tested. For each combination, beginning with the starting dose level, cohorts of 3-6 participants will be enrolled, treated, and monitored during the 28-day DLT-evaluation period (Cycle 1).

Nine evaluable participants are needed to be treated at RP2D if no DLT is observed, and 12 evaluable participants if at least 1 DLT is observed.

Data from Phase 1b participants with SCCHN will also be used for the Phase 2 efficacy assessment at the RP2D.

In Phase 2, with 20 (Combination B), 40 including Phase 1b participants (Combination A) and 40 (Combination C) treated participants in Combinations B, A and C, respectively, soft tissue ORR, ORR, and PSA response rate can be estimated with a maximum standard error of 0.112 (Combination B) or 0.079 (Combinations A and C), respectively.

Assuming beta-binomial distributions for ORR (Combination A), soft tissue ORR (Combination B), and PSA response rate (Combination C) and a non-informative beta (0.5, 0.5) prior:

- For Combination A (1L SCCHN), if 20 responders (out of 40 participants, ORR = 50%) are observed, the probability of a true ORR≥ 40 % (considered a clinically relevant effect) will be ≥90% (90.1%).
- For Combination B (DDR defect positive mCRPC post chemotherapy), if 12 responders (out of 20 participants, soft tissue ORR = 60%) are observed, the probability of a true soft tissue ORR≥ 50% (considered a clinically relevant effect) will be ≥80% (81.4%).

- For Combination C (mCRPC post abiraterone), if 20 PSA responders (out 40 participants, PSA response rate = 50%) are observed, the probability of a true PSA response rate ≥ 40% (considered a clinically relevant effect) will be ≥90% (90.1%).

The determination of what constitutes a clinically meaningful response rate was based upon a review of historical ORR (for SSCHN), soft tissue ORR (for mCRPC, Combination B), PSA response rate (for mCRPC, Combination C) in clinical studies.

5.1.2. Decision rules

Identification of a recommended dose

The dosing decision and estimation of the MTDs of the doublet (Combination A) and the triplets (Combination B and C) will be guided by the estimation of the probability of DLT in Cycle 1. However, other evidence such as safety data beyond DLT, clinical activity, PK, and PD data will play an important role in the final decision. A RP2D below the MTD may be determined based on these considerations.

A dose level combination is a potential candidate for being the MTD level when all the following criteria are met:

- ≥6 participants have been treated at that dose;
- Probability of target dosing >0.50;
- Probability of overdosing <0.25.

Combination A will be evaluated first to determine the RP2D. Upon the completion of the dose finding of the doublet, Combinations B and C will then be evaluated to determine the RP2D for these triplet combinations. Guidance for Phase 1b dosing (dose level to be evaluated in the next cohort) and enrollment (number of participants to be enrolled in the next cohort) decisions will be based on a Bayesian Logistic Regression Model (BLRM). The BLRM incorporates single-agent and available combination DLT data (historical and prospectively across dose combinations) to estimate the posterior probability of under-dosing, target dosing and overdosing, thereby reducing participant risk and increasing efficiency and precision during dose finding with combination treatments. Refer to Appendix 3, Appendix 4, and Appendix 5 for the full details of the BLRM designs for Combinations A, B, and C, respectively.

Bayesian adaptive approach

Doublet combination model:

For Combination A, the Bayesian model consists of three parts, representing:

- Single-agent avelumab toxicity;
- Single-agent bempegaldesleukin (NKTR-214) toxicity;

- Interaction between bempegaldesleukin (NKTR-214) and avelumab.

Triplet combination model:

For Combination B, the Bayesian model consists of seven parts, representing:

- Single-agent talazoparib toxicity;
- Single-agent bempegaldesleukin (NKTR-214) toxicity;
- Single-agent avelumab toxicity;
- Interaction between talazoparib and bempegaldesleukin (NKTR-214);
- Interaction between talazoparib and avelumab;
- Interaction between bempegaldesleukin (NKTR-214) and avelumab;
- Triple interaction among talazoparib, bempegaldesleukin (NKTR-214), and avelumab.

For the Combination C, the Bayesian model consists of seven parts, representing:

- Single-agent enzalutamide toxicity;
- Single-agent bempegaldesleukin (NKTR-214) toxicity;
- Single-agent avelumab toxicity;
- Interaction between enzalutamide and bempegaldesleukin (NKTR-214);
- Interaction between enzalutamide and avelumab;
- Interaction between bempegaldesleukin (NKTR-214) and avelumab;
- Triple interaction among enzalutamide, bempegaldesleukin (NKTR-214), and avelumab.

Single-agent toxicities are modelled using logistic regression for the probability of a participant experiencing a DLT against log-dose. The odds of a DLT are then calculated under no interaction for the two/three single-agent toxicities, and interaction is accounted for by adjusting these odds with an additional model parameter (odds multiplier).

Assessment of participant risk

After each cohort of participants completes the DLT-evaluation period, the posterior distribution for the risk of DLT for different combination doses of interest will be evaluated.

The posterior distributions will be summarized to provide the posterior probability that the risk of DLT lies within the following intervals:

- Underdosing: [0, 0.16)
- Target toxicity: [0.16, 0.33)
- Excessive toxicity or overdosing: [0.33, 1]

The EWOC principle

Dosing decisions are guided by the EWOC principle[1]. A combination dose may only be used for the next cohort of participants if the risk of excessive toxicity ([0.33, 1]) at that combination dose is less than 0.25.

Prior distributions

A meta-analytic-predictive (MAP) approach was used to derive the prior distribution for the single-agent model parameters. The MAP prior for the logistic model parameters for this study is the conditional distribution of the parameters given the historical data[9, 10, 11]. MAP priors are derived using Bayesian hierarchical models, which take into account possible differences between the studies.

The prior distribution for the interaction parameters (doublet and triplets) were based on the prior understanding of possible drug safety interactions. This prior allows for the possibility of either synergistic or antagonistic interaction.

Starting dose levels

The starting dose for the Combination A is 800 mg avelumab IV Q2W, and 0.006 mg/kg bempegaldesleukin [NKTR-214] Q2W IV. For this dose the prior risk of excessive toxicity is 0.137, which satisfies the EWOC criterion.

The starting dose for the triplets (Combinations B and C) will be determined based on all available data after completion of the dose finding for Combination A.

5.2. General Methods

The definition of '**treatment group**' in this study is provided in Table 2.

Table 3 provides an overview of the planned summaries for this study for each endpoint, treatment group and study phase.

Table 3. Study Summaries

Summaries	Analysis Sets	Phase 1b	Phase 2	Phase 1b and Phase 2 combined
Baseline characteristics	FAS	- by treatment group - pooled: A1+A2 - pooled: B1 +…+ B6 [a] - pooled: C1 +…+ C6 [b] - pooled: all participants	- by treatment group - pooled: all participants	All participants treated at the RP2D for each combination
Disposition	FAS	- by treatment group - pooled: A1+A2 - pooled: B1 +…+ B6 [a] - pooled: C1 +…+ C6 [b]	- by treatment group	All participants treated at the RP2D for each combination
DLTs	DLT-evaluable set	- by treatment group - pooled: A1+A2 - pooled: B1 +…+ B6 [a] - pooled: C1 +…+ C6 [b]	Not Done	Not Done
Efficacy data	FAS	- by treatment group	- by treatment group	All participants treated at the RP2D for Combination A and for Combination C
Other safety data (including AESI), exposure data, concomitant medications, non-drug treatments	Safety analysis set	- by treatment group - pooled: A1+A2 - pooled: B1 +…+ B6 [a] - pooled: C1 +…+ C6 [b]	- by treatment group	All participants treated at the RP2D for each combination
PK data for avelumab	PK analysis set	- by treatment group	- by treatment group	Not Done
PK data for bempegaldesleukin (NKTR-214) and IL-2	PK analysis set	- by treatment group	- by treatment group	Not Done
PK data for talazoparib	PK analysis set	- by treatment group	- by treatment group	Not Done
PK data for enzalutamide and N-Desmethyl-Enzalutamide	PK analysis set	- by treatment group	- by treatment group	Not Done
Biomarker data	Biomarker analysis set	- pooled: A1+A2 - pooled: B1 +…+B6 [a] - pooled: C1 +…+C6 [b]	- by treatment group	- by combination [c]
Immunogenicity for avelumab	Immunogenicity analysis set	- pooled: A1+A2 - pooled: B1 +…+B6 [a] - pooled: C1 +…+C6 [b] - pooled: all participants	- by treatment group - pooled: all participants	- by combination [c] - pooled: all participants

Immunogenicity for bempegaldesleukin (NKTR-214) and IL-2	Immunogenicity analysis set	- pooled: A1+A2 - pooled: B1 +…+B6 [a] - pooled: C1 +…+C6 [b] - pooled: all participants	- by treatment group - pooled: all participants	- by combination [c] - pooled: all participants

[a] B1 +…+B6 = B1+ B2+ B3+ B4+ B5+ B6;
[b] C1 +…+C6 = C1+ C2+ C3+ C4+ C5+ C6;
[c] Combination A=A1+A2+ cohort A; Combination B= B1+ B2+ B3+ B4+ B5+ B6 + Cohort B; Combination C= C1+ C2+ C3+ C4+ C5+ C6 + Cohort C.

5.2.1. Data handling after the cut-off date

Data after the cut-off date may not undergo the cleaning process and will not be displayed in any listings or used for summary statistics, statistical analyses or imputations.

5.2.2. Pooling of centers

In order to provide overall estimates of treatment effects, data will be pooled across centers. The 'center' factor will not be considered in statistical models or for subgroup analyses due to the high number of participating centers in contrast to the anticipated small number of participants treated at each center.

5.2.3. Presentation of continuous and qualitative variables

Continuous variables will be summarized using descriptive statistics ie, number of non-missing values and number of missing values [ie, n (missing)], mean, median, standard deviation (SD), minimum, maximum and first and third quartile (Q1 and Q3).

Qualitative variables will be summarized by frequency counts and percentages. Unless otherwise specified, the calculation of proportions will include the missing category. Therefore, counts of missing observations will be included in the denominator and presented as a separate category.

In case the analysis refers only to certain visits, percentages will be based on the number of participants still present in the study at that visit, unless otherwise specified.

5.2.4. Definition of study day

Start day of study treatment is the day of the first dose of study treatment.

The study day for assessments occurring on or after the start of study treatment (eg, adverse event onset, tumor measurement) will be calculated as:

Study day = Date of the assessment/event - start of study treatment + 1.

The study day for assessments occurring prior to the first dose of study treatment (eg, baseline characteristics, medical history) will be negative and calculated as:

Study day = Date of the assessment/event - start of study treatment.

The study day will be displayed in all relevant data listings.

5.2.5. Definition of start of new anti-cancer drug therapy

Start date of new anti-cancer drug therapy is used to determine the end of the on-treatment period (see Section 5.2.7).

The start date of new anti-cancer drug therapy is the earliest start date of anti-cancer drug therapy recorded in the 'Follow-up Cancer Therapy' eCRF pages that is after the first dose of study treatment. When start date of anti-cancer drug therapy is missing or partially missing, the imputation rules described in Section 5.3.3.4 should be applied using only data from the 'Follow-up Cancer Therapy' eCRF pages.

5.2.6. Definition of start of new anti-cancer therapy

Start date of new anti-cancer therapy (drug, radiation, surgery) is used for censoring in efficacy analyses (see Sections 6.1.2, 6.1.3, 6.1.4, and Section 6.2.2).

The start date of new anti-cancer therapy is the earliest date after the first dose of study treatment amongst the following:

- Start date of anti-cancer drug therapy recorded in the 'Follow-up Cancer Therapy' eCRF pages
- Start date of radiation therapy recorded in 'Concomitant Radiation Therapy', and 'Follow-up Radiation Therapy' eCRF pages with 'Treatment Intent' = 'Curative in intent'
- Surgery date recorded in 'Concomitant Surgery', and 'Follow-up Surgery' eCRF pages when 'Surgery Outcome' = 'Resected' or 'Partially Resected'.

When start date of anti-cancer therapy is missing or partially missing, the imputation rules described in Section 5.3.3.4 should be applied using 'Follow-up Cancer Therapy', 'Concomitant Radiation Therapy', 'Follow-up Radiation Therapy', 'Concomitant Surgery', and 'Follow-up Surgery' eCRF pages.

5.2.7. Definition of on-treatment period

Safety endpoints will be summarized based on the on-treatment period unless otherwise specified.

On-treatment period is defined as the time from the first dose of study treatment through minimum (30 days + last dose of study treatment, start day of new anti-cancer drug therapy – 1 day).

Safety data collected outside the on-treatment period as described above will be listed and flagged in listings but not summarized.

5.2.8. Standard derivations and reporting conventions

The following conversion factors will be used to convert days into weeks, months or years: 1 week = 7 days, 1 month = 30.4375 days, 1 year = 365.25 days.

Demographics and physical measurements:

- Age [years]:
  - (date of given informed consent - date of birth + 1) / 365.25
  - In case of missing day, day only: Age [years]: (year/month of given informed consent – year/month of birth)
  - In case only year of birth is given: Age [years]: (year of given informed consent - year of birth)

The integer part of the calculated age will be used for reporting purposes.

- BMI (kg/m^2) = weight (kg)/[height (m)]^2

For reporting conventions, mean and median should generally be displayed one more decimal place than the raw data and standard deviation should be displayed to two more decimal places than the raw data. Percentages will be reported to one decimal place. The rounding will be performed to closest integer / first decimal using the common mid-point between the two consecutive values. Eg, 5.1 to 5.4 will be rounded to an integer of 5, and 5.5 to 5.9 will be rounded to an integer of 6.

5.2.9. Unscheduled visits

Generally, data collected at unscheduled visits will be included and analyzed for both safety and efficacy analyses in the same fashion as the data collected at scheduled visits except where otherwise noted in the sections that follow. Descriptive statistics (mean, SD, median, minimum, maximum, quartiles) by nominal visit or time point for safety endpoints such as laboratory measurements, ECGs and vital signs will include only data from scheduled visits.

5.2.10. Adequate baseline tumor assessment

Adequate baseline is defined using the following criteria:

- All baseline assessments must be within 28 days prior to and including the date of first dose of study treatment.
- All documented lesions must have non-missing assessments (ie, non-missing measurements for target lesions and non-missing lesions assessment status at baseline for non-target lesions).

5.2.11. Adequate post-baseline tumor assessment

An adequate post-baseline assessment is defined as an assessment where a response of CR, PR, SD, non-CR/non-PD, or PD can be determined (see Section 6.1.2.1 and Section 6.1.3.1). Time points where the response is not evaluable (NE) or no assessment was performed will not be used for determining the censoring date.

5.3. Methods to Manage Missing Data

5.3.1. Missing data

Unless otherwise specified, all data will be evaluated as observed, and no imputation method for missing values will be used.

In all participant data listings imputed values will be presented. In all listings imputed information will be flagged.

Missing statistics, eg when they cannot be calculated, should be presented as 'ND' or 'NA'. For example, if N=1, the measure of variability (SD) cannot be computed and should be presented as 'ND' or 'NA'.

5.3.1.1. Pharmacokinetic concentrations

Concentrations Below the Limit of Quantification

For all calculations, figures and estimation of individual pharmacokinetic parameters, all concentrations assayed as below the level of quantification (BLQ) will be set to zero. In log-linear plots these values will not be represented. The BLQ values will be excluded from calculations of geometric means and their CIs. A statement similar to 'All values reported as BLQ have been replaced with zero' should be included as a footnote to the appropriate tables and figures.

Deviations, Missing Concentrations and Anomalous Values

In summary tables and plots of median profiles, concentrations will be set to missing if one of the following cases is true:

1. A concentration has been reported as ND (ie, not done) or NS (ie, no sample);
2. A deviation in sampling time is of sufficient concern or a concentration has been flagged as anomalous by the clinical pharmacologist.

Summary statistics will not be presented at a particular time point if more than 50% of the data are missing. For analysis of pharmacokinetic concentrations, no values will be imputed for missing data.

5.3.1.2. Pharmacokinetic parameters

Whether actual or nominal PK sampling time will be used for the derivation of PK parameters will be determined by the results of interim PK analyses. If a PK parameter cannot be derived from a participant's concentration data, the parameter will be coded as NC (ie, not calculated). NC values will not be generated beyond the day that a participant discontinues.

In summary tables, statistics will be calculated by setting NC values to missing. Statistics will not be presented for a particular treatment if more than 50% of the data are NC. For statistical analyses (ie, analysis of variance), PK parameters coded as NC will also be set to missing.

If an individual participant has a known biased estimate of a PK parameter (due for example to a deviation from the assigned dose level), this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical analyses.

5.3.2. Handling of incomplete dates

5.3.2.1. Disease history

Incomplete dates for disease history (eg, initial diagnosis date, date of documented, locally advanced, inoperable or metastatic disease diagnosis, date of response or progression in prior treatment) will be imputed as follows:

- If the day is missing, it will be imputed to the 15th day of the month.
- If both day and month are missing and the year is prior to the year of the first study treatment, the month and day will be imputed as July 1st.
- If both day and month are missing and the year is same as the year of the first study treatment, the month and day will be imputed as January 1st.
- If the date is completely missing, no imputation will be performed.

5.3.2.2. Adverse events

Incomplete AE-related dates will be imputed as follows:

- If the AE onset date is missing completely, then the onset date will be replaced by the start of study treatment.
- If only the day part of the AE onset date is missing, but the month and year are equal to the start of study treatment, then the AE onset date will be replaced by the start of study treatment. For example, if the AE onset date is --/JAN/2015, and study treatment start date is 15/JAN/2015, then the imputed AE onset date will be 15/JAN/2015.
- If both the day and month of the AE onset date are missing but the onset year is equal to the start of study treatment, then the onset date will be replaced by the start of study treatment. For example, if AE onset date is --/---/2014, and study treatment start date is 19/NOV/2014, then the imputed AE onset date will be 19/NOV/2014.
- In all other cases the missing onset day or missing onset month will be replaced by 1.
- Incomplete stop date will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of participant's death. In the latter case the date of death will be used to impute the incomplete stop date.
- In all other cases the incomplete stop date will not be imputed. If stop date of AE is after the date of cut-off outcome of AE is ongoing at cut-off.

5.3.2.3. Prior and concomitant medications

Incomplete prior/concomitant medication dates will be imputed as follows:

- If the medication date is missing completely, then the medication date will be replaced by the start of study treatment.
- If the day of medication date is missing, but the month and year are equal to the start of study treatment, then the medication date will be replaced by the start of study treatment. For example, if the medication start date is --/JAN/2015, and study treatment start date is 15/JAN/2015, then the imputed medication start date will be 15/JAN/2015.

- If both the day and month of medication start date are missing but the start year is equal to the start of study treatment, then the medication date will be replaced by the start of study treatment. For example, if the medication start date is --/---/2014, and study treatment start date is 19/NOV/2014, then the imputed medication start date will be 19/NOV/2014.
- In all other cases the missing medication day or missing medication month will be replaced by 1.
- Incomplete stop date will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of participant's death. In the latter case the date of death will be used to impute the incomplete stop date.
- In all other cases the incomplete medication stop date will not be imputed.

5.3.2.4. Exposure

No imputation will be done for first dose date. Date of last dose of study drug, if unknown or partially unknown, will be imputed as follows:

- If the last date of study drug is completely missing and there is no End of Treatment eCRF page and no death date, the participant should be considered to be ongoing and use the cut-off date for the analysis as the last dosing date
- If the last date of study drug is completely or partially missing and there is EITHER an End of Treatment eCRF page OR a death date available (within the cut-off date), then imputed last dose date is:

  = 31DECYYYY, if only Year is available and Year < Year of min (EOT date, death date)

  = Last day of the month, if both Year and Month are available and Year = Year of min (EOT date, death date) and Month < the month of min (EOT date, death date)

  = min (EOT date, death date), for all other cases.

5.3.3. Imputation rules for date of last contact and efficacy assessments

5.3.3.1. Date of last contact

The date of last contact will be derived for participants not known to have died at the analysis cut-off using the latest complete date among the following:

- All participant assessment dates (blood draws (laboratory, PK), vital signs, performance status, ECG, tumor assessments)
- Start and end dates of anti-cancer therapies administered after study treatment discontinuation
- AE start and end dates
- Last date of contact collected on the 'Survival Follow-up' eCRF (do not use date of survival follow-up assessment unless status is 'alive')
- Study drug start and end dates
- Withdrawal of consent date

- Date of discontinuation on disposition eCRF pages (do not use if reason for discontinuation is lost to follow-up).

Only dates associated with actual examinations of the participant will be used in the derivation. Dates associated with a technical operation unrelated to participant status such as the date a blood sample was processed will not be used. Assessment dates after the cut-off date will not be applied to derive the last contact date.

5.3.3.2. Death date

Missing or partial death dates will be imputed based on the last contact date:

- If the date is missing it will be imputed as the day after the date of last contact
- If the day or both day and month is missing, death will be imputed to the maximum of the full (non-imputed) day after the date of last contact and the following:
  - Missing day: 1st day of the month and year of death
  - Missing day and month: January 1st of the year of death

5.3.3.3. Tumor assessments

All investigation dates (eg, X-ray, CT scan) must be completed with day, month and year.

If there are multiple scan dates associated with an evaluation, ie, radiological assessments occur over a series of days rather than the same day, the choice of date of assessment could impact the date of progression and/or date of response. If there are multiple scan dates associated with an evaluation, the earliest of the scan dates associated with the evaluation will be used as the date of assessment.

If one or more investigation dates for an evaluation are incomplete but other investigation dates are available, the incomplete date(s) are not considered for calculation of the assessment date and assessment date is calculated as the earliest of all investigation dates (eg, X-ray, CT-scan).

If all measurement dates for an evaluation have no day recorded, the 1st of the month is used.

If the month is not completed, for any of the investigations for an evaluation, the respective assessment will be considered to be at the date which is exactly between the previous and the following assessment. If both a previous and following assessments are not available, this assessment will not be used for any calculations.

5.3.3.4. Date of start of new anti-cancer therapy

Incomplete dates for start date of new anti-cancer therapy (drug therapy, radiation, surgery) will be imputed as follows and will be used for determining censoring dates for efficacy analyses and in the derivation of the end of on-treatment period. PD date below refers to PD date by investigator assessment.

- The end date of new anti-cancer therapy will be included in the imputations for start date of new anti-cancer therapy. If the end date of new anti-cancer therapy is
  - completely missing then it will be ignored in the imputations below
  - partially missing with only year (YYYY) available then the imputations below will consider 31DECYYYY as the end date of the new anti-cancer therapy
  - partially missing with only month and year available then the imputations below will consider the last day of the month for MMMYYYY as the end date of the new anti-cancer therapy
- For participants who have not discontinued study treatment at the analysis cut-off date, last dose of study treatment is set to the analysis cut-off date in the imputations below.
- If the start date of new anti-cancer therapy is completely or partially missing, then the imputed start date of new anti-cancer therapy is derived as follows:
  - Start date of new anti-cancer therapy is completely missing

    Imputed start date = min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]
  - Only year (YYYY) for start of anti-cancer therapy is available

    IF YYYY < Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy] THEN imputed start date = 31DECYYYY;

    ELSE IF YYYY = Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]

    THEN imputed start date = min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]

    ELSE IF YYYY > Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]

    THEN imputed start date = 01JANYYYY
  - Both Year (YYYY) and Month (MMM) for start of anti-cancer therapy are available

    IF

    YYYY = Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy], AND

    MMM < Month of min [max(PD date + 1 day, last dose of study treatment + 1 day), end date of new anti-cancer therapy]

    THEN

    imputed start date = DAY (Last day of MMM) MMM YYYY;

    ELSE IF

    YYYY = Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy], AND

MMM = Month of min [max(PD date + 1 day, last dose of study treatment + 1 day), end date of new anti-cancer therapy]

THEN

imputed start date = min [max(PD date + 1 day, last dose of study treatment + 1 day), end date of new anti-cancer therapy]);

ELSE IF

YYYY = Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy], AND

MMM > Month of min [max(PD date + 1 day, last dose of study treatment + 1 day), end date of new anti-cancer therapy]

THEN

imputed start date = 01 MMM YYYY;

ELSE IF

YYYY < Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]

THEN

imputed start date = DAY (Last day of MMM) MMM YYYY;

ELSE IF

YYYY > Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]

THEN

imputed start date = 01 MMM YYYY.

