Title Page

Protocol Title: 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

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Short Title: JAVELIN IL-2 Medley

Acronym: not applicable

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Protocol Amendment Summary of Changes Table

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Original Protocol	03-May-2019
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Amendment 1 (27-JUN-2019)

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

Overall Rationale for the Amendment:

The overall rationale for the changes implemented in the protocol amendment are to expand the Dose Limiting Toxicity (DLT) criteria following the feedback received from the FDA during the Investigational New Drug (IND) application review.


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1.1. Synopsis

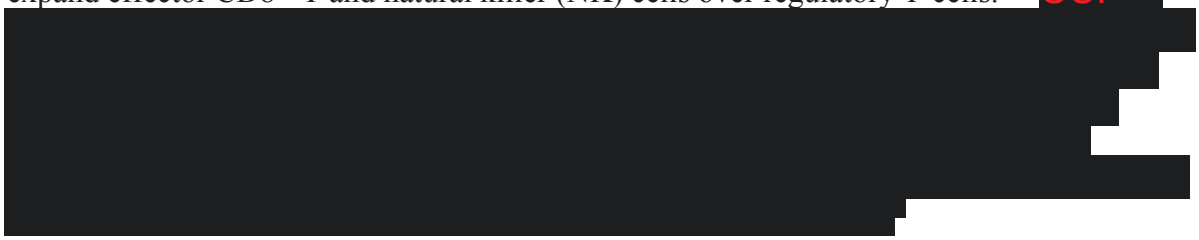
Protocol Title: A Phase 1b/2 Study to Evaluate Safety and Clinical Activity of Avelumab in Combination with Bempegaldesleukin (NKTR-214) with or without Talazoparib or Enzalutamide in Participants with Locally Advanced or Metastatic Solid Tumors
Short Title: JAVELIN IL-2 Medley

Rationale:
Combination A: Avelumab + Bempegaldesleukin (NKTR-214) for treatment of locally recurrent (not amendable for treatment with curative intent) or metastatic squamous cell carcinoma of the head and neck (1L SCCHN)

Avelumab (MSB0010718C) is a human immunoglobulin (Ig)G1 monoclonal antibody (mAb) directed against programmed death receptor ligand 1 (PD-L1). Avelumab selectively binds to PD-L1 and competitively blocks its interaction with the programmed death receptor 1 (PD-1), thereby interfering with this key immune checkpoint inhibition pathway. In March 2017, avelumab received accelerated approval by the United States (US) Food and Drug Administration (FDA) as the first approved treatment for metastatic Merkel cell carcinoma (MCC) followed by approvals in Japan, Australia, European Union, Switzerland, and Israel. In May 2017, avelumab received accelerated approval by the US FDA for the treatment of patients with locally advanced or metastatic urothelial cancer (UC) with disease progression during or following platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy. In January 2018, avelumab was approved for the same indication in Israel.

Currently, there are 2 ongoing Phase 3 studies investigating avelumab and chemoradiotherapy in locally advanced (LA) SCCHN, study B9991016 (NCT02952586) and the Randomized Trial of Avelumab-cetuximab-radiotherapy versus Standard of Cares (SOCs) in LA SCCHN (REACH) study (NCT02999087).

Bempegaldesleukin (NKTR-214) is a CD122-biased cytokine agonist conjugated with multiple releasable chains of polyethylene glycol designed to provide sustained signaling through the heterodimeric interleukin-2 (IL-2) receptor pathway to preferentially activate and expand effector CD8+ T and natural killer (NK) cells over regulatory T-cells.[2,3] CCI



The combination of bempegaldesleukin (NKTR-214) with nivolumab in the PIVOT-02 study has showed preliminary evidence of improved clinical activity with the observed response rates comparing favorably when referencing to anti-PD-1/PD-L1 single agents data sets from phase 3 studies; clinical activity was observed also in patients with PD-L1 negative disease.[5] Consistent with the mechanisms of actions of both agents, increased T-cell infiltration was observed in tumors and conversion of baseline PD-L1 negative disease to PD-L1 positive disease at week 3 of treatment was reported in serial biopsies from 7/10 patients in the PIVOT-02 study.[6]

Similar effect is expected when combining avelumab with bempegaldesleukin, and the combination may lead to increased PD-L1 expression and potentially improved anti-tumor activity over single-agent checkpoint inhibitors in locally recurrent (1L) SCCHN. Indeed, in the KEYNOTE-048 Phase 3 study (NCT02358031) of pembrolizumab or pembrolizumab + chemotherapy vs. EXTREME (platinum-based chemotherapy + 5-fluorouracil [5-FU]) as first-line systemic therapy for R/M SCCHN, the observed clinical benefit correlated with PD-L1 expression level. The confirmed ORR was (pembrolizumab vs EXTREME) 23% vs 36% for PD-L1 combined positive score (CPS) ≥20, 19% vs 35% for CPS ≥1, and 17% vs 36% for the total population. Also, the observed overall survival benefit was dependent on the baseline PD-L1 expression level with a reported hazard ratio favoring pembrolizumab over EXTREME of 0.61 (95% confidence interval [CI] 0.45-0.83) and 0.78 (95% CI 0.64-0.96) for the CPS ≥20 and CPS ≥1 populations, respectively.[7]

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Based on current data, the avelumab + bempegaldesleukin (NKTR-214) combination is expected to enhance anti-tumor activity over single-agent checkpoint inhibitor in study participants with 1L SCCHN whose disease is positive or negative PD-L1 expression at baseline.

Combination B: Avelumab + Bempegaldesleukin (NKTR-214) + Talazoparib for treatment of DNA Damage Repair (DDR) + metastatic castration-resistant prostate cancer (mCRPC)

Single agent treatment with immune checkpoint blockers, including avelumab, delivers only modest clinical benefit in prostate cancer and correlative studies have demonstrated that the prostate tumor microenvironment is predisposed toward immunosuppression.[8]

As previously discussed, the combination of bempegaldesleukin (NKTR-214) with nivolumab in the PIVOT-02 study demonstrated preliminary signs of clinical activity referencing to anti-PD-1/PD-L1 single agents.[5] Combination strategies aimed to enhance the immune recognition of the tumor create the potential for a therapeutically relevant treatment in prostate cancer. One proposed treatment combination for evaluation in this study is the triplet of avelumab + bempegaldesleukin (NKTR-214) + talazoparib (Combination B).

Talazoparib is a potent, small molecule poly (adenosine diphosphate [ADP]-ribose) polymerase inhibitor (PARPi) in development for the treatment of a variety of human cancers. Talazoparib is a particularly potent PARP trapper, a property that is associated with cytotoxicity in preclinical models.[9] Single agent treatment with talazoparib demonstrates potent antitumor effects in tissue culture studies, mouse tumor xenograft models, and in Phase 1 studies in patients with solid tumors. Talazoparib has also been shown to enhance the cytotoxic effects of deoxyribose nucleic acid (DNA) damaging chemotherapy. Talazoparib was approved by the FDA on 16 October 2018 for the treatment of adults with deleterious or suspected deleterious germline Breast Cancer susceptibility gene (BRCA) mutated human epidermal growth factor receptor 2 negative (HER2-) locally advanced or metastatic breast cancer.[10]

Proof of concept of PARPi efficacy in metastatic castration-resistant prostate cancer (mCRPC) with DNA Damage Repair (DDR) deficiency was established in a Phase 2 study (TOPARP-A) with olaparib, which enrolled men heavily pre-treated with taxane based chemotherapy and novel hormonal therapy (NHT). Of the 49 patients evaluable for response (defined either as an objective response according to Response Evaluation Criteria in Solid Tumors [RECIST] v1.1, or as a reduction of at least 50% in the prostate specific antigen [PSA] level or a confirmed reduction in the circulating tumor cell [CTC] count from 5 or more cells per 7.5 mL of blood to less than 5 cells per 7.5 mL), 16 patients achieved a response (33%; 95% CI: 20.0, 48.0). Homozygous deletions, deleterious mutations, or both were identified in DNA repair genes in 16 patients (33%) and 14 of these patients (88%) achieved a response.[11] These results were further confirmed with rucaparib in a similar therapeutic setting in the TRITON2 phase 2 study where the observed confirmed objective response rate (ORR) in mCRPC patients with BRCA1/2 defects was 45.5% (95% CI 16.7-75.6).[12] In addition, the combination of durvalumab and olaparib was evaluated in a Phase 2 study in 17 patients with mCRPC after progression on NHT and chemotherapy.

Overall, 8 out of 17 patients had a reduction in PSA level ≥50% from baseline. PSA level reductions were observed mainly in patients with mutations in DNA repair pathways, but also in some patients without alteration.[13] In alignment with these findings, the combination of pembrolizumab and olaparib in the KEYNOTE-365 study showed early evidence of clinical activity in mCRPC patients whose disease was negative for homologous recombination defects (HRD) after treatment with taxane based chemotherapy and NHT with a reported ORR of 7% (95% CI 1-23), and disease control rate ≥6 months of 32% in patients with measurable disease.[14]

A key aim of the combination B in this study is to extend PARPi activity beyond BRCA deficiency to sustain and prolong responses to PARPi in mCRPC participants whose disease is positive for DDR defects (DDR+). The proposed triple combination has the potential to activate several non-overlapping immune mechanisms to synergize and induce potent anti-tumor immune response. Talazoparib would induce the activation of proinflammatory dentritic cells (DCs) via stimulation of the interferon genes (STING) pathway to prime and differentiate tumor specific CD8 T-cells.[15,16] As such, increased DNA damage via PARP inhibition is expected to enhance effective recognition and infiltration of tumors by immune cells. In keeping with this expectation, talazoparib has been shown to promote T-cell and NK cell infiltration and activation in a mouse model of ovarian cancer.[17] Bempegaldesleukin (NKTR-214) would allow the expansion of these CD8 T-cells as suggested by pre-clinical evidence that demonstrated improved anti-tumor activity for bempegaldesleukin (NKTR-214) + rucaparib in a BRCA-deficient and immuno-competent ovarian cancer model.[2,3] Additionally, talazoparib treatment has been shown to lead to increased expression of PD-L1 by tumor cells[18] suggesting that this may represent a mean by which tumors function to inhibit talazoparib-mediated anti-tumor immunity. Addition of avelumab would release the checkpoint break by overcoming the PD-L1-mediated inhibition resulting in anti-tumor immune response.

In summary, the proposed triple combination may produce enhanced anti-tumor activity with talazoparib, promoting immune priming and tumor immunogenicity and avelumab/bempegaldesleukin (NKTR-214) enhancing the anti-tumor immune response, so offering a therapeutic opportunity to patients with mCRPC after progression to taxane-based chemotherapy in the metastatic setting.

Combination C: Avelumab + Bempegaldesleukin (NKTR-214) + Enzalutamide for Treatment of mCRPC

The second proposed treatment combination for mCRPC for this study is the triplet of avelumab + bempegaldesleukin (NKTR-214) + enzalutamide (Combination C). Results from the PIVOT-02 study of bempegaldesleukin (NKTR-214) with nivolumab as discussed above also support the evaluation of avelumab plus bempegaldesleukin as the backbone of this triplet combination.

Enzalutamide is an androgen receptor inhibitor approved for treating patients with non-metastatic castration-resistant prostate cancer (NM CRPC) as well as mCRPC. Preliminary results from the ARCHES study (NCT02677896) demonstrated that enzalutamide plus androgen deprivation therapy (ADT) also significantly improved

radiographic progression-free survival (rPFS) compared with ADT alone in patients with hormone-sensitive metastatic prostate cancer (mHSPC). Enzalutamide acts by inhibiting the binding of androgens to the androgen receptor, androgen receptor nuclear translocation, and androgen receptor-mediated DNA binding and is currently being evaluated in combination with other anti-cancer therapies in Phase 3 studies, including atezolizumab (NCT03016312) and pembrolizumab (NCT03834493) in patients with mCRPC. The combination of immune checkpoint blockers with androgen receptor blockers and CD8 T-cell stimulants may improve the therapeutic outcome of mCRPC patients. In a study of biochemically recurrent prostate cancer, a preliminary analysis of 12 patients treated with a 3-month course of enzalutamide showed increases in NK cells and decreases in myeloid-derived suppressor cells (MDSC).[19] In addition, patients who experienced progression during enzalutamide treatment showed increased PD-L1 expression on dendritic cells[20] and encouraging evidence of clinical activity in patients were observed with pembrolizumab plus enzalutamide after progression on enzalutamide with PSA level reduction ≥50% reported in 5 out of 28 (18%) patients and radiographic response observed in 3 out of 12 patients (ORR=25%) with measurable disease at baseline.[21] Moreover, the combination of pembrolizumab plus enzalutamide in mCRPC patients after abiraterone therapy failure induced PSA reduction ≥50% in 18 out of 54 patients (33%) and radiographic response observed in 5 out of 25 patients (ORR=20%) with measurable disease at baseline.[22]

Based on the above data, the proposed triplet combination could represent an effective treatment strategy by enzalutamide enhancing NK cells and lowering MDSC, bempegaldesleukin (NKTR-214) generating a robust CD-8 and NK cell level in the tumor tissue, and avelumab providing the release from the checkpoint blockade resulting from PD-L1-mediated inhibition of anti-tumor immune response. Therefore, Combination C may provide an innovative treatment option to mCRPC patients after disease progression on abiraterone treatment.

Objectives, Estimands and Endpoints

Primary Objectives	**Primary Endpoints**
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 ORR of avelumab in combination with bempegaldesleukin (NKTR-214) in participants with locally recurrent or metastatic SCCHN. • **Combination B:** To assess soft tissue ORR of avelumab in combination with bempegaldesleukin (NKTR-214) and talazoparib in participants with DDR defect positive mCRPC. • **Combination C:** To assess the PSA response rate of avelumab in combination with bempegaldesleukin (NKTR-214) and enzalutamide in participants with mCRPC after progression on abiraterone.	**Phase 2:** • **Combination A:** Confirmed objective response (OR) as determined by the investigator using RECIST v1.1 (Appendix 9). • **Combination B**: Confirmed soft tissue OR as determined by the investigator using RECIST v 1.1 (Appendix 9) with no evidence of confirmed bone disease progression on repeat bone scan at least 6 weeks later per PCWG3 criteria (Appendix 10). • **Combination C:** Confirmed prostate specific antigen (PSA) response decrease ≥ 50% from baseline confirmed by a second consecutive assessment at least 3 weeks later.
Secondary Objectives	**Secondary Endpoints**
• 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 antitumor 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 (Appendix 9) with no evidence of confirmed bone disease progression on repeat bone scan at least 6 weeks later per PCWG3 criteria (Appendix 10). • **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 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), talazoparib, enzalutamide, and N-desmethyl-enzalutamide and maximum concentrations (C_{max}) for avelumab and bempegaldesleukin (NKTR-214).
• To assess the immunogenicity of avelumab and bempegaldesleukin when combined together and with talazoparib or enzalutamide.	• Anti-drug antibody (ADA) and neutralizing antibodies (NAb) against avelumab, bempegaldesleukin (NKTR-214) and IL-2 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.

Estimands

This section defines the estimands associated with the primary endpoints and the secondary efficacy endpoints of the study.

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 DDR defect positive 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 dose-limiting toxicity (DLT) during the primary DLT evaluation period (Cycle 1). DLTs are defined in Section 4.1 and the Synopsis. 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 Section 9.4.1) 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 9.4.1) will be calculated.

- Phase 2 tumor-related endpoints (time to tumor response [TTR, Combinations A, B, and C], duration of response [DR, Combinations A, B and C], time to PSA progression [TTPSAP, Combinations B and C only], CTC count conversion and CTC0 [Combination C only]) are defined in Section 9.4.1. 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 9.4.1) 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: Overall survival (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 9.4.1) 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.

Overall Design:
This Phase 1b/2, open-label, multi-center study will include a dose-finding component of avelumab in combination with bempegaldesleukin (NKTR-214; Combination A), avelumab in combination with bempegaldesleukin (NKTR-214) and talazoparib (Combination B), and avelumab in combination with bempegaldesleukin (NKTR-214) and enzalutamide (Combination C).

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 the recommended Phase 2 dose (RP2D). Refer to Table 1 for the potential dose levels. A minimum of 9 participants will be enrolled.

Step 2. Upon the determination of the RP2D for Combination A, the dose-finding for Phase 1b for Combinations B and C in participants with mCRPC will commence and will be conducted in parallel with the Phase 2 Combination A portion of the study to determine the RP2D for Combinations B and C separately. Refer to Table 2 and Table 3 for the potential dose levels for Combinations B and C, respectively. A minimum of 9 participants will be enrolled in each combination.

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). Refer to Appendix 11, Appendix 12, and Appendix 13 for the BLRM designs for Combinations A, B, and C, respectively. 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.

Step 1. Dose-Finding for Combination A

The potential dose levels of avelumab and bempegaldesleukin (NKTR-214) for dose finding for Combination A are shown in Table 1. The starting dose level is 800 mg avelumab intravenous (IV) every 2 weeks (Q2W) plus 0.006 mg/kg bempegaldesleukin Q2W, which satisfies the Escalation With Overdose Control (EWOC) criterion that the risk for excessive toxicity is less than 0.25. For the starting dose level, the risk of excessive toxicity was estimated to be 13.7% based on information from prior single-agent Phase 1 studies and a pharmacokinetic (PK) assessment of no potential significant drug-drug interaction. Dose reduction of bempegaldesleukin (NKTR-214) to 0.003 mg/kg Q2W will be triggered for future participants if higher than expected toxicity is observed at the higher dose (the risk of excessive toxicity ≥ 0.25).

Table 1. Phase 1b Combination A 1L SCCHN Avelumab + Bempegaldesleukin (NKTR-214) Dose Levels

Dose Level	Avelumab dose IV (mg Q2W)	Bempegaldesleukin (NKTR-214) (mg/kg Q2W)
D0	800	0.006
D-1	800	0.003

1L SCCHN= locally recurrent squamous cell carcinoma of the head and neck; D0= starting dose; D-1=reduced dose; IV= intravenous; mg= milligram; Q2W= every 2 weeks.

Step 2. Dose-Finding for Combinations B and C

The potential dose levels of avelumab, bempegaldesleukin (NKTR-214) and talazoparib for dose finding for Combination B are listed in Table 2. The dose level for avelumab is fixed at 800 mg Q2W. The starting dose level for bempegaldesleukin (NKTR-214) and talazoparib will be determined at the completion of the Phase 1b dose finding for Combination A based on available clinical data (including but not limited to safety and PK/pharmacodynamic

data). The lowest allowed dose for bempegaldesleukin (NKTR-214) will be 0.003 mg/kg and the lowest allowed dose for talazoparib will be 0.5 mg once daily, in which case participants with moderate renal impairment cannot be enrolled. The starting dose for talazoparib for participants with moderate renal impairment (creatinine clearance [CrCL] 30-59 mL/min) will be reduced by 1 dose level unless the determined starting dose for talazoparib for participants with no or mild renal impairment is 0.5 mg once daily.

Table 2. Phase 1b Combination B mCRPC Avelumab, Bempegaldesleukin (NKTR-214), and Talazoparib Dose levels

Dose Level	Avelumab Dose IV (mg Q2W)	Bempegaldesleukin (NKTR-214) IV (mg/kg Q2W)	Talazoparib Dose PO (mg once daily)
D0-A*	800	0.006	1.0
D-1A	800	0.006	0.75
D-2A	800	0.006	0.5
D0-B*	800	0.003	1.0
D-1B	800	0.003	0.75
D-2B	800	0.003	0.5

D0= starting dose; D-1=reduced dose; D-2=second reduced dose; IV= intravenous; mCRPC= metastatic castration-resistant prostate cancer; mg= milligram; PO=orally; Q2W= every 2 weeks. *Dose levels for Combination B designated with 'A' are applicable if the bempegaldesleukin (NKTR-214) dose is 0.006 mg/kg Q2W; dose levels for Combination B designated with 'B' are applicable if the bempegaldesleukin (NKTR-214) dose is 0.003 mg/kg Q2W.

The potential dose levels of avelumab, bempegaldesleukin (NKTR-214) and enzalutamide for dose finding for Combination C are listed in Table 3. The starting dose level for bempegaldesleukin (NKTR-214) and enzalutamide will be determined at the completion of the dose finding for Combination A based on available clinical data (including but not limited to safety and PK/pharmacodynamic data). The approved label dose for enzalutamide is 160 mg once daily (QD). The target starting enzalutamide dose to be used in Combination C is 160 mg QD unless unexpected safety issues require its lowering according to the BLRM recommendation. In both the KEYNOTE-199 study (pembrolizumab + enzalutamide in mCRPC) and the IMbassador250 study (atezolizumab + enzalutamide in mCRPC), the full monotherapy dose of enzalutamide was used as the starting dose. The lowest allowed dose for bempegaldesleukin (NKTR-214) will be 0.003 mg/kg and the lowest allowed dose for enzalutamide will be 80 mg once daily.

Table 3. Phase 1b Combination C mCRPC Avelumab, Bempegaldesleukin (NKTR-214) and Enzalutamide Dose levels

Dose Level	Avelumab Dose IV (mg Q2W)	Bempegaldesleukin (NKTR-214) IV (mg/kg Q2W)	Enzalutamide Dose PO (mg once daily)
D0-A*	800	0.006	160
D-1A	800	0.006	120
D-2A	800	0.006	80
D0-B*	800	0.003	160
D-1B	800	0.003	120
D-2B	800	0.003	80

D0= starting dose; D-1=reduced dose; D-2=second reduced dose; IV= intravenous; mCRPC=metastatic castration-resistant prostate cancer; mg= milligram; PO=orally; Q2W= every 2 weeks.
*Dose levels for Combination C with 'A' are applicable if the bempegaldesleukin (NKTR-214) dose is 0.006 mg/kg Q2W; dose levels for Combination C designated with 'B' are applicable if the bempegaldesleukin (NKTR-214) dose is 0.003 mg/kg Q2W.

For each combination, beginning with the starting dose level, participants will be enrolled, treated, and monitored in increments of 3-6 during the 28-day dose-limiting toxicity (DLT) evaluation period (Cycle 1) as follows:

- Participants who withdraw from study treatment in Cycle 1 before receiving at least 2 doses of bempegaldesleukin (NKTR-214) and avelumab and at least 75% of the planned dose of talazoparib (Combination B) or enzalutamide (Combination C) for reasons other than treatment-related toxicity are not evaluable for DLT. All participants deemed non-evaluable for DLT may be replaced.

- A minimum of 3 DLT-evaluable participants in each cohort will be required; additional participants will be enrolled in the specific enrollment cohort to replace participants who are not considered DLT-evaluable, where required.

- When all DLT-evaluable participants treated in a given enrollment cohort have completed the DLT observation period or experienced a DLT, whichever occurs first, the posterior distribution for the risk of DLT for new participants at different dose levels for the combination of interest will be evaluated.

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

    - Underdosing: [0, 0.16)

    - Target toxicity: [0.16, 0.33)

    - Excessive toxicity or overdosing: [0.33, 1]

In addition to accumulating safety data and observed DLTs, decisions on further participant enrollment and dose level selection will be guided by the EWOC criterion. A combination dose may only be used for newly enrolled participants if the risk of excessive toxicity at that combination dose is less than 0.25.

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

- $\geq$6 participants have been treated at that dose;

- Probability of target dosing >0.50;

- Probability of overdosing <0.25.

An RP2D below the MTD may be determined based on other safety, efficacy, PK, and pharmacodynamic data. Nine DLT-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.

Phase 2 Design

Once the Phase 1b component 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.

DLT Determination

The Combinations A, B, and C will be administered in 28-day cycles, and the DLT evaluation period will be limited to the first treatment cycle. The severity of adverse events (AEs) will be graded according to Common Terminology Criteria for Adverse Events (CTCAE) v4.03. For the purpose of dose finding, any of the following AEs occurring in the first cycle of treatment which are attributable to any or all agents 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 $<0.5 \times 10^9/L$) 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 $<1.0 \times 10^9/L$, and Grade >3 infection).
- Grade 3 thrombocytopenia ($25,000/mm^3$ or $25.0 \times 10^9/L$ to $<50,000/ mm^3$ or $<50.0 \times 10^9/L$) with bleeding, or grade 4 thrombocytopenia (platelet count $<25,000/mm^3$ or $<25.0 \times 10^9/L$);

Non-Hematologic:

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

Disclosure Statement:
This is a Dose Finding Treatment study with 3 Arms that has No masking

Number of Participants:
Approximately 160 participants will be screened to achieve approximately 127 participants assigned to study intervention based on eligibility, for an estimated total of 27-36 DLT-evaluable 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.

Intervention Groups and Duration:
Eligible participants will be centrally assigned via an interactive response technology (IRT) to a study combination after providing informed consent and completing the screening procedures for their respective combination. Study drugs will be assigned and given as follows:

Combination A:

- Bempegaldesleukin (NKTR-214) will be supplied as a sterile solution and will be administered as an approximately 30-minute intravenous (IV) infusion at a starting dose of 0.006 mg/kg Q2W on Days 1 and 15 of each 28-day cycle in Phase 1b. The bempegaldesleukin (NKTR-214) dose level may be adjusted in Phase 2 if needed to the minimum dose of 0.003 mg/kg Q2W for this study. Bempegaldesleukin (NKTR-214) will be administered before avelumab. In order to mitigate hypotension, participants will receive IV fluids at each bempegaldesleukin (NKTR-214) administration, as per Section 6.1.2.1.1. In addition, participants may receive pre-medication to treat flu-like symptoms as per Section 6.1.2.1.2.

- Avelumab will be supplied as a sterile solution (20 mg/mL) and will be administered as an approximately 1-hour IV infusion Q2W on Days 1 and 15 of each 28-day cycle at a fixed dose of 800 mg. In order to mitigate infusion-related reactions (IRRs), participants will be pre-medicated with antihistamine and with paracetamol (acetaminophen) as per Section 6.1.1.3.1.

Combination B:

- Avelumab and bempegaldesleukin (NKTR-214) will be supplied and administered as in Combination A (bempegaldesleukin [NKTR-214] dose TBD), in addition to talazoparib (dose TBD) self-administered orally once a day, every day of each 28-day cycle. Talazoparib may be taken before or after avelumab + bempegaldesleukin (NKTR-214) administration is complete and should be taken at approximately the same time each day.

Combination C:

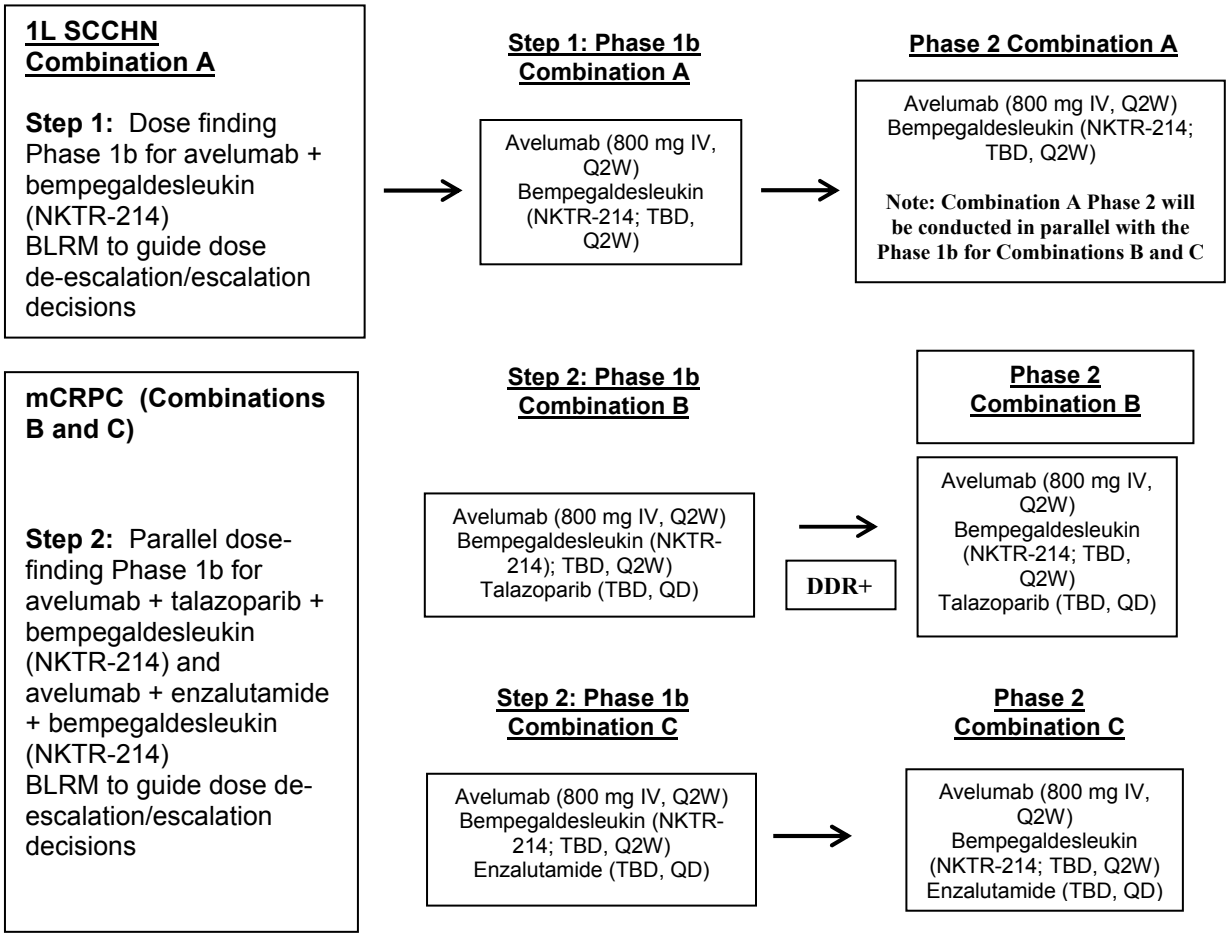
- Avelumab and bempegaldesleukin (NKTR-214) will be supplied and administered as in Combination A (bempegaldesleukin [NKTR-214] dose TBD), in addition to enzalutamide (dose TBD) self-administered orally once a day, every day of each 28-day cycle. Enzalutamide may be taken before or after avelumab + bempegaldesleukin (NKTR-214) administration is complete and should be taken at approximately the same time each day.

- Participants will receive study treatment until progressive disease (PD) based on Investigator assessment per RECIST v1.1 (Appendix 9) for Combination A; RECIST v1.1 and PCWG3 (Appendix 9 and Appendix 10, respectively) for Combinations B and C; unacceptable toxicity, withdrawal of consent, or termination of study at sponsor discretion, whichever is earliest.

Data Monitoring Committee: No

1.2. Schema

Figure 1. B9991040 Study Schematic



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.

1.3. Schedule of Activities (SoA)

The SoA tables provide an overview of the protocol visits and procedures.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA tables in order to conduct evaluations or assessments required to protect the well-being of the participant.

1.3.1. Table 4. SoA for SCCHN Phase 1b and Phase 2 (Combination A): Screening, Cycle 1 and Cycle 2

Table 4. SoA for SCCHN Phase 1b and Phase 2 (Combination A): Screening, Cycle 1 and Cycle 2

Procedure	Screening	Treatment Period (One Cycle = 28 days)								Notes
		Cycle 1					Cycle 2			
		D1	D3	D4	D8	D15	D1	D8	D15	
Visit Window (Days)	**-28 to -1**	**±0**	**±0**	**±0**	**±2**	**±2**	**±2**	**±2**	**±2**	
Clinical Assessments										
Informed consent	X									Refer to Section 10.1.3 in Appendix 1
Medical/Oncological History	X									
Tumor Assessments (including scans)	X									Refer to Section 8.1.1.1 and Appendix 9. Refer to Table 5 regarding continuing assessments for Cycle ≥3 and post-treatment.
Physical Examination	X	X								Complete physical examination at screening; brief physical exam at C1D1. Refer to Section 8.2.1 for details. Refer to Table 5 regarding continuing assessments for Cycle ≥3 and post-treatment.
Contraception Check	X	X					X			**Must be performed D1 of each cycle.** Refer to Appendix 4 and Section 5.3 for contraceptive guidance. Refer to Table 5 regarding continuing assessments for Cycle ≥3 and post-treatment.
ECOG Performance Status	X	X					X			Refer to Section 8.2.7 and Appendix 8 for ECOG performance status criteria. Refer to Table 5 regarding continuing assessments for Cycle ≥3 and post-treatment.