6. ANALYSES AND SUMMARIES

Refer to Section 4 for definitions of analysis sets and Section 5.2 for general methodology.

6.1. Primary Endpoints

6.1.1. DLT for Phase 1b

6.1.1.1. Primary analysis

In Phase 1b, any of the following AEs occurring in the first cycle of treatment which are attributable to any or all study drugs administered in the combination will be classified as DLTs.

Hematologic:

- Grade 4 anemia lasting >5 days (life threatening consequences; urgent intervention indicated).

- Grade 4 neutropenia (absolute neutrophil count [ANC] <500/mm^3 or <0.5×10^9/L) lasting >5 days.

- Grade ≥3 febrile neutropenia, defined as ANC <1000/mm^3 with a single temperature of >38.3°C (>101°F) or a sustained temperature of ≥38°C (100.4°F) for more than 1 hour.

- Grade ≥3 neutropenic infection (ANC <1,000/mm^3 or <1.0×10^9/L, and Grade >3 infection).

- Grade 3 thrombocytopenia (25,000/mm^3 or 25.0×10^9/L to <50,000/ mm^3 or <50.0×10^9/L) with bleeding, or grade 4 thrombocytopenia (platelet count <25,000/mm^3 or <25.0×10^9/L).

Non-Hematologic:

- Potential Hy's Law cases defined as: ALT or AST >3×upper limit of normal (ULN) if normal at baseline OR >3×ULN and doubling the baseline (if >ULN at baseline) associated with total bilirubin >2×ULN and an alkaline phosphatase (AP) <2×ULN.

- Grade ≥3 toxicities of any duration **except:**

  - Grade 3 nausea, vomiting, or diarrhea and Grade 4 vomiting or diarrhea that resolves in 72 hours;

  - Grade 3 hypotension that occurs within 5 days post-dosing and resolves with adequate medical intervention;

  - Grade 3 non-hematologic laboratory abnormalities without a clinical correlate.

Non-adherence to Treatment Schedule:

- Delay of the subsequent cycle of two weeks or more due to toxicity occurring during the DLT observation period.

- Failure to deliver ≥75% of the planned doses of all study interventions during the first cycle of treatment due to treatment related toxicities.

While the rules for adjudicating DLTs in the context of the Phase 1b are specified above, an AE not listed above, or an AE meeting the DLT criteria above but occurring outside of the DLT observation period, may be defined as a DLT based on the emerging safety profile for the combinations.

The following analyses will be based on the DLT-evaluable set for participants in the Phase 1b. DLTs by SOC and PT will be listed and summarized by number and percentage of participants in decreasing frequency as shown in Table 3.

The posterior distribution of DLT rate [posterior probabilities that DLT rate is in the intervals of underdosing (<0.16), target toxicity (≥0.16 and <0.33) and overdosing (≥0.33 and ≤1)] at the end of Phase 1b will be provided as shown in Table 3.

6.1.2. Objective response as assessed by the Investigator per RECIST v1.1 in participants with SCCHN

6.1.2.1. Primary analysis

The following analyses will be based on the FAS for participants with SCCHN in Combination A as shown in Table 3. Assessment of response will be made based on investigator assessment using RECIST v1.1.

Best overall response (BOR) will be assessed based on reported overall lesion responses at different evaluation time points from the date of first dose of study treatment until the first documentation of PD, according to the following rules. Only tumor assessments performed on or before the start date of any further anti-cancer therapies will be considered in the assessment of BOR. Clinical deterioration will not be considered as documentation of disease progression.

BOR Based on Confirmed Responses:

- CR = at least two determinations of CR at least 4 weeks apart and before first documentation of PD
- PR = at least two determinations of PR or better (PR followed by PR or PR followed by CR) at least 4 weeks apart and before first documentation of PD (and not qualifying for a CR)
- SD (applicable only to participants with measurable disease at baseline) = at least one SD assessment (or better) ≥ 6 weeks after the date of first dose of study treatment and before first documentation of PD (and not qualifying for CR or PR).
- Non-CR/non-PD (applicable only to participants with non-measurable disease at baseline) = at least one non-CR/non-PD assessment (or better) ≥ 6 weeks after the date of first dose of study treatment and before first documentation of PD (and not qualifying for CR or PR).
- PD = first documentation of PD ≤ 12 weeks after the date of first dose of study treatment (and not qualifying for CR, PR, SD or non-CR/non-PD).
- NE: all other cases.

An objective status of PR or SD cannot follow one of CR. SD can follow PR only in the rare case that tumor increases by less than 20% from the nadir, but enough that a previously documented 30% decrease from baseline no longer holds. If this occurs, the sequence PR-SD-PR is considered a confirmed PR. A sequence of PR – SD – SD – PD would be a best response of SD if the window for SD definition has been met.

Objective Response (OR) is defined as confirmed BOR of CR or PR according to RECIST v1.1.

Participants who do not have a post-baseline radiographic tumor assessment due to early progression, who receive anti-cancer therapies other than the study treatments prior to reaching a CR or PR, or who die, progress, or drop out for any reason prior to reaching a CR or PR will be counted as non-responders in the assessment of OR. Each participant will have an objective response status (0: no OR; 1: OR). OR rate (ORR) is the proportion of participants with OR in the analysis set.

ORR by treatment group will also be calculated along with the 2-sided 95% CI using the Clopper-Pearson method[3] (exact CI for a binomial proportion as computed by default by the FREQ procedure using the EXACT option).

In addition, the frequency (number and percentage) of participants with a confirmed BOR of CR, PR, SD, non-CR/non-PD (applicable only to participants with non-measurable disease at baseline), PD, and NE will be tabulated. Participants with confirmed BOR of NE will be summarized by reason for having NE status. The following reasons will be used:

- No baseline assessment
- No post-baseline assessments due to death
- No post-baseline assessments due to other reasons
- All post-baseline assessments have overall response NE
- New anti-cancer therapy started before first post-baseline assessment
- SD of insufficient duration (<6 weeks after the date of first dose of study treatment without further evaluable tumor assessments)
- PD too late (>12 weeks after the date of first dose of study treatment)

Special and rare cases where BOR is NE due to both SD of insufficient duration and late PD will be classified as 'SD too early' (ie, SD of insufficient duration).

6.1.3. Soft tissue objective response as assessed by the Investigator per RECIST v1.1 and PCWG3 criteria in participants with mCRPC

6.1.3.1. Primary analysis

The following analyses will be based on the FAS for participants with mCRPC as shown in Table 3. Assessment of response will be made based on investigator assessment.

Soft tissue best overall response (BOR) (for Combinations B and C) will be assessed based on reported overall soft tissue responses and bone scan assessment at different evaluation time points from the date of first dose of study treatment until the first documentation of radiographic PD, according to the following rules. The documentation required for the determination of PD is shown in Table 5. Only assessments performed on or before the start date of any further anti-cancer therapies will be considered in the assessment of soft tissue BOR. Clinical deterioration will not be considered as documentation of disease progression.

- CR = at least two determinations of CR in soft tissue per RECIST v1.1 at least 4 weeks apart and before first documentation of PD (PD in soft tissue per RECIST v1.1 or in bone by PCWG3 criteria).

- PR = at least two determinations of PR or better (PR followed by PR or PR followed by CR) in soft tissue per RECIST v1.1 at least 4 weeks apart and before first documentation of PD (PD in soft tissue per RECIST v1.1 or in bone by PCWG3 criteria), and not qualifying for a CR.

- SD (applicable only to participants with measurable disease at baseline) = at least one SD assessment (or better) ≥ 6 weeks after the date of first dose of study treatment and before first documentation of PD (PD in soft tissue per RECIST v1.1 or in bone by PCWG3 criteria), and not qualifying for CR or PR.

- Non-CR/non-PD (applicable only to participants with non-measurable disease at baseline) =at least one non-CR/non-PD assessment (or better) ≥ 6 weeks after the date of first dose of study treatment and before first documentation of PD (PD in soft tissue per RECIST v1.1 or in bone by PCWG3 criteria), and not qualifying for CR or PR.

- PD = progression ≤ 12 weeks after the date of first dose of study treatment (and not qualifying for CR, PR, SD or non-CR/non-PD).

- NE: all other cases.

An objective status of PR or SD cannot follow one of CR. SD can follow PR only in the rare case that tumor increases by less than 20% from the nadir, but enough that a previously documented 30% decrease from baseline no longer holds. If this occurs, the sequence PR-SD-PR is considered a confirmed PR. A sequence of PR – SD – SD – PD would be a best response of SD if the window for SD definition has been met.

Soft tissue Objective Response (OR) is defined as confirmed BOR of CR or PR in soft tissue.

Participants who do not have a post-baseline radiographic assessment of soft tissue or bone lesions due to early progression, who receive anti-cancer therapies other than the study treatments prior to reaching a CR or PR, or who die, progress, or drop out for any reason prior to reaching a CR or PR will be counted as non-responders in the assessment of soft tissue OR. Each participant will have an objective response status (0: no OR; 1: OR). Soft tissue OR rate (ORR) is the proportion of participants with soft tissue OR in the analysis set.

Soft tissue ORR by treatment group will also be calculated along with the 2-sided 95% CI using the Clopper-Pearson method[3] (exact CI for a binomial proportion as computed by default by the FREQ procedure using the EXACT option).

In addition, the frequency (number and percentage) of participants with a confirmed soft tissue BOR of CR, PR, SD, non-CR/non-PD (applicable only to participants with non-measurable disease at baseline), PD, and NE will be tabulated. Participants with confirmed

BOR of NE will be summarized by reason for having NE status. The following reasons will be used:

- No baseline assessment
- No post-baseline assessments due to death
- No post-baseline assessments due to other reasons
- All post-baseline assessments have overall response NE
- New anti-cancer therapy started before first post-baseline assessment
- SD of insufficient duration (<6 weeks after the date of first dose of study treatment without further evaluable tumor assessments)
- PD too late (>12 weeks after the date of first dose of study treatment)

Special and rare cases where soft tissue BOR is NE due to both SD of insufficient duration and late PD will be classified as 'SD too early' (ie, SD of insufficient duration).

6.1.4. PSA response for participants with mCRPC

6.1.4.1. Primary analysis

The following analyses will be based on the FAS for participants with mCRPC as shown in Table 3.

PSA response is defined as PSA decline ≥50% compared to baseline. PSA response must be confirmed by a second, consecutive PSA assessment ≥ 3 weeks later.

PSA response will be assessed based on PSA assessments at different evaluation time points from the date of first dose of study treatment until PSA progression. Only PSA assessments performed on or before the start of any further anti-cancer therapies will be considered in the assessment of PSA response and PSA progression.

- PSA response = at least 2 assessments, at least 3 weeks apart with ≥ 50% reduction in PSA level from baseline.

- No PSA response = all other cases.

Each participant will have a PSA response status (0: no PSA response; 1: PSA response). PSA response rate is the proportion of participants with PSA response in the analysis set.

PSA response rate by treatment group will be calculated along with the 2-sided 95% CI using the Clopper-Pearson method[3] (exact CI for a binomial proportion as computed by default by the FREQ procedure using the EXACT option).

For patients with PSA declines after baseline, the PSA progression date is defined as the date that a ≥ 25% increase and an absolute increase of ≥ 2 µg/L (2 ng/mL) above the nadir is documented, which is confirmed by a second consecutive value obtained at least 3 weeks later.

Early rises (before week 12) should be ignored in determining progression. As such, for patients with no PSA declines after baseline, the PSA progression date is defined as the date that a ≥ 25% increase and an absolute increase of ≥ 2 µg/L (2 ng/mL) above the baseline is documented after 12 weeks of treatment, which is confirmed by a second consecutive value at least 3 weeks later.

6.2. Secondary Endpoint(s)

6.2.1. Safety endpoints

Refer to Section 6.6.

6.2.2. Efficacy endpoints

The following analyses will be based on the FAS as shown in Table 3. Assessment of tumor response will be made using RECIST v1.1 (for Combination A) and PCWG3 criteria (for Combinations B and C). Tumor-related endpoints will be analyzed based on investigator assessment.

6.2.2.1. Tumor shrinkage from baseline

Tumor shrinkage will be summarized as the percent change from baseline in target lesions (sum of longest diameter for non-nodal lesion and short axis for nodal lesion) per time point. It will be derived as:

- ((Sum of target lesions at week XX – sum of target lesions at baseline)/sum of target lesions at baseline) × 100

The maximum reduction in target lesions from baseline will be derived across all the post-baseline assessments until documented disease progression, excluding assessments after start of subsequent anti-cancer therapy, as:

- Minimum of ((sum of target lesions at week XX – sum of target lesions at baseline)/sum of target lesions at baseline) × 100

A waterfall plot of maximum percent reduction in the sum of longest diameter for non-nodal lesions and short axis for nodal lesions from baseline will be created by treatment group. These plots will display the best percentage change from baseline in the sum of the diameter of all target lesions for each participant with measurable disease at baseline and at least one post-baseline assessment.

6.2.2.2. PSA reduction from baseline

For patients with mCRPC, the level of PSA will be summarized as the percent change from baseline per time point. It will be derived as:

- ((PSA at week XX – PSA at baseline)/PSA at baseline) × 100

The maximum reduction in PSA from baseline will be derived across all the post-baseline assessments until PSA progression, excluding assessments after start of subsequent anti-cancer therapy, as:

- Minimum of ((PSA at week XX – PSA at baseline)/PSA at baseline) × 100

A waterfall plot of maximum percent decrease in PSA value from baseline will be created. The plot will display the best percentage change from baseline in PSA value for each participant with a baseline assessment and at least one post-baseline assessment.

6.2.2.3. Disease control

Disease Control (DC) is defined as BOR (for Combination A) or soft tissue BOR (for Combinations B and C) of CR, PR, non-CR/non-PD or SD. DC rate (DCR) is the proportion of participants with DC.

DCR will be summarized by frequency counts and percentages.

6.2.2.4. Duration of tumor response

For participants with SCCHN in Combination A, Duration of Response (DR) is defined, for participants with OR, as the time from the first documentation of objective response (CR or PR) to the date of first documentation of PD or death due to any cause. The documentation of PD is defined using RECIST v1.1.

If a participant has not had an event (PD or death), DR is censored at the date of last adequate tumor assessment. The censoring rules for DR are described in Table 4.

DR (months) = [date of event or censoring– first date of OR +1]/30.4375

Table 4. Outcome and Event Dates for DR Analyses

Scenario	Date of event/censoring	Outcome
PD or death - After at most one missing or inadequate post-baseline tumor assessment, OR - ≤ 16 weeks after the date of first dose of study treatment	Date of PD or death	Event
PD or death - After 2 or more missing or inadequate post-baseline tumor assessments	Date of last adequate tumor assessment [a] documenting no PD before new anti-cancer therapy is given or missed tumor assessments	Censored
No PD and no death	Date of last adequate tumor assessment [a] documenting no PD before new anti-cancer therapy is given or missed tumor assessments	Censored
Treatment discontinuation due to 'Disease progression' without documented progression	Not applicable	Information is ignored. Outcome is derived based on documented progression only.
New anti-cancer therapy given	Date of last adequate tumor assessment [a] documenting no PD before new anti-cancer therapy is given or missed tumor assessments	Censored

[a] If there are no adequate post-baseline assessments prior to PD or death, then the time without adequate assessment should be measured from the date of first dose of study treatment; if the criteria were met the censoring will be on the date of first dose of study treatment.

For participants with mCRPC who achieve soft tissue OR in Combinations B and C, DR is defined as the time from the first documentation of soft tissue response per RECIST v1.1 and no evidence of confirmed bone disease progression by PCWG3 criteria to the first subsequent documentation of PD by soft tissue evaluated per RECIST v1.1 or bone disease evaluated per PCWG3 criteria, or death due to any cause. The documentation of PD is defined by either soft tissue progression using RECIST v1.1 or by bone disease using PCWG3 criteria, as described in Table 5.

If a participant has not had an event (PD or death), DR is censored at the date of last adequate tumor assessment. The censoring rules for DR are described in Table 4.

DR (months) = [date of event or censoring– first date of soft tissue OR +1]/30.4375

Table 5. Criteria for Evidence of Radiographic Progression for Participants with mCRPC

Date Progression Detected [a]	Criteria for Progression	Criteria to Confirm Progression	Criteria to Document Disease Progression on Confirmatory Scan
Week 8	Bone lesions: 2 or more new lesions compared to screening bone scan by PCWG3 [a]	Timing: At least 6 weeks after progression identified or at Week 16 visit [b]	2 or more new bone lesions on bone scan compared to Week 8 scan
	Soft tissue lesions: Progressive disease on CT or MRI by RECIST v1.1	No confirmatory scan required for soft tissue disease progression	No confirmatory scan required for soft tissue disease progression
Week 16 or later	Bone lesions: 2 or more new lesions on bone scan compared to Week 8 bone scan	Timing: At least 6 weeks after progression identified or at next imaging time point [b]	Persistent or increase in number of bone lesions on bone scan compared to prior scan [c]
	Soft tissue lesions: Progressive disease on CT or MRI by RECIST v1.1	No confirmatory scan required for soft tissue disease progression	No confirmatory scan required for soft tissue disease progression

[a] Progression detected by bone scan at an unscheduled visit either before Week 8 or between scheduled visits will require a confirmatory scan at least 6 weeks later and should follow confirmation criteria outlined in the table for the next scheduled scan.
[b] Confirmation must occur at the next available scan.
[c] For confirmation, at least 2 of the lesions first identified as new must be present at the next available scan (confirmation scan).

Kaplan-Meier estimates[6] (product-limit estimates) will be presented by treatment group together with a summary of associated statistics including the median DR time with 2-sided 95% CIs. In particular, the event free rates at 2, 4, 6, 8, 10, 12, 15 and 18 months will be estimated with corresponding 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley (1982)[2] and the CIs for the survival function estimates at the time points defined above will be derived using the log-log transformation according to Kalbfleisch and Prentice (2002)[5] (conftype=loglog default option in SAS Proc LIFETEST) with back transformation to a CI on the untransformed scale. The estimate of the standard error will be computed using Greenwood's formula.

DR will be displayed graphically and analyzed using Kaplan-Meier methodology. If the number of participants with OR (for participants with SCCHN in Combination A) and soft tissue OR (for participants with mCRPC in Combinations B and C) is small, the Kaplan-Meier method may not provide reliable estimates. In this case, only descriptive statistics or listings will be provided.

Frequency (number and percentage) of participants with each event type (PD or death) and censoring reasons will be presented by treatment group. Reasons for censoring will be summarized according to the categories in Table 6 following the hierarchy shown.

Table 6. DR Censoring Reasons and Hierarchy

Hierarchy	Condition	Censoring Reason
1	Start of new anti-cancer therapy	Start of new anti-cancer therapy
2	Event after 2 or more missing or inadequate post-baseline tumor assessments/date of randomization	Event after 2 or more missing assessments [a]
3	No event and [withdrawal of consent date ≥ date of randomization OR End of study (EOS) = Participant refused further follow-up]	Withdrawal of consent
4	No event and lost to follow-up in any disposition page	Lost to follow-up
5	No event and [EOS present OR disposition page for any epoch after screening says participant will not continue into any subsequent phase of the study] and no adequate post-baseline tumor assessment	No adequate post-baseline tumor assessment
6	No event and none of the conditions in the prior hierarchy are met	Ongoing without an event

[a] 2 or more missing or inadequate post-baseline tumor assessments.

The DR time or censoring time and the reasons for censoring will also be presented in a participant listing.

6.2.2.5. Duration of PSA response

For participants with mCRPC in Combinations B and C and PSA response, duration of PSA response is defined as the time from the first documentation of PSA response to the date of the date that a ≥25% increase in PSA with an absolute increase of ≥2 µg/L (2 ng/mL) above the nadir (or baseline for participants with no PSA decline) is documented. PSA progression must be confirmed by a second, consecutive PSA assessment ≥3 weeks later.

Duration of PSA response will be censored on the date of the last PSA assessment for participants who do not have an event (confirmed PSA progression), for participants who start a new anti-cancer therapy prior to an event (see Section 5.2.6) or for participants with an event after 2 or more missing PSA assessments. The censoring rules for duration of PSA response are described in Table 7.

> Duration of PSA response (months)= [date of event or censoring– first date of PSA response +1]/30.4375

Table 7. Outcome and Event Dates for Duration of PSA Response Analysis

Scenario	Date of event/censoring	Outcome
PSA progression (subsequently confirmed), after at most one missing PSA assessment.	Date of first PSA progression	Event
PSA progression (subsequently confirmed) after 2 or more missing PSA assessments	Date of last PSA assessment documenting no PSA progression before new anti-cancer therapy is given or missed PSA assessments	Censored
PSA progression not confirmed or no PSA progression	Date of last PSA assessment documenting no PSA progression before new anti-cancer therapy is given or missed PSA assessments	Censored
New anti-cancer therapy prior to confirmed PSA progression	Date of last PSA assessment documenting no PSA progression before new anti-cancer therapy is given or missed PSA assessments	Censored

Kaplan-Meier estimates[6] (product-limit estimates) will be presented by treatment group together with a summary of associated statistics including the median duration of PSA response time with 2-sided 95% CIs. In particular, the event free rates at 2, 4, 6, 8, 10, 12, 15, and 18 months will be estimated with corresponding 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley (1982)[2] and the CIs for the survival function estimates at the time points defined above will be derived using the log-log transformation according to Kalbfleisch and Prentice (2002)[5] (conftype=loglog default option in SAS Proc LIFETEST) with back transformation to a CI on the untransformed scale. The estimate of the standard error will be computed using Greenwood's formula.

Duration of PSA will be displayed graphically and analyzed using Kaplan-Meier methodology. If the number of participants with PSA response is small, the Kaplan-Meier method may not provide reliable estimates. In this case, only descriptive statistics or listings will be provided.

Frequency (number and percentage) of participants with an event and censoring reasons will be presented. Reasons for censoring will be summarized according to the categories in Table 8 following the hierarchy shown.

Table 8. Duration of PSA Response Censoring Reasons and Hierarchy

Hierarchy	Condition	Censoring Reason
1	Start of new anti-cancer therapy	Start of new anti-cancer therapy
2	Event after 2 or more missing post-baseline PSA assessments/date of first dose of study treatment	Event after missing assessments [a]
3	No event and [withdrawal of consent date ≥ date of first dose of study treatment OR End of study (EOS) = Participant refused further follow-up]	Withdrawal of consent
4	No event and lost to follow-up in any disposition page	Lost to follow-up
5	No event and [EOS present OR disposition page for any epoch after screening says participant will not continue into any subsequent phase of the study] and no post-baseline PSA assessment	No post-baseline PSA assessment
6	No event and none of the conditions in the prior hierarchy are met	Ongoing without an event

[a] 2 or more missing post-baseline PSA assessments.

The duration of PSA response time or censoring time and the reasons for censoring will also be presented in a participant listing.

6.2.2.6. Time to tumor response

For participants with SCCHN in Combination A, time to tumor response (TTR) is defined, for participants with OR, as the time from the date of first dose of study treatment to the first documentation of objective response (CR or PR) which is subsequently confirmed.

TTR (in months) = [first date of OR – date of first dose of study treatment +1]/30.4375

For participants with mCRPC in Combinations B and C who achieve soft tissue OR, TTR is defined is defined as the time from the date of first dose of study treatment to the first documentation of soft tissue response which is subsequently confirmed with no evidence of bone disease progression per PCWG3 criteria.

TTR (in months) = [first date of soft tissue OR – date of first dose of study treatment +1]/30.4375

TTR will be summarized using simple descriptive statistics (mean, SD, median, min, max. Q1, Q3).

6.2.2.7. Time to PSA response

For participants with mCRPC in Combinations B and C and PSA response, time to PSA response (TTPSAR) is defined as the time from the date of first dose of study treatment to the date that PSA decline ≥50% compared to baseline which is subsequently confirmed a second, consecutive PSA assessment ≥ 3 weeks later.

TTPSAR (in months) = [first date of PSA response – date of first dose of study treatment +1]/30.4375

TTPSAR will be summarized using simple descriptive statistics (mean, SD, median, min, max. Q1, Q3).

6.2.2.8. Progression-free survival

For participants with SCCHN in Combination A, Progression-Free Survival (PFS) is defined as the time from the date of first dose of study treatment to the date of the first documentation of PD or death due to any cause, whichever occurs first.

PFS for participants with mCRPC in Combinations B and C is defined as the time from the date of first dose of study treatment to the date of the first documentation of radiographic progression in soft tissue per RECIST v1.1, or bone per PCWG3 criteria, or death due to any cause, whichever occurs first.

PFS data will be censored on the date of the last adequate tumor assessment for participants who do not have an event (PD or death), for participants who start a new anti-cancer therapy prior to an event (see Section 5.2.6) or for participants with an event after 2 or more missing tumor assessments. Participants who do not have an adequate baseline tumor assessment or who do not have an adequate post-baseline tumor assessment will be censored on the date of first dose of study treatment unless death occurred on or before the time of the second planned tumor assessment (ie ≤ 16 weeks after the date of first dose of study treatment) in which case the death will be considered an event.

Antitumor activity in participants with SCCHN will be assessed through radiological tumor assessments conducted at screening and every 8 weeks (± 7 days) until PD regardless of initiation of subsequent anti-cancer therapy. After 52 weeks from the date of first dose of study treatment, tumor assessments will be conducted less frequently, ie, at 16-week (± 7 days) intervals.

Antitumor activity in participants with mCRPC will be assessed through radiological tumor assessments conducted at screening and every 8 weeks (± 7 days) until PD regardless of initiation of subsequent anti-cancer therapy. After 52 weeks from the date of first dose of study treatment, tumor assessments will be conducted less frequently, ie, at 12-week (± 7 days) intervals.

The censoring and event date options to be considered for the PFS analysis are presented in Table 9.

PFS (months) = [date of event or censoring– date of first dose of study treatment +1]/30.4375

Table 9. Outcome and Event Dates for PFS Analyses

Scenario	Date of event/censoring	Outcome
No adequate baseline assessment	Date of first dose of study treatment [a]	Censored [a]
PD or death - After at most one missing or inadequate post-baseline tumor assessment, OR - ≤ 16 weeks after the date of first dose of study treatment	Date of PD or death	Event
PD or death - After 2 or more missing or inadequate post-baseline tumor assessments	Date of last adequate tumor assessment [b] documenting no PD before new anti-cancer therapy is given or missed tumor assessments	Censored
No PD and no death	Date of last adequate tumor assessment [b] documenting no PD before new anti-cancer therapy is given or missed tumor assessments	Censored
Treatment discontinuation due to 'Disease progression' without documented progression	Not applicable	Information is ignored. Outcome is derived based on documented progression only.
New anti-cancer therapy given	Date of last adequate tumor assessment [b] documenting no PD before new anti-cancer therapy is given or missed tumor assessments	Censored

[a] However if the participant dies ≤16 weeks after the date of first dose of study treatment the death is an event with date on death date

[b] If there are no adequate post-baseline assessments prior to PD or death, then the time without adequate assessment should be measured from the date of first dose of study treatment; if the criteria were met the censoring will be on the date of first dose of study treatment

Kaplan-Meier estimates[6] (product-limit estimates) will be presented by treatment group together with a summary of associated statistics including the median PFS time with 2-sided 95% CIs. In particular, the PFS rates at 2, 4, 6, 8, 10, 12, 15, 18, and 24 months will be estimated with corresponding 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley (1982)[2] and the CIs for the survival function estimates at the time points defined above will be derived using the log-log transformation according to Kalbfleisch and Prentice (2002)[5] (conftype=loglog default option in SAS Proc LIFETEST) with back transformation to a CI on the untransformed scale. The estimate of the standard error will be computed using Greenwood's formula.

Frequency (number and percentage) of participants with each event type (PD or death) and censoring reasons will be presented by treatment group. Reasons for censoring will be summarized according to the categories in Table 10 following the hierarchy shown.

Table 10. PFS Censoring Reasons and Hierarchy

Hierarchy	Condition	Censoring Reason
1	No adequate baseline assessment	No adequate baseline assessment
2	Start of new anti-cancer therapy	Start of new anti-cancer therapy
3	Event after 2 or more missing or inadequate post-baseline tumor assessments/date of first dose of study treatment	Event after missing assessments [a]
4	No event and [withdrawal of consent date ≥ date of first dose of study treatment OR End of study (EOS) = Participant refused further follow-up]	Withdrawal of consent
5	No event and lost to follow-up in any disposition page	Lost to follow-up
6	No event and [EOS present OR disposition page for any epoch after screening says participant will not continue into any subsequent phase of the study] and no adequate post-baseline tumor assessment	No adequate post-baseline tumor assessment
7	No event and none of the conditions in the prior hierarchy are met	Ongoing without an event

[a] 2 or more missing or inadequate post-baseline tumor assessments.

The PFS time or censoring time and the reasons for censoring will also be presented in a participant listing.

Time of Follow-Up for PFS

A plot will be generated to compare planned and actual relative day of tumor assessments by treatment group. A Kaplan-Meier plot for PFS follow-up duration will also be generated to assess the follow-up time in the treatment groups reversing the PFS censoring and event indicators. Kaplan-Meier estimates (product-limit estimates) will be presented by treatment group together with a summary of associated statistics including the median time of follow-up for PFS with 2-sided 95% CIs. In particular, the rates at 2, 4, 6, 8, 10, 12, 16, 18, and 24 months will be estimated with corresponding 2-sided 95% CIs.

6.2.2.9. Time to PSA progression for participants with mCRPC

Time to PSA progression for participants with mCRPC is defined as the time from the date of first dose of study treatment to the date of PSA progression, as defined in Section 6.1.4.1.

Time to PSA progression will be censored on the date of the last PSA assessment for participants who do not have an event (confirmed PSA progression), for participants who start a new anti-cancer therapy prior to an event (see Section 5.2.6) or for participants with an event after 2 or more missing PSA assessments. Participants who do not have a baseline PSA assessment or who do not have a post-baseline PSA assessment will be censored on the date of first dose of study treatment.

PSA assessments will be conducted at screening, every 4 weeks ± 7 days and at EOT.

The censoring and event date options to be considered for the time to PSA progression analysis are presented in Table 11.

Time to PSA progression (months) = [date of PSA progression or censoring– date of first dose of study treatment +1]/30.4375

Table 11. Outcome and Event Dates for Time to PSA Progression Analysis

Scenario	Date of event/censoring	Outcome
No PSA assessment at baseline	Date of first dose of study treatment	Censored
PSA progression (subsequently confirmed), after at most one missing PSA assessment.	Date of first PSA progression	Event
PSA progression (subsequently confirmed) after 2 or more missing PSA assessments	Date of last PSA assessment documenting no PSA progression before new anti-cancer therapy is given or missed PSA assessments	Censored
PSA progression not confirmed or no PSA progression	Date of last PSA assessment documenting no PSA progression before new anti-cancer therapy is given or missed PSA assessments	Censored
New anti-cancer therapy prior to confirmed PSA progression	Date of last PSA assessment documenting no PSA progression before new anti-cancer therapy is given or missed PSA assessments	Censored

Kaplan-Meier estimates6[6] (product-limit estimates) will be presented together with a summary of associated statistics including the median time to PSA progression with 2-sided 95% CIs. In particular, the PSA progression rates at 2, 4, 6, 8, 10, 12, 15, 16, 18, and 24 months will be estimated with corresponding 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley (1982)[2] and the CIs for the survival function estimates at the time points defined above will be derived using the log-log transformation according to Kalbfleisch and Prentice (2002)[5] (conftype=loglog default option in SAS Proc LIFETEST). The estimate of the standard error will be computed using Greenwood's formula.

Frequency (number and percentage) of participants with an event and censoring reasons will be presented. Reasons for censoring will be summarized according to the categories in Table 12 following the hierarchy shown.

Table 12. PSA Progression Censoring Reasons and Hierarchy

Hierarchy	Condition	Censoring Reason
1	No baseline PSA assessment	No baseline PSA assessment
2	Start of new anti-cancer therapy	Start of new anti-cancer therapy
3	Event after 2 or more missing post-baseline PSA assessments/date of first dose of study treatment	Event after missing assessments [a]
4	No event and [withdrawal of consent date ≥ date of first dose of study treatment OR End of study (EOS) = Participant refused further follow-up]	Withdrawal of consent
5	No event and lost to follow-up in any disposition page	Lost to follow-up
6	No event and [EOS present OR disposition page for any epoch after screening says participant will not continue into any subsequent phase of the study] and no post-baseline PSA assessment	No post-baseline PSA assessment
7	No event and none of the conditions in the prior hierarchy are met	Ongoing without an event

[a] 2 or more missing post-baseline PSA assessments.

The PSA progression-free interval or censoring time and the reasons for censoring will also be presented in a participant listing.

6.2.2.10. Overall Survival

Overall survival (OS) is defined as the time from the date of first dose of study treatment to the date of death due to any cause. Participants last known to be alive will be censored at date of last contact.

OS (months) = [date of death or censoring– date of first dose of study treatment +1]/30.4375

Kaplan-Meier estimates[6] (product-limit estimates) will be presented by treatment group together with a summary of associated statistics including the median OS time with 2-sided 95% CIs. In particular, the OS rates at 3, 6, 9, 12, 15, 18, 24, and 30 months will be estimated with corresponding 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley (1982)[2] and the CIs for the survival function estimates at the time points defined above will be derived using the log-log transformation according to Kalbfleisch and Prentice (2002)[5] (conftype=loglog default option in SAS Proc LIFETEST) with back transformation to a CI on the untransformed scale. The estimate of the standard error will be computed using Greenwood's formula.

Frequency (number and percentage) of participants with an event (death) and censoring reasons will be presented by treatment group. Reasons for censoring will be summarized according to the categories in Table 13 following the hierarchy shown.

Table 13. OS Censoring Reasons and Hierarchy

Hierarchy	Condition	Censoring Reason
1	No event and [withdrawal of consent date ≥ date of first dose of study treatment OR End of study (EOS) = Participant refused further follow-up]	Withdrawal of consent
2	No event and [lost to follow-up in any disposition page OR data cut-off date – last contact date > 14 weeks]	Lost to follow-up
3	No event and none of the conditions in the prior hierarchy are met	Alive

The OS time or censoring time and the reasons for censoring will also be presented in a participant listing.

Time of Follow-Up for OS

A Kaplan-Meier plot for OS follow-up duration will also be generated to assess the follow-up time in the treatment groups reversing the OS censoring and event indicators. Kaplan-Meier estimates[6] (product-limit estimates) will be presented by treatment group together with a summary of associated statistics including the median time of follow-up for OS with 2-sided 95% CIs. In particular, the rates at 3, 6, 9, 12, 15, 18, 24, and 30 months will be estimated with corresponding 2-sided 95% CIs.

6.2.2.11. CTC count conversion and CTC0 for participants with mCRPC

CTC count conversion is defined as a decrease in CTC count from ≥ 5 CTC per 7.5 mL of blood at baseline to < 5 CTC per 7.5 mL of blood on study. Only the CTC count assessments performed on or before the start of any further anti-cancer therapies will be considered in the assessment of CTC count conversion. The analysis set will include all participants with CTC count ≥ 5 CTC per 7.5 mL at baseline. All other participants will be considered as non-evaluable. The participants in the analysis set will be counted as:

- CTC count conversion = one or more post-baseline assessment(s) of CTC count < 5 CTC per 7.5 mL
- No CTC count conversion = all other cases.

Participants with CTC count ≥ 5 CTC per 7.5 mL at baseline and who do not have a post-baseline CTC count assessment will be counted as no CTC count conversion. Each participant in the analysis set will have a CTC count conversion status (0: no CTC count conversion; 1: CTC count conversion). The CTC count conversion rate is the proportion of participants with CTC count conversion rate in the analysis set.

A waterfall plot of maximum percent decrease in CTC count from baseline will be created for all participants with CTC count ≥ 5 CTC per 7.5 mL at baseline. The plot will display the best percentage change from baseline in CTC count for each participant with a baseline assessment and at least one post-baseline assessment.

CTC0 is defined as a decrease in CTC count from ≥ 1 CTC per 7.5 mL of blood at baseline to an undetectable level on study. Only the CTC count assessments performed on or before the start of any further anti-cancer therapies will be considered in the assessment of CTC0. The analysis set will include all participants with CTC count ≥ 1 CTC per 7.5 mL at baseline. All other participants will be considered as non-evaluable. The participants in the analysis set will be counted as:

- CTC0 = one or more post-baseline CTC count are at undetectable level(s)
- No CTC0 = all other cases.

Participants with CTC count ≥ 1 CTC per 7.5 mL at baseline and who do not have a post-baseline CTC count assessment will be counted as no CTC0. Each participant in the analysis set will have a CTC0 status (0: no CTC0; 1: CTC0). The CTC0 rate is the proportion of participants with CTC0 in the analysis set.

The CTC count conversion rate and CTC0 rate will be calculated along with the 2-sided 95% CI using the Clopper-Pearson method[3] exact CI for a binomial proportion as computed by default by the FREQ procedure using the EXACT option).

6.2.3. Pharmacokinetic endpoints

The following pharmacokinetic analyses will be based on the PK analysis sets by treatment group as shown in Table 3.

PK parameters to be determined for avelumab, bempegaldesleukin (NKTR-214), IL-2, talazoparib, enzalutamide, and N-desmethyl-enzalutamide are defined in Table 14.

Table 14. PK Parameters to be Determined for Avelumab, Bempegaldesleukin (NKTR-214), IL-2, Talazoparib and Enzalutamide

Parameter	Definition	Method of Determination
C_{max} for avelumab, bempegaldesleukin (NKTR-214) and IL-2	Maximum observed plasma concentration at the end of infusion	Observed directly from data
C_{trough} for avelumab, bempegaldesleukin (NKTR-214), IL-2, talazoparib, enzalutamide, and N-desmethyl-enzalutamide	Predose concentration at the end of dosing interval	Observed directly from data
C_{trough} (dn) [a] for talazoparib, enzalutamide, and N-desmethyl-enzalutamide	Dose-normalized C_{trough}	C_{trough}/dose
T_{max} [a] for bempegaldesleukin and IL-2	Time for C_{max}	Observed directly from data as time of first occurrence
AUC_{last} [a] for bempegaldesleukin and IL-2	Area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (C_{last})	Linear/Log trapezoidal method
$t_{½}$ [a] for bempegaldesleukin and IL-2	Terminal half-life	$Log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline were used in the regression.

[a] If data permit.
IL-2 is the active form of (NKTR-214)

C_{trough} for avelumab, bempegaldesleukin (NKTR-214), IL-2, talazoparib, enzalutamide and N-desmethyl-enzalutamide, and C_{max} for avelumab, bempegaldesleukin (NKTR-214) and IL-2 will be summarized descriptively (n, mean, SD, CV, median, minimum, maximum, geometric mean, its associated CV, and 95% CI) by treatment group, dose level, cycle, day and nominal time. Other PK parameters including T_{max}, $AUC_{last,}$ and $t_{1/2}$ will be calculated for bempegaldesleukin (NKTR-214) and IL-2 after first dose as appropriate, and summarized using similar descriptive statistics.

Concentration dose normalized C_{trough} (CDN- C_{trough}) will be reported for talazoparib, enzalutamide, and N-desmethyl-enzalutamide, as appropriate, using similar descriptive statistics described above.

Pharmacokinetic parameters for avelumab, bempegaldesleukin (NKTR-214), IL-2, talazoparib, enzalutamide, and N-desmethyl-enzalutamide will be taken from observed values.

Presentation of pharmacokinetic data will include:

- Linear-linear plots of mean and median plasma concentrations by nominal time for bempegaldesleukin (NKTR-214) and IL-2 after the first dose will be presented for PK sampling days by treatment group, cycle, and study day. Similar plots will be presented for each individual participant concentrations. Participants who have undergone intraparticipant dose reduction or escalation will be excluded from the median plasma concentration-time plots.
- Pharmacokinetic parameters for avelumab, bempegaldesleukin (NKTR-214), IL-2, talazoparib, enzalutamide, and N-desmethyl-enzalutamide will be listed and summarized by treatment group/dose level, cycle and study day using descriptive statistics (n, mean, SD, %CV, median, minimum, maximum, geometric mean and its associated %CV, and 95% CI). PK parameters with zero values will be excluded from the calculation of geometric means and its associated %CV. For talazoparib, enzalutamide, and N-desmethyl-enzalutamide, if an intraparticipant dose escalation or reduction occurs, dose-dependent PK C_{trough} for that participant may be dose-normalized or may only be included in descriptive statistics and summary plots up to the time of the dose change.
- Box plots for C_{trough} for avelumab, bempegaldesleukin (NKTR-214), IL-2, talazoparib, enzalutamide, and N-desmethyl-enzalutamide and C_{max} for avelumab, bempegaldesleukin (NKTR-214) and IL-2 will be generated by treatment group/dose level, cycle and study day to assess the attainment of steady-state. Individual data points, the geometric mean and the median of the parameter in each treatment will be overlaid on the box plots. If a treatment group has limited evaluable PK data (n<4), matchstick plots showing changes in and C_{max} for avelumab, bempegaldesleukin (NKTR-214) and IL-2 and C_{trough} for each drug and its active metoblites in individual participants will then be generated.
- PK parameters of avelumab, bempegaldesleukin (NKTR-214), IL-2 talazoparib, enzalutamide, and N-desmethyl-enzalutamide from this study may be compared with the historical PK parameters when avelumab, bempegaldesleukin (NKTR-214), IL-2, talazoparib, and enzalutamide were administered as single agents.

6.2.4. Population pharmacokinetic endpoints

Pharmacokinetic and pharmacodynamic data from this study may be analyzed using modeling approaches and may also be pooled with data from other studies to investigate any association between avelumab, bempegaldesleukin (NKTR-214), IL-2, talazoparib enzalutamide and N-desmethyl-enzalutamide exposure and biomarkers or significant safety/efficacy endpoints. The results of these analyses, if performed, may be reported separately.

6.2.5. Biomarker endpoints

Secondary biomarker endpoints include PD-L1 expression level in baseline tumor tissue for combinations A, B, and C, and PD-L1 expression level in on-treatment tumor tissue for Combination A as described in Table 15.

Table 15. Biomarker Definition and Determination

Parameter	Definition	Method of Determination
PD-L1 expression level in baseline tumor tissue, and in on-treatment tumor tissue (Combination A only)	The number of PD-L1 positive cells and/or qualitative assessment of PD-L1 staining on tumor and/or inflammatory cells in regions of interest	Pathologist, assisted by image analysis

Biomarker data will be analyzed based on the biomarker analysis sets as defined in Section 4.3.3. Data will be summarized as shown in Table 3.

Biomarker values at screening will be listed and summarized.

For PD-L1 expression, participants will be classified as positive or negative according to scoring algorithms and cut-offs established from internal or external sources.

For continuous measurement biomarker results, summary statistics (eg, the mean, standard deviation, median, percent of coefficient of variation, and minimum/maximum levels) will be determined at baseline and on-treatment/end of treatment time points, as appropriate.

For discrete measurement biomarker results, frequencies and percentages of categorical biomarker measures will be determined at baseline and on-treatment/end of treatment time points. Shift tables may also be provided as appropriate.

Change from baseline measurements will be provided, as appropriate.

BOR rate (for participants with SCCHN in Combination A) and soft tissue BOR rate (for participants with mCRPC in Combinations B and C) will be summarized and for each category following the methodology outlined in Section 6.1.2 and Section 6.1.3. The number of responders (participants with BOR of CR or PR) will be tabulated relative to biomarker classifications using a contingency table.

PSA response rate (for participants with mCRPC in Combinations B and C) will be summarized and for each category following the methodology outlined in Section 6.1.4. The number of responders will be tabulated relative to biomarker classifications using a contingency table.

DR, duration of PSA response (for participants with mCRPC only), PFS, time to PSA progression (for participants with mCRPC only), and OS (if meaningful) will be summarized for each category of the biomarkers following the methodology outlined in Sections 6.2.2.4, 6.2.2.5, 6.2.2.8, 6.2.2.9, and 6.2.2.10.

6.2.6. Endpoints for immunogenicity data of avelumab, bempegaldesleukin (NKTR-214), and IL-2

All analyses described below are performed as shown in Table 3.

Blood samples for avelumab, bempegaldesleukin (NKTR-214), and IL-2 immunogenicity testing will be collected pre-dose on day 1 of Cycle 1, 2, 3, 6, 9, 12 and EOT. All samples should be drawn within 2 hours before start of infusion for avelumab and bempegaldesleukin (NKTR-214).

Samples positive for ADA will be analyzed for titer and may be analyzed for nAb. The analyses of nAb data described in the following sections will only be conducted contingent upon assay and data availability at the time of reporting.

Participants will be characterized into different ADA categories based on the criteria defined in Table 16.

Table 16. Participants Characterized Based on Anti-Drug Antibody Results (ADA Status)

Category	Definition	Participants at Risk (Denominator for Incidence)
ADA never-positive	No positive ADA results at any time point; ADA-negative participants (titer < cutpoint)	Number of participants with at least one valid ADA result at any time point
ADA ever-positive	At least one positive ADA result at any time point; ADA-positive participants (titer ≥ cutpoint)	Number of participants with at least one valid ADA result at any time point
Baseline ADA positive	A positive ADA result at baseline	Number of participants with valid baseline ADA result
Treatment-boosted ADA	A positive ADA result at baseline and the titer ≥ 8×baseline titer at least once after treatment with avelumab/ bempegaldesleukin (NKTR-214)	Number of participants with valid baseline ADA results and at least one valid post-baseline ADA result
Treatment-induced ADA	Participant is ADA-negative at baseline and has at least one positive post-baseline ADA result; or if participant does not have a baseline sample, the participant has at least one positive post-baseline ADA result	Number of participants with at least one valid post-baseline ADA result and without positive baseline ADA result (including missing, NR)
Transient ADA response	If participants with treatment-induced ADA have (a single positive ADA result or duration between first and last positive result <16 weeks) and ADA result at the last assessment is not positive.	Number of participants with at least one valid post-baseline ADA result and without positive baseline ADA result (including missing, NR)
Persistent ADA response	If participants with treatment-induced ADA have duration between first and last positive ADA result ≥16 weeks or a positive ADA result at the last assessment	Number of participants with at least one valid post-baseline ADA result and without positive baseline ADA result (including missing, NR)

ADA: anti-drug antibody, NR = not reportable.