Table 4. SoA for SCCHN Phase 1b and Phase 2 (Combination A): Screening, Cycle 1 and Cycle 2

Procedure	Screening	Treatment Period (One Cycle = 28 days)								Notes
		Cycle 1					Cycle 2			
		D1	D3	D4	D8	D15	D1	D8	D15	
Visit Window (Days)	**-28 to -1**	**±0**	**±0**	**±0**	**±2**	**±2**	**±2**	**±2**	**±2**	
Vital Signs	X	X	X*	X*	X*	X	X		X	Record blood pressure, heart rate, height, and weight at screening; ***collect BP and HR only on C1 D3, D4 (72-96) hour window for D4 from D1, refer to PK assessments) and D8**; collect BP and HR pre-dose at all other visits, and include weight pre-dose at D1 of each cycle. Refer to Section 8.2.2. Refer to Table 5 regarding continuing assessments for Cycle ≥3 and post-treatment.
12-Lead ECG	X	X					X			**Phase 1b**: 12-lead ECGs should be performed at screening (singlet) and on Day 1 of Cycles 1 and 2 (triplicate), prior to any pre-dose PK collection (within 2 hours) and prior to post-dose avelumab PK collection (within 10 minutes after the end of avelumab infusion); then singlet 12-lead ECGs should be performed as clinically indicated. **Phase 2:** Singlet 12-lead ECGs should be performed if clinically indicated. Refer to Section 8.2.5 for details.
ECHO/MUGA (LVEF determination)	X*									*Perform within six months prior to screening. Refer to Section 8.2.6
CCI [redacted]		[redacted]					[redacted]			[redacted]
Laboratory assessments (must be performed pre-dose during the treatment period). Laboratory tests may be performed up to 3 days prior to the scheduled clinic visit so that results will be available for review before study treatment administration. Unless otherwise noted, refer to Section 8.2.3 and Appendix 2 for additional information on Laboratory Assessments. Refer to Table 5 regarding continuing assessments for Cycle ≥3 and post-treatment.										

Table 4. SoA for SCCHN Phase 1b and Phase 2 (Combination A): Screening, Cycle 1 and Cycle 2

Procedure	Screening	Treatment Period (One Cycle = 28 days)								Notes
		Cycle 1					Cycle 2			
		D1	D3	D4	D8	D15	D1	D8	D15	
Visit Window (Days)	**-28 to -1**	**±0**	**±0**	**±0**	**±2**	**±2**	**±2**	**±2**	**±2**	
Hematology/Blood for lymphocyte count	X	X	X	X*	X	X	X		X	Collect approximately 8-mL whole blood **(*72-96 hour window from D1 for D4).** Refer to Section 8.1.2.1, Section 8.2.3 and Appendix 2 for further details. Prior to study drug administration on Days 1 and 15 of each treatment cycle, hematology (ie, hemoglobin, platelets, and white blood cells) tests must be performed and results reviewed by the treating physician prior to study drug administration. Refer to Table 5 regarding continuing assessments for Cycle ≥3 and post-treatment.
Blood Chemistry	X	X				X	X		X	Collect approximately 4 mL whole blood prior to study drug administration on Days 1 and 15 of each treatment cycle. Chemistry (ie, ALT, AST, alkaline phosphatase, total bilirubin, blood urea nitrogen, creatinine, sodium, potassium, lipase, amylase, and glucose) tests must be performed and results reviewed by the treating physician prior to study drug administration. Refer to Section 8.2.3, and also Table 5 regarding continuing assessments for Cycle ≥3 and post-treatment.
Coagulation	X	X*					X*			Collect approximately 4 mL whole blood. Conduct at screening and then ***at D1 for C1 and C2 for Phase 1b only**.
Thyroid Function and ACTH Tests*	X									Collect approximately 4 mL whole blood. *Free T4, TSH, and ACTH must be performed at screening and at least every 8 weeks during study treatment (ie, every two cycles; D1 of C3, C5, C7, etc.). Refer to Table 5 regarding continuing assessments for Cycle ≥ 3 and post-treatment.
Pregnancy Test	X	X*					X			Collect approximately 5 mL whole blood if using a serum-based pregnancy test. Refer to Section 8.2.4 and Appendix 4 for details. *WOCBP must have a negative highly sensitive pregnancy test ([urine or serum] as required by local regulations) at C1D1. Results from pregnancy tests must be available for review prior to dosing.
Urinalysis	X									Conduct at screening and then additionally if clinically indicated.

Table 4. SoA for SCCHN Phase 1b and Phase 2 (Combination A): Screening, Cycle 1 and Cycle 2

Procedure	Screening	Treatment Period (One Cycle = 28 days)								Notes
		Cycle 1					Cycle 2			
		D1	D3	D4	D8	D15	D1	D8	D15	
Visit Window (Days)	**-28 to -1**	**±0**	**±0**	**±0**	**±2**	**±2**	**±2**	**±2**	**±2**	
Hepatitis B and C Virus tests	X									Collect approximately 5 mL whole blood for HBV surface antigen and anti-HCV antibody tests. If anti-HCV antibody test is positive, participants must be tested for HCV RNA.
Enrollment, Study Treatment, and Safety										
Enrollment/treatment assignment		X								Refer to Section 6.3 for details.
Pre-treatment for bempegaldesleukin (NKTR-214)		X				X	X		X	Participants should receive at least one liter of IV fluids at each dosing of bempegaldesleukin (NKTR-214) to prevent hypotension as per Section 6.1.2.1.1 (particularly in Cycle 1 and Cycle 2). Consider if anti-hypertensive medications should be withheld. Refer to Table 5 regarding continuing treatments for Cycle ≥3.
Study treatment (bempegaldesleukin [NKTR-214])		X				X	X		X	Refer to Section 6.1.2 for treatment details. Refer to Table 5 regarding continuing treatments for Cycle ≥3. Participants should be carefully monitored for infusion reactions during administration. If an acute infusion reaction is noted, participants should be managed according to Table 12 in Section 6.6.1.
Pre-medication for avelumab		X				X	X		X	In order to mitigate IRRs, premedication with an antihistamine and with paracetamol (acetaminophen) 30 to 60 minutes prior to the first 4 infusions of avelumab is mandatory, as per Section 6.1.1.3.1. Refer to Table 5 regarding continuing treatments for Cycle ≥3.
Study treatment (avelumab)		X				X	X		X	Refer to Section 6.1.1 for treatment details. Refer to Table 5 regarding continuing treatments for Cycle ≥3. Participants should be carefully monitored for infusion reactions during administration. If an acute infusion reaction is noted, participants should be managed according to Table 11 in Section 6.6.1.

Table 4. SoA for SCCHN Phase 1b and Phase 2 (Combination A): Screening, Cycle 1 and Cycle 2

Procedure	Screening	Treatment Period (One Cycle = 28 days)								Notes
		Cycle 1					Cycle 2			
		D1	D3	D4	D8	D15	D1	D8	D15	
Visit Window (Days)	**-28 to -1**	**±0**	**±0**	**±0**	**±2**	**±2**	**±2**	**±2**	**±2**	
Concomitant Therapy	X	→	→	→	→	→	→	→	→	Refer to Section 6.5 for details. Refer to Table 5 regarding continuing assessments for Cycle ≥3 and post-treatment.
Reporting of AEs and SAEs	X	→	→	→	→	→	→	→	→	Refer to Appendix 3 for details. Refer to Table 5 regarding continuing assessments for Cycle ≥3 and post-treatment.
Tumor Biopsies										
Mandatory Tumor Tissue	X									Refer to Section 8.8.1.1
On-Study Tumor Tissue		An on-treatment biopsy is required to be collected on Cycle 1 between Days 9 and 14. When this is not feasible, a biopsy may be collected on Cycle 1 between Days 15 and 21. These on-treatment biopsies are required except in instances where the procedure poses unacceptable risks per Investigator.								Refer to Section 8.8.1.4
Pharmacodynamic, Biomarker and Immunogenicity Assessments										
Saliva sample for germline comparator		X								Collect pre-dose. Refer to Section 8.8.2.1
CCI [redacted]		[redacted]								[redacted]
[redacted]		[redacted]								[redacted]

Table 4. SoA for SCCHN Phase 1b and Phase 2 (Combination A): Screening, Cycle 1 and Cycle 2

Procedure	Screening	Treatment Period (One Cycle = 28 days)								Notes
		Cycle 1					Cycle 2			
		D1	D3	D4	D8	D15	D1	D8	D15	
Visit Window (Days)	**-28 to -1**	**±0**	**±0**	**±0**	**±2**	**±2**	**±2**	**±2**	**±2**	
CCI [redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]				[redacted]	[redacted]			[redacted]
Immunogenicity for avelumab (ADA and NAb)		X					X			Collect approximately 3.5 mL whole blood. Collections are pre-dose, within 2 hours prior to infusion. Refer to Section 8.8.3.1 for details. Refer to Table 5 regarding continuing assessments for Cycle ≥3 and post-treatment.
Immunogenicity for bempegaldesleukin (NKTR-214; ADA and NAb)		X					X			Collect approximately 3.5 mL whole blood. Collections are pre-dose, within 2 hours prior to infusion. Refer to Section 8.8.3.2 for details. Refer to Table 5 regarding continuing assessments for Cycle ≥3 and post-treatment.
Pharmacokinetic Assessments										
PK for avelumab		X				X	X		X	Collect approximately 3.5 mL whole blood**.** All collections should occur within 2 hours prior to IV infusion and within 10 minutes after EOI. Refer to Section 8.5.1 for details. Refer to Table 5 regarding continuing assessments for Cycle ≥3 and post-treatment.

Table 4. SoA for SCCHN Phase 1b and Phase 2 (Combination A): Screening, Cycle 1 and Cycle 2

Procedure	Screening	Treatment Period (One Cycle = 28 days)								Notes
		Cycle 1					Cycle 2			
		D1	D3	D4	D8	D15	D1	D8	D15	
Visit Window (Days)	**-28 to -1**	**±0**	**±0**	**±0**	**±2**	**±2**	**±2**	**±2**	**±2**	
PK for Bempegaldesleukin (NKTR-214)		X*	X	X†	X		X	X		**Phase 1b: all participants. Phase 2: a subset of approximately 20 participants from Combination A receiving RP2D.** CCI [redacted] Collect approximately 3.5 mL whole blood**.** *Collect a 3.5-mL whole blood sample at the following timepoints for C1D1: within 2 hours prior to IV infusion and within 10 minutes after, and 2 hours since the start of infusion (approximately 1.5 hours post-EOI). For C2D1, collect within 2 hours prior to IV infusion and within 10 minutes after EOI. †72-96 hour window from C1D1 for C1D4 collection. Refer to Section 8.5.2 for details. Refer to Table 5 regarding continuing assessments for Cycle ≥3 and post-treatment.

Abbreviations: ACTH=adrenocorticotropic hormone, ADA=anti-drug antibodies; AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BP=blood pressure; C=Cycle; C1D1=Cycle 1 Day 1; CRF=case report form; CCI [redacted] D=Day; ECG=electrocardiogram; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; EOI=end of infusion; CCI [redacted] H&N=head and neck; HBV=hepatitis B virus; HCV=hepatitis C virus; HR=heart rate; IRR=infusion-related reaction; IV=intravenous; NAb=neutralizing antibodies; LVEF=left ventricular ejection fraction; MUGA=multigated acquisition; PD=progressive disease; PK=pharmacokinetic; QLQ=quality of life; RNA=ribonucleic acid; RP2D=recommended Phase 2 dose; SAE=serious adverse event; SCCHN=squamous cell carcinoma of the head and neck; CCI [redacted]; T4=thyroxine; CCI [redacted] TSH=thyroid stimulating hormone; WOCBP=women of childbearing potential.

1.3.2. Table 5. SoA for SCCHN Phase 1b and Phase 2 (Combination A): Cycle ≥ 3 and Post-Treatment

Table 5. SoA for SCCHN Phase 1b and Phase 2 (Combination A): Cycle ≥ 3 and Post-Treatment

Procedure	Treatment Period (One Cycle = 28 Days)		Post-Treatment Period			Notes
	Cycle ≥ 3		ED or EOT	Short-Term Follow-up (30, 60, or 90 days post-dose)	Long-Term Follow-up (Every 12 Weeks)	Refer to Section 7.1 for additional information regarding ED, EOT, Short-term Follow-up, and Long-Term Follow-up.
	D1	D15				
Visit Window (Days)	±2	±2	+7	±3	±14	
Clinical Assessments						
Tumor Assessments (including scans)	Every 8 weeks (±7 days) after C1D1. After 52 weeks from C1D1, then every 16 weeks (±7 days) until progressive disease, including during follow-up and long-term follow-up after end of treatment, for participants who discontinue treatment due to reasons other than PD.					Refer to Section 8.1.1.1 and Appendix 9 for details.
Physical Examination	X		X	X (30 day visit only)		Brief physical exam. Refer to Section 8.2.1 for details.
Contraception Check	X		X	X (30 day visit only)		**Must be performed D1 of each cycle**. Refer to Appendix 4 and Section 5.3 for contraceptive guidance.
ECOG Performance Status	X		X	X (30 day visit only)		Refer to Section 8.2.7 and Appendix 8 for ECOG performance status criteria.
Vital Signs*	X	X	X	X (30 day visit only)		***Collect BP and HR (pre-dose on D1 and D15 of all Cycles) at all visits, and include weight pre-dose at D1 of each cycle, EOT, and at the 30-day follow-up visit.** Refer to Section 8.2.2.
12-Lead ECGs						Conduct a 12-lead singlet reading if clinically indicated.

Table 5. SoA for SCCHN Phase 1b and Phase 2 (Combination A): Cycle ≥ 3 and Post-Treatment

Procedure	Treatment Period (One Cycle = 28 Days)		Post-Treatment Period			Notes
	Cycle ≥ 3		ED or EOT	Short-Term Follow-up (30, 60, or 90 days post-dose)	Long-Term Follow-up (Every 12 Weeks)	Refer to Section 7.1 for additional information regarding ED, EOT, Short-term Follow-up, and Long-Term Follow-up.
	D1	D15				
Visit Window (Days)	**±2**	**±2**	**+7**	**±3**	**±14**	
CCI [redacted]	[redacted]		[redacted]	[redacted]		[redacted]
Laboratory Assessments (must be performed pre-dose during the treatment period). Laboratory tests may be performed up to 3 days prior to the scheduled clinic visit so that results will be available for review before study treatment administration. Unless otherwise stated, refer to Section 8.2.3 and Appendix 2 for additional information on Laboratory Assessments.						
Hematology/Blood for lymphocyte count	X	X	X	X (30 Day Visit only)		Collect approximately 8 mL whole blood. Prior to study drug administration on Days 1 and 15 of each treatment cycle, hematology (ie, hemoglobin, platelets, and white blood cells) tests must be performed and results reviewed by the treating physician prior to study drug administration. Refer to Section 8.1.2.1, Section 8.2.3, and Appendix 2 for details.
Blood Chemistry	X	X	X	X (30 Day Visit only)		Collect approximately 4 mL whole blood prior to study drug administration on Days 1 and 15 of each treatment cycle. Chemistry (ie, ALT, AST, alkaline phosphatase, total bilirubin, blood urea nitrogen, creatinine, sodium, potassium, lipase, amylase, and glucose) tests must be performed and results reviewed by the treating physician prior to study drug administration. Refer to Section 8.2.3 and Appendix 2 for details.
Thyroid Function and ACTH Tests*	X		X	X (30 Day Visit only)		Collect approximately 4 mL whole blood. *Free T4, TSH, and ACTH must be performed at least every 8 weeks during study treatment (ie, D1 of every two cycles; C3, C5, C7, etc.), at EOT, and at the 30-day short-term follow-up visit.

Table 5. SoA for SCCHN Phase 1b and Phase 2 (Combination A): Cycle ≥ 3 and Post-Treatment

Procedure	Treatment Period (One Cycle = 28 Days)		Post-Treatment Period			Notes
	Cycle ≥ 3		ED or EOT	Short-Term Follow-up (30, 60, or 90 days post-dose)	Long-Term Follow-up (Every 12 Weeks)	Refer to Section 7.1 for additional information regarding ED, EOT, Short-term Follow-up, and Long-Term Follow-up.
	D1	D15				
Visit Window (Days)	**±2**	**±2**	**+7**	**±3**	**±14**	
Pregnancy Test	X		X	X (30 Day Visit only)		Collect approximately 5 mL whole blood if using a serum-based pregnancy test. Refer to Section 8.2.4 and Appendix 4 for details. Results from pregnancy tests must be available for review prior to dosing.
Urinalysis						Conduct if clinically indicated.
Study Treatments and Safety						
Pre-treatment for bempegaldesleukin (NKTR-214)	X*	X*				Participants may or may not receive at least one liter of IV fluids at each dosing of bempegaldesleukin (NKTR-214) to prevent hypotension as per Section 6.1.2.1.1 ***as per clinical judgement.** Consider if anti-hypertensive medications should be withheld.
Study treatment (bempegaldesleukin [NKTR-214])	X	X				Refer to Section 6.1.2 for treatment details. Participants should be carefully monitored for infusion reactions during administration. If an acute infusion reaction is noted, participants should be managed according to Table 12 in Section 6.6.1.
Pre-medication for avelumab						Not mandatory for Cycles ≥3 (ie, beyond the first four infusions); premedication should be administered for subsequent avelumab doses based on clinical judgment and presence/severity of prior infusion reactions, as per Section 6.1.1.3.1.

Table 5. SoA for SCCHN Phase 1b and Phase 2 (Combination A): Cycle ≥ 3 and Post-Treatment

Procedure	Treatment Period (One Cycle = 28 Days)		Post-Treatment Period			Notes
	Cycle ≥ 3		ED or EOT	Short-Term Follow-up (30, 60, or 90 days post-dose)	Long-Term Follow-up (Every 12 Weeks)	Refer to Section 7.1 for additional information regarding ED, EOT, Short-term Follow-up, and Long-Term Follow-up.
	D1	D15				
Visit Window (Days)	±2	±2	+7	±3	±14	
Study treatment (avelumab)	X	X				Refer to Section 6.1.1 for treatment details. Participants should be carefully monitored for infusion reactions during administration. If an acute infusion reaction is noted, participants should be managed according to Table 11 in Section 6.6.1.
Concomitant Therapy	→	→	→	X		Refer to Section 6.5 for details.
Reporting of AEs and SAEs	→	→	→	X	X	Refer to Appendix 3.
Tumor Biopsies						
On-study tumor tissue			X			Refer to Section 8.8.1.4. An optional biopsy at End of Treatment is requested except in instances where the procedure poses unacceptable risks per Investigator documentation. The End of Treatment tumor biopsy should be performed before initiation of subsequent anti-cancer therapy and preferably no later than 7 days after the EOT visit.
Pharmacodynamic, Biomarker, and Immunogenicity Assessments						

Table 5. SoA for SCCHN Phase 1b and Phase 2 (Combination A): Cycle ≥ 3 and Post-Treatment

Procedure	Treatment Period (One Cycle = 28 Days)		Post-Treatment Period			Notes
	Cycle ≥ 3		ED or EOT	Short-Term Follow-up (30, 60, or 90 days post-dose)	Long-Term Follow-up (Every 12 Weeks)	Refer to Section 7.1 for additional information regarding ED, EOT, Short-term Follow-up, and Long-Term Follow-up.
	D1	D15				
Visit Window (Days)	±2	±2	+7	±3	±14	
[redacted]	[redacted]		[redacted]			[redacted]
[redacted]	[redacted]					[redacted]
Immunogenicity for avelumab (ADA and NAb)	X*		X			Collect approximately 3.5 mL whole blood. *Collections are within 2 hours prior to IV infusion on D1 for Cycles 3, 6, 9, and 12, and at EOT. Refer to Section 8.8.3.1 for details.
Immunogenicity for bempegaldesleukin (NKTR-214; ADA and NAb)	X*		X			Collect approximately 3.5 mL whole blood. *Collections are within 2 hours prior to IV infusion on D1 for Cycles 3, 6, 9, and 12, and at EOT. Refer to Section 8.8.3.2 for details.
Pharmacokinetic Assessments						

Table 5. SoA for SCCHN Phase 1b and Phase 2 (Combination A): Cycle ≥ 3 and Post-Treatment

Procedure	Treatment Period (One Cycle = 28 Days)		Post-Treatment Period			Notes
	Cycle ≥ 3		ED or EOT	Short-Term Follow-up (30, 60, or 90 days post-dose)	Long-Term Follow-up (Every 12 Weeks)	Refer to Section 7.1 for additional information regarding ED, EOT, Short-term Follow-up, and Long-Term Follow-up.
	D1	D15				
Visit Window (Days)	±2	±2	+7	±3	±14	
PK for avelumab	X*					Collect approximately 3.5 mL whole blood. *Collections are within 2 hours prior to IV infusion on D1 of Cycles 3, 6, 9, and 12. Refer to Section 8.5.1 for details.
PK for bempegaldesleukin (NKTR-214)	X*					**Phase 1b: all participants. Phase 2: a subset of approximately 20 participants from Combination A receiving RP2D.** Collect approximately 3.5 mL whole blood on *D1 of Cycles 3, 6, 9, and 12. Collections are within 2 hours prior to IV infusion and within 10 minutes after EOI. Refer to Section 8.5.2 for details.
Follow-up Assessments						
Subsequent Cancer Treatment				X	X	Refer to Section 7.1 for details.
Survival Assessment					X	Refer to Section 7.1 for details.

Table 5. SoA for SCCHN Phase 1b and Phase 2 (Combination A): Cycle ≥ 3 and Post-Treatment

Procedure	Treatment Period (One Cycle = 28 Days)		Post-Treatment Period			Notes
	Cycle ≥ 3		ED or EOT	Short-Term Follow-up (30, 60, or 90 days post-dose)	Long-Term Follow-up (Every 12 Weeks)	Refer to Section 7.1 for additional information regarding ED, EOT, Short-term Follow-up, and Long-Term Follow-up.
	D1	D15				
Visit Window (Days)	±2	±2	+7	±3	±14	

Abbreviations: ACTH=adrenocorticotropic hormone, ADA=anti-drug antibodies; AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BP=blood pressure; C=Cycle; C1D1=Cycle 1 Day 1; CRF=case report form; CCI [redacted] D=Day; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; ED=early discontinuation; EOI=end of infusion; EOT=end of treatment; CCI [redacted]; H&N=head and neck; HBV=hepatitis B virus; HCV=hepatitis C virus; HR=heart rate; IRR=infusion-related reaction; IV=intravenous; NAb=neutralizing antibodies; PD=progressive disease; PK=pharmacokinetic; CCI [redacted]; RNA=ribonucleic acid; SAE=serious adverse event; RP2D=recommended Phase 2 dose; SCCHN=squamous cell carcinoma of the head and neck; CCI [redacted] T4=thyroxine; CCI [redacted] TSH=thyroid stimulating hormone; WOCBP=women of childbearing potential.

1.3.3. Table 6. SoA for mCRPC Phase 1b and Phase 2 (Combinations B and C): Screening, Cycle 1, and Cycle 2

Table 6. SoA for mCRPC Phase 1b and Phase 2 (Combinations B and C): Screening, Cycle 1 and Cycle 2

Procedure	Screening	Treatment Period (One Cycle = 28 days)							Notes
		Cycle 1					Cycle 2		
		D1	D3	D4	D8	D15	D1	D8	D15	
Visit Window (Days)	-28 to -1	±0	±0	±0	±2	±2	±2	±2	±2	
Clinical Assessments										

Table 6. SoA for mCRPC Phase 1b and Phase 2 (Combinations B and C): Screening, Cycle 1 and Cycle 2

Procedure	Screening	Treatment Period (One Cycle = 28 days)								Notes
		Cycle 1					Cycle 2			
		D1	D3	D4	D8	D15	D1	D8	D15	
Visit Window (Days)	**-28 to -1**	**±0**	**±0**	**±0**	**±2**	**±2**	**±2**	**±2**	**±2**	
Informed consent	X									Refer to Section 10.1.3 in Appendix 1
Medical/Oncological History	X									
Tumor Assessments (including scans)	X									Refer to Section 8.1.1.2, Appendix 9 (RECIST v1.1), and Appendix 10 (PCWG3). Refer to Table 7 regarding continuing assessments for Cycle ≥3 and post-treatment.
Physical Examination	X	X								Complete physical examination at screening; brief physical exam at C1D1. Refer to Section 8.2.1 for details. Refer to Table 7 regarding continuing assessments for Cycle ≥3 and post-treatment.
Contraception Check	X	X					X			**Must be performed D1 of each cycle.** Refer to Appendix 4 and Section 5.3 for contraceptive guidance. Refer to Table 7 regarding continuing assessments for Cycle ≥3 and post-treatment.
ECOG Performance Status	X	X					X			Refer to Section 8.2.7 and Appendix 8 for ECOG performance status criteria. Refer to Table 7 regarding continuing assessments for Cycle ≥3 and post-treatment.
Vital Signs	X	X	X*	X*	X*	X	X		X	Record blood pressure, heart rate, height, and weight at screening; ***collect BP and HR only on C1 D3, D4 (72-96 hour window from D1 for D4, refer to PK assessments) and D8**; collect BP and HR pre-dose at all other visits, and include weight pre-dose at D1 of each cycle. Refer to Section 8.2.2. Refer to Table 7 regarding continuing assessments for Cycle ≥3 and post-treatment.

Table 6. SoA for mCRPC Phase 1b and Phase 2 (Combinations B and C): Screening, Cycle 1 and Cycle 2

Procedure	Screening	Treatment Period (One Cycle = 28 days)								Notes
		Cycle 1					Cycle 2			
		D1	D3	D4	D8	D15	D1	D8	D15	
Visit Window (Days)	**-28 to -1**	**±0**	**±0**	**±0**	**±2**	**±2**	**±2**	**±2**	**±2**	
12-Lead ECG	X	X					X			**Phase 1b**: 12-lead ECGs should be performed at screening (singlet) and on Day 1 of Cycles 1 and 2 (triplicate), prior to any pre-dose PK collection (within 2 hours) and prior to post-dose avelumab PK collection (within 10 minutes after the end of avelumab infusion); then singlet 12-lead ECGs should be performed as clinically indicated. **Phase 2:** Singlet 12-lead ECGs should be performed if clinically indicated. Refer to Section 8.2.5 for details.
ECHO/MUGA (LVEF determination)	X*									*Perform prior to six months of screening. Refer to Section 8.2.6.
CCI [redacted]		[redacted]					[redacted]			[redacted]
Laboratory assessments (must be performed pre-dose during the treatment period). Laboratory tests may be performed up to 3 days prior to the scheduled clinic visit so that results will be available for review before study treatment administration. Unless otherwise noted, refer to Section 8.2.3 and Appendix 2 for additional information on Laboratory Assessments. Refer to Table 7 regarding continuing assessments for Cycle ≥3 and post-treatment.										
Hematology/Blood for lymphocyte count	X	X	X	X*	X	X	X		X	Collect approximately 8 mL whole blood **(*72-96 hour window from D1 for D4).** Refer to Section 8.1.2.1, Section 8.2.3, and Appendix 2 for further details. Prior to study drug administration on Days 1 and 15 of each treatment cycle, hematology (ie, hemoglobin, platelets, and white blood cells) tests must be performed and results reviewed by the treating physician prior to study drug administration. Refer to Table 7 regarding continuing assessments for Cycle ≥3 and post-treatment.

Table 6. SoA for mCRPC Phase 1b and Phase 2 (Combinations B and C): Screening, Cycle 1 and Cycle 2

Procedure	Screening	Treatment Period (One Cycle = 28 days)								Notes
		Cycle 1					Cycle 2			
		D1	D3	D4	D8	D15	D1	D8	D15	
Visit Window (Days)	**-28 to -1**	**±0**	**±0**	**±0**	**±2**	**±2**	**±2**	**±2**	**±2**	
Blood Test for Circulating Tumor Cells (CTC)	X	X								**Combination C only**. Collect approximately 10-mL blood within 2 hours pre-dose on D1. Refer to Section 8.1.2.2. Refer to Table 7 regarding continuing assessments for Cycle ≥3.
PSA Antibody Test*	X	X†					X			Collect approximately 5 mL whole blood. Refer to Section 8.1.2.3. *Conduct at screening and then every 4 weeks (D1 of each cycle) within 2 hours pre-dose. †There is a 7-day window allowed for PSA labs from C1D1. Refer to Table 7 regarding continuing assessments for Cycle ≥3 and post-treatment.
Testosterone	X									Collect approximately 5 mL whole blood. Refer to Section 8.1.2.4.
Blood Chemistry	X	X				X	X		X	Collect approximately 4 mL whole blood prior to study drug administration on Days 1 and 15 of each treatment cycle. Chemistry (ie, ALT, AST, alkaline phosphatase, total bilirubin, blood urea nitrogen, creatinine, sodium, potassium, lipase, amylase, and glucose) tests must be performed and results reviewed by the treating physician prior to study drug administration. Refer to Section 8.2.3 and Appendix 2 for further details. Refer to Table 7 regarding continuing assessments for Cycle ≥3 and post-treatment.
Coagulation	X	X*					X*			Collect approximately 4 mL whole blood. Conduct at screening and then ***at D1 for C1 and C2 for Phase 1b only.**
Thyroid Function and ACTH Tests*	X									Collect approximately 4 mL whole blood. *Free T4, TSH, and ACTH must be performed at screening and at least every 8 weeks during study treatment (ie, every two cycles; D1 of C3, C5, C7, etc.). Refer to Table 7 regarding continuing assessments for Cycle ≥ 3 and post-treatment.
Urinalysis	X									Conduct at screening and then additionally if clinically indicated.
Hepatitis B and C Virus tests	X									Collect approximately 5 mL whole blood for HBV surface antigen and anti-HCV antibody tests. If anti-HCV antibody test is positive, participants must be tested for HCV RNA.

Table 6. SoA for mCRPC Phase 1b and Phase 2 (Combinations B and C): Screening, Cycle 1 and Cycle 2

Procedure	Screening	Treatment Period (One Cycle = 28 days)								Notes
		Cycle 1					Cycle 2			
		D1	D3	D4	D8	D15	D1	D8	D15	
Visit Window (Days)	**-28 to -1**	**±0**	**±0**	**±0**	**±2**	**±2**	**±2**	**±2**	**±2**	
Enrollment, Study Treatment, and Safety										
Enrollment/treatment assignment		X								Refer to Section 6.3 for details.
Pre-treatment for bempegaldesleukin (NKTR-214)		X				X	X		X	Participants should receive at least one liter of IV fluids at each dosing of bempegaldesleukin (NKTR-214) to prevent hypotension as per Section 6.1.2.1.1 (particularly in Cycle 1 and Cycle 2). Consider if anti-hypertensive medications should be withheld. Refer to Table 7 regarding continuing treatments for Cycle ≥3.
Study treatment (bempegaldesleukin [NKTR-214])		X				X	X		X	Refer to Section 6.1.2 for treatment details. Refer to Table 7 regarding continuing treatments for Cycle ≥3. Participants should be carefully monitored for infusion reactions during administration. If an acute infusion reaction is noted, participants should be managed according to Table 12 in Section 6.6.1
Pre-medication for avelumab		X				X	X		X	In order to mitigate IRRs, premedication with an antihistamine and with paracetamol (acetaminophen) 30 to 60 minutes prior to the first 4 infusions of avelumab is mandatory, as per Section 6.1.1.3.1. Refer to Table 7 regarding continuing treatments for Cycle ≥3.
Study treatment (avelumab)		X				X	X		X	Refer to Section 6.1.1 for treatment details. Refer to Table 7 regarding continuing treatments for Cycle ≥3. Participants should be carefully monitored for infusion reactions during administration. If an acute infusion reaction is noted, participants should be managed according to Table 11 in Section 6.6.1
Study treatment Combination B (Talazoparib)		→	→	→	→	→	→	→	→	Daily dosing until EOT. Refer to Section 6.1.3.2 for details.