Participants will be characterized into different nAb categories based on the criteria in Table 17. For nAb, treatment-boosted is not applicable since no titer result is available.

Table 17. Participants Characterized Based on Neutralizing Antibody Results (nAb Status)

Category	Definition	Participants at Risk (Denominator for Incidence)
nAb never-positive	No positive nAb results at any time point	Number of participants with at least one valid ADA result at any time point
nAb ever-positive	At least one positive nAb result at any time point	Number of participants with at least one valid ADA result at any time point
Baseline nAb positive	A positive nAb result at baseline	Number of participants with valid baseline ADA result
Treatment-induced nAb	Participant is not nAb positive at baseline and has at least one positive post-baseline nAb result; or if participant does not have a baseline sample, the participant has at least one positive past-baseline ADA result	Number of participants with at least one valid post-baseline ADA result and without positive baseline nAb result (including missing, NR)
Transient nAb response	If participants with treatment-induced nAb have (a single positive nAb result or duration between first and last positive result <16 weeks) and nAb result at the last assessment is not positive.	Number of participants with at least one ADA valid post-baseline result and without positive baseline nAb result (including missing, NR)
Persistent nAb response	If participants with treatment-induced nAb have duration between first and last positive nAb result ≥16 weeks or a positive nAb result at the last assessment	Number of participants with at least one valid post-baseline ADA result and without positive baseline nAb result (including missing, NR)

ADA = antidrug antibody, nAb = neutralizing antibody, NR = no result.

The number and percentage of participants in each ADA and nAb category will be summarized.

6.2.6.1. Time to and Duration of ADA and nAb response

The ADA and nAb analyses described below will include participants with treatment-induced ADA or nAb, respectively.

Time (weeks) to ADA response is defined as:

(Date of first positive ADA result – date of first dose of avelumab + 1)/7.

Time to ADA response will be summarized using simple descriptive statistics (mean, SD, median, min, max. Q1, Q3).

Duration (weeks) of ADA response is defined as:

(Date of last positive ADA result – date of first positive ADA result + 1)/7.

Duration of ADA response will be censored if:

- the last ADA assessment is positive AND participant is ongoing treatment with avelumab, or

- the last ADA assessment is positive AND participant discontinued treatment with avelumab AND the last planned ADA assessment (End of Treatment) is after the cut-off date.

Time to nAb response and duration of nAb response are defined similarly based on first and last positive nAb result.

Kaplan-Meier estimates[6] (product-limit estimates) will be presented together with a summary of associated statistics including the median ADA response time with 2-sided 95% CIs. ADA response rates at different timepoints will be estimated with corresponding 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley (1982)[2] and the CIs for the survival function estimates will be derived using the log-log transformation according to Kalbfleisch and Prentice (2002)[5] (conftype=loglog default option in SAS Proc LIFETEST) with back transformation to a CI on the untransformed scale. The estimate of the standard error will be computed using Greenwood's formula.

Duration of ADA response will be displayed graphically and analyzed using Kaplan-Meier methodology. If the number of participants with ADA response is small, the Kaplan-Meier method may not provide reliable estimates. In this case, only descriptive statistics or listings will be provided

As data permit, the analyses described above will be repeated for participants with treatment-induced nAb.

6.2.6.2. ADA titer

For participants who are ADA ever positive, the maximum observed ADA titer for a participant will be summarized, overall and by ADA subcategories (baseline ADA positive, treatment-boosted ADA, treatment-induced ADA, transient ADA response, persistent ADA response) of participants having each discrete maximum titer value will be tabulated. The denominator to calculate the percentages will be the total number of participants in the associated ADA subcategory.

For participants with treatment-induced ADA, a cross tabulation of duration of ADA response and maximum ADA titer will be provided. The following categories for duration of ADA response will be used: ≤1, >1 to ≤3, >3 to ≤5, >5 to ≤7, >7 to ≤13, >13 to ≤16, >16 to ≤25, >25 weeks. In this categorization, the censoring in duration of ADA response is ignored.

6.2.6.3. Analysis of PK and safety by immunogenicity status

The following ADA and nAb status will be used for the analyses described below.

ADA

- ADA ever-positive versus ADA never-positive
- ADA: treatment-induced ADA versus ADA never-positive or baseline ADA positive

nAb

- nAb ever-positive versus nAb never-positive
- nAb: treatment-induced nAb versus nAb never-positive or baseline nAb positive

Data listings will include immunogenicity data together with relevant PK, and safety data.

PK parameters and immunogenicity status

The following analyses will include participants in both the immunogenicity analysis set and in the PK parameter analysis set. The PK endpoints pertinent to the immunogenicity analyses are C_{trough} and C_{max} for avelumab, bempegaldesleukin (NKTR-214) and IL2.

Blood samples for avelumab PK will be collected as outlined in the "Schedule for Pharmacokinetic Sample Collection" table of the Schedule of Assessments section of the protocol.

C_{trough} and C_{max} will be summarized descriptively (n, mean, SD, CV, median, minimum, maximum, geometric mean, its associated CV, and 95% CI) by nominal time and ADA status. Linear-linear and log-linear plots of mean and median for C_{trough} and C_{max} over nominal time and by ADA status will be presented.

Among participants with treatment-induced ADA, analyses will be conducted to assess whether C_{trough} and C_{max} have any changes before and after the first positive ADA assessment. To be included in this analysis, participants must have the same PK parameter available both before and after the first positive ADA assessment. Relative PK day will be calculated as:

(PK assessment nominal day) – (first positive ADA assessment nominal day).

Nominal day is the protocol scheduled timing for an assessment. For example, if C_{trough} is collected on Day 1 of Cycle 2 and the first positive ADA result is observed on Day 1 of Cycle 3, then the relative PK day for this C_{trough} is -14. Linear-linear and log-linear plots of mean and median for C_{trough} and C_{max} over relative PK day will be presented.

As data permit, the analyses described above will be repeated for nAb.

Safety and immunogenicity status

The following analyses will include participants in the immunogenicity analysis set.

The frequency (number and percentage) of participants with each of the following will be presented by ADA status.

- TEAEs, by SOC and PT
- TEAEs leading to dose reduction of avelumab, by SOC and PT

- TEAEs leading to dose reduction of bempegaldesleukin (NKTR-214), by SOC and PT
- TEAEs leading to discontinuation of avelumab, by SOC and PT
- TEAEs leading to discontinuation of bempegaldesleukin (NKTR-214), by SOC and PT
- TEAEs leading to discontinuation of any study drug, by SOC and PT
- Grade ≥ 3 TEAEs, by SOC and PT
- SAEs, by SOC and PT
- IRRs, by PT

For participants who had at least one IRR and have treatment-induced ADA, time related to first onset of an IRR (infusion 1, infusion 2, infusion 3, infusion 4 or later) will be summarized taking into account whether the IRR occurred on or after the first ADA positive assessment or whether the IRR occurred before the first ADA positive assessment.

As data permit, the analyses described above will be repeated for nAb.

CCI [redacted]

6.4. Subset Analyses

Applicable to efficacy assessments only. For Combinations A and C, phase 1b participants treated at the RP2D will combined with Phase 2 participants. For Combination B, the subset analyses will only include Phase 2 participants.

The following efficacy endpoints (if meaningful) will be summarized by PD-L1 expression at baseline (negative vs positive)

- OR and DR in participants with SCCHN in Combination A

- Soft tissue OR and DR in participants after progression on taxane-based chemotherapy with mCRPC in Combination B

- Soft tissue OR and DR, PSA response and duration of PSA response in participants with mCRPC after progression on abiraterone in Combination C

In addition, soft tissue OR and DR in participants with mCRPC after progression on abiraterone in Combination C will be summarized for participants with measurable disease at baseline.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline summaries

The following analyses will be based on the FAS as shown in Table 3.

6.5.1.1. Demographic characteristics

Demographic characteristics and physical measurements will be summarized by treatment group using the following information from the 'Screening/Baseline Visit' eCRF pages.

- Demographic characteristics
  - Gender: Male, Female
  - Race: White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Multiracial, Not Reported
  - Ethnic origin:
    - Hispanic or Latino
    - Not Hispanic or Latino
    - Not Reported
  - Age (years): summary statistics
  - Age categories:
    - < 65 years, ≥ 65 years
    - < 65, 65-<75, 75-<85, ≥ 85 years
  - Pooled Geographical Region (as applicable):
    - North America
    - Europe
    - Asia
    - Rest of the World (Australasia, Latin America, Africa and/or Middle East will be included as additional pooled geographical regions if including > 10% of the overall treated population)
  - Geographic Region (as applicable):

  - North America
  - Latin America
  - Western Europe
  - Eastern Europe
  - Middle East
  - Australasia
  - Asia
  - Africa
- Eastern Cooperative Oncology Group (ECOG) Performance Status: 0, 1, 2, 3, and 4

- Physical measurements
  - Height (cm)
  - Weight (kg)
  - Body Mass Index (BMI) (kg/m^2)

Center codes will be used for the determination of the participant's geographic region.

The listing of demographics and baseline characteristics will include the following information: participant identifier, treatment group, age, sex, race, ethnicity, height (cm), weight (kg), BMI (kg/m^2), and ECOG performance status.

6.5.1.2. Medical history

Medical history will be coded using the most current available version of Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized from the 'Medical History' eCRF page. Medical history will be summarized as the numbers and percentages of participants by MedDRA preferred term (PT) as event category and MedDRA primary system organ class (SOC) as summary category. Each participant will be counted only once within each PT or SOC.

Medical history will be displayed in terms of frequency tables: ordered by primary SOC and PT in alphabetical order.

6.5.1.3. Disease characteristics

Information on disease characteristics collected on 'Primary Diagnosis', 'Substance Use' and RECIST eCRF pages will be summarized overall and by treatment group. Summary statistics will be presented for the following.

From the 'Primary Diagnosis' eCRF page:

- Site of primary tumor
- Primary diagnosis (summarize all categories collected in the 'Primary Diagnosis' eCRF page)

- Time since initial diagnosis to date of first dose of study treatment (months), defined as (date of first dose of study treatment – date of initial diagnosis)/30.4375

From the RECIST eCRF page:

- Measurable disease (lesions) at baseline (Yes, No, No disease)
- Involved tumor sites at baseline

From the 'Substance Use' eCRF page:

- Smoking history (never smoker vs current vs former smoker)

Listing of disease history will be provided with all relevant data (as collected on the 'Primary Diagnosis' and 'Substance Use' eCRF pages) and derived variables as above.

6.5.1.4. Prior anti-cancer therapies

The prior anti-cancer therapies are collected under the 'Prior Cancer Therapy', 'Prior Radiation Therapy' and 'Prior Surgery' eCRF pages.

The number and percentage of participants in each of the following anti-cancer therapy categories will be tabulated:

- Participants with at least one type of prior anti-cancer therapy
- Participants with at least one prior anti-cancer drug therapy
- Participants with at least one prior anti-cancer radiotherapy
- Participants with at least one prior anti-cancer surgery

Prior anti-cancer drug therapy will be summarized as follows based on the number and percentage of participants with the following:

- At least one prior anti-cancer drug therapy
- Number of prior anti-cancer drug therapy regimens: missing, 1, 2, 3, ≥4
- Best response: CR, PR, SD, PD, Unknown, Not applicable. Best response is derived from the last treatment regimen.

The prior anti-cancer drugs will also be summarized based on the number and percentage of participants by the drug class and preferred term. A participant will be counted only once within a given drug class and within a given drug name, even if he/she received the same medication at different times. The summary will be sorted on decreasing frequency of drug class and decreasing frequency of drug name in a given drug class. In case of equal frequency regarding drug class (respectively drug name), alphabetical order will be used.

Prior anti-cancer therapies will be included in the listings that follow with a flag to identify prior therapies. These will include the participant identification number, and all the relevant collected data-fields on the corresponding eCRF pages.

- Listing of anti-cancer drug therapies

- Listing of anti-cancer radiotherapy
- Listing of anti-cancer surgeries

6.5.2. Study conduct and participant disposition

The following analyses will be performed based on the FAS as shown in Table 3.

6.5.2.1. Patient disposition

The percentages below will be calculated based on the number of participants in the FAS.

- Total number of participants screened overall
- Number of participants who discontinued from the study prior to treatment with study drug overall and by the main reason for discontinuation
- Number and percentage of treated participants in each of the analysis sets defined in Section 4
- Number and percentage of participants with study drug ongoing (separately for each study drug administered in combination)
- Number and percentage of participants who discontinued study drug overall and by the main reason for discontinuation of study drug (separately for each study drug administered in combination)
- Number and percentage of participants who entered follow-up
- Number and percentage of participants who discontinued follow-up overall and by the main reason for discontinuation

In addition, the following will be summarized:

- Number and percentage of treated participants overall, by region (Europe, EEA (required by EudraCT), North America, Latin America, Middle East, Asia, Australasia, Africa), by country within region
- Number and percentage of treated participants by center

6.5.2.2. Protocol deviations

All protocol violations that impact the safety of the participants and/or the conduct of the study and/or its evaluation will be reported. These include:

- Participants who are dosed on the study despite not satisfying the inclusion criteria
- Participants who develop withdrawal criteria whilst on the study but are not withdrawn
- Participants who receive the wrong treatment or an incorrect dose
- Participants who receive an excluded concomitant medication
- Deviations from GCP.

The identification of these and other CSR-reportable deviations will be based on the inclusion/exclusion criteria or other criteria presented in the protocol.

6.5.3. Study treatment compliance and exposure

The following analyses will be based on the safety analysis set as shown in Table 3.

Cycle definitions for study drugs that are administered in combination apply to all the study drugs in the combination. Ie, cycle is participant-dependent, rather than study-drug-dependent when study drugs are administered in combination.

For Cycle X, actual cycle start date for each participant is

- the earliest start date of dosing in the Cycle X day 1 visit eCRF exposure page, if the participant received study treatment on that visit (ie, any study drug with dose>0 at that visit)
- the first day of assessments in the Cycle X day 1 visit, if the participant did not receive study treatment on that visit (ie, all study drugs had dose=0 at that visit). Use start date in the exposure page if available; if start date is not available then use date of collection of vital signs on Cycle X day 1 visit.

Actual cycle end date for each participant is,

- for all cycles X except the last cycle, actual cycle end date = actual cycle (X+1) start date – 1 day;
- for the last cycle, actual cycle end date = actual cycle start date + 28 (in days) – 1 day

Cycle duration (weeks) = (actual cycle end date – actual cycle start date + 1)/7

When summarizing exposure for each study drug, only cycles from first dose of study treatment until the last cycle with non-zero dose of at least one of the study drugs should be included.

Exposure may be summarized as dose received (cumulative dose, actual dose intensity) and as dose received relative to intended dose (relative dose intensity [RDI]).

The information that will be summarized depends on how the study drug is dosed (eg, infusion cyclical, oral daily, oral cyclical).

The formulae below should be applied to each study drug separately even when study drugs are administered in combination.

The derivations below are provided assuming 1 cycle = 4 weeks and for the following study drugs:

- Avelumab administered as a 1-hour IV infusion at a dose of 800 mg once every 2 weeks in 4-week cycles.
- NKTR-214 administered as a 30-minute IV infusion at a dose of 0.006 or 0.003 mg/kg once every 2 weeks in 4-week cycles.
- Talazoparib administered orally QD PO at a dose of 0.5, 0.75, or 1.0 mg.

- Enzalutamide administered orally QD PO at a dose of 80, 120 or 160 mg.

6.5.3.1. Exposure to avelumab

The dose level for avelumab is calculated as actual dose administered (mg).

Intended duration of treatment with avelumab (weeks) =

(end date–date of first dose of study drug +1)/7,

where end date = start date of last cycle with non-zero dose of avelumab + 28 – 1

Duration of exposure to avelumab (weeks) =

(last dose date of avelumab – first dose date of avelumab + 14)/7

Cumulative dose is the sum of the actual doses of avelumab received.

Actual Dose Intensity (DI)

- Overall actual DI (mg/4-week cycle) = [overall cumulative dose (mg)] / [intended duration of treatment with avelumab (weeks)/4].

Relative Dose Intensity (RDI)

- Intended DI (mg/4-week cycle) = [intended cumulative dose per cycle] / [intended number of 4-weeks in a cycle] = [1600 (mg)] / [1 (4-week cycle)] = 1600 (mg/4-week cycle)
- Overall RDI (%) = 100 × [overall actual DI] / [intended DI]
  = 100 × [overall actual DI] / [1600 (mg/4-week cycle)]

6.5.3.2. Exposure to NKTR-214

The dose level for NKTR-214 is calculated as actual dose administered/weight (mg/kg). The last available weight of the participant on or prior to the day of dosing will be used.

Intended duration of treatment with NKTR-214 (weeks) =

(end date–date of first dose of study drug +1)/7,

where end date = start date of last cycle with non-zero dose of NKTR-214 + 28 – 1

Duration of exposure to NKTR-214 (weeks) =

(last dose date of NKTR-214 – first dose date of NKTR-214 + 14)/7

Cumulative dose is the sum of the actual doses of NKTR-214 received.

Actual Dose Intensity (DI)

- Overall actual DI (mg/kg/4-week cycle) = [overall cumulative dose (mg/kg)] / [intended duration of treatment with NKTR-214(weeks)/4].

Relative Dose Intensity (RDI)

- Intended DI (mg/kg/4-week cycle) = [intended cumulative dose per cycle] / [intended number of 4-weeks in a cycle] = [d (mg/kg)] / [1 (4-week cycle)] = d (mg/kg/4-week cycle)
- Overall RDI (%) = 100 × [overall actual DI] / [intended DI]
  = 100 × [overall actual DI] / [d (mg/kg/4-week cycle)]

  Where d=0.006 mg/kg or 0.003 mg/kg

6.5.3.3. Exposure to talazoparib

The dose level is calculated as actual dose administered (mg/day).

Intended duration of treatment with talazoparib (weeks)= (end date – date of first dose of talazoparib +1)/7,

where end date = date of last dose of talazoparib.

Duration of exposure to talazoparib (weeks) =

(last dose date of talazoparib – first dose date of talazoparib + 1)/7

Cumulative dose is the sum of the actual doses of talazoparib received in the study.

Actual Dose Intensity (DI)

- Overall actual DI (mg/week) = [overall cumulative dose (mg)] / [intended treatment duration (weeks)]

Relative Dose Intensity (RDI)

- RDI (%) = 100 × [overall cumulative dose] / [intended cumulative dose per week × number of weeks from first dose of talazoparib to last dose of talazoparib]

  = 100 × [overall cumulative dose] / [7 × d × duration of exposure to talazoparib in weeks]

  where d=0.5 mg, 0.75 mg, or 1.0 mg.

6.5.3.4. Exposure to enzalutamide

The dose level is calculated as actual dose administered (mg/day).

Intended duration of treatment with enzalutamide (weeks)= (end date – date of first dose of enzalutamide +1)/7,

where end date = date of last dose of enzalutamide.

Duration of exposure to enzalutamide (weeks) =

(last dose date of enzalutamide – first dose date of enzalutamide + 1)/7

Cumulative dose is the sum of the actual doses of enzalutamide received in the study.

Actual Dose Intensity (DI)

- Overall actual DI (mg/week) = [overall cumulative dose (mg)] / [intended treatment duration (weeks)]

Relative Dose Intensity (RDI)

- RDI (%) = 100 × [overall cumulative dose] / [intended cumulative dose per week × number of weeks from first dose of enzalutamide to last dose of enzalutamide]

  = 100 × [overall cumulative dose] / [7 × d × duration of exposure to enzalutamide in weeks]

  where d=160 mg, 120 mg, or 80 mg.

6.5.3.5. Dose reductions

Applicable to avelumab and NKTR-214. Dose reduction is defined as actual non-zero dose < 90% of the planned dose.

Applicable to talazoparib and enzalutamide. Dose reduction is defined as a change to a non-zero dose level lower than that planned in the protocol.

The number and percentage of participants with at least one dose reduction as well as a breakdown of the number of dose reductions (1, 2, 3, ≥4) will be summarized.

6.5.3.6. Dose interruptions

Applicable to talazoparib and enzalutamide only.

An interruption is defined a 0 mg dose administered on one or more days for talazoparib or enzalutamide. What follows defines how dose interruptions will be counted in the case of multiple dose interruptions.

- If an interruption occurs consecutively for at least two days, then it will be counted only once (example: If the actual dose on days 1-3 is not 0 mg and actual dose on days 4-5 is 0 mg, then the total number of dose interruptions is 1).
- If an interruption occurs for more than one day, but the days are not consecutive, ie there is at least one dosing day in between, then each dose interruption will be counted as a different occurrence (example: If the actual dose on days 1, 3 and 5, is not 0 mg and actual dose on days 2 and 4 is 0 mg, the total number of dose interruptions is 2).

A dose interruption is not considered a dose reduction.

The number and percentage of participants with dose interruptions will be summarized.

6.5.3.7. Dose delays

Applicable to avelumab and NKTR-214.

Dose Delay is the difference between the actual time between two consecutive non-zero doses and the planned time between the same two consecutive non-zero doses.

For Cycle 1 Dose 1:

Dose Delay (days) = day of the first day of study drug -1

After Cycle 1 Dose 1:

Dose Delay for Dose x (days) = Date of Dose x – Date of Dose (x-1) – Planned days between two consecutive doses = Date of Dose x – Date of Dose (x-1) – 14.

Dose delays will be grouped into the following categories:

- No delay
- 1-2 days delay
- 3-6 days delay
- 7 or more days delay

For example, for avelumab, administered on a 2-week schedule, if one participant receives avelumab on Day 1, then the next avelumab administration date will be on Day 15; however, if the participant receives avelumab at Day 16 or 17, this is considered as 1-2 days delay.

No delay and 1-2 days delay will also be summarized together.

The number and percentage of participants with delayed study drug administration and maximum length of delay, ie, the worst case of delay if participants have multiple dose delays will be summarized.

6.5.3.8. Infusion rate reductions

Applicable to avelumab and NKTR-214.

The number and percentage of participants with at least one infusion rate reduction of ≥50% compared to the first infusion rate reported in the eCRF as well as the frequency of participants with 1, 2, 3 or ≥4 infusion rate reductions of ≥50% will be summarized.

6.5.3.9. Infusion interruptions

An infusion interruption is defined as an infusion that is stopped and re-started on the same day (ie, for a visit more than one infusion start time and infusion end time are recorded).

The number and percentage of participants with at least one infusion interruption as well as the frequency of participants with 1, 2, 3, or ≥4 infusion interruptions will be summarized.

6.5.4. Concomitant medications and non-drug treatments

The following analyses will be based on the safety analysis set as shown in Table 3.

Concomitant medications are medications, other than study drugs, which started prior to first dose date of study treatment and continued during the on-treatment period as well as those started during the on-treatment period. **Prior medications** are medications, other than study drugs and pre-medications for study drug, which are started before the first dose of study treatment.

Prior and concomitant medications will be summarized from the 'General Concomitant Medications' eCRF page. Pre-medications for study drug will also be summarized separately from the 'Pre-Medication Treatment' eCRF page.

Summary of prior medications, summary of concomitant medications and summary of pre-medications will include the number and percentage of participants by Anatomical Therapeutic Chemical (ATC) Classification level 2 and preferred term. A participant will be counted only once within a given drug class and within a given drug name, even if he/she received the same medication at different times. If any prior or concomitant medication is classified into multiple ATC classes, the medication will be summarized separately under each of these ATC classes. The summary tables will be sorted on decreasing frequency of drug class and decreasing frequency of drug name in a given drug class. In case of equal frequency regarding drug class (respectively drug name), alphabetical order will be used. In case any specific medication does not have ATC classification level 2 coded term, it will be summarized under 'Unavailable ATC classification' category.

A listing of prior medications and a listing of concomitant medications will be created with the relevant information collected on the 'General Concomitant Medications' eCRF page. A listing of pre-medications will be created with the relevant information collected on the 'Pre-Medication Treatment' eCRF page.

All concurrent procedures, which were undertaken any time during the on-treatment period, will be listed according to the eCRF page 'General Non-drug Treatments'.

A listing of concurrent procedures will be created with the relevant information collected on the 'General Non-drug Treatments' eCRF page.

6.5.5. Subsequent anti-cancer therapies

The following analyses will be based on the FAS as shown in Table 3.

Anti-cancer treatment will be provided in a data listing with data retrieved from 'Follow-up Cancer Therapy', 'Concomitant Radiation Therapy', 'Follow-up Radiation Therapy', 'Concomitant Surgery', and 'Follow-up Surgery' eCRF pages.

Number and percentage of participants with any anti-cancer therapy after discontinuation will be tabulated overall and by type of therapy based on the data collected from the 'Follow-up Cancer Therapy', 'Follow-up Radiation Therapy' and 'Follow-up Surgery' eCRF pages.

6.6. Safety Summaries and Analyses

The Safety Analysis Set will be the primary population for safety evaluations. Summaries of AEs and other safety parameters will be based on the safety analysis set as shown in Table 3.

6.6.1. Adverse events

Treatment-emergent adverse events (TEAEs) are those events with onset dates occurring during the on-treatment period as defined in Section 3.2.1.

All analyses will be based on TEAEs (started during the on-treatment period) if not otherwise specified. The AE listings will include all AEs (whether treatment-emergent or not). AEs outside the on-treatment period will be flagged in the listings.

- **Related Adverse Events:** adverse events with relationship to study treatment (as recorded on the AE eCRF page, Relationship with study treatment = Related) reported by the investigator and those of unknown relationship (ie, no answer to the question 'Relationship with study treatment'). Related AEs are those related to any study drug (ie, at least one of the study drugs).
- **Serious Adverse Events (SAE):** serious adverse events (as recorded on the AE eCRF page, Serious Adverse Event = Yes).
- **Adverse Events Leading to Dose Reduction:** adverse events leading to dose reduction of study treatment (as recorded on the AE eCRF page, Action taken with study treatment = Dose reduced).
- **Adverse Events Leading to Interruption of Study Treatment:** adverse events leading to interruption of study treatment (as recorded on the AE eCRF page, Action taken with study treatment = Drug interrupted). The eCRF does not allow for a clear separation between interruption of an infusion and delays of administration for a parenteral drug as both are recorded using the same term on the eCRF ("Drug interrupted"). IRRs will be excluded in the analysis of AEs leading to Drug Interruption in case they only led to an interruption of the infusion.
- **Adverse Events Leading to Permanent Treatment Discontinuation:** adverse events leading to permanent discontinuation of study treatment (as recorded on the AE eCRF page, Action taken with study treatment = Drug withdrawn).
- **Adverse Events Leading to Death:** adverse event leading to death (as recorded on the AE eCRF page, Outcome = Fatal, as well as AEs of Grade 5).
- **Immune-related Adverse Events (irAE):** irAEs (as identified according to the methodology outlined in Appendix 1 for a pre-specified search list of MedDRA PTs, documented in the Safety Review Plan (SRP) and finalized for analysis of the current studies data prior to DB lock)
- **Infusion-related Reactions (IRR)**: IRRs (as identified according to the methodology outlined in Appendix 2 for a pre-specified search list of MedDRA PTs documented in the SRP and finalized for analysis of the current study data prior to DB lock.

Unless otherwise specified, AEs will be summarized by number and percentage of participants with the AE in the category of interest as described above, primary SOC and PT in decreasing frequency.

Each participant will be counted only once within each SOC or PT. If a participant experiences more than one AE within a SOC or PT for the same summary period, only the AE with the strongest relationship or the worst severity, as appropriate, will be included in the summaries of relationship and severity.

6.6.1.1. All adverse events

Adverse events will be summarized by worst severity (according to NCI-CTCAE version 4.03) per participant, using the latest version of MedDRA preferred term (PT) as event category and MedDRA primary system organ class (SOC) body term as Body System category.

In case a participant has events with missing and non-missing grades, the maximum of the non-missing grades will be displayed. No imputation of missing grades will be performed.

The following tables will be created:

- The overall summary of AEs table will include the frequency (number and percentage) of participants with each of the following by treatment group:
  - TEAEs
  - TEAEs, Grade ≥ 3
  - Related TEAEs
  - Related TEAEs, Grade ≥ 3
  - TEAEs leading to dose reduction of avelumab
  - TEAEs leading to dose reduction of NKTR-214
  - TEAEs leading to dose reduction of talazoparib
  - TEAEs leading to dose reduction of enzalutamide
  - TEAEs leading to interruption of avelumab
  - TEAEs leading to interruption of NKTR-214
  - TEAEs leading to interruption of talazoparib
  - TEAEs leading to interruption of enzalutamide
  - TEAEs leading to discontinuation of avelumab
  - TEAEs leading to discontinuation of NKTR-214
  - TEAEs leading to discontinuation of talazoparib
  - TEAEs leading to discontinuation of enzalutamide
  - TEAEs leading to discontinuation of any study drug

- TEAEs leading to discontinuation of all study drugs
- Related TEAEs leading to discontinuation of avelumab
- Related TEAEs leading to discontinuation of NKTR-214
- Related TEAEs leading to discontinuation of talazoparib
- Related TEAEs leading to discontinuation of enzalutamide
- Related TEAEs leading to discontinuation of any study drug
- Related TEAEs leading to discontinuation of all study drugs
- Serious TEAEs
- Related Serious TEAEs
- TEAEs leading to death
- Related TEAEs leading to death
- irAEs
- IRRs

- TEAEs by SOC and PT and worst grade
- TEAEs related to avelumab by SOC and PT and worst grade
- TEAEs related to NKTR-214 by SOC and PT and worst grade
- TEAEs related to talazoparib by SOC and PT and worst grade
- TEAEs related to enzalutamide by SOC and PT and worst grade
- TEAEs related to any study drug by SOC and PT and worst grade
- TEAEs leading to death by SOC and PT
- Related TEAEs leading to death by SOC and PT

6.6.1.2. Adverse events leading to dose reduction

The frequency (number and percentage) of participants with each of the following will be presented for TEAEs leading to dose reduction of each study drug by treatment group:

- TEAEs leading to dose reduction of avelumab by SOC and PT
- TEAEs leading to dose reduction of NKTR-214 by SOC and PT
- TEAEs leading to dose reduction of talazoparib by SOC and PT
- TEAEs leading to dose reduction of enzalutamide by SOC and PT

The listing of all AEs leading to dose reduction will also be provided with the relevant information.

6.6.1.3. Adverse events leading to interruption of study treatment

The eCRF does not allow for a clear separation between interruption of an infusion and delays of administration for a parenteral drug as both are recorded using the same term on the eCRF ("Drug interrupted"). IRRs will be excluded in the analysis of AEs leading to Drug Interruption in case they only led to an interruption of the infusion (ie, did not lead to a dose reduction or a dose delay).

As such, AEs leading to interruption will be defined as AEs identified in the AE eCRF page with an action taken with study treatment of 'drug interrupted' excluding

- IRRs that occurred on the day of infusion with ≥90% of the planned dose given (ie IRRs that did not lead to a dose reduction) and subsequent administration of study drug had no delay (as defined in Section 6.5.3.7). These IRRs will be considered as IRRs leading to interruption of infusion.
- IRRs occurring on the day after infusion and subsequent dose administration had no delay (as defined in Section 6.5.3.7).

The frequency (number and percentage) of participants with each of the following will be presented for TEAEs leading to interruption of each study drug by treatment group:

- TEAEs leading to interruption of avelumab by SOC and PT
- TEAEs leading to interruption of NKTR-214 by SOC and PT
- TEAEs leading to interruption of talazoparib by SOC and PT
- TEAEs leading to interruption of enzalutamide by SOC and PT

The listing of all AEs leading to interruption of study treatment will also be provided with the relevant information.

In addition, the frequency (number and percentage) of participants with each of the following will be presented for TEAEs leading to dose interruption and dose reduction of each study drug by treatment group:

- TEAEs leading to both interruption and dose reduction of avelumab by SOC and PT
- TEAEs leading to both interruption and dose reduction of NKTR-214 by SOC and PT
- TEAEs leading to both interruption and dose reduction of talazoparib by SOC and PT
- TEAEs leading to both interruption and dose reduction of enzalutamide by SOC and PT

This summary will take into account PTs with both actions as defined in Section 6.6.1, even though the actions may be captured for different PT records (ie, different onset for the PT with action "drug interrupted" and the PT with action "dose reduced".

6.6.1.4. Adverse events leading to discontinuation of study treatment

The frequency (number and percentage) of participants with each of the following will be presented for TEAEs leading to permanent discontinuation of each study drug and study treatment, by treatment group:

- TEAEs leading to discontinuation of avelumab by SOC and PT
- Related TEAEs leading to discontinuation of avelumab by SOC and PT
- TEAEs leading to discontinuation of NKTR-214 by SOC and PT
- Related TEAEs leading to discontinuation of NKTR-214 by SOC and PT
- TEAEs leading to discontinuation of talazoparib by SOC and PT
- Related TEAEs leading to discontinuation of talazoparib by SOC and PT
- TEAEs leading to discontinuation of enzalutamide by SOC and PT
- Related TEAEs leading to discontinuation of enzalutamide by SOC and PT
- TEAEs leading to discontinuation of any study drug by SOC and PT
- Related TEAEs leading to discontinuation of any study drug by SOC and PT
- TEAEs leading to discontinuation of all study drugs by SOC and PT
- Related TEAEs leading to discontinuation of all study drugs by SOC and PT

The listing of all AEs leading to treatment discontinuation will also be provided with the relevant information.

6.6.2. Deaths

The frequency (number and percentage) of participants in the safety analysis set who died and who died within 30 days after last dose of study treatment as well as the reason for death, will be tabulated based on information from the 'Notice of Death' and 'Survival Follow-Up' eCRFs, by treatment group.

- All deaths
- Deaths within 30 days after last dose of study treatment
- Reason for Death
  - Disease progression
  - Study treatment toxicity
  - AE not related to study treatment
  - Unknown
  - Other.

In addition, date and cause of death will be provided in individual participant data listing together with selected dosing information (study treatment received, date of first / last administration, dose) and will include the following information:

- AEs with fatal outcome (list preferred terms of AEs with outcome=Fatal, as well as AEs of Grade 5),
- Flag for death within 30 days of last dose of study treatment.

6.6.3. Serious adverse events

The frequency (number and percentage) of participants with each of the following will be presented for treatment-emergent SAEs by treatment group:

- SAEs by SOC and PT
- Related SAEs by SOC and PT

The listings of all SAEs will also be provided with the relevant information with a flag for SAEs with onset outside of the on-treatment period.

6.6.4. Other significant adverse events

The frequency (number and percentage) of participants with each of the following will be presented for irAEs, by treatment group:

- irAEs leading to death, by Cluster and PT
- irAEs, by Cluster and PT
- irAEs, Grade ≥ 3, by Cluster and PT
- irAEs leading to discontinuation of avelumab, by Cluster and PT
- irAEs leading to discontinuation of NKTR-214, by Cluster and PT
- irAEs leading to discontinuation of talazoparib, by Cluster and PT
- irAEs leading to discontinuation of enzalutamide, by Cluster and PT
- irAEs leading to discontinuation of any study drug, by Cluster and PT
- irAEs leading to discontinuation of all study drugs, by Cluster and PT
- Serious irAEs, by Cluster and PT

The listing of all irAEs will also be provided with the relevant information with a flag for irAEs with onset outside of the on-treatment period.

The frequency (number and percentage) of participants with each of the following will be presented for IRRs, by treatment group:

- IRRs leading to death, by PT
- IRRs, by PT

- IRRs, Grade ≥ 3, by PT
- IRRs leading to discontinuation of avelumab, by PT
- IRRs leading to discontinuation of NKTR-214, by PT
- IRRs leading to discontinuation of any study drug, by PT
- IRRs leading to discontinuation of all study drugs, by PT
- Serious IRRs, by PT
- Time related to first onset of an IRR (infusion 1, infusion 2, infusion 3, infusion 4 or later). For IV study drugs administered in combination the infusion numbers are those associated with the regimen, rather than the individual study drugs.

The listing of all IRRs will also be provided with the relevant information with a flag for IRRs with onset outside of the on-treatment period.

6.6.5. Laboratory data

6.6.5.1. Hematology and chemistry parameters

Laboratory results will be classified according to the NCI-CTCAE criteria version 4.03. Non-numerical qualifiers (with the exception of fasting flags) will not be taken into consideration in the derivation of CTCAE criteria (eg, hypokalemia Grade 1 and Grade 2 are only distinguished by a non-numerical qualifier and therefore Grade 2 will not be derived). Additional laboratory results that are not part of NCI-CTCAE will be presented according to the categories: below normal limit, within normal limits and above normal limit (according to the laboratory normal ranges).

Abnormalities classified according to NCI-CTCAE toxicity grading v.4.03 will be described using the worst grade. For those parameters which are graded with two toxicities such as potassium (hypokalemia/hyperkalemia), the toxicities will be summarized separately. Low direction toxicity (eg, hypokalemia) grades at baseline and post baseline will be set to 0 when the variables are derived for summarizing high direction toxicity (eg, hyperkalemia), and vice versa.

For **WBC differential counts** (total neutrophil [including bands], lymphocyte, monocyte, eosinophil, and basophil counts), the absolute value will be used when reported. When only percentages are available (this is mainly important for neutrophils and lymphocytes, because the CTCAE grading is based on the absolute counts), the absolute value is derived as follows:

$$\text{Derived differential absolute count} = (\text{WBC count}) \times (\text{Differential \%value} / 100)$$

If the range for the differential absolute count is not available (only range for value in % is available) then Grade 1 will be attributed to as follows:

- Lymphocyte count decreased:
  - derived absolute count does not meet Grade 2-4 criteria, and
  - % value < % LLN value, and

  - derived absolute count ≥ 800/mm3
- Neutrophil count decreased
  - derived absolute count does not meet Grade 2-4 criteria, and
  - % value < % LLN value, and
  - derived absolute count ≥ 1500/mm3

For **calcium**, CTCAE grading is based on Corrected Calcium and Ionized Calcium (CALCIO). Corrected Calcium is calculated from Albumin and Calcium as follows

Corrected calcium (mmol/L) = measured total Calcium (mmol/L) + 0.02 (40 - serum albumin [g/L])

Liver function tests: Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin (TBILI) are used to assess possible drug induced liver toxicity. The ratios of test result over upper limit of normal (ULN) will be calculated and classified for these three parameters during the on-treatment period.

Summary of liver function tests will include the following categories. The number and percentage of participants with each of the following during the on-treatment period will be summarized by treatment group:

- ALT ≥ 3×ULN, ALT ≥ 5×ULN, ALT ≥ 10×ULN, ALT ≥ 20×ULN
- AST ≥ 3×ULN, AST ≥ 5×ULN, AST ≥ 10×ULN, AST ≥ 20×ULN
- (ALT or AST) ≥ 3×ULN, (ALT or AST) ≥ 5×ULN, (ALT or AST) ≥ 10×ULN, (ALT or AST) ≥ 20×ULN
- TBILI ≥ 2×ULN
- Concurrent ALT ≥ 3×ULN and TBILI ≥ 2×ULN
- Concurrent AST ≥ 3×ULN and TBILI ≥ 2×ULN
- Concurrent (ALT or AST) ≥ 3×ULN and TBILI ≥ 2×ULN
- Concurrent (ALT or AST) ≥ 3×ULN and TBILI ≥ 2×ULN and ALP > 2×ULN
- Concurrent (ALT or AST) ≥ 3×ULN and TBILI ≥ 2×ULN and (ALP ≤ 2×ULN or missing)

Concurrent measurements are those occurring on the same date.

Categories will be cumulative, ie, a participant with an elevation of AST ≥10×ULN will also appear in the categories ≥5×ULN and ≥3×ULN. Liver function elevation and possible Hy's Law cases will be summarized using frequency counts and percentages.

An evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) plot will also be created, with different symbols for different treatment groups, by graphically displaying

- peak serum ALT(/ULN) vs peak total bilirubin (/ULN) including reference lines at ALT=3×ULN and total bilirubin =2×ULN.

- peak serum AST(/ULN) vs peak total bilirubin (/ULN) including reference lines at AST=3×ULN and total bilirubin =2×ULN .

In addition, a listing of all TBILI, ALT, AST and ALP values for patients with concurrent (ALT or AST) ≥ 3×ULN and TBILI ≥ 2×ULN and (ALP ≤ 2×ULN or missing) will be provided.

Parameters with NCI-CTC grades available:

The laboratory toxicities will be tabulated using descriptive statistics (number of participants and percentages) during the on-treatment period. The denominator to calculate percentages for each laboratory parameter is the number of participants evaluable for CTCAE grading (ie those participants for whom a Grade 0, 1, 2, 3 or 4 can be derived).

- The summary of laboratory parameters by CTCAE grade table will include number and percentage of participants with Grade 1, 2, 3, 4, Grade 3/4 and any grade (Grades 1-4), laboratory abnormalities during the on-treatment period.
- The shift table will summarize baseline CTCAE grade versus the worst on-treatment CTCAE grade. The highest CTCAE grade during the on-treatment period is considered as the worst grade for the summary.
- The number and percentage of participants with newly occurring or worsening laboratory abnormalities during the on-treatment period will be summarized by worst grade on-treatment (Grade 1, 2, 3, 4, Grade 3/4 and any grade (Grades 1-4)).

The above analyses apply to hematology and chemistry evaluations which can be graded per CTCAE, ie:

- Hematology:

  Hemoglobin (HB), white blood cell count (white blood cell count decreased), Lymphocytes (lymphocyte count increased/decreased), Neutrophils / Absolute Neutrophils Count (ANC) (neutrophil count decreased), Platelet Count (PLT) (platelet count decreased).

- Serum Chemistry:

  Albumin (hypoalbuminemia), Alkaline Phosphatase (alkaline phosphatase increased), Alanine Aminotransferase (ALT) (ALT increased), Amylase (serum amylase increased), Aspartate Aminotransferase (AST) (AST increased), Total Bilirubin (blood bilirubin increased, Creatinine (creatinine increased), Potassium (hypokalemia/ hyperkalemia), Sodium (hyponatremia/ hypernatremia), Magnesium (hypomagnesemia/hypermagnesemia), Calcium (hypocalcemia/ hypercalcemia), Glucose (hypoglycemia/hyperglycemia, non-fasted), Gamma Glutamyl Transferase (GGT) (GGT increased), Lipase (lipase increased), Phosphates (hypophosphatemia).

Parameters with NCI-CTC grades not available:

Hematology and chemistry evaluations which cannot be graded per CTCAE criteria will be summarized as frequency (number and percentage) of participants with:

- shifts from baseline normal to at least one result above normal during on-treatment period

- shifts from baseline normal to at least one result below normal during on-treatment period

In this study, these apply to the following parameters:

- Hematology: Absolute Monocytes, Absolute Eosinophils, Absolute Basophils
- Serum Chemistry: Chloride, Total Urea, Uric Acid, Total Protein, C-Reactive Protein, Lactate Dehydrogenase (LDH)

6.6.5.2. Other laboratory parameters

The listings of laboratory results will be provided for all laboratory parameters. The listings will be sorted by parameters and assessment dates or visits for each participant. Laboratory values that are outside the normal range will also be flagged in the data listings, along with corresponding normal ranges. A listing of CTCAE grading will also be generated for those laboratory tests.

In addition, listings of abnormal values will be provided for hematology, chemistry, urinalysis, coagulation parameters. If there is at least one abnormal assessment for any parameter, all the data for that laboratory parameter will be included into the listing.

For all tests not mentioned above but present in the clinical data, a listing of participants with at least one result for the relevant test will be provided.

6.6.6. Vital signs

Weight for the purposes of dose calculation will be recorded pre-dose on Day 1 of each cycle. Weight will also be recorded at screening, End of Treatment, and at the 30-day follow-up visit. Height will be measured at screening only.

Vital sign summaries will include all vital sign assessments from the on-treatment period. All vital sign assessments will be listed, and those collected outside the on-treatment period will be flagged in the listing.

All vital sign parameters will be summarized using descriptive statistics (mean, SD, median, Q1, Q3, minimum, and maximum) of actual values and changes from baseline for each visit over time. End of Treatment visit will be summarized separately. The changes computed will be the differences from baseline.

6.6.7. Electrocardiogram

ECG summaries will include all ECG assessments from the on-treatment period. All ECG assessments will be listed, and those collected outside the on-treatment period will be flagged in the listing. QTcB and QTcF will be derived based on RR and QT (see below). When triplicate ECG are performed, the average of the replicate measurements should be determined after the derivation of the individual parameter at each time point.

Selecting Primary QT Correction for Heart Rate

The analysis of QT data is complicated by the fact that the QT interval is highly correlated with heart rate. Because of this correlation, formulas are routinely used to obtain a corrected

value, denoted QTc, which is independent of heart rate. This QTc interval is intended to represent the QT interval at a standardized heart rate. Several correction formulas have been proposed in the literature. For this analysis we will use some of those methods of correction, as described below. The QT interval corrected for heart rate by the Bazett's formula, QTcB, is defined as

$$QTcB = \frac{QT}{\sqrt{RR}},$$

the QT interval corrected for heart rate by the Fridericia's formula, QTcF, is defined as

$$QTcF = \frac{QT}{\sqrt[3]{RR}},$$

where RR represents the RR interval of the ECG, in seconds, and can be estimated as 60/Heart Rate.

Although Bazett's correction is the historical standard, it does not perform well when heart rate fluctuates. Fridericia's formula may perform better under these conditions. If QTcB and QTcF methods do not adequately correct for HR and there are a sufficient number of participants (eg >30) with baseline ECGs, an alternate correction to achieve the goal of getting uncorrelated QTc and RR is based on a linear regression method which yields, theoretically, uncorrelated QTc and RR.

Linear regression method:

- Fit a model QT = a + b × RR to baseline data
- Use the estimated slope, $\hat{b}$, to correct QT
- Corrected QT for heart rate will be computed as follows:

$$QTcP = QT + \hat{b} \times (1 - RR)$$

Data will be summarized using QTcF and QTcB. However, if these are not appropriate for the data set due to an observed large correlation between corrected QT and HR using the baseline assessments, the results will also be summarized using QTcP.

ECG Summaries

The following analyses will be performed for each applicable ECG parameters (RR, PR, QRS, QT, ventricular rate -denoted as HR in what follows-, and QTc) by treatment group, during the on-treatment period. The denominator to calculate percentages for each category is the number of participants evaluable for the category.