Table 6. SoA for mCRPC Phase 1b and Phase 2 (Combinations B and C): Screening, Cycle 1 and Cycle 2

Procedure	Screening	Treatment Period (One Cycle = 28 days)								Notes
		Cycle 1					Cycle 2			
		D1	D3	D4	D8	D15	D1	D8	D15	
Visit Window (Days)	**-28 to -1**	**±0**	**±0**	**±0**	**±2**	**±2**	**±2**	**±2**	**±2**	
Study treatment Combination C (Enzalutamide)		→	→	→	→	→	→	→	→	Daily dosing until EOT. Refer to Section 6.1.4.2 for details.
Concomitant Therapy	X	→	→	→	→	→	→	→	→	Refer to Section 6.5 for details. Refer to Table 7 regarding continuing assessments for Cycle ≥3 and post-treatment.
Reporting of AEs and SAEs	X	→	→	→	→	→	→	→	→	Refer to Appendix 3 for details. Refer to Table 7 regarding continuing assessments for Cycle ≥3 and post-treatment.
Tumor Biopsies										
Mandatory Tumor Tissue	X									Refer to Section 8.8.1.2
Mandatory baseline tumor tissue for DDR Defect Assessment (**Combination B only**)	X									Refer to Section 8.8.1.3 **Phase 2 only**. Tissue should be sent in the form of 15 unstained slides, positively charged and unbaked at 4-5 microns thick, and one original (not recut) H&E slide. The portion of the tumor sections used should optimally measure 5×5 mm and contain minimally 20% and optimally 40% or greater tumor nuclei.

Table 6. SoA for mCRPC Phase 1b and Phase 2 (Combinations B and C): Screening, Cycle 1 and Cycle 2

Procedure	Screening	Treatment Period (One Cycle = 28 days)								Notes
		Cycle 1					Cycle 2			
		D1	D3	D4	D8	D15	D1	D8	D15	
Visit Window (Days)	**-28 to -1**	**±0**	**±0**	**±0**	**±2**	**±2**	**±2**	**±2**	**±2**	
CCI [redacted]		[redacted]								[redacted]
Pharmacodynamic, Biomarker, and Immunogenicity Assessments										
Saliva sample for germline comparator		X								Collect pre-dose. Refer to Section 8.8.2.1
Saliva sample for targeted germline DDR assessment (Combination B only)		X								**Collect pre-dose for Phase 2 Combination B only**. Refer to Section 8.8.2.2.
CCI [redacted]		[redacted]								[redacted]
[redacted]		[redacted]								[redacted]

Table 6. SoA for mCRPC Phase 1b and Phase 2 (Combinations B and C): Screening, Cycle 1 and Cycle 2

Procedure	Screening	Treatment Period (One Cycle = 28 days)								Notes
		Cycle 1					Cycle 2			
		D1	D3	D4	D8	D15	D1	D8	D15	
Visit Window (Days)	**-28 to -1**	**±0**	**±0**	**±0**	**±2**	**±2**	**±2**	**±2**	**±2**	
CCI [redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]				[redacted]	[redacted]			[redacted]
Immunogenicity for avelumab (ADA and NAb)		X					X			Collect approximately 3.5 mL whole blood. Collections are pre-dose, within 2 hours prior to infusion. Refer to Section 8.8.3.1 for details. Refer to Table 7 regarding continuing assessments for Cycle ≥3 and post-treatment.
Immunogenicity for bempegaldesleukin (NKTR-214; ADA and NAb)		X					X			Collect approximately 3.5 mL whole blood. Collections are pre-dose, within 2 hours prior to infusion. Refer to Section 8.8.3.2 for details. Refer to Table 7 regarding continuing assessments for Cycle ≥3 and post-treatment.
Pharmacokinetic Assessments										
PK for avelumab		X				X	X		X	Collect approximately 3.5 mL whole blood. All collections are within 2 hours prior to IV infusion and within 10 minutes after EOI. Refer to Section 8.5.1 for details. Refer to Table 7 regarding continuing assessments for Cycle ≥3 and post-treatment.

Table 6. SoA for mCRPC Phase 1b and Phase 2 (Combinations B and C): Screening, Cycle 1 and Cycle 2

Procedure	Screening	Treatment Period (One Cycle = 28 days)								Notes
		Cycle 1					Cycle 2			
		D1	D3	D4	D8	D15	D1	D8	D15	
Visit Window (Days)	**-28 to -1**	**±0**	**±0**	**±0**	**±2**	**±2**	**±2**	**±2**	**±2**	
PK for bempegaldesleukin (NKTR-214)		X*	X	X†	X		X	X		**Phase 1b: all participants. Phase 2: a subset of approximately 20 participants from each Combinations B and C receiving RP2D.** CCI [redacted] a 3.5-mL whole blood. *Collect approximately 3.5 mL whole blood at the following timepoints for C1D1: within 2 hours prior to IV infusion, within 10 minutes after EOI, and 2 hours from start of infusion (approximately 1.5 hours post-EOI). For C2D1, collect within 2 hours pre-dose and within 10 minutes after EOI. †72-96 hour window from C1D1 for C1D4 collection. Refer to Section 8.5.2 for details. Refer to Table 7 regarding continuing assessments for Cycle ≥3 and post-treatment.
PK for talazoparib (Combination B only)		X					X			Collect approximately 3.0-mL whole blood. Collections are within 2 hours pre-dose. Refer to Section 8.5.3 for details. Refer to Table 7 regarding continuing assessments for Cycle ≥3 and post-treatment.
PK for enzalutamide and N-desmethyl-enzalutamide (Combination C only)		X					X			Collect approximately 3.0-mL whole blood and isolate plasma for analysis. Collections are within 2 hours pre-dose. Refer to Section 8.5.4 for details. Refer to Table 7 regarding continuing assessments for Cycle ≥3 and post-treatment.

Abbreviations: ACTH=adrenocorticotropic hormone, ADA=anti-drug antibodies; AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BP=blood pressure; C=Cycle; C1D1=Cycle 1 Day 1; CRF=case report form; CTC=circulating tumor cells; CCI [redacted] D=Day; ECG=electrocardiogram; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; EOI=end of infusion; CCI [redacted] HBV=hepatitis B virus; HCV=hepatitis C virus; HR=heart rate; IRR=infused-related reaction; IV=intravenous; LVEF=left ventricular ejection fraction; mCRPC=metastatic castration-resistant prostate cancer; MUGA=multigated acquisition; NAb=neutralizing antibodies; PK=pharmacokinetic; PCWG3=prostate cancer working group 3; PD=progressive disease; PSA=prostate-specific antigen; CCI [redacted] RNA=ribonucleic acid; RP2D=recommended Phase 2 dose; SAE=serious adverse event; CCI [redacted] T4=thyroxine; CCI [redacted] TSH=thyroid stimulating hormone.

1.3.4. Table 7. SoA for mCRPC Phase 1b and Phase 2 (Combinations B and C): Cycle ≥ 3 and Post-treatment

Table 7. SoA for mCRPC Phase 1b and Phase 2 (Combinations B and C): Cycle ≥ 3 and Post-Treatment

Procedure	Treatment Period (One Cycle = 28 Days)		Post-Treatment Period			Notes
	Cycle ≥ 3		ED or EOT	Short-Term Follow-up (30, 60, or 90 days post-dose)	Long-Term Follow-up (Every 12 Weeks)	Refer to Section 7.1 for additional information regarding ED, EOT, Short-term Follow-up, and Long-Term Follow-up.
	D1	D15				
Visit Window (Days)	**±2**	**±2**	**+7**	**±3**	**±14**	
Clinical Assessments						
Tumor Assessments (including scans)	Every 8 weeks (±7 days) after C1D1. After 52 weeks from C1D1, then every 12 weeks (±7 days) until progressive disease, including during follow-up and long-term follow-up after end of treatment, for participants who discontinue treatment due to reasons other than PD.					Refer to Section 8.1.1.2, Appendix 9 (RECIST v1.1) and Appendix 10 (PCWG3) for details.
Physical Examination	X		X	X (30 day visit only)		Brief physical exam. Refer to Section 8.2.1 for details.
Contraception Check	X		X	X (30 day visit only)		**Must be performed D1 of each cycle**. Refer to Appendix 4 and Section 5.3 for contraceptive guidance.
ECOG Performance Status	X		X	X (30 day visit only)		Refer to Section 8.2.7 and Appendix 8 for ECOG performance status criteria.
Vital Signs*	X	X	X	X (30 day visit only)		***Collect BP and HR (pre-dose on D1 and D15 of all Cycles) at all visits, and include weight pre-dose at D1 of each cycle, EOT, and at the 30-day follow-up visit.** Refer to Section 8.2.2.
12-Lead ECGs						Conduct a 12-lead singlet reading if clinically indicated.

Table 7. SoA for mCRPC Phase 1b and Phase 2 (Combinations B and C): Cycle ≥ 3 and Post-Treatment

Procedure	Treatment Period (One Cycle = 28 Days)		Post-Treatment Period			Notes
	Cycle ≥ 3		ED or EOT	Short-Term Follow-up (30, 60, or 90 days post-dose)	Long-Term Follow-up (Every 12 Weeks)	Refer to Section 7.1 for additional information regarding ED, EOT, Short-term Follow-up, and Long-Term Follow-up.
	D1	D15				
Visit Window (Days)	**±2**	**±2**	**+7**	**±3**	**±14**	
CCI [redacted]	[redacted]		[redacted]	[redacted]		[redacted]
Laboratory Assessments (must be performed pre-dose during the treatment period). Laboratory tests may be performed up to 3 days prior to the scheduled clinic visit so that results will be available for review before study treatment administration. Unless otherwise stated, refer to Section 8.2.3 and Appendix 2 for additional information on Laboratory Assessments.						
Hematology	X	X	X	X (30 Day Visit only)		Collect approximately 8 mL whole blood**.** Prior to study drug administration on Days 1 and 15 of each treatment cycle, hematology (ie, hemoglobin, platelets, and white blood cells) tests must be performed and results reviewed by the treating physician prior to study drug administration. Refer to Section 8.1.2.1, Section 8.2.3, and Appendix 2 for details.
Blood Test for Circulating Tumor Cells (CTC)	X*					**Combination C only**. Collect approximately 10 mL whole blood within 2 hours pre-dose ***on D1 of C3 and C4 only**. Refer to Section 8.1.2.2.
PSA Antibody Test*	X		X			Collect approximately 5 mL whole blood. Refer to Section 8.1.2.3. *Conduct every 4 weeks (D1 each cycle) within 2 hours pre-dose, and at EOT.

Table 7. SoA for mCRPC Phase 1b and Phase 2 (Combinations B and C): Cycle ≥ 3 and Post-Treatment

Procedure	Treatment Period (One Cycle = 28 Days)		Post-Treatment Period			Notes
	Cycle ≥ 3		ED or EOT	Short-Term Follow-up (30, 60, or 90 days post-dose)	Long-Term Follow-up (Every 12 Weeks)	Refer to Section 7.1 for additional information regarding ED, EOT, Short-term Follow-up, and Long-Term Follow-up.
	D1	D15				
Visit Window (Days)	±2	±2	+7	±3	±14	
Blood Chemistry	X	X	X	X (30 Day Visit only)		Collect approximately 4 mL whole blood prior to study drug administration on Days 1 and 15 of each treatment cycle. Chemistry (ie, ALT, AST, alkaline phosphatase, total bilirubin, blood urea nitrogen, creatinine, sodium, potassium, lipase, amylase, and glucose) tests must be performed and results reviewed by the treating physician prior to study drug administration. Refer to Section 8.2.3 and Appendix 2 for details.
Thyroid Function and ACTH Tests*	X		X	X (30 Day Visit only)		Collect approximately 4 mL whole blood. *Free T4, TSH, and ACTH must be performed at least every 8 weeks during study treatment (ie, D1 of every two cycles; C3, C5, C7, etc.), at EOT, and at the 30-day short-term follow-up visit.
Urinalysis						Conduct if clinically indicated.
Study Treatments and Safety						
Pre-treatment for bempegaldesleukin (NKTR-214)	X*	X*				Participants may or may not receive at least one liter of IV fluids at each dosing of bempegaldesleukin (NKTR-214) to prevent hypotension as per Section 6.1.2.1.1 ***as per clinical judgement.** Consider if anti-hypertensive medications should be withheld.
Study treatment (bempegaldesleukin [NKTR-214])	X	X				Refer to Section 6.1.2 for treatment details. Participants should be carefully monitored for infusion reactions during administration. If an acute infusion reaction is noted, participants should be managed according to Table 12 in Section 6.6.1

Table 7. SoA for mCRPC Phase 1b and Phase 2 (Combinations B and C): Cycle ≥ 3 and Post-Treatment

Procedure	Treatment Period (One Cycle = 28 Days)		Post-Treatment Period			Notes
	Cycle ≥ 3		ED or EOT	Short-Term Follow-up (30, 60, or 90 days post-dose)	Long-Term Follow-up (Every 12 Weeks)	Refer to Section 7.1 for additional information regarding ED, EOT, Short-term Follow-up, and Long-Term Follow-up.
	D1	D15				
Visit Window (Days)	±2	±2	+7	±3	±14	
Pre-medication for avelumab						Not mandatory for Cycles ≥3 (ie, beyond the first four infusions); premedication should be administered for subsequent avelumab doses based on clinical judgment and presence/severity of prior infusion reactions, as per Section 6.1.1.3.1.
Study treatment (avelumab)	X	X				Refer to Section 6.1.1 for treatment details. Participants should be carefully monitored for infusion reactions during administration. If an acute infusion reaction is noted, participants should be managed according to Table 11 in Section 6.6.1
Study treatment Combination B (Talazoparib)	→	→				Daily dosing until EOT. Refer to Section 6.1.3.2 for details.
Study treatment Combination C (Enzalutamide)	→	→				Daily dosing until EOT. Refer to Section 6.1.4.2 for details.
Concomitant Therapy	→	→	→	X		Refer to Section 6.5 for details.

Table 7. SoA for mCRPC Phase 1b and Phase 2 (Combinations B and C): Cycle ≥ 3 and Post-Treatment

Procedure	Treatment Period (One Cycle = 28 Days)		Post-Treatment Period			Notes
	Cycle ≥ 3		ED or EOT	Short-Term Follow-up (30, 60, or 90 days post-dose)	Long-Term Follow-up (Every 12 Weeks)	Refer to Section 7.1 for additional information regarding ED, EOT, Short-term Follow-up, and Long-Term Follow-up.
	D1	D15				
Visit Window (Days)	**±2**	**±2**	**+7**	**±3**	**±14**	
Reporting of AEs and SAEs	→	→	→	X	X	Refer to Appendix 3.
Tumor Biopsies						
[redacted]	[redacted] CCI					[redacted]
Pharmacodynamic, Biomarker, and Immunogenicity Assessments						

Table 7. SoA for mCRPC Phase 1b and Phase 2 (Combinations B and C): Cycle ≥ 3 and Post-Treatment

Procedure	Treatment Period (One Cycle = 28 Days)		Post-Treatment Period			Notes
	Cycle ≥ 3		ED or EOT	Short-Term Follow-up (30, 60, or 90 days post-dose)	Long-Term Follow-up (Every 12 Weeks)	Refer to Section 7.1 for additional information regarding ED, EOT, Short-term Follow-up, and Long-Term Follow-up.
	D1	D15				
Visit Window (Days)	±2	±2	+7	±3	±14	
[redacted]	CCI					[redacted]
[redacted]	CCI					[redacted]
Immunogenicity for avelumab (ADA and NAb)	X*		X			Collect approximately 3.5 mL whole blood. *Collections are within 2 hours pre-dose on D1 for Cycles 3, 6, 9, and 12, and at EOT. Refer to Section 8.8.3.1 for details.
Immunogenicity for bempegaldesleukin (NKTR-214; ADA and NAb)	X*		X			Collect approximately 3.5 mL whole blood. *Collections are within 2 hours pre-dose on D1 for Cycles 3, 6, 9, and 12, and at EOT. Refer to Section 8.8.3.2 for details.
Pharmacokinetic Assessments						

Table 7. SoA for mCRPC Phase 1b and Phase 2 (Combinations B and C): Cycle ≥ 3 and Post-Treatment

Procedure	Treatment Period (One Cycle = 28 Days)		Post-Treatment Period			Notes
	Cycle ≥ 3		ED or EOT	Short-Term Follow-up (30, 60, or 90 days post-dose)	Long-Term Follow-up (Every 12 Weeks)	Refer to Section 7.1 for additional information regarding ED, EOT, Short-term Follow-up, and Long-Term Follow-up.
	D1	D15				
Visit Window (Days)	±2	±2	+7	±3	±14	
PK for avelumab	X*					Collect approximately 3.5 mL whole blood. *Collections are within 2 hours pre-dose on D1 of Cycles 3, 6, 9, and 12. Refer to Section 8.5.1 for details.
PK for bempegaldesleukin (NKTR-214)	X*					Phase 1b: all participants. Phase 2: a subset of approximately 20 participants from each Combinations B and C receiving RP2D. Collect approximately 3.5 mL whole blood on *D1 of Cycles 3, 6, 9, and 12. Collections are within 2 hours prior to IV infusion and within 10 minutes after EOI. Refer to Section 8.5.2 for details.
PK for talazoparib (Combination B only)	X*					Collect approximately 3.0-mL whole blood *within 2 hours pre-dose on D1 of C3 only. Refer to Section 8.5.3 for details.
PK for enzalutamide and N-desmethyl-enzalutamide (Combination C only)	X*					Collect approximately 3.0-mL whole blood and isolate plasma for analysis**.** *Collections are within 2 hours prior to IV infusion on D1 of Cycles 3 and 6 only. Refer to Section 8.5.4 for details.
Follow-up Assessments						

Table 7. SoA for mCRPC Phase 1b and Phase 2 (Combinations B and C): Cycle ≥ 3 and Post-Treatment

Procedure	Treatment Period (One Cycle = 28 Days)		Post-Treatment Period			Notes
	Cycle ≥ 3		ED or EOT	Short-Term Follow-up (30, 60, or 90 days post-dose)	Long-Term Follow-up (Every 12 Weeks)	Refer to Section 7.1 for additional information regarding ED, EOT, Short-term Follow-up, and Long-Term Follow-up.
	D1	D15				
Visit Window (Days)	±2	±2	+7	±3	±14	
Subsequent Cancer Treatment				X	X	Refer to Section 7.1 for details.
Survival Assessment					X	Refer to Section 7.1 for details.

Abbreviations: ACTH=adrenocorticotropic hormone, ADA=anti-drug antibodies; AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BP=blood pressure; C=Cycle; C1D1=Cycle 1 Day 1; CRF=case report form; CTC=circulating tumor cells; CCI [redacted] D=Day; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; ED=early discontinuation; EOI=end of infusion; EOT=end of treatment; CCI [redacted] HBV=hepatitis B virus; HCV=hepatitis C virus; HR=heart rate; IV=intravenous; IRR=infused-related reaction; mCRPC=metastatic castration-resistant prostate cancer; NAb=neutralizing antibodies; PCWG3=prostate cancer working group 3; PD=progressive disease; PK=pharmacokinetic; CCI [redacted] PSA=prostate-specific antigen; CCI [redacted] RNA=ribonucleic acid; RP2D=recommended Phase 2 dose; SAE=serious adverse event; CCI [redacted] T4=thyroxine; CCI [redacted] TSH=thyroid stimulating hormone.

2. INTRODUCTION

This Phase 1b/2 study will evaluate the combination of avelumab + bempegaldesleukin (NKTR-214; Combination A) in locally advanced (not amenable for curative intent) or metastatic squamous cell carcinoma of the head and neck (1L SCCHN) in a Phase 1b dose finding component followed by Phase 2 and avelumab + bempegaldesleukin (NKTR-214) + talazoparib (Combination B) or enzalutamide (Combination C) in metastatic castration-resistant prostate cancer (mCRPC) in Phase 1b dose finding components followed by Phase 2 in both combinations.

2.1. Study Rationale

2.1.1. Rationale for Combination A (Avelumab + Bempegaldesleukin [NKTR-214]) for SCCHN

Currently, there are 2 ongoing Phase 3 studies investigating avelumab and chemoradiotherapy in locally advanced (LA) SCCHN, study B9991016 (NCT02952586) and the Randomized Trial of Avelumab-cetuximab-radiotherapy versus SOCs in LA SCCHN (REACH) study (NCT02999087).

The combination of bempegaldesleukin (NKTR-214) with nivolumab in the PIVOT-02 study has shown preliminary evidence of clinical activity when referencing to anti-PD-1/PD-L1 single agents with significant clinical activity observed also in patients with PD-L1 negative disease. Consistent with the mechanisms of actions of both agents, increased T-cell infiltration was observed in the tumor micro-environment and conversion of baseline PD-L1 negative disease to PD-L1 positive disease was reported in serial biopsies from the PIVOT-02 study.[6]

Similar effect is expected when combining avelumab with bempegaldesleukin, and the combination may lead to increased PD-L1 expression and potentially improved anti-tumor activity over single-agent checkpoint inhibitors in 1L SCCHN. Indeed, in the KEYNOTE-048 Phase 3 study (NCT02358031) of pembrolizumab or pembrolizumab + chemotherapy vs. EXTREME (platinum-based chemotherapy + 5-fluorouracil [5-FU]) as

first-line systemic therapy for R/M SCCHN the observed clinical benefit was dependent on the PD-L1 expression level. The confirmed ORR was (pembrolizumab vs EXTREME) was 23% vs 36% for PD-L1 combined positive score (CPS) ≥20, 19% vs 35% for CPS ≥1, and 17% vs 36% for the total population. Also the observed overall survival benefit was dependent on the baseline PD-L1 expression level with a reported hazard ratio favoring pembrolizumab over EXTREME of 0.61 (95% CI :0.45-0.83) and 0.78 (95% CI: 0.64-0.96) for the CPS≥20 and CPS ≥1 populations, respectively.[7]

Therefore, the avelumab + bempegaldesleukin combination is expected to enhance anti-tumor activity over single-agent checkpoint inhibitor and provide a chemotherapy-free regimen to study participants with 1L SCCHN whose disease is positive or negative PD-L1 expression at baseline.

2.1.2. Rationale for Combination B (Avelumab + Bempegaldesleukin [NKTR-214] + Talazoparib) for mCRPC

Single agent treatment with immune checkpoint blockers, including avelumab, delivers only modest clinical benefit in prostate cancer and correlative studies have demonstrated that the prostate tumors are predisposed toward immunosuppression. As discussed above, the combination of bempegaldesleukin (NKTR-214) with nivolumab in the PIVOT-02 study demonstrated improved clinical activity referencing to anti-PD-1/PD-L1 single agents. Combination strategies aimed to enhance the immune recognition of the tumor create the potential for a therapeutically relevant treatment in prostate cancer. One proposed treatment combination for evaluation in this study is the triplet of avelumab + bempegaldesleukin + talazoparib (Combination B).

Proof of concept of PARPi efficacy in mCRPC with DNA Damage Repair (DDR) deficiency was established in a Phase 2 study (TOPARP-A) with olaparib, which enrolled men heavily pre treated with taxane based chemotherapy and novel hormonal therapy (NHT).[11] These results were further confirmed with rucaparib in a similar therapeutic setting in the TRITON2 phase 2 study where the observed confirmed ORR in mCRPC patients with BRCA1/2 defects was 45.5.0% (95% CI: 16.7, 76.6).[12]

A key aim of the Combination B in this study is to extend PARPi activity beyond BRCA deficiency to sustain and prolong responses to PARPi in mCRPC participants whose disease is positive for DDR defects (DDR+). The proposed triple combination has the potential to activate several non-overlapping immune mechanisms to synergize and induce potent anti-tumor immune response. Talazoparib would induce the activation of proinflammatory dentritic cells (DCs) via stimulation of the interferon genes (STING) pathway to prime and differentiate tumor specific CD8 T-cells.[15,16] As such, increased DNA damage via PARP inhibition is expected to enhance effective recognition and infiltration of tumors by immune cells. In keeping with this expectation, talazoparib has been shown to promote T-cell and NK cell infiltration and activation in a mouse model of ovarian cancer.[17] Bempegaldesleukin would allow the expansion of these CD8 T-cells as suggested by pre-clinical evidence that demonstrated improved anti-tumor activity for bempegaldesleukin + rucaparib in a BRCA-deficient and immuno-competent ovarian cancer model.[2,3] Additionally, talazoparib treatment has been shown to lead to increased expression of PD-L1 by tumor cell[18] suggesting that this may represent a mean by which tumors function to inhibit talazoparib-

mediated anti-tumor immunity. Addition of avelumab would release the checkpoint break with avelumab by overcoming PD-L1-mediated inhibition resulting in anti-tumor immune response.

In summary, the proposed triple combination may produce additive or synergistic anti-tumor activity with talazoparib, promoting immune priming and tumor immunogenicity and avelumab/bempegaldesleukin enhancing the anti-tumor immune response, so offering a therapeutic opportunity to patients with mCRPC after progression to taxane-based chemotherapy in the metastatic setting that currently represent an urgent unmet medical need.

2.1.3. Rationale for Combination C (Avelumab + Bempegaldesleukin [NKTR-214] + Enzalutamide) for mCRPC

The other proposed treatment combination for mCRPC for this study is the triplet of avelumab + bempegaldesleukin + enzalutamide (Combination C).

Results from the PIVOT-02 study of bempegaldesleukin with nivolumab also support the evaluation of avelumab plus bempegaldesleukin as the backbone of this triplet combination.[4]

Combination of immune checkpoint blockers with androgen receptor blockers and CD8 T-cell stimulants could improve the therapeutic outcome of mCRPC patients. In a study of enzalutamide in biochemically recurrent prostate cancer a preliminary analysis of 12 patients treated with a 3-month course of enzalutamide showed increases in NK cells and decreases in MDSC.[19] In addition, patients who experienced progression during enzalutamide treatment showed increased PD-L1 expression on dendritic cells[20] and encouraging evidence of clinical activity in patients were observed with pembrolizumab plus enzalutamide after progression on enzalutamide with prostate specific antigen (PSA) reduction ≥50% reported in 5 out of 28 (18%) patients and radiographic response observed in 3 out of 12 patients (ORR=25%) with measurable disease at baseline.[21] Moreover, the combination of pembrolizumab plus enzalutamide in mCRPC patients after abiraterone therapy failure induced PSA reduction ≥50% in 18 out of 54 patients (33%) and radiographic response observed in 5 out of 25 patients (ORR=20%) with measurable disease at baseline.[22]

Based on the above data, the proposed triplet combination could represent an effective strategy by enzalutamide enhancing NK cells and lowering MDSC, bempegaldesleukin generating a robust CD8 and NK cell level in the tumor tissue, and avelumab providing the release from the checkpoint blockade resulting from PD-L1-mediated inhibition of anti-tumor immune response. Therefore, Combination C may provide an innovative chemo-free treatment option to mCRPC patients after disease progression on abiraterone treatment.

2.1.4. Rationale for Phase 1b Study Design: Bayesian Logistic Regression Model (BLRM) Design

The relatively distinct safety profiles of avelumab, bempegaldesleukin (NKTR-214), talazoparib and enzalutamide support the clinical evaluation of the doublet (Combination A) and triplet (Combinations B and C) combinations. Overlapping adverse events observed with all 4 study interventions include fatigue and nausea. Diarrhea is common to avelumab and

talazoparib. Additionally, decreased appetite has been observed with avelumab, talazoparib and bempegaldesleukin (NKTR-214). Refer to the Investigator Brochures (IBs) for each respective study intervention for further information. In summary, there are a low number of overlapping severe adverse events (or immune-related AEs) reported at the dose levels proposed for testing in the present study.

Guidance for 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 BLRM. The BLRM provides an optimal design for dose finding with combination treatments as it 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 patient risk and increasing efficiency and precision during dose finding with combination treatments.

Refer to Appendix 11, Appendix 12, and Appendix 13 for the BLRM designs for Combinations A, B, and C, respectively.

2.2. Background

2.2.1. SCCHN

Head and neck cancers, including cancers of the oral cavity, nasopharynx, pharynx, and larynx, account for approximately 5% of cancers worldwide (excluding non-melanoma skin cancers).[23,24] Approximately 680,000 new cases of head and neck cancer were diagnosed in 2012 with 370,000 deaths attributed to this disease; of these new cases reported, almost 140,000 were in Europe, and over 90% were squamous cell histology. In the US, it is estimated that over 61,000 people will be diagnosed with head and neck cancer in 2016 and over 13,000 will die from this cancer.[25] Head and neck cancers are predominately squamous carcinomas. SCCHN involving the oral cavity, larynx, oropharynx, and hypopharynx account for 75% SCCHN overall and are closely associated with alcohol and tobacco use.

Of newly-diagnosed patients with SCCHN, approximately 60% present with locally or regionally advanced disease.[25,26] Combination modality therapy is generally employed for these patients and may include surgery with adjuvant radiotherapy for early stage disease and which is standard for more advanced disease.[25,27] The most widely used standard regimen used in this setting consists of 100 mg/m2 cisplatin administered every 3 weeks (Q3W), combined with ~70 Gray radiation delivered in 1.8-2.0 Gray daily fractions. Although associated with increased local control rates and overall survival (OS) compared to radiotherapy alone, this combination is also associated with increased toxicity. Additionally, depending on the tumor site, stage, and resectability, locoregional failure rates can range between 35% and 65%. With a median PFS of 1.9 years and reported 3-year PFS rate of 61.2%, this disease will ultimately recur locally in a large proportion of treated patients, with distant metastases developing in 10% to 30% of these patients.[26,28,29]

Treatment options for patients with recurrent SCCHN are limited to palliative chemotherapy and, in patients suitable for more aggressive treatment, combination systemic chemotherapy regimens.[25] Response rates to single-agent chemotherapy range from 15% to 35%, with a median OS of 6 months. There remains an unmet medical need for improved therapy for

locally recurrent (not amenable for curative intent) or metastatic SCCHN. In the KEYNOTE-048 study, the activity of pembrolizumab was determined to be dependent on PD-L1 expression, as evaluated in participants with squamous cell carcinoma of the head and neck (HNSCC).[7] The study met a primary endpoint of overall survival (OS) as monotherapy in participants whose tumors expressed PD-L1 (combined proportion score [CPS] ≥ 20).

2.2.2. Prostate Cancer

Prostate cancer is the second leading cause of cancer death in men. The American Cancer Society estimates that up to 174,650 men in the United States (US) were diagnosed with prostate cancer and approximately 31,620 will die of the disease in 2019.[30] In Europe in 2012, prostate cancer was the third most common cancer, with an estimated 416,700 new cases and 92,200 deaths.[30,23]

The androgen receptor (AR) signaling axis, the principal driver of prostate cancer growth, has been targeted by castration and other systemic therapies. However, a proportion of tumors progress despite castrate levels of testosterone, at which point the disease is considered castration resistant. Metastatic castration-resistant prostate cancer (mCRPC) represents a lethal transition in the progression of prostate cancer, with most patients ultimately succumbing to the disease.[31] Molecular profiling studies have revealed that the AR remains functional in a majority of progressing tumors. Rationally designed therapies targeting the AR signaling pathway in the castrate setting include enzalutamide, a novel AR signaling inhibitor active in the presence of AR overexpression; and abiraterone acetate/prednisone, an inhibitor of 17,20 lyase (an androgen biosynthetic enzyme overexpressed in castration-resistant prostate cancer (CRPC).[32] These therapies have conferred improved overall survival and radiographic progression free survival (PFS) benefit compared with prednisone or placebo in patients with mCRPC, in both pre- and post-chemotherapy settings. Enzalutamide plus androgen-derived therapy (ADT) versus ADT alone was evaluated also in 1,401 patients with non-metastatic castration-resistant prostate cancer (NM CRPC) in the PROSPER study. This study met its primary endpoint, demonstrating that the use of enzalutamide plus ADT significantly reduced the risk of developing metastasis or death compared to ADT alone. The median for the primary endpoint, metastasis free survival (MFS), was 36.6 months for men who received enzalutamide compared to 14.7 months with ADT alone (n=1401; hazard ratio=0.29 [95% CI: 0.24, 0.35]; p<0.0001.[33] As such, the Food and Drug Administration (FDA) has approved enzalutamide also for the treatment of patients with NM CRPC in July 2018 based on the results of the study.