- Pearson correlation between QT and HR, QTc (QTcB, QTcF and, if applicable, QTcP) and HR using individual (non-averaged) baseline assessments
- For each of the ECG parameters (HR, and QT, QTc, QRS, PR intervals), descriptive statistics at baseline, at each post-baseline time point and changes from baseline at each post-baseline time point

- Frequency (number and percentage) of participants with notable ECG values according to the following categories:
  - QT/QTc increase from baseline >30 ms, >60 ms
  - QT/QTc > 450 ms, > 480 ms, > 500 ms
  - HR ≤ 50 bpm and decrease from baseline ≥ 20 bpm
  - HR ≥ 120 bpm and increase from baseline ≥ 20 bpm
  - PR ≥ 220 ms and increase from baseline ≥ 20 ms
  - QRS ≥ 120 ms

Participants with notable ECG interval values and qualitative ECG abnormalities will be listed for each participant and time point and the corresponding notable values and abnormality findings will be included in the listings.

Unscheduled ECG measurements will not be used in computing the descriptive statistics for change from baseline at each post-baseline time point. However, they will be used in the analysis of notable ECG changes and the shift table analysis of notable QT parameters.

6.6.8. ECOG performance status

The ECOG shift from baseline to highest score during the on-treatment period will be summarized by treatment group.

7. INTERIM ANALYSES

There is no formal interim analysis planned for this study.

8. REFERENCES

1. Babb J, Rogatko A, Zacks S. Cancer Phase I clinical trials: efficient dose escalation with overdose control. Statistics in Medicine 17(10):1103-20, 1998.

2. Brookmeyer R, Crowley JJ. A confidence interval for the median survival time. Biometrics. 38: 29-41, 1982.

3. Clopper CJ, Pearson ES . The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika; 26, 404-413, 1934.

4. de Bono J, Ramanathan RK, Mina L. Phase I, Dose-Escalation, Two-Part Trial of the PARP Inhibitor Talazoparib in Patients with Advanced Germline BRCA1/2 Mutations and Selected Sporadic Cancers. Cancer Discov;7(6):620-9, 2017.

5. Kalbfleisch JD, Prentice, RL. Statistical Analysis of Failure Time Data, 2nd Edition. Hoboken, Wiley Interscience. 2002.

6. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc. 53: 457-81, 1958.

cci [redacted]

[redacted]

9. Neuenschwander B, Capkun-Niggli G, Branson M, and Spiegelhalter DJ. Summarizing Historical Information on Controls in Clinical Trials. Clinical Trials 7:5-18, 2010.

10. Neuenschwander B, Matano A, Tang Z, et al. A Bayesian Industry Approach to Phase I Combination Trials in Oncology. In *Statistical Methods in Drug Combination Studies. Zhao W and Yang H (eds)*; Chapman & Hall/CRC; 2014.

11. Spiegelhalter DJ, Abrams KR, Myles JP. Bayesian Approaches to Clinical Trials and Health-Care Evaluation. John Wiley & Sons; New York; 2004.

12. S-3100-1-01 clinical study report. Medivation, Inc. 10 Feb 2012.

9. APPENDICES

Appendix 1. Immune-Related Adverse Events

The MedDRA PTs and clusters for irAEs are defined in the SRP for avelumab.

Immune-related AEs (irAEs) will be programmatically identified as outlined in Table 18. This case definition is hierarchical, ie, each step is only checked for participants and events that have already met the prior step.

Table 18. Case Definition for irAEs

Step	Selection Criteria	Additional Notes
1	Event selected based on a list of pre-specified MedDRA PTs within clusters. These are included in the SRP as Tier1 events (Immune-mediated xxxx). If AE matches the list, then it is in for the next step	
2	AE onset during 1st study drug administration or anytime thereafter through 90 days after last dose of study treatment.	This is regardless of start of new anti-cancer drug therapy and regardless of TEAE classifications
3	Answer in the AE eCRF page to 'Was another treatment given because of the occurrence of the event' is 'YES'	
4	AE treated with corticosteroids or other immunosuppressant therapy. For endocrinopathies only: AE required hormone replacement	Look in the conmed pages for AE identifiers that match the AEs from Step 3. For each of such AEs if A) OR B) OR C) below are met then the AE is in for the next step A) conmed ATC code is in (H02A, H02B, D07, A01AC, S01BA, S01BB, L04AA, L04AB, L04AC, L04AD, L04AX, A07EA) and AE PT is in any of the irAE clusters. B) conmed ATC code is in (H03A, H03B) and AE PT is in one of the irAE clusters associated with "Immune-mediated endocrinopathies" C) conmed ATC code is A10A and AE PT is in the irAE cluster associated with "Immune-mediated endocrinopathies: Type I Diabetes Mellitus"

5	A) No clear etiology (other than immune mediated etiology) B) Histopathology / biopsy consistent with immune-mediated event Event is in if [Answer to 5B1 and 5B2 is YES (regardless of answer to 5A)] OR [Answer to 5B1 is YES AND answer to 5B2 is NO AND answer to 5A is NO] OR [Answer to 5B1 is NO AND answer to 5A is NO]	A) From the AE eCRF page. Is the AE clearly related to an etiology other than immune-mediated etiology? Yes / No If answer is Yes, check all that apply: • Underlying malignancy / progressive disease. • Other medical conditions. • Prior or concomitant medications / procedures. • Other. Specify. B) From the AE eCRF page. B1) Was there a pathology / histology evaluation performed to investigate the AE? Y/N B2) If answer to the above is Yes, does the pathology/histology evaluation confirms an immune mediated mechanism for the AE? Y/N B3) If pathology / histology evaluation performed to investigate the AE, provide summary of relevant findings of the pathology /histology report. (Free Text)

The data set associated with irAEs may be refined based on medical review. The final data set including any changes based on medical review (eg, addition of cases that are not selected by the programmatic algorithm) will be the basis of the irAE analyses.

Appendix 2. Infusion Related Reactions

For defining an AE as IRR, the onset of the event in relation to the infusion of study drug and time to resolution of the event will be considered.

- All AEs identified by the MedDRA PT query describing signs and symptoms will be considered potential IRRs when onset is on the day of study drug infusion (during or after infusion) and the event resolved with end date within 2 days after onset.
- All AEs identified by the MedDRA PTs of Infusion related reaction, Drug hypersensitivity, Anaphylactic reaction, Hypersensitivity, Type 1 hypersensitivity, will be considered potential IRRs when onset is on the day of study drug infusion (during or after the infusion) or the day after the study drug infusion (irrespective of resolution date).

The list of MedDRA PTs for 'IRRs SIGNS and SYMPTOMS' and PTs 'IRRs CORE' are defined in the SRP for avelumab.

Infusion-related reactions (IRRs) will be programmatically identified as outlined in Table 19 or Table 20 and will be identified for IV drugs only.

Table 19. Case Definition for IRRs – IV Study Drugs Administered Alone Or In Combination With Non-IV Study Drugs

Condition	Selection criterion
If AE meets [1 AND 2] OR [3 AND (4A OR 4B)] then AE is classified as an IRR	
1	PT is included in the 'IRRs SIGNS and SYMPTOMS' list
2	• AE onset date = date of infusion of study drug AND • AE timing related to study drug ('DURING', 'AFTER') AND • AE outcome in ('RECOVERED/RESOLVED', 'RECOVERED/RESOLVED WITH SEQUELAE', 'RECOVERING/RESOLVING') AND • AE end date – AE onset date ≤2
3	PT is included in the 'IRRs CORE' list
4A	• AE onset date = date of infusion of study drug AND • AE timing related to study drug in ('DURING', 'AFTER')
4B	AE onset on the day after infusion

Table 20. Case Definition for IRRs – IV Study Drugs Administered in Combination (eg, Doublets or Triplets)

Condition	Selection criterion
IRR can be associated with the first IV drug and/or subsequent IV drugs that are administered in combination. Without loss of generality assume triplet IV with D_1 administered first then D_2 then D_3. The IV study drug or drugs associated with the IRR need to be identified in the analysis data set to enable subsequent analysis. The following are not sequential and an AE can be classified as an IRR associated with multiple D_J from one or more of I, II, III, IV, V below: I - If the AE meets [1 AND 2A1] for a D_J then the AE is classified as an IRR associated with the D_J that meets the 2A1 criterion II - If the AE meets [1 AND 2A2] for a D_J then the AE is classified as an IRR associated with the D_J and associated with D_{J+1} that meets the 2A2 criterion III - If the AE meets [3 AND 4B] for any D_J then the AE is classified as an IRR associated with all D_J that meet the 4B criterion. IV- If the AE meets [3 AND 4A1] for a D_J then the AE is classified as an IRR associated with the D_J that meets the 4A1 criterion V- If the AE meets [3 AND 4A2] for a D_J then the AE is classified as an IRR associated with the D_J and associated with D_{J+1} that meets the 4A2 criterion	
1	PT is included in the 'IRRs SIGNS and SYMPTOMS' list
2A1	• AE onset date = date of infusion of study drug D_J AND • AE timing related to study drug D_J ('DURING', 'AFTER') AND • [AE timing related to study drug D_{J+1} ('BEFORE') OR AE onset date < date of infusion of study drug D_{J+1}] AND • AE outcome in ('RECOVERED/RESOLVED', 'RECOVERED/RESOLVED WITH SEQUELAE', 'RECOVERING/RESOLVING') AND • AE end date – AE onset date ≤2
2A2	• AE onset date = date of infusion of study drug D_J AND • AE timing related to study drug D_J ('DURING', 'AFTER') AND • AE timing related to study drug D_{J+1} ('DURING', 'AFTER') AND • AE outcome in ('RECOVERED/RESOLVED', 'RECOVERED/RESOLVED WITH SEQUELAE', 'RECOVERING/RESOLVING') AND • AE end date – AE onset date ≤2
3	PT is included in the 'IRRs CORE' list
4A1	• AE onset date = date of infusion of study drug D_J AND • AE timing related to study drug D_J ('DURING', 'AFTER') AND • [AE timing related to study drug D_{J+1} ('BEFORE') OR AE onset date < date of infusion of study drug D_{J+1}]
4A2	• AE onset date = date of infusion of study drug D_J AND • AE timing related to study drug D_J ('DURING', 'AFTER') AND • AE timing related to study drug D_{J+1} ('DURING', 'AFTER')
4B	AE onset on the day after infusion of study drug D_J

Appendix 3. BLRM Design for Avelumab and Bempegaldesleukin (NKTR-214) Doublet - Combination A

This appendix provides the details of the statistical model, the derivation of prior distributions of the single-agent model parameters from historical data, the results of the Bayesian analyses and respective dosing decisions for some hypothetical data scenarios, and a simulation study of the operating characteristics of the model for the bempegaldesleukin (NKTR-214) + avelumab treatment (Combination A).

In this appendix, the reported avelumab dose is 10 mg/kg. Note that the fixed dose of 800 mg to be investigated in this study is expected to be equivalent to the 10 mg/kg dose.

Statistical Model

The statistical model for dose-DLT data for this doublet combination comprises single-agent toxicity parts, which allow the incorporation of single-agent toxicity data, and an interaction part.

Single Agent Parts

Let $\pi_1(d_1)$ be the risk of DLT for bempegaldesleukin (NKTR-214) given as a single agent at dose d_1; and $\pi_2(d_2)$ be the risk of DLT for avelumab given as a single agent at dose d_2. These single agent dose-DLT models are logistic:

bempegaldesleukin (NKTR-214): $\text{logit}\left(\pi_1(d_1)\right) = \log(\alpha_1) + \beta_1 \log(d_1/d_1^*)$

avelumab: $\text{logit}\left(\pi_2(d_2)\right) = \log(\alpha_2) + \beta_2 \log(d_2/d_2^*)$

where d_1^*=0.006 mg/kg, and d_2^* =10 mg/kg, are used to scale the doses of bempegaldesleukin (NKTR-214), and avelumab, respectively. Hence, α_1, α_2 (all >0) are the single-agent odds of a DLT at d_1^* mg/kg, and d_2^* mg/kg, respectively; and β_1,and β_2, (all>0) are the increase in the log-odds of a DLT by a unit increase in log-dose.

Interaction Part

Under an assumption that there is no interaction, the risk of a DLT at dose d_1 of bempegaldesleukin (NKTR-214), and dose d_2 of avelumab is:

$$\pi_{12}^0(d_1, d_2,) = 1 - \left(1 - \pi_1(d_1)\right)\left(1 - \pi_2(d_2)\right)$$

To model the interaction between bempegaldesleukin (NKTR-214) and avelumab, the following odds multiplier is introduced.

- η_{12}: Two-way interaction between bempegaldesleukin (NKTR-214) and avelumab

The risk of DLT for combination dose (d_1, d_2) is then given by:

$$\text{odds}\left(\pi_{12}(d_1, d_2)\right) = g(\eta_{12}) \times \text{odds}\left(\pi_{12}^{0}(d_1, d_2)\right)$$

$$g(\eta_{12}) = \exp(\eta_{12} \times d_1/d_1^* \times d_2/d_2^*)$$

where $\text{odds}(\pi) = \pi/(1-\pi)$; η_{ij} is the log-odds ratio between the interaction and no interaction model at the reference doses of drug i and j. For example, η_{12} is the log-odds ratio between the interaction and no interaction model at avelumab = 10 mg/kg, bempegaldesleukin (NKTR-214) = 0.006 mg/kg. Therefore, η_{12} is the log-odds ratio between the interaction and no interaction model at the reference doses for two drugs. Here $\eta = 0$ corresponds to no interaction, with $\eta > 0$ and $\eta < 0$ representing synergistic and antagonistic toxicity, respectively.

Prior Specifications

The Bayesian approach requires the specification of prior distributions for all model parameters, which include the single agent parameters $\log(\alpha_1)$, $\log(\beta_1)$ for bempegaldesleukin (NKTR-214), and $\log(\alpha_2)$, $\log(\beta_2)$ for avelumab, and the interaction parameter (η_{12}). A meta-analytic-predictive (MAP) approach was used to derive the prior distribution for the single-agent model parameters.

Prior Distribution for the Logistic Parameters for Single Agent

This section illustrates the derivation of prior distributions for single agent model parameters $(\log(\alpha_s), \log(\beta_s))$'s using the available single agent dose-DLT information via a MAP approach.

Description of the Meta-Analytic-Predictive Approach

The aim of the MAP approach is to derive a prior distribution for the logistic parameters $\left(\log(\alpha^*), \log(\beta^*)\right)$ of the new trial using DLT data from historical studies. Let r_{ds} and n_{ds} be the number of participants with a DLT, and the total number of participants at dose d in historical trial s $(s = 1, \ldots, \langle S \rangle)$. The corresponding probability of a DLT is π_{ds}. The model specifications are as follows:

$$r_{ds} \mid \pi_{ds} \sim \text{Binomial}(\pi_{ds}, n_{ds})$$

$$\text{logit}(\pi_{ds}) = \log(\alpha_s) + \beta_s \log(d/d^*)$$

$$\left(log(\alpha_s), log(\beta_s)\right) \mid \mu, \psi_{g(s)} \sim \text{Bivariate Normal (BVN)}\left(\mu, \psi_{g(s)}\right), \qquad s = 1, \ldots, \langle S \rangle$$

$$\left(log(\alpha^*), log(\beta^*)\right) \mid \mu, \psi_{g(*)} \sim \text{BVN}\left(\mu, \psi_{g(*)}\right)$$

The historical trials are partitioned into $\langle G \rangle$ exchangeability groups, with the exchangeability group membership of historical trial s being represented by $g(s)$. The new trial is assigned to exchangeability group $g(*)$. The parameter $\mu = (\mu_1, \mu_2)$ is the mean for the logistic

parameters, and ψ_g is the between-trial covariance matrix for exchangeability group $g = 1, \ldots, \langle G \rangle$. Covariance matrix ψ_g is defined by the standard deviations (τ_{g1}, τ_{g2}), and correlation ρ (a common value for ρ is used across all groups). The parameters τ_{g1} and τ_{g2} quantify the degree of between trial heterogeneity for exchangeability group g. With different prior distributions for the parameter sets (τ_{g1}, τ_{g2}) it is possible to allow for differential discounting for the historical strata. In this way the quality and relevance of historical data can be accounted for in the meta-analysis. The following priors will be used for these parameters:

- normal priors for μ_1 and μ_2,
- log-normal priors for τ_{g1} and τ_{g2}, and
- uniform prior for ρ.

The MAP prior for single-agent model parameters in the new trial, $(log(\alpha^*), log(\beta^*))$, is the predictive distribution

$$(log(\alpha^*), log(\beta^*)) \mid (r_{ds}, n_{ds} : s = 1, \ldots, \langle S \rangle)$$

Since the predictive distribution is not available analytically, the Markov chain Monte Carlo (MCMC) method is used to simulate values from this distribution. This is implemented using Just Another Gibbs Sampler (JAGS) version 4.8.

Single Agent Bempegaldesleukin (NKTR-214)

Dose-DLT data for bempegaldesleukin (NKTR-214) from study EXCEL[8] as presented in Table 21 are used to derive the priors of the single agent logistic parameters for bempegaldesleukin (NKTR-214). In deriving the priors, the Q3W schedule was mapped to the Q2W schedule assuming linear relationship between PK with accumulation for bempegaldesleukin (NKTR-214) based on clinical-pharmacology assessment.

Table 21. Historical Dose Limiting Toxicity Data From Study EXCEL

Bempegaldesleukin (NKTR-214) dose (mg/kg IV)	Number of patients	Number of patients with DLTs
0.003 Q3W	4	0
0.006 Q3W	11	0
0.006 Q2W	6	0
0.009 Q3W	6	0
0.012 Q3W	1	1

Abbreviations: IV=intravenous; mg/kg=milligrams per kilogram; Q2W=every 2 weeks; Q3W=every 3 weeks; DLT=dose limiting toxicity.

Weakly informative normal priors are assumed for μ_{1b} and μ_{2b}, with means corresponding to a 50% chance of DLT at bempegaldesleukin (NKTR-214) =0.006 mg/kg, and a doubling in dose leading to a doubling in the odds of the risk of a DLT, respectively. Priors for τ_{1b} and

τ_{2b} are assigned such that (1) their medians correspond to moderate between trial heterogeneity, and (2) their uncertainty (95% prior interval) cover plausible between-trial standard deviations[10].

The prior distributions for the model used for deriving the MAP priors are specified in Table 22.

Table 22. Prior Distributions for the Parameters of the MAP Model Used to Derive the Prior for the Single-Agent Bempegaldesleukin (NKTR-214) Model Parameters

Parameter	Prior distribution
μ_{1b}	N(mean = 0, sd =2)
μ_{2b}	N(mean = 0, sd=1)
τ_{1b}	log-normal(mean = log(0.25), sd = log(2)/1.96)
τ_{2b}	log-normal(mean = log(0.125), sd = log(2)/1.96)
ρ_b	uniform(-1,1)

Abbreviations: N=normally distributed; sd=standard deviation.

Single Agent Avelumab

Dose-DLT data in the avelumab IB from study EMR100070-001[7] as presented in Table 23 are used to derive the prior of the single agent logistic parameters for avelumab. Based on clinical assessment, the population of the current study is moderately similar to study EMR100070-001.

Table 23. Historical Dose Limiting Toxicity Data from Study EMR100070-001

Avelumab dose (mg/kg Q2W)	Number of patients	Number of patients with DLTs
1	4	0
3	3	0
10	6	0
20	6	1

Abbreviations: mg/kg=milligrams per kilogram; DLT=dose limiting toxicity; Q2W=every 2 weeks.

Weakly informative normal priors are assumed for μ_{1a} and μ_{2a}, with means corresponding to a 50% chance of DLT at avelumab=10 mg/kg, and a doubling in dose leading to a doubling in the odds of the risk of a DLT, respectively. Priors for τ_{1a} and τ_{2a} are assigned such that (1) their medians correspond to moderate between trial heterogeneity, and (2) their uncertainty (95% prior interval) cover plausible between-trial standard deviations[10].

The prior distributions for the model used for deriving the MAP priors are specified in.

Table 24. Prior Distributions for the Parameters of the MAP Model Used to Derive the Prior for the Single-Agent Avelumab Model Parameters

Parameter	Prior distribution
μ_{1a}	N(mean = 0, sd = 2)
μ_{2a}	N(mean = 0, sd=1)
τ_{1a}	log-normal(mean = log(0.25), sd = log(2)/1.96)
τ_{2a}	log-normal(mean = log(0.125), sd = log(2)/1.96)
ρ_a	uniform(-1,1)

Abbreviations: N=normally distributed; sd=standard deviation.

Prior Distribution for the Interaction Parameter

Based on pharmacometrics assessment, no drug-drug interaction is expected between avelumab and bempegaldesleukin (NKTR-214), although uncertainty remains. Based upon this, normal prior for the log-odds multiplier η_{12} is used. The prior is centered on an assumption of no drug-drug interaction, but with appropriate uncertainty that allows for both synergistic and antagonistic toxicity. The prior for $\boldsymbol{\eta_{12}}$ is specified as percentiles of increase in the odds of DLT due to possible interaction in combination therapy at reference doses:

η_{12} is normally distributed, with mean 0 and standard deviation 0.561 (corresponds to no increase in DLT odds at median and 3.0-fold increase in DLTs at 97.5th percentile).

Summary of Prior Distributions

The prior distributions of the model parameters are provided in Table 25. Table 26 illustrates the resulting prior distribution of DLT rate derived from the priors given in Table 25. Based on the available information, the starting dose avelumab = 10 mg/kg and bempegaldesleukin (NKTR-214) = 0.006 mg/kg satisfies the EWOC criterion.

Table 25. Prior Distribution for the Model Parameters

Parameter	Mean	Standard deviations	Correlation
Bempegaldesleukin (NKTR-214) single agent parameters: BVN MAP Prior			
$(\log(\alpha_1), \log(\beta_1))$	-2.612, 0.946	0.932, 1.153	0.056
Avelumab single agent parameters: BVN MAP Prior			
$(\log(\alpha_2), \log(\beta_2))$	-2.67, -0.047	0.972, 0.822	-0.233
Interaction parameter: Normal prior			
η_{12}	0	0.561	

η_{12}: Two-way interaction between bempegaldesleukin (NKTR-214) and avelumab.
Abbreviations: BVN=bivariate normal; MAP=meta-analytic-predictive.

Table 26. Summary of Prior Distribution of Dose Limiting Toxicity Rates for the Doublet Combination of Avelumab in Combination with Bempegaldesleukin (NKTR-214)

Bempegaldesleukin (NKTR-214) dose (mg/kg Q2W IV)	Prior probabilities that DLT rate is in the interval:			Mean	SD	Quantiles		
	[0, 0.16)	[0.16, 0.33)	[0.33,1]			2.5%	50%	97.5%
0.003	0.771	0.192	0.037	0.115	0.093	0.015	0.089	0.369
0.006	0.528	0.335	0.137	0.186	0.132	0.029	0.151	0.529

Avelumab dose fixed at 10 mg/kg every 2 weeks.
Abbreviations: IV=intravenous; mg/kg=milligrams per kilogram; Q2W=every 2 weeks; DLT=dose limiting toxicity; SD=Standard Deviation.

Hypothetical on-Study Data Scenarios

To illustrate the performance of the Bayesian model used to guide dose finding, hypothetical dose finding scenarios following the provisional dose levels specified in the protocol are displayed. In each case, the possible recommended dose that can be used in the next cohort of participants is shown. These recommended doses are determined using the model-based assessment of the risk of DLT in future participants, EWOC criteria and maximum amount of escalation allows (100% of current dose). In practice, the dose recommended by the adaptive Bayesian logistic model may be regarded as guidance. The final recommendation will be based on overall safety profile and PK data.

Table 27 shows some hypothetical dose escalation data scenarios for Combination A and the corresponding recommendations for the next dose. For example, in Scenario 1, if no DLT is observed among 3 DLT-evaluable participants at the starting dose, the recommendation is to remain at the same dose level with probability of overdosing of 0.044. Note that the starting dose is already the maximum possible dose for Combination A. In Scenario 3, if 2 participants experience a DLT out of 3 DLT-evaluable participants at the starting dose, the recommendation is to de-escalate the dose of bempegaldesleukin (NKTR-214) to 0.003 mg/kg with avelumab remaining at 10 mg/kg; this lower dose combination has a probability of overdosing of 0.139. Scenarios 1 through 7 show clinically plausible next dose recommendations.

Table 27. Combination A: Data Scenarios, Next Dose Recommendation, and the Interval Probability of Target Toxicity and Overdosing at Next Dose.

	Dose Evaluated			D/N*	Next Dose (ND)			Pr(TT) at ND	Pr(OD) at ND
Scenarios	Ave (mg/kg IV Q2W)	NKTR (mg/kg IV Q2W)			Ave (mg/kg IV Q2W)	NKTR (mg/kg IV Q2W)			
1	(10)	0.006		0/3	(10)	0.006		0.265	0.044
2	(10)	0.006		1/3	(10)	0.006		0.435	0.179
3	(10)	0.006		2/3	(10)	0.003		0.378	0.139
4	(10)	0.006		2/6	(10)	0.006		0.518	0.210
5	(10)	0.006		3/6	(10)	0.003		0.418	0.121
6	(10) (10)	0.006 0.003		3/6 1/3	(10)	0.003		0.518	0.164
7	(10)	0.006		1/6 0/3	(10)	0.006		0.309	0.027

Abbreviations: Ave=avelumab; NKTR=bempegaldesleukin (NKTR-214); *D=number of participants with DLT, N=number of DLT-evaluable participants; IV=intravenous; mg/kg=milligrams per kilogram; ND=next dose; Pr(TT)=probability of target toxicity; Pr(OD)=probability of overdosing; Q2W=every 2 weeks.

Operating Characteristics

A simulation study is used to illustrate the properties of the dose finding model guided by BLRM. Several example scenarios were investigated and in each scenario 1000 trials were simulated.

Simulation Scenarios

Several scenarios are considered for Combination A (Table 28). Scenario 1 represents the case when the distribution of DLT coincides with prior, ie, the true DLT probability equals to mean of prior DLT. Scenarios 2-3 represent an increase in DLT rate compared to Scenario 1.

Table 28. Combination A: Dose Limiting Toxicity Rate Scenarios (Fixed Avelumab Dose 10 mg/kg every 2 Weeks)

Ture DLT rate scenarios	Bempegaldesleukin (NKTR-214) mg/kg Q2W IV	
	0.003	**0.006**
1. Prior means	0.115	0.186
2. 25% more toxic than prior means	0.144	0.232
3. Higher dose is overly toxic	0.250	0.500

Abbreviations: IV=intravenous; mg/kg=milligrams per kilogram; Q2W=every 2 weeks

Simulation Details

Simulations were performed using R version 3.5.3 (The R-project for Statistical Computing. https://www.r-project.org/), and JAGS 4.8 to perform the MCMC analyses.

For each scenario, data for 1000 trials were generated, with a cohort size of 3-6. At any time during the course of dose finding, escalation to doses where the risk of overdose exceeds 25% is not permitted. The 'next dose recommendation' is the dose with maximum probability of overdose among all dose levels that meet the EWOC criteria.

For Combination A, the starting dose was avelumab 10 mg/kg and bempegaldesleukin (NKTR-214) 0.006 mg/kg. The maximum number of participants per trial was set to 30. The trial was stopped when the following criteria were met:

- At least 6 participants have been treated at the recommended MTD $\tilde{d}$.
- The dose $\tilde{d}$ satisfies one of the following conditions:
    - The probability of target toxicity at dose $\tilde{d}$ exceeds 50%, ie, $\Pr(0.16 \leq \pi_{\tilde{d}} < 0.33) \geq 50\%$;
    - A minimum of 9 participants have been treated in the trial;

The following metrics were assessed in the simulations:

- Percentage of participants receiving dose combination(s) in the target toxicity interval;
- Percentage of participants receiving an overdose;
- Percentage of participants receiving an under dose;
- Probability that recommended MTD at the end of the trial is in the target toxicity interval;
- Probability that recommended MTD is an overdose;
- Probability that recommended MTD is an under dose;
- Percentage of trials stopped without MTD declaration;
- Average sample size.

Simulation Results

Operating characteristics for Combination A are presented in Table 29. The percentage of trials with a correctly identified MTD ranges from 67.3% to 84.4%. The average sample size is 10-11 participants.

Table 29. Combination A: Operating Characteristics

True DLT rate scenarios	% Participant allocation			% declare MTD			% stop (no MTD)	Average sample size
	TT	OD	UD	TT	OD	UD		
1. Prior means	91.1	0	8.9	84.4	0	15.0	0.6	10
2. 25% more toxic than prior means	87.8	0	12.2	78.4	0	20.6	1.0	10
3. Higher dose is overdose	40.7	59.3	0	67.3	9.5	0	23.2	11

Abbreviations: MTD=maximum tolerated dose: OD=overdose; TT=target toxicity; UD=under dose.

Appendix 4. BLRM Design for Talazoparib Triplet - Combination B

This appendix provides the details of the statistical model, the derivation of prior distributions for the single agent model parameters from historical data, the results of the Bayesian analyses and respective dosing decisions for some hypothetical data scenarios, and a simulation study of the operating characteristics of the model for the talazoparib, bempegaldesleukin (NKTR-214), and avelumab triplet combination (Combination B).

In this appendix, the reported avelumab dose is 10 mg/kg. Note that the fixed dose of 800 mg to be investigated in this study is expected to be equivalent to the 10 mg/kg dose.

Statistical Model

The statistical model for Combination B dose-DLT data comprises single-agent toxicity parts, which allow the incorporation of single-agent toxicity data, and interaction parts.

Single Agent Parts

Let $\pi_1(d_1)$ be the risk of DLT for talazoparib given as a single agent at dose d_1; $\pi_2(d_2)$ be the risk of DLT for bempegaldesleukin (NKTR-214) given as a single agent at dose d_2; and $\pi_3(d_3)$ be the risk of DLT for avelumab given as a single agent at dose d_3. These single agent dose-DLT models are logistic:

talazoparib: $$\text{logit}\big(\pi_1(d_1)\big) = \log(\alpha_1) + \beta_1 \log(d_1/d_1^*)$$

bempegaldesleukin (NKTR-214): $$\text{logit}\big(\pi_2(d_2)\big) = \log(\alpha_2) + \beta_2 \log(d_2/d_2^*)$$

avelumab: $$\text{logit}\big(\pi_3(d_3)\big) = \log(\alpha_3) + \beta_3 \log(d_3/d_3^*)$$

where d_1^*=1.0 mg, d_2^* =0.006 mg/kg, and d_3^* =10 mg/kg are used to scale the doses of talazoparib, bempegaldesleukin (NKTR-214), and avelumab, respectively. Hence, α_1, α_2, and α_3 (all >0) are the single-agent odds of a DLT at d_1^* mg, d_2^* mg/kg, and d_3^* mg/kg, respectively; and β_1, β_2, and β_3(all >0) are the increase in the log-odds of a DLT by a unit increase in log-dose.

Interaction Parts

Under an assumption that there is no interaction, the risk of a DLT at dose d_1 of talazoparib, dose d_2 of bempegaldesleukin (NKTR-214), and dose d_3 of avelumab is:

$$\pi_{123}^0(d_1, d_2, d_3) = 1 - \big(1 - \pi_1(d_1)\big)\big(1 - \pi_2(d_2)\big)\big(1 - \pi_3(d_3)\big)$$

To model the interaction between talazoparib, bempegaldesleukin (NKTR-214), and avelumab, the following four odds multipliers are introduced.

- η_{12}: Two-way interaction between talazoparib and bempegaldesleukin (NKTR-214)
- η_{13}: Two-way interaction between talazoparib and avelumab

- η_{23}: Two-way interaction between bempegaldesleukin (NKTR-214) and avelumab
- η_{123}: Three-way interaction among talazoparib, bempegaldesleukin (NKTR-214), and avelumab

The risk of DLT for combination dose (d_1, d_2, d_3) is then given by:

$$\text{odds}\left(\pi_{123}(d_1,d_2,d_3)\right) = g(\eta_{12},\eta_{13},\eta_{23},\eta_{123}) \times \text{odds}\left(\pi^0_{123}(d_1,d_2,d_3)\right)$$

$$\begin{aligned} g(\eta_{12},\eta_{13},\eta_{23},\eta_{123}) = \; & \exp(\eta_{12} \times d_1/d_1^* \times d_2/d_2^*) \\ & \times \exp(\eta_{13} \times d_1/d_1^* \times d_3/d_3^*) \\ & \times \exp(\eta_{23} \times d_2/d_2^* \times d_3/d_3^*) \\ & \times \exp(\eta_{123} \times d_1/d_1^* \times d_2/d_2^* \times d_3/d_3^*) \end{aligned}$$

where $\text{odds}(\pi) = \pi/(1-\pi)$; η_{ij} is the log-odds ratio between the interaction and no interaction model at the reference doses of drug *i* and *j* and a zero dose of the third drug. For example, η_{23} is the log-odds ratio between the interaction and no interaction model at avelumab = 10 mg/kg, bempegaldesleukin (NKTR-214) = 0.006 mg/kg, and talazoparib=0 mg. Therefore, $\eta_{12} + \eta_{13} + \eta_{23} + \eta_{123}$ is the log-odds ratio between the interaction and no interaction model at the reference doses for all three drugs. Here $\eta = 0$ corresponds to no interaction, with $\eta > 0$ and $\eta < 0$ representing synergistic and antagonistic toxicity, respectively.

Inclusion of the Doublet Data

Based on the preliminary data from the Phase 1b portion of study B9991025, a total 12 participants were enrolled at the starting dose level of 800 mg avelumab Q2W in combination with talazoparib at 1.0 mg once daily. All 12 participants were DLT-evaluable with a DLT rate of 3/12. This information from study B9991025 was incorporated in the assessment of prior distribution of DLT, starting dose, data scenarios, and simulations of Combination B via a direct down-weighting approach. The weight was calculated using the formula below assuming substantial heterogeneity between the populations included in the avelumab + talazoparib doublet and Combination B in terms of DLT;

$$w = \frac{1}{1 + \frac{2\tau^2}{\sigma^2} N}$$

where, N= Total number of participants enrolled in the B9991025 avelumab + talazoparib doublet combination (N=12)

σ = population standard deviation (σ =2)

τ = heterogeneity between populations in the B9991025 doublet and triplet (τ =0.5)

The on-study bempegaldesleukin (NKTR-214) and avelumab doublet DLT data was also utilized in the assessment of starting dose and data scenarios of Combination B via a direct down-weighting approach, assuming a moderate heterogeneity between the populations included in this on-trial doublet and Combination B in terms of DLT. The weight was calculated using the down-weighting formula shown above with (σ =2) and (τ = 0.25).

The on-study bempegaldesleukin (NKTR-214) and avelumab doublet DLT data was not considered in the simulations.

Prior Specifications

The Bayesian approach requires the specification of prior distributions for all model parameters, which include the single agent parameters $\log(\alpha_1)$, $\log(\beta_1)$ for talazoparib, $\log(\alpha_2)$, $\log(\beta_2)$ for bempegaldesleukin (NKTR-214), $\log(\alpha_3)$, $\log(\beta_3)$ for avelumab, and the interaction parameters $\eta = (\eta_{12}, \eta_{13}, \eta_{23}, \eta_{123})$. **A meta-analytic-predictive (MAP) approach was used to derive the prior distribution for the single-agent model parameters**.

Prior Distribution for the Logistic Parameters for Single Agent Avelumab and Bempegaldesleukin (NKTR-214)

For derivation of the prior distribution of the logistic parameters for single agent avelumab and single agent bempegaldesleukin (NKTR-214), refer to Appendix 3.

Single Agent Talazoparib

Dose-DLT data from study PRP-001 (C3441007, NCT01286987)[4] presented in Table 30 are used to derive the prior of the single agent logistic parameters for talazoparib.

Table 30. Historical Dose Limiting Toxicity data from Study PRP-001

Talazoparib dose (mg QD)	Number of Patients	Number of Patients with DLTs
0.025	3	0
0.05	3	0
0.1	3	0
0.2	3	0
0.4	3	0
0.6	6	0
0.9	6	1
1.0	6	0
1.1	6	2

Abbreviations: DLT=dose limiting toxicity; mg=milligrams; QD=once daily.

Weakly informative normal priors are assumed for μ_{1t} and μ_{2t}, with means corresponding to a 50% chance of DLT at talazoparib=1.0 mg, and a doubling in dose leading to a doubling in the odds of the risk of a DLT, respectively. Priors for τ_{1t} and τ_{2t} are assigned such that (1)

their medians correspond to moderate between trial heterogeneity, and (2) their uncertainty (95% prior interval) cover plausible between-trial standard deviations.

Table 31. Prior Distributions for the Parameters of the MAP Model Used to Derive the Prior for the Single-Agent Talazoparib Model Parameters

Parameter	Prior distribution
μ_{1t}	N(mean = 0, sd = 2)
μ_{2t}	N(mean = 0, sd=1)
τ_{1t}	log-normal(mean = log(0.25), sd = log(2)/1.96)
τ_{2t}	log-normal(mean = log(0.125), sd = log(2)/1.96)
ρ_t	uniform(-1,1)

Abbreviations: N=normally distributed; sd=standard deviation.

Prior Distribution for the Interaction Parameters

Normal priors for the log-odds multipliers $\eta_{12}, \eta_{13}, \eta_{23}, \eta_{123}$ are used. The prior for $\eta_{12}, \eta_{13}, \eta_{23}, \eta_{123}$ are specified as percentiles of increase in the odds of DLT due to possible interaction in combination therapy at reference doses:

- η_{12} is normally distributed, with mean 0.095 and standard deviation 0.305 (corresponds to 10% increase in DLT odds at median and 2.0 fold increase in DLTs at 97.5th percentile)
- η_{13} is normally distributed, with mean 0.095 and standard deviation 0.305 (corresponds to 10% increase in DLT odds at median and 2.0 fold increase in DLTs at 97.5th percentile)
- η_{23} is normally distributed, with mean 0 and standard deviation 0.561 (corresponds to no increase in DLT odds at median and 3.0 fold increase in DLTs at 97.5th percentile)
- η_{123} is normally distributed, with mean 0 and standard deviation 0.093 (corresponds to no increase in DLT odds at median and 1.20 fold increase in DLTs at 97.5th percentile).

η_{12}: Two-way interaction between talazoparib and bempegaldesleukin (NKTR-214);
η_{13}: Two-way interaction between talazoparib and avelumab;
η_{23}: Two-way interaction between bempegaldesleukin (NKTR-214) and avelumab;
η_{123}: Three-way interaction between talazoparib, bempegaldesleukin (NKTR-214) and avelumab.

Summary of Prior Distributions

The prior distributions of the model parameters are provided in Table 32.

Table 32. Prior Distribution for the Model Parameters

Parameter	Mean	Standard deviations	Correlation
Talazoparib single agent parameters: BVN MAP Prior			
$(\log(\alpha_1), \log(\beta_1))$	-1.770, 0.651	0.720, 0.890	0.188
Bempegaldesleukin (NKTR-214) single agent parameters: BVN MAP Prior			
$(\log(\alpha_2), \log(\beta_2))$	-2.612, 0.946	0.932, 1.153	0.056
Avelumab single agent parameters: BVN MAP Prior			
$(\log(\alpha_3), \log(\beta_3))$	-2.672, -0.047	0.972, 0.822	-0.233
Interaction parameters: Normal prior			
η_{12}	0.095	0.305	
η_{13}	0.095	0.305	
η_{23}	0	0.561	
η_{123}	0	0.093	

η_{12}: Two-way interaction between talazoparib and bempegaldesleukin (NKTR-214);
η_{13}: Two-way interaction between talazoparib and avelumab;
η_{23}: Two-way interaction between bempegaldesleukin (NKTR-214) and avelumab;
η_{123}: Three-way interaction between talazoparib, bempegaldesleukin (NKTR-214) and avelumab.
Abbreviations: BVN=bivariate normal; MAP=meta-analytic-predictive.

From Table 33, in absence of the B9991025 avelumab + talazoparib doublet data and the on-trial avelumab + bempegaldesleukin (NKTR-214) data, the dose levels of avelumab= 10 mg/kg, bempegaldesleukin (NKTR-214) = 0.003 mg/kg and talazoparib= 0.75 mg or talazoparib= 0.50 mg are acceptable starting doses for Combination B. However, the final starting dose for Combination B will be determined after the dose-DLT data for the on-trial doublet is available.

Table 33. Summary of Prior Distribution of DLT Rates for the Triplet Combination of Avelumab in Combination with Bempegaldesleukin (NKTR-214) and Talazoparib

NKTR dose (mg/kg Q2W)	Tala dose (mg QD)	Prior probabilities that DLT rate is in the interval:			Mean	SD	Quantiles		
		[0, 0.16)	[0.16, 0.33)	[0.33,1]			2.5%	50%	97.5%
0.003	0.5	0.547	0.359	0.094	0.173	0.111	0.031	0.148	0.454
0.003	0.75	0.379	0.450	0.171	0.218	0.123	0.049	0.194	0.520
0.003	1.0	0.187	0.457	0.356	0.294	0.145	0.078	0.271	0.627
0.006	0.5	0.344	0.403	0.253	0.246	0.151	0.045	0.214	0.617
0.006	0.75	0.243	0.400	0.357	0.292	0.165	0.058	0.262	0.677
0.006	1.0	0.139	0.341	0.521	0.364	0.185	0.079	0.341	0.761

Avelumab dose fixed at 10 mg/kg every 2 weeks.
Abbreviations: mg=milligrams; mg/kg=milligrams per kilogram; Q2W= Every 2 weeks; NKTR= bempegaldesleukin (NKTR-214); QD=once daily; SD=Standard Deviation; Tala=Talazoparib

Hypothetical on-Study Data Scenarios

To illustrate the performance of the Bayesian model used to guide dose finding, hypothetical dose finding scenarios following the provisional dose levels specified in the protocol are displayed. In each case, the possible recommended dose that can be used in the next group of participants is shown. These recommended doses are determined using the model-based assessment of the risk of DLT in future participants, EWOC criteria and maximum amount of escalation allows (100% of current dose). In practice, the dose recommended by the adaptive Bayesian logistic model may be regarded as guidance. The final recommendation will be based on overall safety profile and PK data.

Table 34 shows the plausible starting dose level(s) for Combination B given hypothetical data from the on-study bempegaldesleukin (NKTR-214) and avelumab doublet (Combination A). If the dose-DLT profile of Combination A is safe at avelumab= 10 mg/kg, bempegaldesleukin (NKTR-214) = 0.006 mg/kg (Scenario 1), triplet dose escalation can begin at avelumab= 10 mg/kg, bempegaldesleukin (NKTR-214) = 0.006 mg and talazoparib= 0.75 mg, or avelumab= 10 mg/kg, bempegaldesleukin (NKTR-214) = 0.003 mg and talazoparib= 1.0 mg. If 2 participants with DLT observed out of 12 DLT-evaluable participants at avelumab= 10 mg/kg, bempegaldesleukin (NKTR-214) = 0.006 mg/kg (Scenario 2), the starting dose can be avelumab= 10 mg/kg, bempegaldesleukin (NKTR-214) = 0.006 mg/kg and talazoparib= 0.5 mg or avelumab= 10 mg/kg, bempegaldesleukin (NKTR-214) = 0.003 mg/kg and talazoparib= 0.75 mg. All other scenarios (3, 4, and 5) are plausible starting doses for Combination B.

Table 34. Combination B: Clinically Meaningful Starting Dose Given Hypothetical Data from the Combination A, and the Interval Probability of Target Toxicity and Overdosing at Starting Dose.

Scenarios	Doublet Dose			D/N*	Triplet starting dose (SD)			Pr(TT) at SD	Pr(OD) at SD
	Ave (mg/kg Q2W)	NKTR (mg/kg Q2W)	Tala (mg QD)		Ave (mg/kg Q2W)	NKTR(mg/kg Q2W)	Tala (mg QD)		
1	(10)	0.006	-	0/9	(10) (10)	0.006 0.003	0.75 1.0	0.443 0.553	0.137 0.196
2	(10)	0.006	-	2/12	(10) (10)	0.006 0.003	0.50 0.75	0.517 0.534	0.175 0.107
3	(10)	0.006	-	3/12	(10)	0.003	0.75	0.567	0.160
4	(10) (10)	0.006 0.003	-	2/4 1/12	(10)	0.003	0.75	0.569	0.155
5	(10) (10)	0.006 0.003	-	2/4 3/12	(10)	0.003	0.50	0.607	0.187

Abbreviations: Ave=avelumab; NKTR= bempegaldesleukin (NKTR-214); *D=number of participants with DLT; N=number of DLT-evaluable participants; mg=milligrams; mg/kg=milligrams per kilogram; ND=next dose; Pr(TT)=probability of target toxicity; Pr(OD)=probability of overdosing; Tala= Talazoparib; QD=once daily; Q2W=every 2 weeks.

Table 35 shows data scenarios for Combination B and the corresponding recommendations for the next dose. The recommended next dose is adequate for all considered scenarios.

Table 35. Combination B: Data Scenarios (Given Hypothetical Combination A Data), Next Dose Recommendation, and the Interval Probability of Target Toxicity and Overdosing at Next Dose.

Scenarios	Dose evaluated			D/N*	Next Dose (ND)			Pr(TT) at ND	Pr(OD) at ND
	Ave (mg/kg Q2W)	NKTR (mg/kg Q2W)	Tala (mg QD)		Ave (mg/kg Q2W)	NKTR (mg/kg Q2W)	Tala (mg QD)		
1	(10) (10)	0.006 0.006	- 0.75	0/9 0/3	(10)	0.006	1.0	0.477	0.190
2	(10) (10)	0.006 0.006	- 0.75	0/9 1/3	(10)	0.006	0.75	0.527	0.171
3	(10) (10)	0.006 0.006	- 0.75	0/9 2/3	(10) (10)	0.006 0.003	0.50 0.75	0.554 0.601	0.189 0.150
4	(10) (10)	0.006 0.006	- 0.75	0/9 3/3	(10)	0.003	0.50	0.564	0.111
5	(10) (10)	0.006 0.003	- 0.75	3/12 0/3	(10) (10)	0.006 0.003	0.50 0.75	0.553 0.530	0.197 0.075
6	(10) (10)	0.006 0.003	- 0.75	3/12 1/3	(10)	0.003	0.75	0.617	0.186
7	(10) (10)	0.006 0.003	- 0.75	3/12 2/3	(10)	0.003	0.50	0.618	0.177

Abbreviations: Ave=avelumab; NKTR= bempegaldesleukin (NKTR-214); *D=number of participants with DLT; N=number of DLT-evaluable participants; mg=milligrams; mg/kg=milligrams per kilogram; ND=next dose Pr(TT)=probability of target toxicity; Pr(OD)=probability of overdosing; QD=once daily; Q2W=every 2 weeks; Tala=Talazoparib.

Operating Characteristics

A simulation study is used to illustrate the properties of the dose finding model guided by BLRM. Several example scenarios were investigated and each scenario 1000 trials were simulated, with results summarized below.

Simulation Scenarios

Several scenarios are considered for Combination B (Table 36). Scenario 1 represents the case when the distribution of DLT coincides with prior, ie, the true DLT probability equals to mean of prior DLT. Scenario 2 represents an increased DLT rate compared to Scenario 1. Scenario 3 represents a true toxicity profile with dose combinations in both under-dose and over-dose regions.