In the same setting, in February 2018, the FDA approved apalutamide, next generation nonsteroidal antiandrogen, for patients with NM CRPC. In the SPARTAN study, apalutamide significantly improved MFS in patients with nonmetastatic castration resistant prostate cancer. The estimated median MFS was 40.5 months for patients receiving apalutamide and 16.2 months for those receiving placebo (hazard ratio = 0.28; 95% CI: 0.23, 0.35; p<0.0001.[34]

Taxane-based chemotherapy (docetaxel, cabazitaxel) has been shown to improve PFS and OS with mCRPC. At present, patients whose disease progresses on novel hormonal agents are recommended treatment with taxane-based chemotherapy, based on retrospective series

supporting efficacy, although no randomized study data are available. Additionally, many patients with advanced prostate cancer may not be candidates for taxane-based chemotherapy due to their comorbidities or performance status or may prefer to delay treatment with such chemotherapy as a last resort. Thus, a significant unmet medical need remains for new therapeutic options for men with mCRPC whose disease progresses on novel hormonal agents or on taxane-based chemotherapy. In addition to improved characterization of the heterogeneity of the disease and advances in predictive biomarkers to better identify specific genomic aberrations to inform patient care, innovative combination treatment remains a critical need.

2.2.3. Avelumab

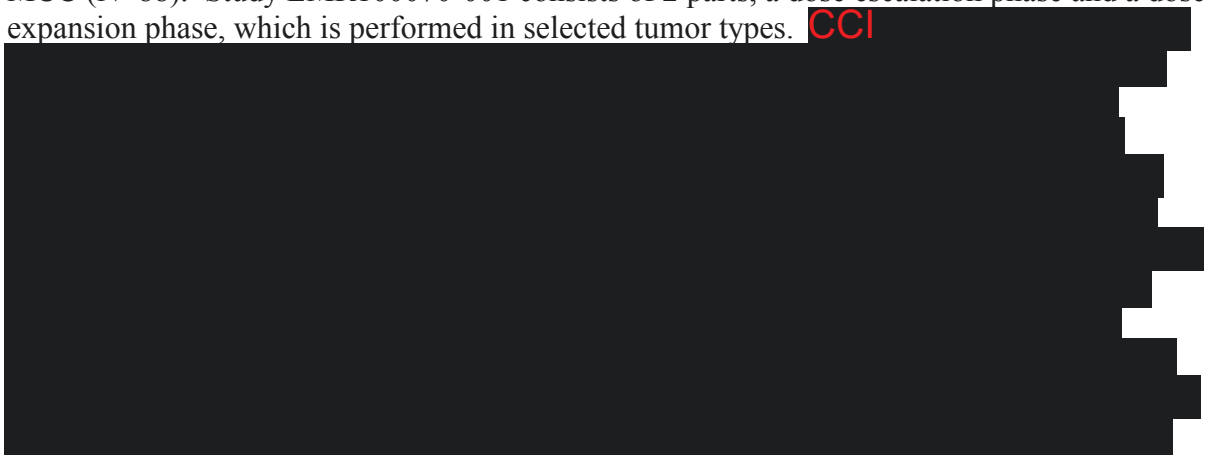
Avelumab is a human immunoglobulin (Ig)G1 monoclonal antibody (mAb) directed against programmed death ligand 1 (PD-L1). Avelumab is currently being investigated as single agent and in combination with other anti-cancer therapies in patients with locally advanced or metastatic solid tumors and various hematological malignancies. In March 2017, avelumab received accelerated approval by the United States (US) Food and Drug Administration (FDA) as the first approved treatment for metastatic Merkel cell carcinoma (MCC) followed by approvals in Japan, Australia, European Union, Switzerland, and Israel. In May 2017, avelumab received accelerated approval by the US Food and Drug Administration (FDA) for the treatment of patients with locally advanced or metastatic urothelial cancer (UC) with disease progression during or following platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy. In January 2018, avelumab was approved for the same indication in Israel.

2.2.3.1. Avelumab Mechanism of Action

Avelumab selectively binds to PD-L1 and competitively blocks its interaction with programmed death receptor 1 (PD-1), thereby interfering with this key immune checkpoint inhibition pathway.

2.2.3.2. Avelumab Clinical Experience

The safety profile of avelumab administered intravenously (IV) as single agent at a dose of 10 mg/kg every 2 weeks (Q2W) has been characterized primarily in 1738 adult patients from studies EMR100070-001 in various solid tumors (N=1650) and EMR100070-003 Part A in MCC (N=88). Study EMR100070-001 consists of 2 parts, a dose escalation phase and a dose expansion phase, which is performed in selected tumor types. CCI



CCI [redacted]

2.2.4. Bempegaldesleukin (NKTR-214)

Bempegaldesleukin (NKTR-214) is a CD122-biased cytokine agonist conjugated with multiple releasable chains of polyethylene glycol designed to provide sustained signaling through the heterodimeric interleukin-2 (IL-2) receptor pathway to preferentially activate and expand effector CD8+ T and NK cells over regulatory T-cells in the tumor microenvironment developed by Nektar Therapeutics. CCI [redacted]

Bempegaldesleukin (NKTR-214) is currently being evaluated in combination with other anti-cancer therapies, including anti-PD1 (Nektar study PIVOT-02), in patients with advanced locally advanced or metastatic solid tumors.

2.2.4.1. Bempegaldesleukin (NKTR-214) Mechanism of Action

Bempegaldesleukin (NKTR-214) is a prodrug of a conjugated cancer immunotherapy cytokine that exerts its biological activity by binding to the IL-2 receptor and subsequent activation of effector T-cells. As a polyethylene glycol (PEG)ylated human recombinant IL-2 molecule of aldesleukin with six releasable polyethylene glycol chains, bempegaldesleukin (NKTR-214) can be administered conveniently in the outpatient setting using an antibody-like dosing regimen. The polymer conjugation renders the cytokine initially inactive; upon intravenous administration, the PEG chains slowly release via hydrolysis to generate the active cytokine species (2-PEG-IL-2 and 1-PEG-IL-2) that have a peak plasma concentration 24 to 48 hours after infusion. The slow generation of the 2-PEG-IL-2 and 1 PEG IL 2 significantly mitigates the rapid-onset, systemic cytokine-related toxicities associated with high dose IL-2.

The polymer conjugation of bempegaldesleukin (NKTR-214) promotes biased signaling through the IL-2 receptor beta gamma (IL-2Rβγ). This unique feature preferentially increases the proliferation, activation, and effector functions of tumor antigen-specific CD8+ T-cells and NK cells within the tumor microenvironment without expanding unwanted intra-tumoral regulatory T-cells that are activated through IL-2Rαβγ.[2,3] Specifically, the location of the bempegaldesleukin (NKTR-214) PEG chains interferes with the IL-2 alpha subunit responsible for the undesirable effect of activating regulatory T-cells in the tumor while continuing to permit binding to the IL-2Rβγ (CD122) receptor.

Bempegaldesleukin (NKTR-214) also correspondingly promotes expression of PD-1 on the surface of CD8+ T cells and induction of a Type II interferon gene signature, driving cell surface expression of programmed cell death ligand 1 (PD-L1) on tumor cells.[5]

The immunogenic properties of bempegaldesleukin (NKTR-214) with the induction of tumor infiltrating lymphocytes and upregulation of the PD-1/PD-L1 axis makes this compound a potentially promising combination therapy for use with immune checkpoint inhibitors that target and inhibit the PD-1/PD-L1 pathway. Moreover, the side effect profile of bempegaldesleukin (NKTR-214) generally does not overlap with that of checkpoint inhibitors, further supporting the use of this compound as a potentially complimentary combination partner with immune checkpoint inhibitors.

2.2.4.2. Bempegaldesleukin (NKTR-214) Clinical Experience

CCI

CCI

2.2.4.3. Bempegaldesleukin (NKTR-214) plus Nivolumab Clinical Experience

The PIVOT-02 study was a Phase 1/2 open-label, multicenter, dose-escalation and dose expansion study of bempegaldesleukin (NKTR-214) in combination with nivolumab in patients with local advanced or metastatic solid tumors.

CCI [redacted]

The combination of bempegaldesleukin (NKTR-214) with nivolumab in the PIVOT-02 study has showed preliminary evidence of improved clinical activity with the observed response rates comparing favorably when referencing to anti-PD-1/PD-L1 single agents data sets from phase 3 studies; clinical activity was observed also in patients with PD-L1 negative disease.[5] Consistent with the mechanisms of actions of both agents, increased T-cell infiltration was observed in tumors and conversion of baseline PD-L1 negative disease to PD-L1 positive disease at week 3 of treatment was reported in serial biopsies from 7/10 patients in the PIVOT-02 study.[6]

Efficacy data for the dose escalation population alone or for those patients enrolled in the dose escalation phase at the RP2D in combination with patients enrolled in dose expansion populations are presented below for the efficacy evaluable population (defined as having received one dose of study treatment and having undergone at least one scan).

Dose Escalation Phase

CCI [redacted]

Dose Expansion Phase

As of the 07 February 2018 cutoff date, ORR and disease control rate (DCR) in 24 RCC (1L) patients was 54% and 79%; 20/24 of the RCC patients had known PD-L1 status. ORR was 4/7 (57%) for PD-L1(+) patients and 7/13 (54%) for PD-L1(-) pts. ORR and DCR in 6 NSCLC (1-2L) patients was 50% and 67%; 5/6 patients had known PD-L1 status. ORR was 3/5 (60%) in PD-L1(-) patients.[5] As of 11 October 2018, in the urothelial cancer (UC) expansion cohort, the ORR was 48%, (13 of 27 efficacy-evaluable patients) with 19% (5/27)

CR and 30% (8/27) PR. There was no significant difference in the ORR between PD-L1 negative and PD-L1 positive tumors.[6]

Refer to the bempegaldesleukin (NKTR-214) IB for additional information on clinical study outcomes for efficacy and safety.

2.2.5. Talazoparib

Talazoparib is a potent, orally bioavailable poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor, which is cytotoxic to human cancer cell lines harboring gene mutations that compromise deoxyribonucleic acid (DNA) repair, an effect referred to as synthetic lethality, and by trapping PARP protein on DNA thereby preventing DNA repair, replication, and transcription.[9] Talazoparib was approved by the Food and Drug Administration (FDA) on 16 October 2018 for the treatment of adults with deleterious or suspected deleterious germline Breast Cancer susceptibility gene (BRCA) mutated human epidermal growth factor receptor 2 negative (HER2-) locally advanced or metastatic breast cancer.[10]

2.2.5.1. Talazoparib Mechanism of Action

Talazoparib is a particularly potent PARP trapper, a property that is associated with cytotoxicity in preclinical models.[9] Single agent treatment with talazoparib demonstrates potent antitumor effects in tissue culture studies, mouse tumor xenograft models, and in Phase 1 studies in patients with solid tumors. Talazoparib has also been shown to enhance the cytotoxic effects of DNA damaging chemotherapy.

PARP1 and PARP2 play important roles in DNA repair.[35,36] Following DNA damage, PARP1 and PARP2 bind to single stranded DNA breaks, cleave nicotinamide adenine dinucleotide, and attach multiple ADP ribose units to the target protein, including itself.[15,36,37,38] The outcome is a highly negatively charged protein, which leads to the unwinding of the DNA strands and recruitment of proteins to repair the damaged DNA through the base excision repair process. When PARP1 and PARP2 are inhibited, single strand DNA breaks persist, resulting in stalled replication forks and conversion of single strand breaks into double strand breaks. These breaks must be repaired by homologous recombination or nonhomologous end joining or they may become lethal. Thus, inhibition of PARP catalytic activity results in synthetic lethality as defects in homologous recombination DNA repair prevent double strand breaks from being repaired, thereby killing the cell, including cancer cells.

In addition, PARP inhibitors bind to PARP DNA complexes (ie, become trapped), thereby inhibiting DNA repair, replication, and transcription, which is cytotoxic to cancer cells. Although other PARP inhibitors possess both activities (ie, inhibition of PARP catalytic activity and PARP trapping), in vitro studies demonstrated that talazoparib is a more potent PARP trapper than other PARP inhibitors in clinical development, a property that has been associated with significant cytotoxicity in preclinical models.[9,39]

2.2.5.2. Talazoparib Clinical Experience

In the Phase 1 Study PRP-001, in patients treated with talazoparib 1.0 mg/day with advanced breast cancer, ovarian/peritoneal cancer, and pancreatic cancer, an ORR of 50.0% (7 of 14)) and 20% (2 of 10) was observed, respectively.

Proof of concept of PARPi efficacy in metastatic castration-resistant prostate cancer (mCRPC) with DNA Damage Repair (DDR) deficiency was established in a Phase 2 study (TOPARP-A) with olaparib, which enrolled men heavily pre- treated with taxane based chemotherapy and novel hormonal therapy (NHT). Of the 49 patients evaluable for response (defined either as an objective response according to Response Evaluation Criteria in Solid Tumors [RECIST] v1.1, or as a reduction of at least 50% in the prostate specific antigen [PSA] level or a confirmed reduction in the circulating tumor cell [CTC] count from 5 or more cells per 7.5 mL of blood to less than 5 cells per 7.5 mL), 16 patients achieved a response (33%; 95% CI: 20.0, 48.0). Homozygous deletions, deleterious mutations, or both were identified in DNA repair genes in 16 patients (33%) and 14 of these patients (88%) achieved a response.[11] These results were further confirmed with rucaparib in a similar therapeutic setting in the TRITON2 Phase 2 study where the observed confirmed objective response rate (ORR) in mCRPC patients with BRCA1/2 defects was 45.5.0% (95% CI 16.7-76.6).[12] In addition, the combination of durvalumab and olaparib was evaluated in a Phase 1/2 study in 17 patients with mCRPC after progression on NHT and chemotherapy. Overall, 8 out of 17 patients had a reduction in PSA level ≥50% from baseline. PSA level reductions were observed mainly in patients with mutations in DNA repair pathways, but also in some patients without alteration.[13] In alignment with these findings, the combination of pembrolizumab and olaparib in the KEYNOTE-365 study showed early evidence of clinical activity in mCRPC patients whose disease was negative for homologous recombination defects (HRD) after treatment with taxane based chemotherapy and NHT with a reported ORR of 7% (95% CI 1-23), and disease control rate ≥6 months of 32% (95% CI 16–52) in patients with measurable disease.[14]

Study B9991025 is an ongoing Phase 1b/2, open-label, multi-center, study of avelumab in combination with talazoparib in adult patients with locally advanced (primary or recurrent) or metastatic solid tumors. During Phase 1b, 12 patients with locally advanced or metastatic solid tumors who met eligibility criteria were treated with talazoparib 1.0 mg administered orally once daily in combination with a fixed dose of avelumab 800 mg IV Q2W in 28-day cycles (dose level D0), and were evaluated for DLTs. The modified toxicity probability interval (mTPI) method was used to identify the RP2D for talazoparib in combination with avelumab using a DLT rate of <0.33.[40] The target patient enrollment for each cohort was 3-6 patients. Three DLTs were reported among the 12 DLT-evaluable patients enrolled in phase 1b (grade 3 neutropenia n=1 and grade 3 thrombocytopenia n=2) so the MTD and RP2D for the combination was estimated to be dose level D0. The most frequently reported treatment-emergent adverse events (TEAEs) were cytopenias and chills, which are consistent with the risk profiles of talazoparib and avelumab, respectively. Although Phase 1b was comprised of only 12 DLT-evaluable patients, the frequency of the TEAEs following administration of avelumab in combination with talazoparib were generally consistent with the frequency of TEAEs following administration of the study drugs as single agents. The TEAEs leading most frequently to dose interruptions were thrombocytopenias and

neutropenias, and were generally consistent with events leading to dose interruptions of talazoparib single agent in the talazoparib development program. In summary, the safety profile of the combination of avelumab with talazoparib at full dose remains aligned to the safety profiles from the individual components and is generally manageable.

In the ongoing Phase 2 study in patients with locally advanced or metastatic breast cancer harboring BRCA mutations (Study 673201, ABRAZO), independently assessed objective response (OR) has been observed in 21% of 48 participants with disease progression after prior response to platinum containing regimens and in 37% of 35 patients with disease progression after 3 or more non-platinum cytotoxic regimens.[41]

In the ongoing Phase 3, open-label, randomized, parallel-group study (protocol no. 673-301 [EMBRACA]), talazoparib was evaluated in patients with germline BRCA 1/2 mutations who received no more than 3 prior chemotherapy regimens for locally advanced or metastatic breast cancer. Median progression-free survival (PFS) was 8.6 months (95% confidence interval (CI): 7.2, 9.3) for patients treated with talazoparib and 5.6 months (95% CI: 4.2, 6.7) for those treated with chemotherapy [hazard ratio: 0.54 (95% CI: 0.41, 0.71), p<0.0001].[42] Talazoparib is currently being investigated as a single-agent (including Pfizer Study TALAPRO-1 in men with mCRPC positive for DDR defects who have previously received taxane-based chemotherapy and progressed on at least 1 novel hormonal agent) and in combination with other anti-cancer therapies, including avelumab (Pfizer studies B9991025, B9991032, and B9991033) and enzalutamide (Pfizer study TALAPRO-2 in men with mCRPC with no prior systemic treatments initiated after documentation of mCRPC) in patients with locally advanced or metastatic solid tumors. Refer to the talazoparib IB for additional information on clinical study outcomes for efficacy and safety.[43]

2.2.6. Enzalutamide

Enzalutamide is an androgen receptor inhibitor currently being evaluated in combination with other anti-cancer therapies, including anti-PD1 or anti-PD-L1 and PARPi, in patients with mCRPC. Enzalutamide has demonstrated single-agent clinical activity in patients with mCRPC. The benefit of enzalutamide on this population has been consistently observed across multiple studies. The clinical safety profile of enzalutamide supports its use as both a single agent and in combination with other cancer therapies. Enzalutamide was approved by the FDA in August 2012 for the treatment of patients with late-stage mCRPC, and subsequently was approved for the treatment of patients with non-metastatic (NM) CRPC in July 2018.

2.2.6.1. Enzalutamide Mechanism of Action

Enzalutamide acts by inhibiting the binding of androgens to the androgen receptor (AR), androgen receptor nuclear translocation, and androgen receptor-mediated DNA binding. In multiple prostate cancer cell lines that specifically model CRPC (LNCaP/AR, VCaP, W741C LNCaP), the consequences of enzalutamide treatment include inhibition of AR-induced gene transcription, reduced cell proliferation, increased cell death by apoptosis and tumor regression. In a mouse xenograft model of CRPC using prostate cancer cells that overexpress the AR (LNCaP/AR), enzalutamide inhibits tumor growth and reduces tumor size.[44]

2.2.6.2. Enzalutamide Clinical Experience

Enzalutamide prolonged overall survival (OS) versus placebo for chemotherapy-naïve men with mCRPC and men who had progressed on docetaxel therapy (PREVAIL and AFFIRM studies, respectively).

The efficacy of enzalutamide in study participants with mCRPC has and continues to be assessed in > 10 clinical studies including participants who were chemotherapy-naïve as well as those who previously received docetaxel: 3 Phase 4 open-label studies: MDV3100-10, 9785-CL-0410 and 9785-MA-1008; and 2 additional Phase 3, randomized, placebo-controlled studies: 9785-CL-0232 and 9785-MA-1001.

Preliminary results from the ARCHES study (NCT02677896) demonstrated that enzalutamide plus androgen deprivation therapy (ADT) also significantly improved radiographic progression-free survival (rPFS) compared with ADT alone in patients with hormone-sensitive metastatic prostate cancer (mHSPC). Enzalutamide acts by inhibiting the binding of androgens to the androgen receptor, androgen receptor nuclear translocation, and androgen receptor-mediated DNA binding and is currently being evaluated in combination with other anti-cancer therapies in Phase 3 studies, including atezolizumab (NCT03016312) and pembrolizumab (NCT03834493) in patients with mCRPC.

Efficacy is also being assessed in participants with nonmetastatic prostate cancer in 2 Phase 3, randomized, placebo-controlled studies (MDV3100-13 and MDV3100-14). MDV3100-14 (PROSPER Study) enzalutamide in combination with androgen deprivation therapy (ADT) reduced the risk of developing metastases or death by 71% compared to ADT alone in participants with non-metastatic (M0) CRPC. As of the data cutoff date for the IB, data for study MDV3100-13 (in participants with high-risk, nonmetastatic hormone sensitive prostate cancer progressing after definitive therapy) has not yet been analyzed.

Enzalutamide has been evaluated in more than 8000 participants enrolled worldwide in completed and ongoing clinical trials, including more than 5500 participants with prostate cancer who received at least 1 dose of enzalutamide (160 mg daily [QD]). Refer to the enzalutamide IB[44] for additional information on clinical study outcomes for efficacy and safety.

2.3. Benefit/Risk Assessment

The benefit risk relationship has been carefully considered in the planning of this trial.

Avelumab was initially dosed per body weight at a dose of 10 mg/kg Q2W in the expansion cohorts of the ongoing Phase 1 Study EMR 100070-001, as described in Section 2.2.3.2.

CCI [redacted]

The 10 mg/kg Q2W avelumab dosing regimen was approved by the FDA in 2017 as the first treatment for Merkel cell carcinoma. In this clinical study a flat dose regimen of 800 mg IV Q2W, as approved by the FDA in 2018, will be used throughout all combinations.

CCI [redacted] and no differences in the overall safety profile for patients with SCCHN and mCRPC relative to all patients. Most of the observed adverse events in patients were either in line with those expected in patients with advanced solid tumors or with similar class effects of mAbs blocking the PD-1/PD-L1 axis. Infusion-related reactions (IRRs), manifesting most frequently as low grade chills during or shortly after the first infusion and managed by infusion interruption and infusion rate reduction, as well as immune-related adverse events (irAEs; mostly represented by thyroid disorders) have been identified as important risks for avelumab. Respective risk mitigation measures have been implemented in all ongoing clinical studies with avelumab, including this study. These measures include guidelines for treatment interruption and discontinuation in case of toxicities, guidelines for steroid treatment implementation, and mandatory pre-treatment with an antihistamine and acetaminophen prior to the first 4 infusions of avelumab and as clinically indicated thereafter.

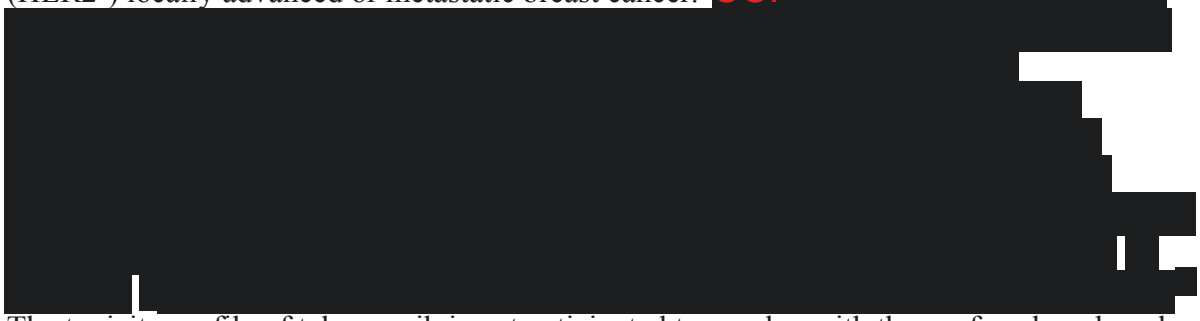
The bempegaldesleukin (NKTR-214) clinical development program has included Phase 1/2 studies in patients with multiple tumor types, including melanoma, renal cell cancer (RCC), non-small cell lung cancer (NSCLC), urothelial carcinoma, bladder cancer, triple-negative breast cancer (TNBC), colorectal cancer (CRC), and sarcoma. Bempegaldesleukin (NKTR-214) has been generally well-tolerated both as single-agent and in combination with nivolumab in clinical trials to date at doses up to 0.009 mg/kg Q3W, as described in Section 2.2.4.2, Section 2.2.4.3, [redacted] CCI .

CCI [redacted] While infusion related reactions are reported for both assets, they are expected to be distinguishable by the timing of onset of symptoms and risk mitigation measures with mandatory pre-treatment to prevent events will be implemented. Further close participant monitoring during the first 8 days and treatment guidelines in case AEs occur will also be implemented in order to safeguard participants.

Based on the manageable safety profiles of avelumab and bempegaldesleukin (NRTR-214) and the anticipated enhanced anti-tumor activity, the benefit-risk relationship of avelumab given in combination with bempegaldesleukin (NKTR-214) is expected to be favorable and it is considered appropriate to proceed with the proposed clinical investigation in participants with 1L SCCHN.

Talazoparib has shown anti-tumor activity in patients with breast, ovarian, peritoneal and pancreatic cancers, as described in Section 2.2.5.2 [redacted] CCI The anti-tumor activity of single agent talazoparib has been demonstrated in the EMBRACA study in

BRCA1/2 positive patients with locally advanced and/or metastatic breast cancer, in which talazoparib provided a significantly superior ORR and PFS benefit as compared to standard chemotherapy.[42,45] Based on these results, talazoparib was approved by the FDA in 2018 for the treatment of adults with deleterious or suspected deleterious germline Breast Cancer susceptibility gene (BRCA) mutated human epidermal growth factor receptor 2 negative (HER2-) locally advanced or metastatic breast cancer. CCI



The toxicity profile of talazoparib is not anticipated to overlap with those of avelumab and bempegaldesleukin (NKTR-214) and the same mitigation measures and participant monitoring as described above for the doublet combination will be implemented in order to safeguard participants.

Based on the manageable safety profiles of avelumab, bempegaldesleukin (NRTR-214) and talazoparib and the anticipated enhanced anti-tumor activity, the benefit-risk relationship of avelumab given in combination with bempegaldesleukin (NKTR-214) and talazoparib is expected to be favorable and it is considered appropriate to proceed with the proposed clinical investigation in participants with mCRPC.

Enzalutamide has demonstrated single-agent clinical activity in patients with mCRPC, as described in Section 2.2.6.2. The benefit of enzalutamide on this population has been consistently observed across multiple studies and is approved in this indication. Enzalutamide was approved in the United States in 2012 for the treatment of patients with mCRPC who have previously received docetaxel. Enzalutamide has subsequently been approved for the treatment of adult men with mCRPC who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy (ADT) in whom chemotherapy is not yet clinically indicated. The clinical safety profile of enzalutamide at a dose of 160 mg daily supports its use as both a single agent and in combination with other cancer therapies.

The grade ≥ 3 TEAEs that were identified in ≥ 1% of patients with non-metastatic or metastatic CRPC treated with enzalutamide, and with ≥ 0.5% higher incidence over placebo, in combined Phase 3 studies (2799 patients total) are as follows: hypertension (4.6% enzalutamide vs 1.8% placebo), fatigue (3.5% vs 2.5%), fall (1.0% vs 0.5%), asthenia (1.6% vs 1.1%), pneumonia (1.4% vs 0.8%) and spinal cord compression (3.1% vs 2.2%).[44] Based on the manageable safety profiles of avelumab, bempegaldesleukin (NRTR-214) and enzalutamide and the anticipated enhanced anti-tumor activity, the benefit risk relationship of avelumab given in combination with bempegaldesleukin (NKTR-214) and enzalutamide is expected to be favorable and it is considered appropriate to proceed with the proposed clinical investigation in participants with mCRPC. The toxicity profile of enzalutamide is not anticipated to overlap with those of avelumab and bempegaldesleukin (NKTR-214) and

the same mitigation measures and patient monitoring as described above for the doublet combination will be implemented in order to safeguard participants.

In summary, based on the available clinical safety and efficacy data for each single agent, and the strength of the scientific hypotheses under evaluation for the combination of avelumab with bempegaldesleukin (NKTR-214) as a doublet in 1L SCCHN participants (Combination A) and as triplets adding either talazoparib (Combination B) or enzalutamide (Combination C), respectively in mCRPC participants, and the anticipated positive benefit-risk ratio, this clinical trial is being proposed for evaluation in patient populations having currently limited treatment options available.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of avelumab, bempegaldesleukin (NKTR-214), talazoparib, or enzalutamide may be found in the Investigator's Brochures, which are the single reference safety documents (SRSDs) for this study.

2.4. Drug-Drug Interactions

CCI [redacted]

Likewise, the DDI potential among avelumab, bempegaldesleukin (NKTR-214) and talazoparib or enzalutamide is minimal because the DDI between small molecule drugs (talazoparib & enzalutamide) and biologics (avelumab & bempegaldesleukin (NKTR-214)) is uncommon given each class of drug has distinct clearance pathways.

Although no DDI is expected in each combination, PK samples for each drug (avelumab, talazoparib and enzalutamide) will be collected from all enrolled participants in Phase 1b and Phase 2. For bempegaldesleukin (NKTR-214), PK samples will be collected from all enrolled participants in Phase 1B and a subset of approximately 20 participants receiving RP2D in each combination in Phase 2. Concentrations will be measured and compared to historical PK data for each drug when administered alone to rule out any potential DDI.

3. OBJECTIVES, ESTIMANDS AND ENDPOINTS

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	**Phase 1b:** • DLT during the DLT evaluation period (Cycle 1)

(**Combination B)** or enzalutamide (**Combination C)** in order to determine the recommended Phase 2 dose (RP2D) for the combinations.	
Phase 2: • **Combination A**: To assess ORR of avelumab in combination with bempegaldesleukin (NKTR-214) in participants with locally recurrent or metastatic SCCHN. • **Combination B:** To assess soft tissue ORR of avelumab in combination with bempegaldesleukin (NKTR-214) and talazoparib in participants with DDR defect positive mCRPC. • **Combination C:** To assess the PSA response rate of avelumab in combination with bempegaldesleukin (NKTR-214) and enzalutamide in participants with mCRPC after progression on abiraterone.	**Phase 2:** • **Combination A**: Confirmed objective response (OR) as determined by the investigator using RECIST v1.1 (Appendix 9). • **Combination B**: Confirmed soft tissue OR as determined by the investigator using RECIST v 1.1 (Appendix 9) 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 (Appendix 10). • **Combination C:** Confirmed prostate specific antigen (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	• Time-to-event endpoints as determined by the investigator, using RECIST v1.1

activity.	(**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 (Appendix 9) with no evidence of confirmed bone disease progression on repeat bone scan at least 6 weeks later per PCWG3 criteria (Appendix 10). • **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 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), talazoparib, enzalutamide and N-desmethyl-enzalutamide and maximum concentrations (C_{max}) for avelumab and

	bempegaldesleukin (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 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.

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Estimands

This section defines the estimands associated with the primary endpoints of the study. For all estimands, refer to Section 9.1.

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 DDR defect positive 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 4.1. 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 Section 9.4.1) 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 9.4.1) will be calculated.

4. STUDY DESIGN

4.1. Overall 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). Refer to the study schema, Section 1.2.

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 the recommended Phase 2 dose (RP2D). Refer to Table 8 for the potential dose levels. A minimum of 9 participants will be enrolled.

Step 2. Upon the determination of the RP2D for Combination A, the dose-finding for Phase 1b for Combinations B and C in participants with mCRPC will commence and will be conducted in parallel with the Phase 2 Combination A portion of the study to determine the RP2D for Combinations B and C separately. A minimum of 9 participants will be enrolled in each combination.

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). Refer to Appendix 11, Appendix 12, and Appendix 13 for the BLRM designs for Combinations A, B, and C, respectively. 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.

Step 1. Dose-Finding for Combination A

The potential dose levels of avelumab and bempegaldesleukin for dose finding for Combination A are shown in Table 8. The starting dose level is 800 mg avelumab intravenous (IV) every 2 weeks (Q2W) plus 0.006 mg/kg bempegaldesleukin IV Q2W, which satisfies the Escalation With Overdose Control (EWOC) criterion that the risk for excessive toxicity is less than 0.25. For the starting dose level, the risk of excessive toxicity was estimated to be 13.7% based on information from prior single-agent Phase 1 studies and a pharmacokinetic (PK) assessment of no potential significant drug-drug interaction. Dose reduction of bempegaldesleukin (NKTR-214) to 0.003 mg/kg Q2W will be triggered if higher than expected toxicity is observed at the higher dose (risk of excessive toxicity ≥ 0.25).

Table 8. Phase 1b Combination A 1L SCCHN Avelumab + Bempegaldesleukin (NKTR-214) Dose Levels

Dose Level	Avelumab dose IV (mg Q2W)	Bempegaldesleukin dose IV (NKTR-214) (mg/kg Q2W)
D0	800	0.006
D-1	800	0.003

1L SCCHN= locally recurrent squamous cell carcinoma of the head and neck; D0=starting dose; D-1=reduced dose; IV= intravenous; mg= milligram; Q2W= every 2 weeks.

Step 2: Dose-Finding for Combinations B and C

The potential dose levels of avelumab, bempegaldesleukin (NKTR-214) and talazoparib for dose finding for Combination B are listed in Table 9. The dose level for avelumab is fixed at 800 mg Q2W. The starting dose level for bempegaldesleukin (NKTR-214) and talazoparib will be determined at the completion of the dose finding for Combination A based on available clinical data (including but not limited to safety and PK/pharmacodynamic data). The lowest allowed dose for bempegaldesleukin (NKTR-214) will be 0.003 mg/kg and the lowest allowed dose for talazoparib will be 0.5 mg once daily, in which case participants with moderate renal impairment cannot be enrolled. The starting dose for talazoparib for participants with moderate renal impairment (creatinine clearance [CrCL] 30-59 mL/min) will be reduced by 1 dose level unless the determined starting dose for talazoparib for participants with no or mild renal impairment is 0.5 mg once daily.

Table 9. Phase 1b Combination B mCRPC Avelumab, Bempegaldesleukin (NKTR-214), and Talazoparib Dose levels

Dose Level	Avelumab Dose IV (mg Q2W)	Bempegaldesleukin (NKTR-214) IV (mg/kg Q2W)	Talazoparib Dose PO (mg once daily)
D0-A*	800	0.006	1.0
D-1A	800	0.006	0.75
D-2A	800	0.006	0.5
D0-B*	800	0.003	1.0
D-1B	800	0.003	0.75
D-2B	800	0.003	0.5

Table 9. Phase 1b Combination B mCRPC Avelumab, Bempegaldesleukin (NKTR-214), and Talazoparib Dose levels

Dose Level	Avelumab Dose IV (mg Q2W)	Bempegaldesleukin (NKTR-214) IV (mg/kg Q2W)	Talazoparib Dose PO (mg once daily)

D0= starting dose; D-1=reduced dose; D-2=second reduced dose; IV= intravenous; mCRPC=metastatic castration-resistant prostate cancer; mg= milligram; PO=orally; Q2W= every 2 weeks.
*Dose levels for Combination B designated with 'A' are applicable if the bempegaldesleukin (NKTR-214) dose is 0.006 mg/kg Q2W; dose levels for Combination B designated with 'B' are applicable if the bempegaldesleukin (NKTR-214) dose is 0.003 mg/kg Q2W.

The potential dose levels of avelumab, bempegaldesleukin (NKTR-214), and enzalutamide for dose finding for Combination C are listed in Table 10. The starting dose level for bempegaldesleukin (NKTR-214) and enzalutamide will be determined at the completion of the dose finding for Combination A based on available clinical data (including but not limited to safety and PK/pharmacodynamic data). The approved label dose for enzalutamide is 160 mg QD. The target starting enzalutamide dose to be used in Combination C is 160 mg QD unless unexpected safety issues require its lowering according to the BLRM recommendation. In both the KEYNOTE-199 study (pembrolizumab + enzalutamide in mCRPC) and the IMbassador250 study (atezolizumab + enzalutamide in mCRPC), the full monotherapy dose of enzalutamide was used as the starting dose. The lowest allowed dose for bempegaldesleukin (NKTR-214) will be 0.003 mg/kg and the lowest allowed dose for enzalutamide will be 80 mg once daily.

Table 10. Phase 1b Combination C mCRPC Avelumab, Bempegaldesleukin (NKTR-214), and Enzalutamide Dose levels

Dose Level	Avelumab Dose IV (mg Q2W)	Bempegaldesleukin (NKTR-214) IV (mg/kg Q2W)	Enzalutamide Dose PO (mg once daily)
D0-A*	800	0.006	160
D-1A	800	0.006	120
D-2A	800	0.006	80
D0-B*	800	0.003	160
D-1B	800	0.003	120
D-2B	800	0.003	80

D0= starting dose; D-1=reduced dose; D-2=second reduced dose; IV= intravenous; mCRPC=metastatic castration resistant prostate cancer; mg= milligram; PO=orally; Q2W= every 2 weeks.
*Dose levels for this Combination C designated with 'A' are applicable if the bempegaldesleukin (NKTR-214) dose is 0.006 mg/kg Q2W; dose levels for Combination C designated with 'B' are applicable if the bempegaldesleukin (NKTR-214) dose is 0.003 mg/kg Q2W.

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) as follows:

- Participants who withdraw from study treatment in Cycle 1 before receiving at least 2 doses of bempegaldesleukin (NKTR-214) and avelumab and at least 75% of the planned dose of talazoparib (Combination B) or enzalutamide (Combination C) for reasons other than treatment-related toxicity are not evaluable for DLT. All participants deemed non-evaluable for DLT may be replaced.

- A minimum of 3 DLT-evaluable participants from each cohort will be required; additional participants will be enrolled in the specific enrollment cohort to replace participants who are not considered DLT-evaluable, where required.

- When all DLT-evaluable participants treated in a given enrollment cohort have completed the DLT observation period or experienced a DLT, whichever occurs first, the posterior distribution for the risk of DLT for new participants at different dose levels for the combination of interest will be evaluated.

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

    - Underdosing: [0, 0.16)

    - Target toxicity: [0.16, 0.33)

    - Excessive toxicity or overdosing: [0.33, 1]

In addition to accumulating safety data and observed DLTs, decisions on further participant enrollment and dose level selection will be guided by the EWOC criterion. A combination dose may only be used for newly enrolled participants if the risk of excessive toxicity at that combination dose is less than 0.25.

A dose level combination is a potential candidate for being the maximum tolerated dose (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.

An RP2D below the MTD may be determined based on other safety, clinical activity, PK, and pharmacodynamic (PD) data. Nine DLT-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.

Phase 2 Design

Once the Phase 1b component 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. Refer to Table 9 and Table 10 for the potential dose levels for Combinations B and C, respectively.

4.1.1. DLT Determination

The Combinations A, B, and C will be administered in 28-day cycles, and the DLT evaluation period will be the first treatment cycle. The severity of AEs will be graded according to CTCAE v. 4.03. For the purpose of dose finding, any of the following AEs occurring in the first cycle of treatment which are attributable to any or all agents 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 x 109/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 x 10^9/L, and Grade >3 infection).
- Grade 3 thrombocytopenia (25,000/mm^3 or 25.0 x 10^9/L to <50,000/ mm^3 or <50.0 x 10^9/L) with bleeding, or grade 4 thrombocytopenia (platelet count <25,000/mm^3 or <25.0 x 10^9/L.

Non-Hematologic:

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

4.2. Scientific Rationale for Study Design

Refer to Section 2.1 for the Study Rationale. CCI [redacted]

4.3. Justification for Dose

4.3.1. Avelumab + Bempegaldesleukin (NKTR-214): Combination A

Modeling and simulation was performed to support the use of a flat dose regimen in selected clinical studies. Avelumab was developed using a mg/kg regimen in order to reduce inter-subject variability in drug exposure. However, emerging data for mAbs, including the marketed PD-1 and PD-L1 immune checkpoint inhibitors nivolumab,[46] pembrolizumab, and atezolizumab[47] reveal that body weight based dose regimens do not result in less variability in measures of exposure compared to fixed (ie, body weight independent) dose regimens. The same has been confirmed for avelumab using simulations based on population PK models. Simulation showed that exposures to avelumab across the available range of body weights are less variable with 800 mg IV Q2W compared with 10 mg/kg IV Q2W; exposures were similar near the population median weight.[47] Furthermore, the 800 mg IV Q2W dose regimen is expected to result in C_{trough} > 1 mg/mL required to maintain avelumab serum concentrations at > 95% target occupancy (TO) throughout the entire dosing interval in all weight categories. Further, fixed dosing is expected to provide more consistent dosing across body weights, minimize drug wastage, facilitate preparation and administration, and reduce pharmacy errors.

Furthermore, avelumab has been administered safely as a fixed dose regimen of 800 mg IV every 2 weeks in previous Pfizer clinical trials and the fixed dose regimen of 800 mg IV every 2 weeks proposed for this study is currently the FDA approved dose for both UC and MCC.[1]

FDA guidance for co-development of two drugs recommends starting at the maximum dose for both agents if a) single agent toxicity profiles are known and b) no overlapping toxicity is expected. Therefore, it is proposed to start at the maximum dose levels of 800 mg IV and 0.0006 mg/kg IV Q2W for avelumab and bempegaldesleukin (NKTR-214), respectively.

The proposed starting dose level (D0) of 800 mg avelumab intravenous IV Q2W plus 0.006 mg/kg bempegaldesleukin (NKTR-214) IV Q2W, which satisfies the Escalation With Overdose Control (EWOC) criterion.

CCI [redacted]

CCI [redacted] Based on these data, the proposed starting dose in Combination A for bempegaldesleukin (NKTR-214) is 0.006 mg/kg IV Q2W to match the Q2W dosing schedule of avelumab for participant convenience.

CCI [redacted]

The observations noted in the studies described in Section 2.2, coupled with the established avelumab dosing schedule of Q2W, provide support for exploring the evaluation of bempegaldesleukin (NKTR-214) plus avelumab utilizing the Q2W dosing schedule in this study.

4.3.2. Avelumab + Bempegaldesleukin (NKTR-214) + Talazoparib (Combination B); Avelumab + Bempegaldesleukin (NKTR-214) + Enzalutamide (Combination C)

The starting dose levels for bempegaldesleukin (NKTR-214), talazoparib and enzalutamide will be determined at the completion of the dose finding for the Combination A based on the observed clinical data (including but not limited to safety and PK data). An approved dose level for all investigational products as single agents is proposed, provided this is supported by both the DLT data and available combination data to support the claim of these dose levels.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure and visit shown in the Schedule of Activities, has died, withdrawn consent for any further participation in the study or has been lost to follow-up, whichever occurs earlier.

The end of the study is defined as the date of study completion for the last participant in the trial globally or at sponsor discretion if the data support ending the study.

For all combinations, participants clinically benefiting from study treatment without unacceptable toxicity, objective disease progression, or withdrawal of consent will be given the opportunity to continue treatment after study discontinuation by the sponsor. Participants without other options for treatment may continue on treatment with the combination to which they have been assigned upon agreement with the sponsor.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled.

The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a participant is suitable for this protocol.

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

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participants must be ≥ 18 years old.

Type of Participant and Disease Characteristics

2. Participants must have histological diagnosis of solid tumors, as follows:

   a. Combination A: Locally recurrent (not amenable for curative intent) or metastatic squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx; and both of the following:

   - No prior systemic treatment for unresectable locally recurrent or metastatic disease. **Exception:** If prior systemic chemotherapy treatment was given as part of chemoradiotherapy treatment, disease-free interval after the last administration of systemic chemotherapy treatment must be at least 6 months.
   - Measurable disease by RECIST v1.1 (Appendix 9) with at least 1 measurable lesion.

   b. Combination B or C: mCRPC without small cell features meeting all of the following criteria:

   - Castration as defined by both of the following:
     - Serum testosterone ≤1.73 nmol/L (50 ng/dL) at the time of enrollment (prior to treatment with study drug on Cycle 1 Day 1 [C1D1]).
     - Bilateral orchiectomy or ongoing androgen deprivation therapy with a gonadotropin releasing hormone (GnRH) agonist/antagonist (surgical or medical castration).
   - Progressive disease at the time of enrollment (prior to treatment with study drug on C1D1) defined as 1 or more of the following 3 criteria:

- A minimum of 3 consecutive rising PSA values with an interval of at least 1 week between determinations. The screening PSA value must be ≥2 µg/L (2 ng/mL) if qualifying solely by PSA progression;

- Radiographic soft tissue disease progression as defined by RECIST v1.1 (Appendix 9) for soft tissue;

- Radiographic bone disease progression defined by Prostate Cancer Working Group 3 (PCWG3; Appendix 10) with 2 or more new metastatic lesions on bone scan (confirm ambiguous results by other imaging modalities).

- **Combination B participants must meet all of the following:**

  - Progressed on at least 1 line of second generation anti-androgen therapy (eg, enzalutamide and/or abiraterone acetate/prednisone) for treatment of mCRPC.

  - Have received at least 1, but no more than 1, prior taxane-based chemotherapy regimen for mCRPC, or were deemed unsuitable, declined, or did not have access to these therapies. No other prior chemotherapy regimen for mCRPC is allowed. Participants may have received radium-223 or sipuleucel-T, which does not count for a line of prior chemotherapy regimen.

  - Measurable disease by RECIST v1.1 (Appendix 9) with at least 1 measurable lesion.

  - CCI

- **Combination C:**

  - Participants with non-measurable disease (including disease affecting bone only) as determined by RECIST v1.1 (Appendix 9) are allowed.

  - Participants must have progressed on 1 line of abiraterone acetate/prednisone anti-androgen therapy for treatment of mCRPC.

  - Participants must have not had any prior chemotherapy for the treatment of mCRPC. Prior treatment with radium 223 or sipuleucel-T is allowed and it does not count as a prior chemotherapy regimen.

3. All participants must provide tumor tissue as described in Section 8.1.

4. Participants must have an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0 or 1 (Appendix 8).

5. Participants must have adequate bone marrow function without hematopoietic growth factor or transfusion support within 14 days prior to and including C1D1:

   a. Absolute Neutrophil Count (ANC) ≥1,500/mm^3 or ≥1.5 x 10^9/L;

   b. Platelets ≥100,000/mm^3 or ≥100 x 10^9/L;

   c. Hemoglobin ≥9 g/dL (or ≥5.6 mmol/L).

6. Participants must have adequate renal function by C1D1, defined by an estimated creatinine clearance (CrCl) ≥30 mL/min. CrCl should be estimated according to the Cockcroft-Gault formula as:

   CrCl={[(140 − age) × weight)]/(72 x S_{CR}[serum creatinine])} × 0.85 (if female), where CrCl (creatinine clearance) is measured in mL/min, age is expressed in years, weight in kilograms (kg), and S_{CR} in mg/dL.

7. Participants must have adequate liver function by C1D1, including:

   a. Total serum bilirubin ≤1.5 × the upper limit of normal range (ULN);

   b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 x ULN (if liver test abnormalities are due to hepatic metastasis, then AST and ALT ≤5 x ULN)

Sex

8. Male or Female

Contraceptive use by men with the ability to father a child or women of childbearing potential (Combination A only regarding the latter) must meet requirements outlined in

Appendix 4 and should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

a. Male participants:

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 30 days after the last dose of avelumab, at least 3 months after the last dose of enzalutamide or bempegaldesleukin (azospermic males are exempt from contraceptive requirements for bempegaldesleukin [NKTR-214]), and at least 4 months after the last dose of talazoparib, which corresponds to the time needed to eliminate study interventions. In addition, male participants MUST:

- Refrain from donating sperm
- PLUS either:
  - Be abstinent from intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

  OR

  - Use an additional highly effective contraceptive method with a failure rate of <1% per year as described below and in Appendix 4 for a female partner of childbearing potential. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.
- Must agree to use contraception/barrier as detailed below:
  - Agree to use a male condom when engaging in any activity that allows passage of ejaculate to another person.

b. Female participants (Combination A only):

- A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:
  - Is not a woman of childbearing potential (WOCBP)

  OR

  - Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described in Appendix 4 during the intervention period and for at least 30

days after the last dose of avelumab and bempegaldesleukin (NKTR-214); and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

- A WOCBP must have a negative highly sensitive pregnancy test ([urine or serum] as required by local regulations) at C1D1.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Additional requirements for pregnancy testing during and after study intervention are located in Appendix 2.

Informed Consent

9. Participants must be capable of giving signed informed consent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the informed consent document (ICD) and in this protocol.

10. Participants must be willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other procedures.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Known prior sever hypersensitivity to investigational products or any component in their formulations, including known severe hypersensitivity reactions to monoclonal antibodies (NCT CTCAE v4.03 Grade ≥3).

2. Known history of: immune-mediated colitis, inflammatory bowel disease, pneumonitis, or pulmonary fibrosis.

3. Active or prior autoimmune disease that might deteriorate when receiving an immunostimulatory agent. Participants with diabetes type I, vitiligo, psoriasis, or hypo or hyperthyroid disease not requiring immunosuppressive treatment are eligible.

4. Prior organ transplantation including allogenic stem cell transplantation.

5. Vaccination within 4 weeks prior to C1D1 and while on trial is prohibited except for administration of inactivated vaccines.

6. Known symptomatic brain lesions requiring steroids. Exception: participants with previously diagnosed brain lesions are eligible if they meet all of the following criteria: have newly diagnosed small brain lesions which do not require treatment; have completed their treatment and have recovered from the acute effects of radiation therapy or surgery prior to C1D1; have discontinued corticosteroid treatment for these lesions for at least 4 weeks prior to C1D1; and are neurologically stable.

7. Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).

8. Positive hepatitis B virus (HBV) surface antigen, or positive hepatitis C virus (HCV) ribonucleic acid (RNA) if anti-HCV antibody screening tests positive.

9. Active infection requiring systemic therapy within 14 days prior to C1D1.

10. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the participant inappropriate for entry into this study.

11. Clinically significant (ie, active) cardiovascular disease including the following: documented left ventricular ejection fraction (LVEF) < 50% by echocardiogram/multigated ECHO/MUGA (echocardiogram/multigated acquisition; performed within 6 months prior to enrollment); cerebral vascular accident/stroke (<6 months prior to C1D1); myocardial infarction (<6 months prior to C1D1); unstable angina; congestive heart failure (≥New York Heart Association Classification Class II); or serious cardiac arrhythmia (uncontrolled, clinically significant) requiring medication.

12. Diagnosis of any other malignancy within 2 years prior to C1D1, except for adequately treated basal cell or squamous cell skin cancer, carcinoma in situ of the breast, bladder or of the cervix and for Combination A only, low-grade (Gleason 6 or below) prostate cancer on surveillance with no plans for treatment intervention (eg, surgery, radiation, or castration) or prostate cancer that has been adequately treated with prostatectomy or radiotherapy and currently with no evidence of disease or symptoms is allowed.

Prior/Concomitant Therapy

13. Prior immunotherapy with IL-2 agents or anti PD-1, anti PD-L1, anti PD-L2, or anti- cytotoxic T-lymphocyte associated protein 4 (CTLA-4) antibody. Prior treatment with Sipuleucel-T for participants with mCRPC is allowed.

14. **Combination B only:** Prior treatment with a PARP inhibitor.

15. **Combination C only**: Prior treatment with second generation androgen receptor antagonist other than abiraterone/prednisone (eg, enzalutamide, apalutamide).

16. Current use of immunosuppressive medication at the time of C1D1, EXCEPT for the following permitted steroids:
    a. Intranasal, inhaled, topical steroids, eye drops or local steroid injection (eg, intra articular injection);
    b. Systemic corticosteroids at physiologic doses ≤10 mg/day of prednisone or equivalent;
    c. Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication).

17. **Combination B only:** Current (within 7 days prior to C1D1) or anticipated use of medications, including strong P-glycoprotein (P-gp) inhibitors (refer to Section 6.5.5 for a list of strong P-gp inhibitors), strong P-gp inducers (eg: avasimibe, carbamazepine, phenytoin, rifampin, St. John's wort), and strong inhibitors of breast cancer resistance protein (BCRP; eg: curcumin, cyclosporine, elacridar [GF120918], eltrombopag).

18. **Combination C only:** Strong (eg: carbamazepine, phenobarbital, phenytoin, rifabutin, rifapentine) and moderate (eg: bosentan, efavirenz, etravirine, modafinil, nafcillin) inducers for CYP3A4; strong CYP2C8 inducers (eg: rifampin); strong CYP2C8 inhibitors (eg, clopidogrel, gemfibrozil); substrates of CYP3A4 (eg: alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus); substrates of CYP2C9 (eg, phenytoin; per the enzalutamide label, only substrates with narrow therapeutic index [NTI]); and substrates of CYP2C19 (eg, S mephenytoin, substrates with a narrow therapeutic index).

19. Bisphosphonate or denosumab dosage that was not stable (ie, not the same) for at least 2 weeks before C1D1 for participants receiving these therapies.

20. Prior radiation therapy within 14 days prior to C1D1. Prior palliative radiotherapy to metastatic lesion(s) is permitted, provided it has been completed >14 days prior

to C1D1 and no clinically significant toxicities are expected (eg, mucositis, esophagitis).

21. Major surgery within 4 weeks prior to C1D1.

Prior/Concurrent Clinical Study Experience

22. Participation in other studies involving investigational drug(s) within 2 weeks prior to C1D1.

23. Persisting toxicity related to prior therapy (NCI CTCAE v4.03 Grade >1); however, alopecia and sensory neuropathy Grade ≤2, or other Grade ≤2 AEs not constituting a safety risk, based on Investigator's judgment, are acceptable.

Other Exclusions

24. Conditions that may impair intake or absorption of talazoparib (Combination B) or enzalutamide (Combination C), as follows: inability to swallow capsules or tablets; known malabsorption syndrome; or baseline diarrhea ≤ Grade 1.

25. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or participants who are Pfizer employees, including their family members, directly involved in the conduct of the study.

5.3. Lifestyle Considerations

- **Contraception:** Please refer to Appendix 4 regarding definitions for WOCBP and Contraception guidance. The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his or her partner(s) from the permitted list of contraception methods (refer to Appendix 4 Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. **A contraception check must be performed on D1 of every cycle during study treatment** as indicated in the Schedule of Activities (SoA); the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

Please refer to the Inclusion Criteria (Section 5.1) under "Sex" for details on contraception timeframes.

- **Concomitant Therapy:** Refer to Section 6.5.
- **Special Precautions for Administration:** Refer to Section 6.1 and Section 6.6.

5.4. Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

6. STUDY INTERVENTION

Study intervention is defined as any investigational product(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

6.1.1. Avelumab Administration

Avelumab (MSB0010718C) will be supplied for the study by Pfizer Global Clinical Supply, Worldwide Research and Development. Clinical trial supplies will be shipped to the study sites with a Drug Shipment and Proof of Receipt form. This form will be completed, filed, and the shipment confirmed as directed on the bottom of the Drug Shipment and Proof of Receipt form. The Investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational products in accordance with the protocol and any applicable laws and regulations.

6.1.1.1. Avelumab Dosage and Packaging

Avelumab is a sterile, clear, non-pyrogenic, and colorless solution intended for IV administration. It is presented at a concentration of 20 mg/mL with a nominal volume of 10 mL in glass vials closed with a rubber stopper and sealed with an aluminum polypropylene flip-off seal. Each vial is intended for a single use in a single participant only. The contents are free of bacteriostatic preservatives.

Packaging and labeling will be in accordance with applicable local regulatory requirements and applicable Good Manufacturing Guidelines (GMP) guidelines. Avelumab will be packed in boxes each containing one vial. The information on the trial drug will be in accordance with approved submission documents.

Avelumab will be shipped in transport cool containers (2°C to 8°C) with temperature monitoring devices.

Refer to the dosage and administration instructions in the Investigational Product (IP) Manual for instructions on how to prepare the investigational products for administration. Investigational products should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, or pharmacist) as allowed by local, state, and institutional guidance, as well as trained in the procedures specified in this protocol.

Detailed information on infusion bags to be used for the preparation of the dilutions and subsequent administration(s) for avelumab will be provided in the IP Manual.

Only qualified personnel who are familiar with procedures that minimize undue exposure to them and to the environment should undertake the preparation, handling, and safe disposal of study agents.

Any unused portion of the avelumab solution should be discarded in biohazard waste disposal with final disposal by accepted local and national standards of incineration. Any spills that occur should be cleaned up using the facility's standard cleanup procedures for biologic products.

6.1.1.2. Administration of Avelumab

Avelumab will be administered at 800 mg as a 1-hour (-10/+20 minutes) IV infusion starting after the bempegaldesleukin (NKTR-214) and talazoparib or enzalutamide (where applicable) is administered, at the investigational site on an outpatient basis on Day 1 and Day 15 of each 28-day cycle. Investigational sites should make every effort to target the timing of the avelumab infusion to be as close to 1 hour as possible. The exact duration of infusion should be recorded in both the source documents and the case report forms (CRFs). Additionally, the start and stop times of any interruptions to infusion and/or changes in rate of avelumab infusion will also need to be recorded in source documents After Cycle 1 Day 1, avelumab may be administered up to 2 days before or after the scheduled treatment day of each cycle for administrative reasons. Within the 2-day window, avelumab and bempegaldesleukin should be administered on the same day, unless one treatment needs to be delayed/withheld due to toxicity reasons.

Participants should be carefully monitored for infusion reactions during administration. If an acute infusion reaction is noted, participants should be managed according to Table 11 in Section 6.6.1.

Participants should be instructed to report any delayed reactions to the Investigator immediately.

Please refer to the Pharmacy Manual/current Investigator Brochure for details regarding preparation, storage, and administration.

6.1.1.3. Special Precautions for Administration of Avelumab

6.1.1.3.1. Infusion-related reactions

As with all mAb therapies, there is a risk of allergic reactions, including anaphylactic shock. Avelumab should be administered in a setting that allows for immediate access to an intensive care unit or equivalent environment and administration of therapy for anaphylaxis, such as the ability to implement immediate resuscitation measures. Steroids (dexamethasone 10 mg), epinephrine (1:1000 dilution), allergy medications (IV antihistamines), bronchodilators, or equivalents, and oxygen should be available for immediate access. If a hypersensitivity reaction occurs, the participant must be treated according to the best available medical practice. In order to mitigate avelumab IRRs, participants may need to be premedicated.

In order to mitigate IRRs, premedication with an antihistamine and with paracetamol (acetaminophen) 30 to 60 minutes prior to the first 4 infusions of avelumab is mandatory. Premedication is not mandatory for Cycles ≥3 (ie, beyond the first four infusions), but should be administered for subsequent avelumab doses based on clinical judgment and presence/severity of prior infusion reactions. The premedication regimen may be modified based on local treatment standards and guidelines, as appropriate, provided it does not include systemic corticosteroids.

Following the infusions of avelumab, participants must be observed for at least 30 minutes post-infusion for potential infusion-related reactions.

Symptoms of avelumab infusion-related reactions include, but are not limited to, fever, chills, flushing, hypotension, dyspnea, wheezing, back pain, abdominal pain, and urticaria. Management of avelumab IRRs is described in Table 11 (Section 6.6.1). Participants should be instructed to immediately report to the Investigator any delayed reactions that may occur after they leave the clinic.

6.1.2. Administration of Bempegaldesleukin (NKTR-214)

Each participant's bempegaldesleukin (NKTR-214) dose will be determined based on the participant's weight in kilograms on Day 1 of each cycle. If the participant's weight is within 10% of the Cycle 1 Day 1 weight, the study drug doses do not need to be recalculated depending on institutional guidelines/preference.

Bempegaldesleukin (NKTR-214) will be administered prior to avelumab. Bempegaldesleukin (NKTR-214) will be administered IV over 30 (± 5) minutes every 2 weeks (+/- 2 days). Participants should be carefully monitored for infusion reactions during bempegaldesleukin (NKTR-214) administration. If an acute infusion reaction is noted, participants should be managed according to Section 6.1.2.1.2. Within the 2-day window, avelumab and bempegaldesleukin (NKTR-214) should be administered on the same day, unless one treatment needs to be delayed/withheld due to toxicity reasons.

Please refer to the Pharmacy Manual/current Investigator Brochure for details regarding preparation, storage, and administration.

6.1.2.1. Special Precautions for Administration of Bempegaldesleukin (NKTR-214)

6.1.2.1.1. Hypotension

Hypotension has been identified as a clinically significant adverse effect of bempegaldesleukin (NKTR-214). The majority of hypotension cases occur on Day 2-3 post administration of bempegaldesleukin (NKTR-214), are clinically asymptomatic, and are rapidly responsive to fluid administration. Cases of syncope in association with post-dose blood pressure decline have been reported in patients receiving bempegaldesleukin (NKTR-214). Due to the risk of development of hypotension after bempegaldesleukin (NKTR-214) administration, the following risk mitigation measures should be taken:

- Consideration should be given to withholding antihypertensive medications including diuretics, as well as other drugs with hypotensive properties (eg, alpha blockers for benign prostatic hyperplasia), particularly when therapy involves multiple antihypertensive drugs and classes other than thiazide diuretics. If withholding antihypertensive medications, withhold no less than 12 hours and no more than 48 hours prior to each dose of bempegaldesleukin (NKTR-214). Antihypertensive medications may be reinstituted in between doses of bempegaldesleukin (NKTR-214) at any time as clinically indicated (eg, based on blood pressure monitoring result).

- Adequate hydration mitigates the development of hypotension. Participants should be given at least one liter of IV fluids at each dosing of bempegaldesleukin (NKTR-214) (Day 1), particularly in Cycles 1 and 2. During Cycles 3 and beyond, fluids may be given to prevent hypotension as per clinical judgement. For the next 3 days (Days 2-4) after bempegaldesleukin (NKTR-214) administration, instruct participants to take at least 2 liters per day of self-administered oral hydration. Advise participants to restrain from strenuous activity and avoid long hot showers and saunas for Days 1 to 4 of every cycle; and advise participants with orthostatic symptoms to call their treating oncologist to consider increasing oral hydration. Per clinical judgment, IV fluids may be administered in any cycle. The Investigator may decide to forego administering IV fluids to a participant if this is deemed in the best interest of the participant (eg, evidence of fluid overload).

6.1.2.1.2. Infusion-related reactions

Symptoms of bempegaldesleukin (NKTR-214) infusion-related reactions include, but are not limited to, fever, chills, flushing, hypotension, and pyrexia. Management of bempegaldesleukin (NKTR-214) IRRs is described in Table 12 (Section 6.6). Participants should be instructed to immediately report to the Investigator any delayed reactions that may occur after they leave the clinic.

For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg should be administered at least 30 minutes before the infusion.

6.1.3. Talazoparib Administration

6.1.3.1. Talazoparib Pre-medication

No pre-medication is required prior to receiving talazoparib.

6.1.3.2. Administration of Talazoparib

Talazoparib is considered a cytotoxic and clastogenic agent; precautions regarding appropriate secure storage and handling must be used by healthcare professionals, including personal protective clothing, disposable gloves, and equipment. Participants should be advised that oral anticancer agents are toxic substances and that other caregivers (including family members) should always use gloves when handling the study treatment.

Talazoparib will be taken once daily (with a reduced dose for participants with moderate renal impairment) starting on Cycle 1 Day 1, and treatment should continue until End of Treatment/withdrawal. On Days 1 and 15 of each maintenance cycle, when the participant returns to the clinic for bempegaldesleukin (NKTR-214) and avelumab administration, the daily dose of talazoparib should not be taken prior to the study visit and will be taken at the clinic after all procedures/assessments have been completed, before or after the bempegaldesleukin (NKTR-214) and avelumab infusions.

Talazoparib can be administered with or without food as 1.0 mg capsules for the 1.0 mg dose; 0.25 mg capsules will be used to dispense the 0.25, 0.5, and 0.75 mg doses. Talazoparib should be administered at the same time each day. Participants will swallow the investigational product whole with a large glass of water (~250 ml), and will not manipulate or chew, dissolve, or open the capsules prior to swallowing.

If a participant forgets his daily dose of talazoparib at the time he typically takes it, but remembers this on the same day, within 12 hours of the usual dose time, the dose may be taken at that time. Any dose that is missed (not taken within 12 hours of the intended time) should be skipped and should not be replaced or made up on the following day. Participants should not make up vomited doses; dosing should resume on the next calendar day unless otherwise instructed.

Please refer to the Pharmacy Manual/current Investigator Brochure for details regarding preparation, storage, and administration.

6.1.4. Enzalutamide Administration

6.1.4.1. Enzalutamide Pre-medication

No pre-medication is required prior to receiving enzalutamide.

6.1.4.2. Administration of Enzalutamide

Enzalutamide will be taken once daily starting on Cycle 1 Day 1 and treatment should continue until End of Treatment/withdrawal. On Days 1 and 15 of each maintenance cycle, when the participant returns to the clinic for avelumab and bempegaldesleukin (NKTR-214) administration, the daily dose of enzalutamide should not be taken prior to the study visit and

will be taken at the clinic after all procedures/assessments have been completed, and before or after the avelumab and bempegaldesleukin (NKTR-214) infusions.

Participants should self-administer enzalutamide orally once daily, with or without food. The capsules should be swallowed whole with a glass of water without chewing, dissolving, or opening the capsules prior to swallowing.

Participants should be instructed to take enzalutamide at approximately the same time each day and to not take more than the prescribed dose at any time.

If a participant misses a day of treatment or vomits any time after taking a dose, he must be instructed not to "make it up" but to resume subsequent doses the next day as prescribed.