Table 36. Combination B: Dose Limiting Toxicity Rate Scenarios (Fixed Avelumab Dose 10 mg/kg Every 2 Weeks)

NKTR-214 (mg/kg Q2W)	Talazoparib (mg QD)					
	0.5	0.75	1.0	0.5	0.75	1.0
	Scenario 1. prior means			Scenario 2. 50% more toxic than prior means		
0.003	0.173	0.218	0.294	0.259	0.327	0.441
0.006	0.246	0.292	0.364	0.370	0.438	0.545
	Scenario 3. With under dose and overdose					
0.003	0.10	0.20	0.45			
0.006	0.15	0.30	0.55			

Abbreviations: mg/kg=milligrams per kilogram; QD=once daily; Q2W=every 2 weeks.

Simulation Details

Simulations were performed using R version 3.5.3 (The R-project for Statistical Computing. https://www.r-project.org/), and JAGS 4.8 to perform the Markov Chain Monte Carlo (MCMC) analyses.

For each scenario, data for 1000 trials were generated, with a cohort size of 3-6. At any time during the course of dose finding, escalation to doses where the risk of overdose exceeds 25% is not permitted. The 'next dose recommendation' is the dose with maximum probability of overdose among all dose levels that meet the EWOC criteria.

A simulation of Combination B is performed using the starting dose of avelumab 10 mg/kg, bempegaldesleukin (NKTR-214) 0.003 mg/kg, and talazoparib 0.5 mg. B9991025 doublet data is considered in this exercise. The maximum number of participants per trial was set to 60. Each trial was stopped when the following criteria were met:

- At least 6 participants have been treated at the recommended MTD $\tilde{d}$.
- The dose $\tilde{d}$ satisfies one of the following conditions:
    - The probability of target toxicity at dose $\tilde{d}$ exceeds 50%, ie, $\Pr(0.16 \leq \pi_{\tilde{d}} < 0.33) \geq 50\%$;
    - A minimum of 15 participants have been treated in the trial.

The following metrics were assessed in the simulations:

- Percentage of participants receiving dose combination(s) in the target toxicity interval;
- Percentage of participants receiving an overdose;

- Percentage of participants receiving an under dose;
- Probability that recommended MTD at the end of the trial is in the target toxicity interval;
- Probability that recommended MTD is an overdose;
- Probability that recommended MTD is an under dose;
- Percentage of trials stopped without MTD declaration;
- Average sample size.

Simulation Results

Operating characteristics for Combination B are presented in Table 37. The percentage of trials with a correctly identified MTD ranges from 61.2% to 95.1%. The percentage of participants treated at overly toxic doses is well controlled. The average sample size is between 10 to 14 participants.

Table 37. Combination B: Operating Characteristics

True DLT rate scenarios	% Participant allocation			% declare MTD			% stop (no MTD)	Average sample size
	TT	OD	UD	TT	OD	UD		
1. Prior means	100	0	0	95.1	0	0	4.9	13
2. 50% more toxic than prior means	91.6	8.4	0	89.5	0	0	10.5	10
3. With under dose and overdose	46.4	6.0	47.6	61.2	0	37.3	1.5	14

Abbreviations: MTD=maximum tolerated dose; OD=overdose; TT=target toxicity; UD=under dose.

Appendix 5. BLRM Design for Enzalutamide Triplet – Combination C

This appendix provides the details of the statistical model, the derivation of prior distributions for the single agent model parameters from historical data, the results of the Bayesian analyses and respective dosing decisions for some hypothetical data scenarios, and a simulation study of the operating characteristics of the model for the enzalutamide +bempegaldesleukin (NKTR-214) + avelumab treatment combination (Combination C).

In this appendix, the reported avelumab dose is 10 mg/kg. Note that the fixed dose of 800 mg to be investigated in this study is expected to be equivalent to the 10 mg/kg dose.

Statistical Model

The statistical model for Combination C dose-DLT data comprises single-agent toxicity parts, which allow the incorporation of single-agent toxicity data, and interaction parts.

Single Agent Parts

Let $\pi_1(d_1)$ be the risk of DLT for enzalutamide given as a single agent at dose d_1; $\pi_2(d_2)$ be the risk of DLT for bempegaldesleukin (NKTR-214) given as a single agent at dose d_2; and $\pi_3(d_3)$ be the risk of DLT for avelumab given as a single agent at dose d_3. These single agent dose-DLT models are logistic:

Enzalutamide: $$\text{logit}\big(\pi_1(d_1)\big) = \log(\alpha_1) + \beta_1 \log(d_1/d_1^*)$$

Bempegaldesleukin (NKTR-214): $$\text{logit}\big(\pi_2(d_2)\big) = \log(\alpha_2) + \beta_2 \log(d_2/d_2^*)$$

Avelumab: $$\text{logit}\big(\pi_3(d_3)\big) = \log(\alpha_3) + \beta_3 \log(d_3/d_3^*)$$

where d_1^*=160 mg, d_2^* =0.006 mg/kg, and d_3^* =10 mg/kg are used to scale the doses of enzalutamide, bempegaldesleukin (NKTR-214), and avelumab, respectively. Hence, α_1, α_2, and α_3 (all >0) are the single-agent odds of a DLT at d_1^* mg, d_2^* mg/kg, and d_3^* mg/kg, respectively; and β_1, β_2, and β_3(all>0) are the increase in the log-odds of a DLT by a unit increase in log-dose.

Interaction Parts

Under an assumption that there is no interaction, the risk of a DLT at dose d_1 of avelumab, dose d_2 of bempegaldesleukin (NKTR-214), and dose d_3 of enzalutamide is:

$$\pi_{123}^0(d_1, d_2, d_3) = 1 - \big(1 - \pi_1(d_1)\big)\big(1 - \pi_2(d_2)\big)\big(1 - \pi_3(d_3)\big)$$

To model the interaction between avelumab, bempegaldesleukin (NKTR-214), and enzalutamide, the following four odds multipliers are introduced.

- η_{12}: Two-way interaction between enzalutamide and bempegaldesleukin (NKTR-214)

- η_{13}: Two-way interaction between enzalutamide and avelumab
- η_{23}: Two-way interaction between bempegaldesleukin (NKTR-214) and avelumab
- η_{123}: Three-way interaction among enzalutamide, bempegaldesleukin (NKTR-214), and avelumab

The risk of DLT for combination dose (d_1, d_2, d_3) is then given by:

$$\text{odds}\left(\pi_{123}(d_1, d_2, d_3)\right) = g(\eta_{12}, \eta_{13}, \eta_{23}, \eta_{123}) \times \text{odds}\left(\pi^0_{123}(d_1, d_2, d_3)\right)$$

$$\begin{aligned} g(\eta_{12}, \eta_{13}, \eta_{23}, \eta_{123}) = \ & \exp(\eta_{12} \times d_1/d_1^* \times d_2/d_2^*) \\ & \times \exp(\eta_{13} \times d_1/d_1^* \times d_3/d_3^*) \\ & \times \exp(\eta_{23} \times d_2/d_2^* \times d_3/d_3^*) \\ & \times \exp(\eta_{123} \times d_1/d_1^* \times d_2/d_2^* \times d_3/d_3^*) \end{aligned}$$

where $\text{odds}(\pi) = \pi/(1-\pi)$; η_{ij} is the log-odds ratio between the interaction and no interaction model at the reference doses of drug i and j and a zero dose of the third drug. For example, η_{23} is the log-odds ratio between the interaction and no interaction model at avelumab = 10 mg/kg, bempegaldesleukin (NKTR-214) = 0.006 mg/kg, and enzalutamide=0 mg. Therefore, $\eta_{12} + \eta_{13} + \eta_{23} + \eta_{123}$ is the log-odds ratio between the interaction and no interaction model at the reference doses for all three drugs. Here $\eta = 0$ corresponds to no interaction, with $\eta > 0$ and $\eta < 0$ representing synergistic and antagonistic toxicity respectively.

Inclusion of the Doublet Data

The addition of the DLT information from the doublet dose escalation of avelumab and bempegaldesleukin (NKTR-214) was included in the assessment of starting dose and data scenario of Combination C using a direct down-weighting approach (for details, please refer to Appendix 4).

Prior Specifications

The Bayesian approach requires the specification of prior distributions for all model parameters, which include the single agent parameters $\log(\alpha_1)$, $\log(\beta_1)$ for enzalutamide, $\log(\alpha_2)$, $\log(\beta_2)$ for bempegaldesleukin (NKTR-214), $\log(\alpha_3)$, $\log(\beta_3)$ for avelumab, and the interaction parameters $\eta = (\eta_{12}, \eta_{13}, \eta_{23}, \eta_{123})$. **A meta-analytic-predictive (MAP) approach was used to derive the prior distribution for the single-agent model parameters**.

Prior Distribution for the Logistic Parameters for Single Agent Avelumab and Bempegaldesleukin (NKTR-214)

For information regarding the prior distribution of the logistic parameters for single agent avelumab and single agent bempegaldesleukin (NKTR-214), refer to Appendix 3.

Single Agent Enzalutamide

Dose-DLT data from Study S-3100-1-01 (for ENZA)[12] presented in Table 38 are used to derive the prior of the single agent logistic parameters for enzalutamide.

Table 38. Historical Dose Limiting Toxicity data from Study S-3100-1-01

Enzalutamide dose (mg)	Number of patients	Number of patients with DLTs
30	3	0
60	27	0
150	28	0
240	29	0
360	28	1
480	22	1
600	3	2

Abbreviations: DLT=dose limiting toxicity; mg=milligram.

Weakly informative normal priors are assumed for μ_{1e} and μ_{2e}, with means corresponding to a 50% chance of DLT at enzalutamide=160 mg, and a doubling in dose leading to a doubling in the odds of the risk of a DLT, respectively. Priors for τ_{1e} and τ_{2e} are assigned such that (1) their medians correspond to moderate between trial heterogeneity, and (2) their uncertainty (95% prior interval) cover plausible between-trial standard deviations.

Table 39. Prior Distributions for the Parameters of the MAP Model Used to Derive the Prior for the Single-Agent Enzalutamide Model Parameters

Parameter	Prior distribution
μ_{1e}	N(mean = 0, sd = 2)
μ_{2e}	N(mean = 0, sd = 1)
τ_{1e}	log-normal(mean = log(0.25), sd = log(2)/1.96)
τ_{2e}	log-normal(mean = log(0.125), sd = log(2)/1.96)
ρ_e	uniform(-1,1)

Abbreviations: N=normally distributed; sd=standard deviation.

Prior Distribution for the Interaction Parameters

Normal priors for the log-odds multipliers $\eta_{12}, \eta_{13}, \eta_{23}, \eta_{123}$ are used. The priors for $\boldsymbol{\eta_{12}, \eta_{13}, \eta_{23}, \eta_{123}}$ are specified as percentiles of increase in the odds of DLT due to possible interaction in combination therapy at reference doses;

- η_{12} is normally distributed, with mean 0.095 and standard deviation 0.519 (corresponds to 10% increase in DLT odds at median and 3.0-fold increase in DLTs at 97.5th percentile).
- η_{13} is normally distributed, with mean 0.095 and standard deviation 0.519 (corresponds to 10% increase in DLT odds at median and 3.0-fold increase in DLTs at 97.5th percentile).
- η_{23} is normally distributed, with mean 0 and standard deviation 0.561 (corresponds to no increase in DLT odds at median and 3.0-fold increase in DLTs at 97.5th percentile).
- η_{123} is normally distributed, with mean 0 and standard deviation 0.354 (corresponds to no increase in DLT odds at median and 2.0-fold increase in DLTs at 97.5th percentile).

- η_{12}: Two-way interaction between enzalutamide and bempegaldesleukin (NKTR-214);
- η_{13}: Two-way interaction between avelumab and enzalutamide;
- η_{23}: Two-way interaction between bempegaldesleukin (NKTR-214) and avelumab;
- η_{123}: Three-way interaction between avelumab, bempegaldesleukin (NKTR-214) and enzalutamide

Summary of Prior Distributions

The prior distributions of the model parameters are provided in Table 40.

Table 40. Prior Distribution for the Model Parameters

Parameter	Mean	Standard deviations	Correlation
Enzalutamide single agent parameters: BVN MAP Prior			
$(\log(\alpha_1), \log(\beta_1))$	-4.299, 0.359	0.917, 0.657	-0.619
Bempegaldesleukin (NKTR-214) single agent parameters: BVN MAP Prior			
$(\log(\alpha_2), \log(\beta_2))$	-2.612, 0.946	0.932, 1.153	0.056
Avelumab single agent parameters: BVN MAP Prior			
$(\log(\alpha_3), \log(\beta_3))$	-2.672,-0.047	0.972, 0.822	-0.233
Interaction parameters: Normal prior			
η_{12}	0.095	0.519	
η_{13}	0.095	0.519	
η_{23}	0	0.561	
η_{123}	0	0.354	

η_{12}: Two-way interaction between enzalutamide and bempegaldesleukin (NKTR-214);
η_{13}: Two-way interaction between avelumab and enzalutamide;
η_{23}: Two-way interaction between bempegaldesleukin (NKTR-214) and avelumab;
η_{123}: Three-way interaction between avelumab, bempegaldesleukin (NKTR-214) and enzalutamide.
Abbreviations: BVN=bivariate normal; MAP=meta-analytic-predictive.

From Table 41, in absence of avelumab + bempegaldesleukin (NKTR-214) doublet data, all 6 but the highest potential dose levels of Combination C are acceptable starting doses. However, the final starting dose for this triplet will be determined after the dose-DLT data for the avelumab + bempegaldesleukin (NKTR-214) doublet is available.

Table 41. Summary of Prior Distribution of DLT Rates for the Triplet Combination of Enzalutamide in Combination with Bempegaldesleukin (NKTR-214) and Avelumab (Combination C)

NKTR dose (mg/kg Q2W)	Enza dose (mg once daily)	Prior probabilities that DLT rate is in the interval:			Mean	SD	Quantiles		
		[0, 0.16)	[0.16, 0.33)	[0.33,1]			2.5%	50%	97.5%
0.003	80	0.705	0.237	0.058	0.134	0.105	0.019	0.104	0.417
0.003	120	0.665	0.257	0.078	0.146	0.116	0.020	0.113	0.458
0.003	160	0.620	0.273	0.107	0.161	0.130	0.019	0.123	0.511
0.006	80	0.461	0.345	0.194	0.213	0.152	0.030	0.173	0.602
0.006	120	0.434	0.329	0.237	0.230	0.169	0.028	0.185	0.660
0.006	160	0.412	0.305	0.283	0.250	0.191	0.024	0.199	0.724

Avelumab dose fixed at 10 mg/kg every 2 weeks.
Abbreviations: DLT=dose-limiting toxicity; mg/kg=milligrams per kilogram; Q2W=twice a week; NKTR=Bempegaldesleukin (NKTR-214); SD=Standard Deviation; Enza=Enzalutamide

Hypothetical on-Study Data Scenarios

To illustrate the performance of the Bayesian model used to guide dose finding, hypothetical dose finding scenarios following the provisional dose levels specified in the protocol are displayed. In each case, the possible recommended dose(s) that can be used in the next cohort of participants is shown. These recommended doses are determined using the model-based assessment of the risk of DLT in future participants, EWOC criteria and maximum amount of escalation allows (100% of current dose). In practice, the dose recommended by the adaptive Bayesian logistic model may be regarded as guidance. The final recommendation will be based on overall safety profile, PK data and other relevant evidence.

Table 42 shows the plausible starting dose level(s) for Combination C given hypothetical data in the doublet combination. If the dose-DLT profile of the doublet is safe at avelumab = 10 mg/kg, bempegaldesleukin (NKTR-214) = 0.006 mg/kg (Scenario 1), triplet dose escalation can begin at avelumab = 10 mg/kg, bempegaldesleukin (NKTR-214) = 0.006 mg/kg and enzalutamide = 160 mg. If moderate DLT is observed in the dual combination (3participants with DLT out of 12 DLT-evaluable participants at avelumab = 10 mg/kg, bempegaldesleukin (NKTR-214) = 0.006 mg/kg, Scenario 3), the starting dose can be avelumab = 10 mg/kg, bempegaldesleukin (NKTR-214) = 0.006 mg/kg and enzalutamide = 80 mg, or avelumab = 10 mg/kg, bempegaldesleukin (NKTR-214) = 0.003 mg/kg and enzalutamide = 160 mg. Scenarios 4 and 5 also show plausible starting triplet dose levels.

Table 42. Combination C: Clinically Meaningful Starting Dose Given Hypothetical Data from the Doublet Combination, and the Interval Probability of Target Toxicity and Overdosing at Starting Dose.

Scenarios	Doublet Dose			D/N*	Triplet Starting Dose (SD)			Pr(TT) at ND	Pr (OD) at ND
	Ave mg/kg (Q2W)	NKTR mg/kg (Q2W)	Enza (mg QD)		Ave mg/kg (Q2W)	NKTR mg/kg (Q2W)	Enza (mg QD)		
1	(10)	0.006	-	0/9	(10) (10)	0.006 0.006	160 120	0.268 0.262	0.118 0.071
2	(10)	0.006	-	2/12	(10)	0.006	120	0.393	0.188
3	(10)	0.006	-	3/12	(10) (10)	0.006 0.003	80 160	0.479 0.340	0.222 0.119
4	(10) (10)	0.006 0.003	-	2/4 1/12	(10)	0.003	160	0.343	0.105
5	(10) (10)	0.006 0.003	-	2/4 3/12	(10) (10)	0.003 0.003	120 80	0.475 0.507	0.195 0.145

Abbreviations: Ave=avelumab; NKTR=Bempegaldesleukin (NKTR-214); *D=number of participants with DLT, N=number of DLT-evaluable participants; mg=milligram; mg/kg=milligram per kilogram; ND=next dose; Pr(TT)=probability of target toxicity; Pr(OD)=probability of overdosing; Enza= Enzalutamide; Q2W=every 2 weeks; QD=once daily.

Table 43 shows some data scenarios for Combination C and the corresponding recommendations for the next dose.

Table 43. Combination C: Data Scenarios (Given Hypothetical Doublet Data), Next Dose Recommendation, and the Interval Probability of Target Toxicity and Overdosing at Next Dose.

	Dose evaluated			**D/N***	**Next Dose (ND)**			**Pr(TT) at ND**	**Pr(OD) at ND**
Scenarios	Ave (mg/kg Q2W)	NKTR (mg/kg Q2W)	Enza (mg once daily)		Ave (mg/kg Q2W)	NKTR (mg/kg Q2W)	Enza (mg once daily)		
1	(10) (10)	0.006 0.006	- 120	0/9 0/3	(10)	0.006	160	0.213	0.047
2	(10) (10)	0.006 0.006	- 120	0/9 1/3	(10) (10)	0.006 0.006	160 120	0.378 0.393	0.186 0.109
3	(10) (10)	0.006 0.006	- 120	0/9 2/3	(10) (10)	0.006 0.003	80 160	0.524 0.414	0.188 0.139
4	(10) (10)	0.006 0.006	- 120	0/9 3/3	(10)	0.003	120	0.476	0.186
5	(10) (10)	0.006 0.003	- 120	3/12 0/3	(10) (10)	0.006 0.006	120 160	0.426 0.374	0.196 0.249
6	(10) (10)	0.006 0.006	- 120	3/12 1/3	(10) (10)	0.003 0.003	160 120	0.441 0.453	0.171 0.112
7	(10) (10)	0.006 0.003	- 120	3/12 2/3	(10)	0.003	80	0.560	0.203

Abbreviations: Ave=avelumab; mg=milligrams; mg/kg=milligrams per kilogram; NKTR=bempegaldesleukin (NKTR-214); *D=number of participants with DLT; N=number of DLT-evaluable participants; ND=next dose Pr(TT)=probability of target toxicity; Pr(OD)=probability of overdosing; Q2W=every 2 weeks; Enza=enzalutamide.

Operating Characteristics

A simulation study is used to illustrate the properties of the dose finding model guided by BLRM. Several example scenarios were investigated and in each scenario 1000 trials were simulated.

Simulation Scenarios

Several scenarios are considered for Combination C (Table 44). Scenario 1 represents the case when the distribution of DLT coincides with prior, ie, the true DLT probability equals to mean of prior DLT. Scenario 2 represents a 50% increased DLT rate compared to Scenario 1. Scenario 3 represents a true toxicity profile with dose combinations in both under-toxicity and over-toxicity intervals.

Table 44. Combination C: Dose Limiting Toxicity Rate Scenarios (Fixed Avelumab Dose 10 mg/kg Every 2 Weeks)

Bempegaldesleukin (NKTR-214) (mg/kg Q2W)	Enzalutamide (mg once daily)					
	80	120	160	80	120	160
	Scenario 1. prior means			Scenario 2. 50% more toxic than prior means		
0.003	0.134	0.146	0.161	0.201	0.219	0.241
0.006	0.213	0.230	0.250	0.319	0.345	0.376
	Scenario 3. With under and over toxicity					
0.003	0.10	0.20	0.30			
0.006	0.15	0.25	0.40			

Abbreviations: Q2W=every 2 weeks; mg=milligrams; mg/kg=milligrams per kilogram.

Simulation Details

Simulations were performed using R version 3.5.3 (The R-project for Statistical Computing. https://www.r-project.org/), and JAGS 4.8 to perform the MCMC analyses.

For each scenario, data for 1000 trials were generated, with a cohort size of 3-6. At any time during the course of dose finding, escalation to doses where the risk of overdose exceeds 25% is not permitted. The 'next dose recommendation' is the dose with maximum probability of overdose among all dose levels that meet the EWOC criteria.

A simulation of the triplet combination is performed using the starting dose of avelumab 10 mg/kg (fixed), bempegaldesleukin (NKTR-214) 0.003 mg/kg, and enzalutamide 80 mg. No doublet combination data is considered in this exercise. The maximum number of participants per trial was set to 60. Each trial was stopped when the following criteria were met:

- At least 6 participants have been treated at the recommended MTD $\tilde{d}$.

- The dose $\tilde{d}$ satisfies one of the following conditions:
  - The probability of target toxicity at dose $\tilde{d}$ exceeds 50%, ie, $Pr(0.16 \leq \pi_{\tilde{d}} < 0.33) \geq 50\%$;
  - A minimum of 15 participants have been treated in the trial.

The following metrics were assessed in the simulations:

- Percentage of participants receiving dose combination(s) in the target toxicity interval;
- Percentage of participants receiving an overdose;
- Percentage of participants receiving an underdose;
- Probability that recommended MTD at the end of the trial is in the target toxicity interval;
- Probability that recommended MTD is an overdose;
- Probability that recommended MTD is an underdose;
- Percentage of trials stopped without MTD declaration;
- Average sample size.

Simulation Results

Operating characteristics for Combination C are presented in Table 45. The percentage of trials with a correctly identified MTD ranges from 86.3% to 94.5%. The percentage of participants treated at overly toxic doses is well controlled. The average sample size for this triplet combination is between 11 to 14 participants.

Table 45. Combination C: Operating Characteristics

True DLT rate scenarios	% Participant allocation			% declare MTD			% Stop (no MTD)	Average sample size
	TT	OD	UD	TT	OD	UD		
1. Prior means	64.5	0	35.5	89.9	0	3.4	7.0	14
2. 50% more toxic than prior means	89.4	10.6	0	86.3	0	0	13.7	11
3.With under dose and overdose	46.9	15.4	37.7	94.5	0	1.6	3.9	12

Abbreviations: MTD=maximum tolerated dose; OD=overdose; TT=target toxicity; UD=under dose