Please refer to the Pharmacy Manual/current Investigator Brochure for details regarding preparation, storage, and administration.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperature since previously documented for all site storage locations upon return to business.

2. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). All study interventions will be accounted for using an investigational product accountability form/record.

3. Further guidance and information for the final disposition of unused study interventions are provided in the study reference manual. The sponsor or designee will also provide guidance on the destruction of unused study intervention (eg, at the site). If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

4. Any storage conditions stated in the single reference safety document (SRSD) will be superseded by the storage conditions stated on the product label.

5. Study interventions should be stored in their original containers and in accordance with the labels.

6. See the investigational product manual (IP Manual), package insert, or equivalent for storage conditions of the study intervention (once reconstituted and/or diluted).

7. Site staff will instruct participants on the proper storage requirements for take-home study intervention.

8. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer upon discovery. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. It will not be considered a protocol deviation if Pfizer approves the use of the study intervention after the temperature excursion. Use of the study intervention prior to Pfizer approval will be considered a protocol deviation. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label study that will not be randomized.

Allocation to Treatment

At the time that a participant has signed informed consent and entered screening, the site should contact the interactive response technology (IRT) system to obtain the participant identification number. Once a participant has met all eligibility criteria, participant enrollment and allocation of investigational product will be managed by the IRT system. At the time of enrollment, site personnel (study coordinator or specified designee) will be required to enter into or select information from the IRT system including, but not limited to, the user's identification (ID) and password, the protocol number, and the participant number. The IRT system will then provide a treatment assignment and dispensable unit (DU) or vial or bottle number for each investigational product to be dispensed. The IRT system will also provide a confirmation report containing the participant number and DU or vial or bottle numbers assigned. The confirmation report must be stored in the site's files.

There is a 24 hour a day, 365 days a year IRT helpdesk available for any questions or issues. The study specific IRT reference manual will provide the contact information and further details on the use of the IRT system.

6.4. Study Intervention Compliance

Participant compliance with study intervention will be assessed at each visit. Compliance will be assessed by using drug accountability form/record. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

For Investigational Product Administered by IV:

For avelumab and bempegaldesleukin (NKTR-214), the site will complete the required dosage Preparation Record located in the Investigational Product Manual. The use of the

Preparation Record is preferred, but it does not preclude the use of an existing appropriate clinical site documentation system. The existing clinical site's documentation system should capture all pertinent /required information on the preparation and administration of the dose. This may be used in place of the Preparation Record after approval from the Pfizer monitor.

The information related to each trial drug administration, including the date, time, and dose of study drug, will be recorded on the electronic case report form (eCRF). The Investigator will ensure that the information entered into the eCRF regarding drug administration is accurate for each participant. Any reason for noncompliance should be documented.

For Investigational Product Administered Orally:

Participants will be required to return all unused talazoparib and enzalutamide capsules (if applicable) every cycle. The number of capsules returned by each participant will be counted, documented, and recorded by site personnel in the participant's medical record and reconciled with the participant's dosing diary to support the talazoparib/enzalutamide accountability process. Study site personnel must make reasonable efforts to obtain study drug packaging and any unused tablets or capsules from participants who do not routinely return them at study site visits.

Additionally, a participant dosing diary will be provided to the participants to aid in compliance with the dosing instructions. The diary will be maintained by the participant to include missed or changed talazoparib/enzalutamide doses. The time of each talazoparib/enzalutamide dose administration and the total dose of talazoparib/enzalutamide taken each day will be recorded in the dosing diary. Participants will be required to return the completed dosing diary on Day 1 and 15 of every cycle for timely review by site personnel and discussion of missed doses and/or compliance issues to ensure accurate data entry for the Dosing CRF. On days when the participant's talazoparib/enzalutamide dose is given at the clinic due to scheduled PK sample collection, the time of talazoparib/enzalutamide dose administration and the total dose of talazoparib/enzalutamide taken will be recorded in the participant's dosing records that are included in the medical chart.

Treatment compliance (reported as a percent) will be defined as the number of capsules taken during the study divided by the expected number of capsules of talazoparib/enzalutamide multiplied by 100%. Tablets that are not returned will be considered to have been taken unless reported otherwise by the participant.

6.5. Concomitant Therapy

- Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:
    - Dates of administration including start and end dates
    - Dosage information including dose and frequency

- Concomitant medications and treatments, including herbal supplements, will be recorded from 28 days prior to the start of study intervention(s) and up to 90 days after the last dose of study intervention(s). All concomitant medications should be recorded in the CRF including supportive care drugs (eg, antiemetic treatment and prophylaxis), and the drugs used to treat adverse events or chronic diseases, as well as non-drug supportive interventions (eg, transfusions).

- Given that recording of non-serious AEs ends when a participant begins a new anti-cancer therapy (Appendix 3, Section 10.3.3), recording of concomitant medications associated with these non-serious AEs should also end. However, given that SAEs must continue to be recorded up to 90 days after the last dose of study treatment(s) even if the participant begins a new anti-cancer therapy (Appendix 3, Section 10.3.4), concomitant medications associated with these SAEs must also be recorded.

- The sponsor should be contacted if there are any questions regarding concomitant or prior therapy.

- Medications or vaccinations specifically prohibited in the exclusion criteria are also not allowed during the active treatment period, except for administration of inactivated vaccines.

- Concomitant treatment considered necessary for the participant's well-being may be given at the discretion of the treating physician.

- Concurrent anti-cancer therapy with agents other than study treatments is not allowed. Medications intended solely for supportive care (ie, antiemetics, analgesics, megestrol acetate for anorexia) are allowed.

- Recommended pre-medication for avelumab is reported in Section 6.1.1.3. Recommended pre-medication for bempegaldesleukin (NKTR-214) is reported in Section 6.1.2.1.

- Recommended medications to treat infusion related reactions for avelumab and bempegaldesleukin (NKTR-214) are reported in Section 6.1.1.3.1 and Section 6.1.2.1.2, respectively. Recommended medications to treat immune-related events are reported in Section 6.6.3.

6.5.1. Permitted Concomitant Medications

- Prophylaxis for flu-like symptoms with either acetaminophen or ibuprofen is permitted on study per the Investigator's discretion. Prophylaxis for flu-like symptoms can be initiated on either Day 1 or Day 2 of the dosing cycle and may continue through Day 5 or longer as needed.

- Prophylaxis for rash and/or pruritus with anti-histamines is permitted on study per the Investigator's discretion. Prophylaxis for rash and/or pruritus can be initiated on either Day 1 or Day 2 of the dosing cycle and may continue through Day 5 or longer as needed.

- Concomitant palliative and supportive care for disease related symptoms (including bisphosphonates and nuclear factor kappa-B ligand [RANKL] inhibitors) is allowed.

- Participants who need to be on anticoagulant therapy during treatment should be treated with low molecular weight heparin. If low molecular weight heparin cannot be administered, coumadin or other coumarin derivatives or other anti-coagulants (including direct Factor 10a inhibitors) may be allowed; however, appropriate monitoring of prothrombin time/international normalized ratio (PT/INR) should be performed as needed.

6.5.2. Concomitant Radiotherapy

- Prior palliative radiotherapy must have been completed > 14 days before administration of first dose of study drug. On-study radiotherapy to target lesions is not permitted. Palliative radiotherapy to specific **non-target** sites of disease is permitted if considered medically necessary by the treating physician. All attempts should be made to rule out disease progression in the event of increased localized pain. If palliative radiotherapy is needed to control bone pain, the sites of bone disease should be present at screening; otherwise, bone pain requiring radiotherapy will be considered as a sign of disease progression.

- Study intervention should be withheld for the entire duration of palliative radiotherapy and can be restarted upon recovery from any radiotherapy-related toxicities, but no sooner than 48 hours after radiotherapy completion.

6.5.3. Concomitant Surgery

- Caution is advised on theoretical grounds for any surgical procedures during the study. Although involving a limited number of participants, studies have not identified an increased surgical risk in participants treated with immune checkpoint inhibitors.[48,49]

- The appropriate interval of time between surgery and administration of investigational products required to minimize the risk of impaired wound healing and bleeding has not been determined. In case of a surgical procedure, investigational products should be delayed. Postoperatively, the decision to reinitiate investigational products should be discussed with the sponsor.

- In the case that a surgical procedure is required for palliative care, all attempts should be made to rule out disease progression beforehand.

6.5.4. Hematopoietic Growth Factors

Primary prophylactic use of granulocyte-colony stimulating factors (G-CSF) or erythropoietin (or darbepoetin) is not permitted during the first cycle of treatment. These factors may be used at any time to treat emergent neutropenia or anemia as indicated by the current American Society of Clinical Oncology (ASCO) guidelines or as allowed per local guidance.

In subsequent cycles, the use of hematopoietic growth factors is at the discretion of the treating physician in line with local guidelines.

6.5.5. Other Prohibited Concomitant Medicines and Therapies

Participants are prohibited from receiving the following therapies (unless otherwise indicated below) during the treatment phase of this trial:

- Anti-cancer chemotherapy or biological therapy.
- Immunotherapy not specified in this protocol.
- Investigational agents other than investigational products.
- Immunosuppressive drugs, unless otherwise indicated for the treatment of irAEs (refer to Table 16, Management of Immune-Related Adverse Events for Avelumab and Bempegaldesleukin [NKTR-214]). See below **Clarification Regarding Steroid Use.**
- Any vaccine therapies for the prevention of infectious disease (eg, human papilloma virus vaccine) except for inactivated vaccines (eg, influenza vaccine).
- Herbal remedies with immunostimulating properties (eg, mistle toe extract) or those known to potentially interfere with major organ function (eg, hypericin).
- Bisphosphonate or denosumab treatment.
- Radiation therapy (with the exception noted above in the Concomitant Radiotherapy Section).
- **Combination B only:**
  - **Potent P-gp inhibitors** that result in ≥ 2-fold increase in the exposure of an in vivo probe P-gp substrate, according to the FDA website (https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table5-2) and University of Washington Drug-Drug Interaction database (https://www.druginteractioninfo.org/). Other validated sources can also be referenced per local requirements: amiodarone, carvedilol, clarithromycin, cobicistat, dronedarone, erythromycin, glecaprevir/pibrentasvir, indinavir, itraconazole, ketoconazole, lapatinib, lopinavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir, sofosbuvir/velpatasvir/voxilaprevir, telaprevir, tipranavir, valspodar, and verapamil.
  - **Strong P-gp inducers** (eg: avasimibe, carbamazepine, phenytoin, rifampin, St. John's wort)

- **Strong inhibitors of breast cancer resistance protein** (BCRP; eg: curcumin, cyclosporine, elacridar [GF120918], eltrombopag)

- **Combination C only**:
  - **Strong CYP3A4 inducers** (eg: carbamazepine, phenobarbital, phenytoin, rifabutin, rifapentine) and moderate (eg: bosentan, efavirenz, etravirine, modafinil, nafcillin).
  - **Strong CYP2C8 inducers** (eg: rifampin)
  - **Strong CYP2C8 inhibitors** (eg: clopidogrel, gemfibrozil)
  - **Substrates of CYP3A4** (eg: alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus)
  - **Substrates of CYP2C9** (eg, phenytoin; per the enzalutamide label, only substrates with NTI)
  - **Substrates of CYP2C19** (eg, S mephenytoin, substrates with a narrow therapeutic index).

There are no prohibited therapies during the Safety Follow-up or Survival Follow-up Phases.

6.5.6. Corticosteroids

Data indicate that corticosteroids have an adverse effect on T-cell function and that they inhibit and damage lymphocytes.[50,51] Furthermore, as for all immunotherapies intended to augment T-cell-mediated immunity, there is a risk that concomitant immunosuppressives such as steroids will counteract the intended benefit. However, studies with anti-CTLA-4 compounds indicate that short-term use of steroids can be employed without compromising clinical outcomes.[52] Therefore, the use of steroids during this trial is restricted as follows:

- Therapeutic use: for the treatment of infusion-related reactions and for the treatment of irAEs, steroids are permitted according to the modalities indicated in Table 16, Management of Immune-Related Adverse Events for Avelumab and Bempegaldesleukin (NKTR-214).
- Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra-articular injection) are permitted.
- Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication) are acceptable.
- Physiologic use: replacement for adrenal insufficiency at doses to ≤10 mg prednisone or equivalent daily are acceptable.

- Participants with pre-existing adrenal impairment requiring corticosteroid supplementation may be at increased risk for hypotensive episodes during treatment with bempegaldesleukin (NKTR-214). For these participants, their existing corticosteroid dose may be increased by an additional supplementation up to a maximum of 10 mg/day of prednisone or equivalent, for the first 4 days after administration of bempegaldesleukin (NKTR-214) based on an assessment of the degree of adrenal impairment and the extent of existing corticosteroid supplementation.

6.5.7. Rescue Medication and Supportive Care

6.5.7.1. Supportive Care Guidelines

- Participants should receive appropriate supportive care measures as deemed necessary by the treating Investigator including but not limited to the items outlined below:

    - Diarrhea: All participants who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.

    - Nausea/Vomiting: Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Participants should be strongly encouraged to maintain liberal oral fluid intake.

    - Anti-infectives: Participants with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating Investigator for a given infectious condition, according to standard institutional practice, assuming there is no expected drug-drug interaction with study.

    - Anti-inflammatory or narcotic analgesics may be offered as needed (ie, nonsteroidal anti-inflammatory drugs [NSAIDS] and anti-histamines for flu like symptoms).

      For supportive care guidelines regarding growth factors, refer to Section 6.5.4.

6.5.7.2. Treatment after Initial Evidence of Radiological Disease Progression

Immunotherapeutic agents such as avelumab, may produce anti-tumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents and can manifest as a clinical response after an initial increase in tumor burden or even the appearance of new lesions.

If radiologic imaging shows disease progression, participants may continue to receive investigational products, after discussion between the sponsor and Investigator and at the Investigator's discretion, if the following criteria are met:

- Absence of clinical signs and symptoms (including worsening of laboratory values) of disease progression;
- No decline in ECOG performance status (Appendix 8);
- Absence of rapid progression of disease by radiographic imaging;
- Absence of progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention.

Before continuation of treatment, the participant must be re-consented via informed consent addendum and informed that, by continuing to receive the investigational products, the participant may be foregoing approved or investigational therapies with possible clinical benefit(s).

If the participant is subsequently found to have further disease progression at a subsequent tumor assessment, either radiologically according to RECIST v1.1 (Appendix 9) or clinically, then treatment with investigational products should be permanently discontinued. Refer to tumor response assessments in Section 8.1.1.

6.6. Dose Modification

6.6.1. Recommended Dose Modifications

Every effort should be made to administer each investigational product at the planned dose and schedule.

In the event of study treatment toxicity, dosing may be interrupted, delayed and/or reduced, only as described for each investigational product. In the event of multiple toxicities, treatment/dose modifications should be based on the worst toxicity observed (CTCAE v4.03) and/or the most conservative recommendation for any given toxicity. Participants are to be instructed to notify Investigators at the first occurrence of any adverse symptom.

Treatment/dose modifications may occur independently for each investigational product in the combination based on the observed toxicity and the general guidance, as follows:

- Avelumab: No dose reductions are permitted in this study, but the next infusion may be omitted/delayed based on persisting toxicity.
- Bempegaldesleukin (NKTR-214): Dose may be reduced from the starting dose. Dose interruptions are allowed if clinically indicated.
- Talazoparib: Dose modifications (dose interruptions, or dose reductions) may be implemented to manage toxicities.
- Enzalutamide: Dose modifications (dose interruptions, or dose reductions) may be implemented to manage toxicities.

All dose modifications must be clearly documented in the participant's medical chart and in the CRF. Appropriate follow-up assessments should be performed until adequate recovery occurs as assessed by the Investigator. In addition to dose modifications, Investigators are encouraged to employ best supportive care according to local institutional clinical practices.

Table 11. Treatment Modification for Symptoms of Infusion related Reactions Associated with Avelumab

NCI CTCAE Severity Grade	Treatment Modification
Grade 1 – mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease the avelumab infusion rate by 50% and monitor closely for any worsening.
Grade 2 – moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, IV fluids; prophylactic medications indicated for ≤24 hours.	Temporarily discontinue avelumab infusion. Resume avelumab infusion at 50% of previous rate once infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any worsening.[a]
Grade 3 or Grade 4 – severe or life-threatening Grade 3: Prolonged (for example, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. Grade 4: Life-threatening consequences; urgent intervention indicated.	Stop the avelumab infusion immediately and disconnect infusion tubing from the participant. **Participants have to be withdrawn immediately from avelumab treatment and must not receive any further avelumab treatment.**

a. If avelumab infusion rate has been decreased by 50% due to an infusion reaction, it must remain decreased for the next scheduled infusion. If no infusion reaction is observed at the next scheduled infusion, the infusion rate may be returned to baseline at subsequent infusions.
Abbreviations: NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Event; NSAIDs=nonsteroidal anti-inflammatory drugs; IV=intravenous.

Table 12. Treatment Modification for Symptoms of Infusion related Reactions Associated with Bempegaldesleukin (NKTR-214)

NCI CTCAE Severity Grade	Treatment Modification
Grade 1 – mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Remain at the bedside and monitor the participant until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg at least 30 minutes before subsequent infusions.
Grade 2 – moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, IV fluids; prophylactic medications indicated for ≤24 hours.	Stop the infusion, begin an IV infusion of normal saline, and treat the participant with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at the bedside and monitor the participant until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve. If symptoms recur after restarting the infusion, then no further bempegaldesleukin (NKTR-214) will be administered at that visit. Administer diphenhydramine 50 mg IV, remain at the bedside, and monitor the participant until resolution of symptoms.[a]
Grade 3 or Grade 4 – severe or life-threatening Grade 3: Prolonged (for example, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. Grade 4: Life-threatening consequences; urgent intervention indicated.	**Immediately discontinue infusion of bempegaldesleukin (NKTR-214).** Begin an IV infusion of normal saline and treat the participant as follows: recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. **Bempegaldesleukin (NKTR-214) will be permanently discontinued.** The participant should be monitored until the Investigator is comfortable that the symptoms will not recur. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at the bedside and monitor the participant until recovery of the symptoms. In case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine or corticosteroids).

a. If bempegaldesleukin (NKTR-214) infusion rate has been decreased by 50% due to an infusion reaction, it must remain decreased for the next scheduled infusion. If no infusion reaction is observed at the next scheduled infusion, the infusion rate may be returned to baseline at subsequent infusions.
Abbreviations: NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Event; NSAIDs=nonsteroidal anti-inflammatory drugs; IV=intravenous.

6.6.2. Study Treatment Modifications for Drug Related Toxicity (excluding infusion related reactions and immune related adverse events)

Infusion-related reactions are addressed in Table 11 and Table 12 for avelumab and bempegaldesleukin (NKTR-214), respectively. Immune-related AEs are addressed in Section 6.6.3 and Table 16.

Every effort should be made to administer each investigational product at the planned dose and schedule.

In the event of study treatment toxicity, dosing may be interrupted, delayed and/or reduced, only as described for each investigational product. In the event of multiple toxicities, treatment/dose modifications should be based on the worst toxicity observed and/or the most conservative recommendation for any given toxicity. Participants are to be instructed to notify Investigators at the first occurrence of any adverse symptom.

Treatment/dose modifications may occur independently for each investigational product in the combination based on the observed toxicity and the general guidance, as per Table 13, Table 14, and Table 15 for Combinations A, B, and C, respectively.

6.6.2.1. Dose Modifications for Avelumab + Bempegaldesleukin (NKTR-214) Doublet (Combination A)

Refer to Table 13 for dose modifications by severity grade for this combination. Participants who require delay of avelumab and/or bempegaldesleukin (NKTR-214) should be re-evaluated weekly or more frequently if clinically indicated and resume treatment with the combination of avelumab and bempegaldesleukin (NKTR-214) when re-treatment criteria are met. Immuno-oncology agents are associated with AEs that can differ in severity and duration from AEs caused by other therapeutic classes. Avelumab and bempegaldesleukin (NKTR-214) are considered immuno-oncology agents. Early recognition and management of AEs associated with immuno-oncology agents may mitigate severe toxicity.

No dose reductions are permitted for avelumab (dose remains fixed at 800 mg Q2W administered by IV); however, the next infusion may be omitted based on persisting toxicity. Avelumab may be discontinued as clinically indicated.

Dose delays and reductions are permitted for bempegaldesleukin (NKTR-214). Bempegaldesleukin (NKTR-214) may be delayed or the dose reduced from 0.006 mg/kg to 0.003 mg/kg based on observed drug-related toxicities. If the bempegaldesleukin dose is reduced to 0.003 mg/kg, the dose level should remain at this level throughout the remainder of the study. Sponsor consultation is required for dose reduction. Bempegaldesleukin (NKTR-214) dosing may resume when toxicity resolves to Grade 1 or returns to baseline.

Table 13. Avelumab and Bempegaldesleukin (NKTR-214) Treatment Modifications for Drug Related Toxicity (Excluding Infusion Related Reactions and Immune Related AEs)

	Avelumab	Bempegaldesleukin (NKTR-214)
Hematologic toxicities		
• Grade 1 and Grade 2	• Continue as per schedule.	• Continue as per schedule.
Anemia Grade ≥3	• Hold avelumab. • Re-initiate avelumab once toxicity Grade ≤1 or baseline. • Permanently discontinue avelumab if toxicity does not resolve to Grade ≤1 or baseline within 12 weeks or if the same Grade 3 toxicity recurs.	• Hold bempegaldesleukin (NKTR-214). • Re-initiate bempegaldesleukin (NKTR-214) once toxicity Grade ≤1 or baseline. • Permanently discontinue bempegaldesleukin (NKTR-214) if toxicity does not resolve to Grade ≤1 or baseline within 12 weeks or if the same Grade 3 toxicity recurs.
Neutropenia Grade ≥3 (ANC <1000/μL)	• Hold avelumab. • Re-initiate avelumab once toxicity Grade ≤1 (ANC ≥1500/μL) or baseline. • Permanently discontinue avelumab if toxicity does not resolve to Grade ≤1 or baseline within 12 weeks or if the same Grade 3 toxicity recurs.	• Hold bempegaldesleukin (NKTR-214). • Re-initiate bempegaldesleukin (NKTR-214) once toxicity Grade ≤1 (ANC ≥1500/μL) or baseline. • Permanently discontinue bempegaldesleukin (NKTR-214) if toxicity does not resolve to Grade ≤1 or baseline within 12 weeks or if the same Grade 3 toxicity recurs.
Thrombocytopenia Grade ≥3 (platelets <50,000/μL)	• Hold avelumab. • Re-initiate avelumab once toxicity Grade ≤1 or baseline. • Permanently discontinue avelumab if toxicity does not resolve to Grade ≤1 or baseline within 12 weeks or if the same Grade 3 toxicity recurs.	• Hold bempegaldesleukin (NKTR-214). • Re-initiate bempegaldesleukin (NKTR-214) once toxicity Grade ≤1 or baseline. • Permanently discontinue bempegaldesleukin (NKTR-214) if toxicity does not resolve to Grade ≤1 or baseline within 12 weeks or if the same Grade 3 toxicity recurs.
Lymphopenia Grade ≥3(lymphocytes <0.5 x $10e^9$ /L)	• Continue as planned.	• Continue as planned.
Eosinophilia	• Continue as planned.	• If the study participant is suspected to have hypereosinophilic syndrome (symptoms may involve skin, lungs, digestive tract, heart, blood, and nervous system) with AEC at or above 5000/μL (5×10^9/L), bempegaldesleukin (NKTR-214) treatment may need to be held.

Table 13. Avelumab and Bempegaldesleukin (NKTR-214) Treatment Modifications for Drug Related Toxicity (Excluding Infusion Related Reactions and Immune Related AEs)

	Avelumab	Bempegaldesleukin (NKTR-214)
Non-hematologic toxicities		
Grade 1	• Continue as per schedule. • For suspected immune-related toxicity follow guidance in Section 6.6.3 and Table 16.	• Continue as per schedule. • For suspected immune related toxicity follow guidance in Section 6.6.3 and Table 16.
Grade 2	• Continue as per schedule. • For suspected immune-related toxicity follow guidance in Section 6.6.3 and Table 16.	• For persistent Grade 2 related toxicity, delay administration at the discretion of the Investigator. • For suspected immune-related toxicity follow guidance in Section 6.6.3 and Table 16. • Bempegaldesleukin (NKTR-214) dosing may resume at the same dose or at a lower dose level when toxicity resolves to Grade 1 or returns to baseline, except for instances where the potential recurrence of the event poses an undue risk for the participant.
Grade 3	• Hold avelumab. • Resume once toxicity is Grade ≤1 or baseline. • Permanently discontinue if toxicity does not resolve to Grade ≤1 or baseline within 12 weeks or if the same Grade 3 toxicity recurs. • **Exceptions are:** Laboratory values that do not have any clinical correlate. • For suspected immune-related toxicity follow guidance in Section 6.6.3 and Table 16.	• Hold bempegaldesleukin (NKTR-214) • Resume once toxicity is Grade ⩽ 1 or baseline. • Permanently discontinue if toxicity does not resolve to Grade ≤1 or baseline within 12 weeks or if the same Grade 3 toxicity recurs. • **Exceptions are**: Laboratory values that do not have any clinical correlate. • For suspected immune-related toxicity follow guidance in Section 6.6.3 and Table 16.
Grade 4	• Permanently discontinue avelumab. • **Exceptions are:** Laboratory values that do not have any clinical correlate. • For suspected immune-related toxicity follow guidance in Section 6.6.3 and Table 16.	• Permanently discontinue bempegaldesleukin (NKTR-214). • **Exceptions are:** Laboratory values that do not have any clinical correlate. • For suspected immune-related toxicity follow guidance in Section 6.6.3 and Table 16.

Abbreviations: AEC=absolute eosinophil count; AE=adverse event; ANC=absolute neutrophil count.

6.6.2.2. Dose Modifications for Avelumab + Bempegaldesleukin (NKTR-214) + Talazoparib Triplet (Combination B)

Refer to Section 6.6.2.1 for additional information regarding dose delays and reductions for avelumab and bempegaldesleukin (NKTR-214). Refer to Table 13 for dose modifications by severity grade for this doublet combination.

Recommended avelumab, bempegaldesleukin (NKTR-214) and talazoparib treatment modifications in case of investigational product related toxicity are shown in Table 14. The specific guidelines are applicable in cases which can be attributed to one of the investigational products. The instructions should be followed in the column regarding the investigational product that toxicity is attributed to. In cases where an AE is possibly related to more than one investigational product, the guidelines in the relevant columns should be followed. Participants who stop avelumab, bempegaldesleukin (NKTR-214) or talazoparib for unacceptable toxicity may continue treatment with the investigational product that is not considered to be responsible for the toxicity observed.

For hematologic toxicities, it is advisable to hold or reduce talazoparib first, before avelumab and bempegaldesleukin (NKTR-214), since hematologic toxicities have been reported with talazoparib treatment.

The dose level for avelumab is fixed at 800 mg Q2W. No dose reductions are permitted for avelumab; however, the next infusion may be omitted/delayed based on persisting toxicity. Avelumab may be discontinued as clinically indicated. Available dose levels for bempegaldesleukin (NKTR-214) dose are 0.006 and 0.003 mg/kg Q2W. Available dose levels for talazoparib are 1.0, 0.75, and 0.5 mg once daily. These available dose levels are the same regardless of whether the bempegaldesleukin (NKTR-214) dose is 0.006 or 0.003 mg/kg Q2W.

Following dosing interruption due to toxicity, talazoparib may need to be resumed at a reduced dose as per the recommendations.

The starting dose of talazoparib for this study will be determined by the BLRM; a reduced dose will be given to participants with moderate renal impairment (CrCL 30-59 mL/min). CrCL may be repeated prior to talazoparib dose reduction, if low results are suspected to be due to insufficient hydration status of the participant.

Dose reduction of talazoparib by 1 dose level at a time will be allowed depending on the starting dose and type and severity of toxicity encountered. Doses less than 0.5 mg are not permitted. Participants unable to tolerate 0.5 mg QD, will be permanently discontinued from the talazoparib, but may continue on avelumab and bempegaldesleukin (NKTR-214).

Site personnel must ensure the participant is instructed how to take the reduced dose and that the participant has the correct dosage strength for the reduced dose.

Avelumab infusion-related reactions should be managed according to guidelines in Section 6.1.1.3.1.

For participants receiving avelumab and bempegaldesleukin (NKTR-214), as a doublet or in combination with talazoparib, any AE suspected to be immune-related should be managed according to the guidance for management of irAEs in Section 6.6.3.

Table 14. Avelumab + Bempegaldesleukin (NKTR-214) + Talazoparib Triplet Treatment Modifications for Drug Related Toxicity (Excluding Infusion Related Reactions and Immune Related AEs)

	Avelumab	Bempegaldesleukin (NKTR-214)	Talazoparib
Hematologic toxicities			
Grade 1 and Grade 2	Continue as per schedule.	Continue as per schedule.	Continue as per schedule.
Anemia Grade ≥3	• Hold avelumab if toxicity does not resolve after holding/reducing talazoparib. • Re-initiate avelumab once toxicity is Grade ≤1 or baseline. • Permanently discontinue avelumab if toxicity does not resolve to Grade ≤1 or baseline within 12 weeks or if the same Grade 3 toxicity recurs (if talazoparib had already been discontinued and recurrent event occurs on avelumab in combination with bempegaldesleukin [NKTR-214]).	• Hold bempegaldesleukin (NKTR-214) if toxicity does not resolve after holding/reducing talazoparib. • Re-initiate bempegaldesleukin (NKTR-214) once toxicity is Grade ≤1 or baseline. • Permanently discontinue bempegaldesleukin (NKTR-214) if toxicity does not resolve to Grade ≤1 or baseline within 12 weeks or if the same Grade 3 toxicity recurs (if talazoparib had already been discontinued and recurrent event occurs on avelumab in combination with bempegaldesleukin [NKTR-214] only).	• Hold talazoparib first (before holding avelumab in combination with bempegaldesleukin [NKTR-214]) and monitor weekly until resolve to Grade ≤1 or baseline. • Resume talazoparib based on the following recovery times: ≤1 week: No change; >1 week: Talazoparib may be reduced by 1 dose level, per Section 6.6.2.2. • Permanently discontinue talazoparib if toxicity persists for >4 weeks without recovery to baseline. Refer to hematologist for evaluation including assessment of possible MDS/AML.
Neutropenia Grade ≥3 (ANC <1000/µL)	• Hold avelumab if toxicity does not resolve after holding/reducing talazoparib. • Re-initiate avelumab once toxicity is Grade ≤1 (ANC ≥1500/µL) or baseline. • Permanently discontinue avelumab if toxicity does not resolve to Grade ≤1 or baseline within 12 weeks or if the same Grade 3 toxicity recurs (if talazoparib had already been discontinued and	• Hold bempegaldesleukin (NKTR-214) if toxicity does not resolve after holding/reducing talazoparib. • Re-initiate bempegaldesleukin (NKTR-214) once toxicity Grade ≤1 (ANC ≥1500/µL) or baseline. • Permanently discontinue bempegaldesleukin (NKTR-214) if toxicity does not resolve to Grade ≤1 or baseline within 12 weeks or if the same Grade 3 toxicity recurs (if	• Hold talazoparib first (before holding avelumab in combination with bempegaldesleukin [NKTR-214]) and monitor weekly until ANC ≥1500/µL. • Resume talazoparib based on the following recovery times: ≤1 week: No change; >1 week: Talazoparib may be reduced by 1 dose level, per Section 6.6.2.2. • Permanently discontinue talazoparib if persists for >4 weeks

Table 14. Avelumab + Bempegaldesleukin (NKTR-214) + Talazoparib Triplet Treatment Modifications for Drug Related Toxicity (Excluding Infusion Related Reactions and Immune Related AEs)

	Avelumab	Bempegaldesleukin (NKTR-214)	Talazoparib
	recurrent event occurs on avelumab in combination with bempegaldesleukin [NKTR-214] only).	talazoparib had already been discontinued and recurrent event occurs on avelumab in combination with bempegaldesleukin [NKTR-214] only).	without recovery to ANC ≥1500/μL. Refer to hematologist for evaluation including assessment of possible MDS/AML.
Thrombocytopenia Grade ≥3 (platelets <50,000/μL)	• Hold avelumab if toxicity does not resolve after holding/reducing talazoparib. • Re-initiate avelumab once toxicity Grade ≤1 or baseline. • Permanently discontinue avelumab if toxicity does not resolve to Grade ≤1 or baseline within 12 weeks or if the same Grade 3 toxicity recurs (if talazoparib had already been discontinued and recurrent event occurs on avelumab in combination with bempegaldesleukin [NKTR-214] only).	• Hold bempegaldesleukin (NKTR-214) if toxicity does not resolve after holding/reducing talazoparib. • Re-initiate bempegaldesleukin (NKTR-214) once toxicity Grade ≤1 or baseline. • Permanently discontinue bempegaldesleukin (NKTR-214) if toxicity does not resolve to Grade ≤1 or baseline within 12 weeks or if the same Grade 3 toxicity recurs (if talazoparib had already been discontinued and recurrent event occurs on avelumab in combination with bempegaldesleukin [NKTR-214] only).	• Hold talazoparib first (before holding avelumab in combination with bempegaldesleukin [NKTR-214]) and monitor weekly until platelets ≥75,000/μL. • Resume talazoparib based on the following recovery times: ≤1 week: No change; >1 week: Talazoparib may be reduced by 1 dose level, per Section 6.6.2.2. • Permanently discontinue talazoparib if persists for >4 weeks without recovery to platelets ≥75,000/μL. Refer to hematologist for evaluation including assessment of possible MDS/AML.
Lymphopenia Grade ≥3 (lymphocytes <0.5 x $10e^9$/L)	• Continue as planned.	• Continue as planned.	• Continue as planned.
Eosinophilia	• Continue as planned.	• If the study participant is suspected to have hypereosinophilic syndrome (symptoms may involve skin, lungs, digestive tract, heart, blood, and nervous system) with AEC at or above 5000/μL (5×10^9/L), bempegaldesleukin (NKTR-214) treatment	• Continue as planned.

Table 14. Avelumab + Bempegaldesleukin (NKTR-214) + Talazoparib Triplet Treatment Modifications for Drug Related Toxicity (Excluding Infusion Related Reactions and Immune Related AEs)

	Avelumab	Bempegaldesleukin (NKTR-214)	Talazoparib
		may need to be held.	
Non-hematologic toxicities			
Grade 1	• Continue as per schedule. • For suspected immune-related toxicity follow guidance in Section 6.6.3 and Table 16.	• Continue as per schedule. • For suspected immune related toxicity follow guidance in Section 6.6.3 and Table 16.	• Continue as per schedule. • For suspected immune related toxicity follow guidance in Section 6.6.3 and Table 16.
Grade 2	• Continue as per schedule. • For suspected immune-related toxicity follow guidance in Section 6.6.3 and Table 16.	• Continue as per schedule. For persistent Grade 2 related toxicity, delay administration at the discretion of the Investigator. • For suspected immune related toxicities follow guidance in Section 6.6.3 and Table 16.	• Continue as per schedule. • For suspected immune-related toxicity that requires avelumab and/or bempegaldesleukin (NKTR-214) delay or discontinuation as per Section 6.6.3 and Table 16, **talazoparib should also be placed on hold until toxicity is Grade ≤1 or baseline.**
Grade 3	• Hold avelumab. • Resume once toxicity is Grade ≤1 or baseline. • Permanently discontinue if toxicity does not resolve to Grade ≤1 or baseline within 12 weeks or if the same Grade 3 toxicity recurs. • **Exceptions are:** Laboratory values that do not have any clinical correlate. • For suspected immune-related toxicity follow	• Hold bempegaldesleukin (NKTR-214). • Resume once toxicity is Grade ≤1 or baseline. • Permanently discontinue if toxicity does not resolve to Grade ≤1 or baseline within 12 weeks or if the same Grade 3 toxicity recurs. • **Exceptions are:** Laboratory values that do not have any clinical correlate. • For suspected immune related toxicity due to bempegaldesleukin	• Hold talazoparib. • Resume talazoparib reduced by 1 dose level, per Section 6.6.2.2 if toxicity resolves to Grade ≤1 or baseline within 4 weeks. • If the same Grade 3 toxicity recurs, reduce by 1 dose level. • Permanently discontinue if toxicity does not improve to Grade ≤1 or baseline within 4 weeks. • **Exceptions are:** Laboratory values that

Table 14. Avelumab + Bempegaldesleukin (NKTR-214) + Talazoparib Triplet Treatment Modifications for Drug Related Toxicity (Excluding Infusion Related Reactions and Immune Related AEs)

	Avelumab	Bempegaldesleukin (NKTR-214)	Talazoparib
	guidance in Section 6.6.3 and Table 16.	(NKTR-214), follow guidance in Section 6.6.3 and Table 16.	do not have any clinical correlate. • Permanently discontinue if Grade 3 liver test abnormality. • **For suspected immune-related toxicity that requires delay or discontinuation of avelumab and bempegaldesleukin (NKTR-214) as per Section 6.6.3 and Table 16, talazoparib should also be placed on hold until toxicity is Grade ≤1 or baseline.**
Grade 4	• Permanently discontinue avelumab. • **Exceptions are:** Laboratory values that do not have any clinical correlate. • For suspected immune-related toxicity, follow guidance in Section 6.6.3 and Table 16.	• Permanently discontinue bempegaldesleukin (NKTR-214). • **Exceptions are:** Laboratory values that do not have any clinical correlate. • For suspected immune related toxicity, follow guidance in Section 6.6.3 and Table 16.	• Permanently discontinue talazoparib. • **Exceptions are:** Laboratory values that do not have any clinical correlate.

Abbreviations: AEC=absolute eosinophil count; AE=adverse event; AML=acute myeloid leukemia; ANC=absolute neutrophil count; MDS=myelodysplastic syndrome.

6.6.2.3. Dose Modifications for Avelumab + Bempegaldesleukin (NKTR-214) + Enzalutamide Triplet (Combination C)

Refer to Section 6.6.2.1 for additional information regarding dose delays and reductions for avelumab and bempegaldesleukin (NKTR-214). Refer to Table 13 for dose modifications by grade for this combination.

Following dosing interruption due to toxicity, the enzalutamide dose may need to be resumed at a reduced dose.

The dose level for avelumab is fixed at 800 mg Q2W. No dose reductions are permitted for avelumab; however, the next infusion may be omitted/delayed based on persisting toxicity. Avelumab may be discontinued as clinically indicated. . Available dose levels for bempegaldesleukin (NKTR-214) dose are 0.006 and 0.003 mg/kg Q2W. Available dose levels for enzalutamide are 80, 120, and 160 mg once daily, with a lowest allowable dose of 80 mg once daily. These available dose levels are the same regardless of whether the bempegaldesleukin (NKTR-214) dose is 0.006 or 0.003 mg/kg Q2W. Dose reduction of enzalutamide by 1 dose level at a time will be allowed depending on the starting dose.

Since the risk of hematologic toxicities with enzalutamide has been established as low in past clinical studies, if a hematologic toxicity occurs, avelumab/bempegaldesleukin (NKTR-214) should be withheld first; enzalutamide can then be subsequently withheld if the toxicity does not resolve. Refer to Table 15.

Participants who experience a grade 3 or higher toxicity that is attributed to enzalutamide and cannot be ameliorated by the use of adequate medical intervention may interrupt treatment with enzalutamide. Subsequently, the enzalutamide dosing may be restarted at the original dose or a reduced dose. Treatment interruption and reinitiation should be discussed with the sponsor.

Site personnel must ensure the participant is instructed how to take the reduced dose and that the participant has the correct dosage strength for the reduced dose.

Table 15. Avelumab + Bempegaldesleukin (NKTR-214) + Enzalutamide Triplet Treatment Modifications for Drug Related Toxicity (Excluding Infusion Related Reactions and Immune Related AEs)

	Avelumab	Bempegaldesleukin (NKTR-214)	Enzalutamide
Hematologic toxicities			
Grade 1 and Grade 2	Continue as per schedule.	Continue as per schedule.	Continue as per schedule.
Anemia Grade ≥3	• Hold avelumab. • Re-initiate avelumab once toxicity Grade ≤1 or baseline. • Permanently discontinue avelumab if toxicity does not resolve to Grade ≤1 or baseline within 12 weeks or if the same Grade 3 toxicity recurs. • For suspected immune-related toxicity follow guidance in Section 6.6.3 and Table 16.	• Hold bempegaldesleukin (NKTR-214). • Re-initiate bempegaldesleukin (NKTR-214) once toxicity Grade ≤1 or baseline. • Permanently discontinue bempegaldesleukin (NKTR-214) or reduce dose as per Section 6.6.2.1 if toxicity does not resolve to Grade ≤1 or baseline within 12 weeks or if the same Grade 3 toxicity recurs. • For suspected immune-related toxicity follow guidance in Section 6.6.3 and Table 16.	• Continue as planned. • If toxicity is attributed to enzalutamide and does not resolve to Grade ≤1 or baseline, delay or reduce dose as per guidelines in Section 6.6.2.3. • Permanently discontinue enzalutamide if toxicity does not resolve to Grade ≤1 or baseline within 12 weeks or if the same Grade 3 toxicity recurs **(if avelumab in combination with bempegaldesleukin [NKTR-214] had already been discontinued and recurrent event occurs on enzalutamide only).** • For suspected immune-related toxicity follow guidance in Section 6.6.3 and Table 16.
Neutropenia Grade ≥3 (ANC <1000/µL)	• Hold avelumab. • Re-initiate avelumab once toxicity Grade ≤1 (ANC ≥1500/µL) or baseline. • Permanently discontinue avelumab if toxicity does not resolve to Grade ≤1 or baseline within 12 weeks or if the same Grade 3 toxicity recurs. • For suspected immune-related toxicity due to avelumab, follow guidance in Section 6.6.3 and Table 16.	• Hold bempegaldesleukin (NKTR-214). • Re-initiate bempegaldesleukin (NKTR-214) once toxicity Grade ≤1 (ANC ≥1500 µL) or baseline. • Permanently discontinue bempegaldesleukin (NKTR-214) or reduce dose as per Section 6.6.2.1 if toxicity does not resolve to Grade ≤1 or baseline within 12 weeks or if the same	• Continue with enzalutamide if toxicity is not attributed to enzalutamide. • If toxicity is attributed to enzalutamide and does not resolve to Grade ≤1 or baseline, delay or reduce dose as per guidelines in Section 6.6.2.3. • Permanently discontinue enzalutamide if toxicity does not resolve to Grade ≤1 or baseline within 12 weeks or if the same Grade 3 toxicity recurs **(if avelumab in combination with bempegaldesleukin [NKTR-214] had**

Table 15. Avelumab + Bempegaldesleukin (NKTR-214) + Enzalutamide Triplet Treatment Modifications for Drug Related Toxicity (Excluding Infusion Related Reactions and Immune Related AEs)

	Avelumab	Bempegaldesleukin (NKTR-214)	Enzalutamide
		Grade 3 toxicity recurs. • For suspected immune-related toxicity due to bempegaldesleukin (NKTR-214), follow guidance in Section 6.6.3 and Table 16.	**already been discontinued and recurrent event occurs on enzalutamide only).** • For suspected immune-related toxicity follow guidance in Section 6.6.3 and Table 16.
Thrombocytopenia Grade ≥3 (platelets <50,000/μL)	• Hold avelumab. • Re-initiate avelumab once toxicity Grade ≤1 or baseline. • Permanently discontinue avelumab if toxicity does not resolve to Grade ≤1 or baseline within 12 weeks or if the same Grade 3 toxicity recurs. • For suspected immune-related toxicity follow guidance in Section 6.6.3 and Table 16.	• Hold bempegaldesleukin (NKTR-214). • Re-initiate bempegaldesleukin (NKTR-214) once toxicity Grade ≤ 1 or baseline. • Permanently discontinue bempegaldesleukin (NKTR-214) or reduce dose per Section 6.6.2.1 if toxicity does not resolve to Grade ≤1 or baseline within 12 weeks or if the same Grade 3 toxicity recurs. • For suspected immune-related toxicity follow guidance in Section 6.6.3 and Table 16.	• Continue with enzalutamide if toxicity is not attributed to enzalutamide. • If toxicity does not resolve to Grade ≤1 or baseline, delay or reduce dose as per guidelines in Section 6.6.2.3. • Permanently discontinue enzalutamide if toxicity does not resolve to Grade ≤1 or baseline within 12 weeks or if the same Grade 3 toxicity recurs **(if avelumab in combination with bempegaldesleukin [NKTR-214] had already been discontinued and recurrent event occurs on enzalutamide only).** • For suspected immune-related toxicity follow guidance in Section 6.6.3 and Table 16.
Lymphopenia Grade ≥3(lymphocytes <0.5 x $10e^9$ /L)	• Continue as planned.	• Continue as planned.	• Continue as planned.
Eosinophilia	• Continue as planned.	• If the study participant is suspected to have hypereosinophilic syndrome (symptoms may involve skin, lungs, digestive tract,	• Continue as planned.

Table 15. Avelumab + Bempegaldesleukin (NKTR-214) + Enzalutamide Triplet Treatment Modifications for Drug Related Toxicity (Excluding Infusion Related Reactions and Immune Related AEs)

	Avelumab	Bempegaldesleukin (NKTR-214)	Enzalutamide
		heart, blood, and nervous system) with AEC at or above 5000/μL (5×10^9/L), bempegaldesleukin (NKTR-214) treatment may need to be held.	
Non-hematologic toxicities			
Grade 1	• Continue as per schedule. • For suspected immune-related toxicities follow guidance in Section 6.6.3 and Table 16.	• Continue as per schedule. • For suspected immune related toxicities follow guidance in Section 6.6.3 and Table 16.	• Continue as per schedule. • For suspected immune related toxicities follow guidance in Section 6.6.3 and Table 16.
Grade 2	• Continue as per schedule. • For suspected immune-related toxicities follow guidance in Section 6.6.3 and Table 16.	• For persistent Grade 2 related toxicity, delay NK-214 administration at the discretion of the Investigator. • Bempegaldesleukin (NKTR-214) dosing may resume at the same dose or at a lower dose level when toxicity resolves to Grade 1 or returns to baseline, except for instances where the potential recurrence of the event poses an undue risk for the participant. • For suspected immune related toxicities follow guidance in Section 6.6.3 and Table 16.	• Continue as per schedule. • For suspected immune-related toxicities follow guidance in Section 6.6.3 and Table 16.
Grade 3	• Hold avelumab. • Resume avelumab once toxicity is Grade ≤1 or baseline. • Permanently discontinue avelumab if toxicity does not resolve to Grade ≤1 or baseline within	• Hold bempegaldesleukin (NKTR-214). • Resume bempegaldesleukin (NKTR-214) once toxicity is Grade ≤1 or baseline. • Permanently discontinue	• Continue with enzalutamide if toxicity is not attributable to enzalutamide. • Resume enzalutamide once toxicity is Grade ≤1 or baseline. • If toxicity does not resolve to Grade ≤1 or

Table 15. Avelumab + Bempegaldesleukin (NKTR-214) + Enzalutamide Triplet Treatment Modifications for Drug Related Toxicity (Excluding Infusion Related Reactions and Immune Related AEs)

	Avelumab	Bempegaldesleukin (NKTR-214)	Enzalutamide
	12 weeks or if the same Grade 3 toxicity recurs. • **Exceptions are:** Laboratory values that do not have any clinical correlate. • For suspected immune-related toxicities follow guidance in Section 6.6.3 and Table 16.	bempegaldesleukin (NKTR-214) if toxicity does not resolve to Grade ≤1 or baseline within 12 weeks or if the same Grade 3 toxicity recurs. • **Exceptions are:** Laboratory values that do not have any clinical correlate. • For suspected immune related toxicities follow guidance in Section 6.6.3 and Table 16.	baseline, delay or reduce dose as per guidelines in Section 6.6.2.3. • Permanently discontinue enzalutamide if toxicity does not resolve to Grade ≤1 or baseline within 12 weeks or if the same Grade 3 toxicity recurs **(if avelumab in combination with bempegaldesleukin [NKTR-214] had already been discontinued and recurrent event occurs on enzalutamide only).** • For suspected immune related toxicities follow guidance in Section 6.6.3 and Table 16.
Grade 4	• Permanently discontinue avelumab. • **Exceptions are:** Laboratory values that do not have any clinical correlate. • For suspected immune-related toxicities follow guidance in Section 6.6.3 and Table 16.	• Permanently discontinue bempegaldesleukin (NKTR-214). • **Exceptions are:** Laboratory values that do not have any clinical correlate. • For suspected immune-related toxicities follow guidance in Section 6.6.3 and Table 16.	• Permanently discontinue enzalutamide. • **Exceptions are:** Laboratory values that do not have any clinical correlate.

Abbreviations: AEC=absolute eosinophil count; AE=adverse event; AML=acute myeloid leukemia; ANC=absolute neutrophil count; MDS=myelodysplastic syndrome.

6.6.3. Immune-Related AEs

For participants receiving avelumab in combination with bempegaldesleukin (NKTR-214) only (Combination A), in combination with both bempegaldesleukin (NKTR-214) + talazoparib (Combination B) or in combination with both bempegaldesleukin (NKTR-214)+ enzalutamide (Combination C), any AE suspected to be immune-related (ie, an irAE) should be managed according to the guidance for management of irAEs (refer to Table 16).

Treatment of irAEs is mainly dependent on severity (NCI CTCAE grade):

- Grades 1 to 2: treat symptomatically or with moderate dose steroids, more frequent monitoring.
- Grades 1 to 2 (persistent): manage similar to Grades 3 to 4 AE.
- Grades 3 to 4: treat with high dose corticosteroids.

Table 16. Management of Immune Related Adverse Events for Avelumab and Bempegaldesleukin (NKTR-214)

Gastrointestinal irAEs		
Severity of Diarrhea/Colitis (NCI-CTCAE v4.03)	Initial Management	Follow-up Management
Grade 1 Diarrhea: <4 stools/day over Baseline Colitis: asymptomatic	Continue study treatment. Symptomatic treatment (eg loperamide).	Close monitoring for worsening symptoms. Educate participant to report worsening immediately. If worsens: Treat as Grade 2, 3 or 4.
Grade 2 Diarrhea: 4 to 6 stools per day over Baseline; IV fluids indicated <24 hours; not interfering with ADL Colitis: abdominal pain; blood in stool.	Withhold study treatment. Symptomatic treatment.	If improves to Grade ≤1: Resume study treatment If persists >5-7 days or recurs: Treat as Grade 3 or 4.
Grade 3 to 4 Diarrhea (Grade 3): ≥7 stools per day over Baseline; incontinence; IV fluids ≥24 h; interfering with ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs. Grade 4: life-threatening, perforation.	Withhold study treatment for Grade 3. Permanently discontinue for Grade 4 or recurrent Grade 3. 1.0 to 2.0 mg/kg/day prednisone IV or equivalent. Add prophylactic antibiotics for opportunistic infections. Consider lower endoscopy.	If improves: Continue steroids until Grade ≤1, then taper over at least 1 month; resume study treatment following steroids taper (for initial Grade 3). If worsens, persists >3 to 5 days, or recurs after improvement: Add infliximab 5mg/kg (if no contraindication). Note: infliximab should not be used in cases of perforation or sepsis.
Dermatological irAEs		
Grade of Rash (NCI-CTCAE v4.03)	Initial Management	Follow-up Management
Grade 1 to 2 Covering ≤30% body surface area	Continue symptomatic therapy (for example, antihistamines, topical	If persists >1 to 2 weeks or recurs: Withhold study treatment

Table 16. Management of Immune Related Adverse Events for Avelumab and Bempegaldesleukin (NKTR-214)

	steroids).	Consider skin biopsy Consider 0.5-1.0 mg/kg/day prednisone or equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume therapy following steroids taper. If worsens: Treat as Grade 3 to 4.
Grade 3 to 4 Grade 3: Covering >30% body surface area; Grade 4: Life threatening consequences.	Withhold study treatment for Grade 3. Permanently discontinue study treatment for Grade 4 or recurrent Grade 3. Consider skin biopsy. Dermatology consult. 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections.	If improves to Grade ≤1: Taper steroids over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3).
Grade 1 to 2 Covering ≤30% body surface area	Continue study treatment Symptomatic therapy (for example, antihistamines, topical steroids).	If persists >1 to 2 weeks or recurs: Withhold study treatment Consider skin biopsy Consider 0.5-1.0 mg/kg/day prednisone or equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume study treatment following steroids taper. If worsens: Treat as Grade 3 to 4.
Hepatic irAEs		
Grade of Liver Test Elevation (NCI-CTCAE v4.03)	Initial Management	Follow-up Management
Grade 1 Grade 1 AST or ALT >ULN to 3.0 x ULN and/or Total bilirubin >ULN to 1.5 x ULN	Continue study treatment.	Continue liver function monitoring If worsens: Treat as Grade 2 or 3 to 4.
Grade 2 AST or ALT >3.0 to ≤5 x ULN and/or total bilirubin >1.5 to ≤3 x ULN	Withhold study treatment Increase frequency of monitoring to every 3 days.	If returns to Grade ≤1: Resume routine monitoring; resume study treatment. If elevation persists >5 to 7 days or worsens: Treat as Grade 3 to 4.
Grade 3 to 4 AST or ALT >5 x ULN and/or total bilirubin >3 x ULN	Permanently discontinue study treatment. Increase frequency of monitoring to every 1 to 2 days. 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for	If returns to Grade ≤1: Taper steroids over at least 1 month If does not improve in >3 to 5 days, worsens or rebounds: Add mycophenolate mofetil 1 gram (g) twice daily If no response within an additional 3 to

Table 16. Management of Immune Related Adverse Events for Avelumab and Bempegaldesleukin (NKTR-214)

	opportunistic infections. Consult gastroenterologist/ hepatologist. Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted.	5 days, consider other immunosuppressants per local guidelines.
Renal irAEs		
Grade of Creatinine Increased (NCI-CTCAE v4.03)	Initial Management	Follow-up Management
Grade 1 Creatinine increased >ULN to 1.5 x ULN	Continue therapy.	Continue renal function monitoring If worsens: Treat as Grade 2 to 3 or 4.
Grade 2 to 3 Creatinine increased >1.5 and ≤6 x ULN	Withhold therapy. Increase frequency of monitoring to every 3 days 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections. Consider renal biopsy.	If returns to Grade ≤1: Taper steroids over at least 1 month, and resume avelumab therapy following steroids taper. If worsens: Treat as Grade 4.
Grade 4 Creatinine increased >6 x ULN	Permanently discontinue therapy. Monitor creatinine daily 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections. Consider renal biopsy. Nephrology consult.	If returns to Grade ≤1: Taper steroids over at least 1 month.
Cardiac irAEs		
Myocarditis	Initial Management	Follow-up Management
New onset of cardiac signs or symptoms and / or new laboratory cardiac biomarker elevations (eg, troponin, CK-MB, BNP) or cardiac imaging abnormalities suggestive of myocarditis.	Withhold therapy. Hospitalize. In the presence of life threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management. Cardiology consult to establish etiology and rule-out immune-mediated myocarditis. Guideline based supportive treatment as per cardiology consult.* Consider myocardial biopsy if recommended per cardiology consult.	If symptoms improve and immune-mediated etiology is ruled out, re-start therapy. If symptoms do not improve/worsen, viral myocarditis is excluded, and immune-mediated etiology is suspected or confirmed following cardiology consult, manage as immune-mediated myocarditis.
Immune-mediated myocarditis	Permanently discontinue therapy. Guideline based supportive treatment as appropriate as per cardiology consult.* 1.0 to 2.0 mg/kg/day prednisone or equivalent.	Once improving, taper steroids over at least 1 month. If no improvement or worsening, consider additional immunosuppressants (eg, azathioprine, cyclosporine A).

Table 16. Management of Immune Related Adverse Events for Avelumab and Bempegaldesleukin (NKTR-214)

	Add prophylactic antibiotics for opportunistic infections.	
*Local guidelines, or eg ESC or AHA guidelines ESC guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines AHA guidelines website: http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001		
Endocrine irAEs		
Endocrine Disorder	Initial Management	Follow-up Management
Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Continue therapy Endocrinology consult if needed. Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for Type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (ie hypopituitarism / hypophysitis).	Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Grade 3 or Grade 4 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Withhold therapy. Consider hospitalization. Endocrinology consult. Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (ie hypopituitarism / hypophysitis).	Resume therapy once symptoms and/or laboratory tests improve to Grade ≤1 (with or without hormone replacement/suppression). Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Hypopituitarism/Hypophysitis (secondary endocrinopathies)	If secondary thyroid and/or adrenal insufficiency is confirmed (ie, subnormal serum FT4 with inappropriately low TSH and/or low serum cortisol with inappropriately low ACTH): Refer to endocrinologist for dynamic testing as indicated and measurement of other hormones (FSH, LH, GH/IGF-1, PRL, testosterone in men, estrogens in women). Hormone replacement/suppressive therapy as appropriate. Perform pituitary MRI and visual field examination as indicated. If hypophysitis confirmed: Continue avelumab if mild symptoms with normal MRI. Repeat the MRI in	Resume therapy once symptoms and hormone tests improve to Grade ≤1 (with or without hormone replacement). In addition, for hypophysitis with abnormal MRI, resume avelumab only once shrinkage of the pituitary gland on MRI/CT scan is documented. Continue hormone replacement/suppression therapy as appropriate.

Table 16. Management of Immune Related Adverse Events for Avelumab and Bempegaldesleukin (NKTR-214)

	1 month. Withhold study treatment if moderate, severe or life-threatening symptoms of hypophysitis and/or abnormal MRI. Consider hospitalization. Initiate corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) followed by corticosteroids taper during at least 1 month. Add prophylactic antibiotics for opportunistic infections.	
Other irAEs (not described above)		
Grade of other irAEs (NCI-CTCAE v4.03)	Initial Management	Follow-up Management
Grade 2 or Grade 3 clinical signs or symptoms suggestive of a potential irAE	Withhold therapy pending clinical investigation.	If irAE is ruled out, manage as appropriate according to the diagnosis and consider re-starting therapy If irAE is confirmed, treat as Grade 2 or 3 irAE.
Grade 2 irAE or first occurrence of Grade 3 irAE	Withhold therapy. 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections. Specialty consult as appropriate.	If improves to Grade ≤1: Taper steroids over at least 1 month and resume therapy following steroids taper.
Recurrence of same Grade 3 irAEs	Permanently discontinue therapy. to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate.	If improves to Grade ≤1: Taper steroids over at least 1 month.
Grade 4	Permanently discontinue therapy. to 2.0 mg/kg/day prednisone or equivalent and/or other immunosuppressant as needed. Add prophylactic antibiotics for opportunistic infections. Specialty consult.	If improves to Grade ≤1: Taper steroids over at least 1 month
Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks for reasons other than hormonal replacement for adrenal insufficiency Persistent Grade 2 or 3 irAE lasting 12 weeks or longer	Permanently discontinue study treatment. Specialty consult.	

Abbreviations: ACTH=adrenocorticotropic hormone; ADL=activities of daily living; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BNP=B type natriuretic peptide; CK MB=creatine kinase MB; CT= computed tomography; FSH=follicle stimulating hormone; GH=growth hormone; IGF 1=insulin like growth factor 1; irAE=immune related adverse event; IV=intravenous; LH=luteinizing hormone; MRI=magnetic resonance imaging; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; PRL=prolactin;T4=thyroxine; TSH=thyroid stimulating hormone; ULN=upper limit of normal.

6.7. Intervention after the End of the Study

There are no interventions planned after the end of this study. Refer to Section 7.1 for end of treatment, short-term follow-up, and long-term follow-up procedures.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

Participants who only discontinue study intervention (ie, study treatment) should continue in the study and complete all protocol specified activities even after discontinuing study treatment, in order to provide the data required for the study estimands (refer to Section 3).

Reasons for discontinuing study intervention (treatment) may include:

- Objective disease progression; however, participants with disease progression who are continuing to derive clinical benefit from the study treatment will be eligible to continue study treatment as described in Section 6.5.7.2, provided that the treating physician has determined that the benefit/risk for doing so is favorable:
- Global deterioration of health status requiring discontinuation;
- Unacceptable toxicity. If the unacceptable toxicity is attributed to 1 of the investigational products, the Investigator may continue treatment with the other investigational product(s);
- Pregnancy;
- Significant protocol violation;
- Lost to follow-up;
- Participant refused further treatment;
- Study terminated by sponsor;
- Death.

Note that discontinuation of study treatment does not represent withdrawal from the study.

As data on clinical events beyond study treatment discontinuation is required to support the study estimands, data should be planned to be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention (ie, study treatment). The discontinuation of study treatment is defined as the discontinuation of **all**

study drugs; if a participant, for example, discontinues one study drug in Combination A, or one or two study drugs in Combinations B or C, this is not a study treatment discontinuation. All participants who discontinue study treatment should still continue to participate in the study and complete activities as specified in Section 1.3 - Schedule of Activities.

It may be necessary for a participant to permanently discontinue study intervention (ie, study treatment). Subsequent anti-cancer treatments will be documented and recorded for participant who discontinue all study treatments and continue in the Follow-up and Long-term Follow-up.

- **End of Treatment** (discontinuation of all study treatment for any reason): Obtain these assessments as per the Schedule of Activities if not completed in the prior 7 days.

- **Short-term Follow-Up (after Last Dose of Study Treatment**): All participants will be followed for safety every 30 days (±3 days) through 90 days after the last dose of study treatment, unless other anti-cancer treatment is initiated; then only SAE and SAE treatments should continue to be collected. Follow-up beyond 30 days and up to and including 90 days after last dose of investigational products may be performed either via a clinic visit or by remote contact (eg, telephone). Refer to Section 8.1.1 for guidance on tumor assessment during the Follow-up periods.

- **Long-term Follow-up:** Following completion of the initial 90-day follow-up period, all participants will be followed for survival status (independently of time of disease progression) and subsequent anti-cancer treatments every 12 weeks (±14 days) for at least 2 years after enrollment of the last participant in the study or until death, lost-to-follow-up, study discontinued by sponsor, or participant withdrawal of consent, whichever comes first. For those participants without evidence of disease progression at the time of treatment discontinuation who continue to be followed with tumor assessments at Long-Term Follow-Up, survival status will be collected at the time of the scheduled tumor assessments.

7.1.1. Abnormal Electrocardiograms (ECGs)

If a clinically significant finding is identified (including, but not limited to changes from baseline in QT interval corrected using [Bazett's formula [QTcB] or Fridericia's formula [QTcF]]) after enrollment, the investigator or qualified designee will determine if the participant can continue on the study treatment and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE. For criteria for clinically significant ECG findings for oncology studies, refer to Appendix 7.

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

7.2. Participant Discontinuation/Withdrawal from the Study

- Reasons from withdrawal from the study include:
  - Study terminated by sponsor;
  - Lost to follow-up;
  - Withdrawal of consent for further collection of follow-up data;
  - Death.
- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The early discontinuation visit applies only to participants who are enrolled and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal. The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant refuses further visits, they should continue to be followed for survival unless the participant withdraws consent for disclosure of future information or for further contact. In this case, no further study specific evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any remaining samples but data already generated from the samples will continue to be available, and may be used to protect the integrity of existing analyses. The investigator must document any such requests in the site study records.
- Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.
- If a participant does not return for a scheduled visit, every effort should be made to contact them. All attempts to contact the participant and information received during contact attempts must be documented in the participant's medical record. In any circumstance, every effort should be made to document participant outcome, if possible. The Investigator should inquire about the reason for withdrawal, request

that the participant return for a final visit, if applicable, and follow up with the participant regarding any unresolved AEs.

- When a participant withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported on the CT SAE Report.

Withdrawal of Consent:

Participants who request to discontinue receipt of study treatment will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of investigational product or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

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

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

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the Schedule of Activities (SoA). Protocol waivers or exemptions are not allowed.
- The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening and applicable C1D1 evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICD may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

8.1. Efficacy Assessments

8.1.1. Tumor Efficacy Imaging Assessments

8.1.1.1. Tumor Related Endpoints and Definitions for 1L SCCHN (Combination A)

Participants with SCCHN will undergo tumor assessments as per the requirements described in this section. Tumor related endpoints for SCCHN participants will be based on RECIST v1.1 (refer to Appendix 9).

Tumor assessments will include all known or suspected disease sites. Imaging is required for the site of the primary tumor and may include neck, chest, abdomen and pelvis CT or MRI

scans. A baseline brain CT or magnetic resonance imaging (MRI) scan is required for all participants with stable brain lesions and for those for whom Central Nervous System (CNS) involvement is suspected; these participants will continue to have brain CT or MRI scans performed at each tumor assessment. Otherwise, brain CT or MRI imaging is required only when clinically indicated.

CT or MRI scans should be performed with contrast agents unless contraindicated for medical reasons. The same imaging technique used to characterize each identified and reported lesion at screening will be employed in the following tumor assessments.

Anti-tumor activity will be assessed through radiological tumor assessments conducted at screening, during treatment every 8 weeks for 52 weeks from the start of the study treatment, and then every 16 weeks thereafter until disease progression. Anti-tumor activity will also be assessed during follow-up and long-term follow-up after end of treatment, for participants who discontinue treatment due to reasons other than PD, regardless of initiation of subsequent anti-cancer therapy, as specified in the Schedule of Activities (Tables 4 and 5), whenever disease progression is suspected (eg, symptomatic deterioration), and at the time of withdrawal from treatment (if not done in the previous 4 weeks and the prior response is other than PD). Timing of disease assessment should be fixed according to the calendar, starting with C1D1, and should not be adjusted for delays in cycle starts. In case CR or PR, is observed according to RECIST v1.1 (refer to Appendix 9), tumor assessments must be confirmed by repeated imaging at least 4 weeks after initial documentation.

The allowable time window for tumor assessments is ±7 days.

Details of treatment after initial evidence of radiological disease progression are provided in Section 6.5.7.2.

8.1.1.2. Tumor Related Endpoints and Definitions for mCRPC (Combinations B and C)

Assessment of soft tissue response for participants with mCRPC will be made using RECIST v1.1 (refer to Appendix 9). The Investigator will assess response of soft tissue disease by RECIST v1.1. Bone disease will not be considered as non-target lesions assessed by RECIST v1.1, but will be assessed for progressive disease by PCWG3 (refer to Appendix 10).

Tumor assessments will include all known or suspected disease sites. Imaging is categorized as soft tissue or bone. Soft tissue imaging may include CT scans of the chest, abdomen and pelvis or MRIs of the abdomen and pelvis. Bone imaging must be whole body radionuclide bone scan. Brain CT or MRI scans are required for all participants with stable brain lesions and for those for whom Central Nervous System (CNS) involvement is suspected. Participants with stable brain lesions present at screening, will continue to have brain CT or MRI scans performed at each tumor assessment. Otherwise, brain CT or MRI imaging is required only when clinically indicated. Bone scans must be performed at every tumor assessment.

CT or MRI scans should be performed with contrast agents unless contraindicated for medical reasons. The same imaging technique used to characterize each identified and reported lesion at screening will be employed in the following tumor assessments.

Anti-tumor activity will be assessed through radiological tumor assessments conducted at screening, during treatment every 8 weeks for 52 weeks from the start of the study treatment, and then every 12 weeks thereafter until disease progression. Anti-tumor activity will also be assessed during follow-up and long-term follow-up after end of treatment, for participants who discontinue treatment due to reasons other than PD, regardless of initiation of subsequent anti-cancer therapy, as specified in the Schedule of Activities (Tables 6 and 7), whenever disease progression is suspected (eg, symptomatic deterioration), and at the time of withdrawal from treatment (if not done in the previous 4 weeks and the prior response is other than PD). Timing of disease assessment should follow calendar days, starting with C1D1, and should not be adjusted for delays in cycle starts.

An objective response is defined as a best overall response of CR or PR per RECIST v1.1 and must be confirmed on repeated imaging at least 4 weeks after initial documentation. Disease progression in bone disease must be confirmed at least 6 weeks later, as per PCWG3.

The allowable time window for tumor assessments is ±7 days.

Details of treatment after initial evidence of radiological disease progression are provided in Section 6.5.7.2.

8.1.2. Clinical Assessments

8.1.2.1. Blood for Lymphocyte Count

Approximately 8 mL whole blood will be collected in a tripotassium ethylenediaminetetraacetic acid (K_3EDTA) tube as described in the Schedule of Activities and Appendix 2 and analyzed by a local laboratory. This sample will be used to assess the number of lymphocytes. This is the same sample that will be used for the hematology assessment.

8.1.2.2. Circulating Tumor Cells (CTCs) for Participants with mCRPC (Combination C)

For participants in Combination C with mCRPC, approximately 10 mL whole blood will be collected at the time points described in the SoA (Tables 6 and 7) to allow quantitation of CTCs.

8.1.2.3. PSA Antibody Testing for Participants with mCRPC (Combinations B and C)

For participants with mCRPC, approximately 5 mL whole blood will be collected at the time points described in the SoA (Tables 6 and 7) and analyzed at a local laboratory for PSA levels. There is a 7-day window allowed for PSA labs from C1D1.

8.1.2.4. Testosterone for Participants with mCRPC (Combinations B and C)

For participants with mCRPC, approximately 5 mL whole blood will be collected at the time points described in the SoA (Table 6) and analyzed at a local laboratory for testosterone levels.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the Schedule of Activities. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety concerns.

8.2.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal and neurological systems, skin, and vital signs at the time points described in the SoA.

- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

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

8.2.2. Vital Signs

- Weight, height, heart rate, and blood pressure will be assessed as per the SoA.

- Blood pressure and pulse measurements will be assessed in a supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.

- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions.

8.2.3. Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the Schedule of Activities for the timing and frequency. Samples for all laboratory assessments will be drawn at the time points indicated and when clinically indicated.

- Prior to study drug administration on Days 1 and 15 of each treatment cycle, hematology (ie, hemoglobin, platelets, and white blood cells) and chemistry (ie, ALT, AST, alkaline phosphatase, total bilirubin, blood urea nitrogen, creatinine, sodium, potassium, lipase, amylase, and glucose) tests must be performed and results reviewed by the treating physician prior to study drug administration. When applicable, results from pregnancy tests must also be available for review prior to dosing.

- Repeat samples do not have to be drawn on Cycle 1 Day 1 if these samples were drawn in the prior 3 days. Laboratory tests may be performed up to 3 days prior to the scheduled clinic visit, so that results will be available for review before study treatment administration.

- Results from pregnancy tests, if taken, must be available for review prior to dosing.

- Laboratory assessments are conducted only through the Day 30 Safety Follow-up visit. Laboratory assessments are not required at the Day 60 or Day 90 Safety Follow-up visit.

- Laboratory assessments must be performed and results reviewed by the treating physician as soon as they are available.

- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically

significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 90 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or sponsor.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
    - All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the Schedule of Activities.
    - If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

8.2.4. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL as required by local regulatory requirements. Pregnancy tests will be performed in WOCBP(Combination A only) at the times listed in the SoA.

Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will then be required at the baseline visit on C1D1 before the participant may receive the study treatment. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations. Refer to Appendix 2.

8.2.5. Electrocardiograms

- For Phase 1b participants, 12-lead ECGs should be performed at screening (singlet), and on Day 1 of Cycles 1 and 2 (triplicate), prior to any pre-dose PK collection(within 2 hours) and prior to any post-dose avelumab PK collection (within 10 minutes after the end of avelumab infusion). Singlet 12-lead ECGs may be performed as clinically indicated for participants in Phase 1b, and only as clinically indicated in Cycles 1 and 2 for participants in Phase 2.

- In Cycle ≥3, singlet 12-lead ECGs will be performed only as clinically indicated for participants in both Phase 1b and Phase 2.

- Refer to the Schedule of Activities for the ECG collection time points. The parameters to be recorded are RR, QT, QTc, PR, and QRS. A standard 12-lead (with a 10-second rhythm strip) tracing will be used for all ECGs. It is preferable that the machine used has a capacity to calculate the standard intervals automatically. If, during a single measurement, the QTc is prolonged (>500 msec, ie, CTCAE Grade ≥3), then a triplicate ECG will be collected to confirm the original measurement and repeated as clinically indicated.

- Refer to Appendix 7 for QTc withdrawal criteria and any additional QTc readings that may be necessary, as well as ECG values of potential clinical concern.

- At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.

8.2.6. Echocardiogram/Multigated Acquisition Scan (ECHO/MUGA)

LVEF should be assessed by transthoracic ECHO or MUGA and performed within 6 months of screening.

8.2.7. ECOG Performance Status

Refer to Appendix 8 for ECOG Performance Status Criteria.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

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

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE, or that caused the participant to discontinue the study (refer to Section 7).

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

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

The time period for actively eliciting and collecting AEs and SAEs (“active collection period”) for each participant begins from the time the participant provides informed consent, which is obtained before the participant’s participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including a minimum of (90 calendar days) after the last administration of the investigational product, up to the start of new anti-cancer therapy.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.

Follow up by the investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period are reported to Pfizer Safety on the CT SAE Report Form immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

All SAEs occurring in a participant during the active collection period are reported to Pfizer Safety on the CT SAE Report Form.

If a participant begins a new anticancer therapy, SAEs occurring during the above-indicated active collection period must still be reported to Pfizer Safety irrespective of any intervening treatment.

SAEs occurring in a participant after the active collection period has ended are reported to Pfizer Safety if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product must be reported to Pfizer Safety.

8.3.1.2. Recording Non-serious AEs and SAEs on the CRF

During the active collection period, both non-serious AEs and SAEs are recorded on the CRF.

If a participant begins a new anticancer therapy, the recording period for non-serious AEs ends at the time the new treatment is started; however, SAEs must continue to be recorded on the CRF during the above-indicated active collection period.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

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

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

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

- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the investigator's brochure and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the investigational product under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

- Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention and until 90 days after the last dose.

- If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.

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

8.3.5.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

8.3.6. Medication Errors

Medication errors may result from the administration or consumption of the investigational product by the wrong participant, or at the wrong time, or at the wrong dosage strength, or from inadvertent exposure.

Exposures to the investigational product under study may occur in clinical study settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating participant;
- Lack of dose reduction as specified by the protocol;
- Continuation of treatment though participant met discontinuation criteria;
- Incorrect study treatment taken by participant;

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified immediately.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and non-serious, are recorded on an AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE.**

8.4. Treatment of Overdose

For this study, refer to intervention-specific overdose guidelines below.

Overdose of Avelumab

There are limited experiences pertaining to overdose with avelumab in clinical studies. Treatment is directed to symptoms.

Overdose of Bempegaldesleukin (NKTR-214)

The clinical consequences of bempegaldesleukin (NKTR-214) overdose have not been clearly identified. The highest dose to date of bempegaldesleukin administered in the clinic is 0.012 mg/kg, which resulted in cytokine release syndrome and DLTs of hypotension and syncope in one participant who received this dose. There is no specific treatment for

overdose of bempegaldesleukin (NKTR-214). If hypotension occurs as a result of overdose, it should be managed by general supportive measures.

Overdose of Talazoparib

There is no specific treatment in the event of talazoparib overdose, and symptoms of overdose are not established. In the event of overdose, treatment with talazoparib should be stopped, and physicians should consider gastric decontamination, follow supportive measures, and treat symptomatically.

Overdose of Enzalutamide

There is no specific treatment for overdose of enzalutamide. In the event of an overdose, treatment should be stopped and general supportive measures initiated, taking into consideration the amount of overdose and enzalutamide's half-life (5.8 days). Participants may be at an increased risk of seizure following an overdose.

In the event of an overdose for any of the above listed study interventions, the treating physician should:

1. Contact the sponsor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities for at least 28 days.
3. Obtain a plasma sample for PK analysis with clear documentation of the time it is collected relative to the date of the last dose of study intervention, if requested by the sponsor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
5. Overdose is reportable to Safety only when associated with a SAE.

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

8.5. Pharmacokinetics

All efforts should be made to obtain the PK samples at the scheduled nominal time relative to dosing. However, the exact time of the sample collection will always be noted on the CRF. Where noted in the SoA, blood samples for avelumab, bempegaldesleukin (NKTR-214), talazoparib, and enzalutamide concentrations should be collected after triplicate 12-lead ECGs are performed. If a scheduled blood sample collection cannot be completed for any reason, the missed sample may be re-scheduled with agreement of clinical investigators, participant and sponsor. PK sampling schedule may be modified based on emerging PK data.

PK samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures (SOPs).

Details regarding the collection, processing, storage and shipping of the PK blood samples will be provided to the investigator site prior to initiation of the trial. The samples must be

processed and shipped as indicated to maintain sample integrity. Any deviations from the processing steps (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may determine whether sample integrity has been compromised. The details of sample collection, processing and storage are presented in the laboratory manual only. If there is any deviation, it should be considered as manual deviation instead of the protocol deviation.

As part of understanding the PK of the investigational products, samples may be used for metabolite identification and/or further bioanalytical evaluation, as well as for other internal exploratory purposes. These data will not be included in the Clinical Study Report (CSR).

8.5.1. Blood for PK Analysis of Avelumab

Blood samples (approximately 3.5 mL whole blood at each time point) will be collected into appropriately labeled serum separator tubes (SST) for PK analysis of avelumab, as outlined in the Schedule of Activities (Tables 4-7). Blood for PK samples will be drawn from the contralateral arm of the drug infusion.

8.5.2. Blood for PK Analysis of Bempegaldesleukin (NKTR-214) CCI

Blood samples (approximately 3.5 mL whole blood at each time point from which plasma will be isolated and used for analysis) will be collected into appropriately labeled tubes containing sodium heparin for PK analysis of bempegaldesleukin (NKTR-214) as outlined in the Schedule of Activities (Tables 4-7). Blood will be collected in standard tubes and shipped to Pfizer's central lab. CCI This assessment will be performed for all Phase 1b participants, as well as for a subset of Phase 2 participants receiving RP2D (approximately 20 participants from each of the three combinations, for approximately 60 participants total).

8.5.3. Blood for PK Analysis of Talazoparib

Blood samples (approximately 3.0 mL whole blood at each time point from which plasma will be isolated and used for analysis) will be collected into appropriately labeled tubes containing K_3EDTA for PK analysis of talazoparib as outlined in the Schedule of Activities (Tables 6-7).

8.5.4. Blood for PK Analysis of Enzalutamide and N-Desmethyl-Enzalutamide

Blood samples (approximately 3.0 mL whole blood at each time point from which plasma will be isolated and used for analysis) will be collected into appropriately labeled tubes containing dipotassium ethylenediaminetetraacetic acid K_2EDTA for PK analysis of enzalutamide and N-desmethyl-enzalutamide as outlined in the Schedule of Activities (Tables 6-7).

Please refer to the Laboratory Manual for instructions for specific details on collection tubes, processing and shipping for all samples collected.

8.6. Pharmacodynamics

8.6.1. Tumor and other Biospecimens

Refer to Section 8.7 for biomarker analyses for genetics. Refer to Section 8.8 for all other biomarker analyses, including pharmacodynamics biomarkers.

8.6.2. Collection of Samples for Pharmacodynamic Analysis

Samples should be obtained within 2 hours prior to infusion.

As part of understanding the PD of the investigational product, samples may be used for evaluation of the bioanalytical method, as well as for other internal exploratory purposes. These data will not be included in the CSR.

The pharmacodynamic (PD) samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PD sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

8.7. Genetics

8.7.1. Specified Genetics

Genetic assessments will be performed utilizing tumor, saliva, and blood samples as collected and described in the SoA. Refer to relevant subsections in Section 8.8.

CCI [redacted]

8.8. Biomarkers

8.8.1. Tumor Tissue Assessments

The objectives of biomarker analyses applied to pre-treatment (archival or de-novo), on-treatment and end-of-treatment tumor biospecimen are to evaluate candidate predictive biomarkers that may be proven useful in identifying participants who may preferentially benefit from the study treatments and to evaluate mechanisms of action and/or resistance for each of the combinations being assessed. CCI [redacted]

Tumor biospecimens representing tissue samples from tumor resection or biopsy will be used to analyze candidate DNA, RNA, or protein markers, or relevant signature of markers for their ability to identify those participants who are most likely to benefit from treatment with the study drugs.

8.8.1.1. Mandatory Tumor Tissue (1L SCCHN, Combination A)

A formalin-fixed paraffin-embedded (FFPE) tumor tissue block from the most recent tumor resection or biopsy must be provided for all participants enrolled in the study and submitted to the Central Laboratory. This tissue block must be obtained from a biopsy or surgery that was performed within 2 years prior to study enrollment, during which time the participant should have received no more than one line of systemic anti-cancer therapy. If FFPE tissue blocks cannot be provided, the tissue should be submitted in the form of 12 unstained, unbaked, positively-charged glass slides each containing an FFPE tissue section that is 4-5 microns thick. In instances where no such archival tumor sample is available a de novo biopsy from a locally recurrent or metastatic tumor site that is not the only RECIST v1.1 (Appendix 9) target lesion must be performed during screening.

Tumor tissue from cytologic sampling (eg, fine-needle aspiration, including FFPE cell pellet material) or from bone biopsies is not adequate and should not be submitted.

A core biopsy preferably using a minimum 18-gauge needle should be performed, in order to maximize the quality and value of obtained tissue. A minimum of 3 separate cores are requested from the same biopsy site for each biopsy procedure. Additional information on tissue collection procedures can be found in the Laboratory Manual.

8.8.1.2. Mandatory Tumor Tissue (mCRPC, Combinations B and C)

All participants must submit an FFPE tumor tissue block from the most recent tumor resection or biopsy to the Central Laboratory. This tissue block must be obtained from a biopsy or surgery that was performed within 2 years prior to study enrollment, during which time the participant should have received no more than one line of systemic anti-cancer therapy. For mCRPC participants with no lesion that can be biopsied outside of bone at screening, tumor tissue from a biopsy/surgery performed within 5 years prior to study enrollment must be provided. In instances where no such archival tumor sample is available a

de novo biopsy from a locally recurrent or metastatic tumor site that is not the only RECIST v1.1 (Appendix 9) target lesion must be performed during screening, as described in Section 8.8.1.1.

A core biopsy, preferably using a minimum 18-gauge needle should be performed, in order to maximize the quality and value of obtained tissue. A minimum of 3 separate cores are requested from the same biopsy site for each biopsy procedure. Additional information on tissue collection procedures can be found in the Laboratory Manual.

If FFPE tissue blocks cannot be provided, the tissue should be submitted in the form of 12 unstained, unbaked, positively-charged glass slides each containing an FFPE tissue section that is 4-5 microns thick.

Tumor tissue from cytologic sampling (eg, fine needle aspiration, including FFPE cell pellet material) or from bone biopsies is not adequate and should not be submitted.

8.8.1.3. Mandatory Baseline Tumor Tissue for DDR Defect Assessment (Combination B – Phase 2 only)

All mCRPC study participants in Phase 2 Combination B must provide a tumor tissue sample for testing of DDR defects [redacted]

CCI [redacted]

[redacted]

[redacted]

Tumor tissue from cytologic sampling (eg, fine needle aspiration, including FFPE cell pellet material) or from bone biopsies is not adequate and should not be submitted.

8.8.1.4. On-Study Tumor Tissue (SCCHN, Combination A)

An on-treatment biopsy is required to be collected on Cycle 1 between Days 9 and 14. When this is not feasible a biopsy may be collected on Cycle 1 between Day 15 and 21. These on treatment biopsies are required except in instances where the procedure poses unacceptable risks per Investigator documentation. Tumor tissue is also requested for those participants who undergo a biopsy or tumor resection as part of routine clinical care at any time during the treatment period. De novo biopsies should be FFPE as per routine (see Laboratory Manual), and the resulting FPPE tissue block(s) should be submitted to the Central Laboratory.

Mandatory paired baseline and on-treatment tumor tissue is required from SCCHN participants to assess the ability of the combination therapy to increase PD-L1 expression while on treatment, as well as to document changes in the tumor microenvironment. Tumor samples will be assessed to provide data on changes in the tumor that develop over the course of therapy, including acquired mechanisms of resistance that may be demonstrated on analysis of tumor tissue collected at the end of treatment.

CCI [redacted] The End of Treatment tumor biopsy should be performed before initiation of subsequent anti-cancer therapy and preferably no later than 7 days after the End of Treatment visit.

A core biopsy preferably using a minimum 18-gauge needle should be performed, in order to maximize the quality and value of obtained tissue. A minimum of 3 separate cores are requested from the same biopsy site for each biopsy procedure. Additional information on tissue collection procedures can be found in the Laboratory Manual.

CCI [redacted]

CCI

[redacted]

[redacted]

[redacted]

8.8.2. Other Biomarker Assessments

The goal of these analyses is to explore potential correlations between molecular profiling and response to study treatment, which will help identify potential biomarkers of response and biomarkers/mechanisms of acquired resistance to study treatment.

8.8.2.1. Saliva Sample for Germline Comparator

Unless prohibited by local regulations or ethics committee decision, saliva samples will be collected from all participants on Cycle 1 Day 1 before the first dose of study treatment and will be used for exploratory targeted and/or whole exome/genome sequencing. These samples will be used as a germline comparator to identify somatic tumor DNA mutations and will not be used to generate free-standing germline sequencing results.

8.8.2.2. Saliva sample for Targeted Germline DDR Assessment (Phase 2 Combination B only)

In Combination B, an additional saliva sample will be collected and will be used to characterize the germline status of the DDR genes used to assess participant eligibility or a subset thereof in order to explore the potential contribution of germline DDR status to efficacy and safety/tolerability with study treatment.

CCI

[redacted]

[redacted]

[redacted]

CCI

[redacted]

8.8.3. Immunogenicity Assessments

Details regarding the collection, processing, storage and shipping of the Immunogenicity samples will be provided to the investigator site prior to initiation of the trial. The samples must be processed and shipped as indicated to maintain sample integrity. Any deviations from the processing steps (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may determine whether sample integrity has been compromised. Any deviation from the specified sample handling procedure that resulted in compromised sample integrity will be considered a protocol deviation.

As part of understanding the immunogenicity of the investigational products, samples may be used for further bioanalytical evaluation, as well as for other internal exploratory purposes. These data will not be included in the Clinical Study Report (CSR).

8.8.3.1. Analysis of ADAs and NAbs for Avelumab

Blood samples (approximately 3.5 mL whole blood) will be collected into appropriately labeled SSTs for determination of avelumab anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs), as outlined in the Schedule of Activities (Tables 4-7). Please refer to the Laboratory Manual for instructions for specific details on collection tubes, processing and shipping. The actual date and time (24-hour clock time) of each sample will be recorded.

For all participants, blood for ADA samples will be drawn from the contralateral arm of the avelumab infusion.

Samples will be analyzed using a validated analytical method in compliance with applicable SOPs. The sample analysis will follow a tiered approach of screening, confirmation, and titer determination.

8.8.3.2. Analysis of ADAs and NAbs for Bempegaldesleukin (NKTR-214)

Blood samples (approximately 3.5 mL whole blood) will be collected into an appropriately labeled tubes for serum determination of bempegaldesleukin (NKTR-214) anti-drug

antibodies (ADAs) and neutralizing antibodies (NAbs), as outlined in the Schedule of Activities (Tables 4-7). Please refer to the Laboratory Manual for instructions for specific details on collection tubes, processing and shipping.

For all participants, blood for ADA samples will be drawn from the contralateral arm of the bempegaldesleukin (NKTR-214) infusion.

8.9. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Estimands and Statistical Hypotheses

9.1.1. Estimands

This section defines the estimands associated with the primary endpoints and the secondary efficacy endpoints of the study.

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 DDR defect positive 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 4.1. 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 Section 9.4.1) 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 9.4.1) will be calculated.

- Phase 2 tumor-related endpoints: (TTR [Combinations A, B, and C], DR [Combinations A, B, and C], TTPSAP [Combinations B and C only], CTC count conversion [Combination C only] and CTC0 [Combination C only]) are defined in Section 9.4.1. 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 9.4.1) 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 9.4.1) 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.

9.1.2. Statistical Methods and Properties

9.1.2.1. Statistical Methods for Dose Finding: BLRM

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.

The doublet of avelumab in combination with bempegaldesleukin will be evaluated first to determine the RP2D. Upon the completion of the dose finding of the doublet, the triplets of avelumab in combination with bempegaldesleukin (NKTR-214) and talazoparib or enzalutamide will then be evaluated to determine the RP2D for these triplet combinations. Refer to Appendix 11, Appendix 12 and Appendix 13 for BLRM designs for Combinations A, B, and C, respectively.

Bayesian adaptive approach

The dose finding in the Phase 1b of the study will be guided by a Bayesian analysis of Cycle 1 DLTs in DLT-evaluable participants.

a. Doublet combination model:

For the doublet combination of avelumab and bempegaldesleukin (NKTR-214), the Bayesian model consists of three parts, representing:

- Single-agent avelumab toxicity;
- Single-agent bempegaldesleukin (NKTR-214) toxicity;
- Interaction between avelumab and bempegaldesleukin (NKTR-214).

b. Triplet combination model:

For the triplet combination of avelumab, bempegaldesleukin [NKTR-214], and talazoparib, the Bayesian model consists of seven parts, representing:

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

For the triplet combination of avelumab, bempegaldesleukin (NKTR-214), and enzalutamide, the Bayesian model consists of seven parts, representing:

- Single-agent avelumab toxicity;

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

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. 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. 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 doublet in Combination A is D0 (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 13.7%, which satisfies the EWOC criterion.

The starting dose for the triplets will be determined based on all available data after completion of the dose finding for the doublet.

9.2. Sample Size Determination

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.

An RP2D below the MTD may be determined based on other safety, efficacy, PK, and pharmacodynamic data. Nine evaluable participants are needed to be treated at RP2D if no DLT is observed, and 12 evaluable participants if at least a DLT is observed.

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 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. An RP2D below the MTD may be determined based on other safety, clinical activity, PK, and pharmacodynamic data.

Phase 1b participants for 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 combination B, A and C, respectively, soft tissue OR, OR, 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 and PSA response rate and a non-informative beta (0.5, 0.5) prior:

1L SCCHN (Combination A):

- if 20 ORs (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%).

Combination B: mCRPC post chemotherapy

- if 12 ORs (out of 20 participants, ORR = 60%) are observed, the probability of a true ORR≥ 50% (considered a clinically relevant effect) will be ≥80% (81.4%).

Combination C: mCRPC

- if 20 PSA responses (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 PSA response rate and ORR data for clinical studies in SSCHN and mCRPC.

Table 17 provides the exact 95% confidence interval for ORR/ PSA response rate based on different observed numbers of responders in a given combination.

Table 17. B9991040 Sample Size and Exact 95% Confidence Interval for ORR/PSA Response Rate

N per Combination	Number of Responders	Observed ORR/PSA response rate	Exact 95% CI for ORR/PSA response rate
20	6	30%	11.9% - 54.3%
	8	40%	19.1% - 63.9%
	10	50%	27.2% - 72.8%
	12	60%	36.1% - 80.9%
	14	70%	45.7% -88.1%
	15	75%	50.9% - 91.3%
40	14	35%	20.6% - 51.7%
	16	40%	24.9% - 56.7%
	18	45%	29.2% - 61.5%
	20	50%	33.8% - 66.2%
	22	65%	38.5% - 70.7%
	24	60%	48.3% - 79.4%
	26	65%	43.3% - 75.1%
	28	70%	53.5% - 83.4%
	30	75%	58.8% - 87.3%

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Defined populations for analysis	Description
Full Analysis Set (FAS)	All enrolled participants who take at least 1 dose of study drug. Participants will be classified according to the study treatment actually received.
Safety Analysis Set	In this non-randomized study, the Safety Analysis Set is identical to the FAS.
DLT-Evaluable	The DLT-evaluable analysis set is a subset of the safety analysis set and includes all enrolled participants in Phase 1b who receive at

Defined populations for analysis	Description
	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 who withdraw from study treatment in Cycle 1 before receiving at least 2 doses of bempegaldesleukin (NKTR-214) and avelumab and at least 75% of the planned dose of talazoparib (Combination B) or enzalutamide (Combination C) for reasons other than treatment-related toxicity are not evaluable for DLT. All participants deemed non-evaluable for DLT may be replaced.
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), 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), talazoparib, , enzalutamide, or N-desmethyl-enzalutamide.
Biomarker Analysis Set	The biomarker analysis set is a subset of the safety analysis set and will include participants who have at least one baseline biomarker assessment. Analysis sets will be defined separately for blood-based and tumor tissue-based biomarkers.
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.

9.4. Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. Efficacy Analyses

Endpoints	Statistical Analysis Methods
• **Phase 2 Primary**	
• **Combination A**: Confirmed objective response (OR) as determined by the investigator using RECIST v1.1 (Appendix 9).	• **Combination A:** The confirmed objective response rate (ORR) of avelumab in combination with bempegaldesleukin (NKTR-214) in participants with IL SCCHN) will be calculated along with the 2-sided 95% CI using the Clopper-Pearson method. ORR is defined as the proportion of participants with a confirmed CR or PR based on the Investigator's assessment according to RECIST v1.1. Only tumor assessments performed on or before the start date of any further anti-cancer therapies will be considered in the assessment of response. Confirmed responses are those that persist on repeat tumor assessments for at least 4 weeks after initial documentation of response. Otherwise, the participant will be counted as a non-responder in the assessment of ORR. Additionally, participants with inadequate data for tumor assessment (eg, no baseline assessment or no follow-up assessments) will be considered as non-responders in the assessment of ORR.
• **Combination B**: Confirmed soft tissue OR as determined by the investigator using RECIST v 1.1 (Appendix 9) with no evidence of confirmed bone disease progression on repeat bone scan at least 6 weeks later per PCWG3 criteria (Appendix 10).	• **Combination B**: The confirmed soft tissue objective response rate (ORR) of avelumab in combination with bempegaldesleukin (NKTR-214) and talazoparib in participants with DDR defect positive mCRPC will be calculated along with the 2-sided 95% CI using the Clopper-Pearson method. Soft tissue OR is determined by the investigator using RECIST v 1.1 (Appendix 9) with no evidence of confirmed bone disease progression on repeat bone scan at least 6 weeks later per PCWG3 criteria (Appendix 10). Only tumor assessments performed on or before the start date of any further anti-cancer therapies will be considered in the assessment of response. Confirmed responses are those that persist on repeat tumor assessments for at least 4 weeks after initial documentation of response. Otherwise, the participant will be counted as a non-responder in the assessment of soft tissue objective response.
• **Combination C:** Confirmed prostate specific antigen (PSA) response decrease ≥ 50% from baseline confirmed by a second consecutive assessment at least 3 weeks	• **Combination C:** The rate of PSA response decrease ≥50% from baseline, confirmed by a second consecutive evaluation ≥ 3 weeks later, in participants with mCRPC after progression will be calculated along with the 2-sided 95% CI using the Clopper- Pearson method. Only PSA assessments performed on or before the start of any further

Endpoints	Statistical Analysis Methods
later.	anti-cancer therapies will be considered in the assessment of PSA response.
Secondary	
• Time to event endpoints as determined by the investigator, using RECIST v1.1 in participants with SCCHN (**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).	• PFS is defined as the time from the first dose of study treatment to the date of PD 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 new anti-cancer therapy prior to an event, or for participants with an event after two or more missing tumor assessments. Participants who do not have an adequate baseline tumor assessment or who do not have any adequate post-baseline tumor assessments 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, in which case the death will be considered an event. • TTR is defined, for participants with a confirmed OR, as the time from the first dose to the first documentation of OR (CR or PR) which is subsequently confirmed (SSCHN) without evidence of confirmed bone disease on bone scan per PCWG3 (mCRPC). The estimate of the standard error will be computed using Greenwood's formula. • DR is defined, for participants with a confirmed OR, as the time from the first documentation of OR (CR or PR) to the date of first documentation of PD or death due to any cause. • OS is defined as the time from time from the first dose of study treatment to the date of death due to any cause. Participants without an event (death) will be censored at the date of last contact. • TTR will be summarized using simple descriptive statistics (eg, median and range). DR, PFS, and OS will be analyzed using Kaplan-Meier methods. Kaplan-Meier estimates (product-limit estimates) will be presented together with a summary of associated statistics including the median DR, PFS, or OS with 2-sided 95% CIs. In addition, DR, PFS, and OS rates at different time points will be estimated with corresponding 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley and the 95% CIs for the survival function estimates at the time points defined above will be

Endpoints	Statistical Analysis Methods
	derived using the log-log transformation according to Kalbfleisch and Prentice
• **Combination B**: Confirmed PSA response	• **Combination B**: Confirmed PSA response will be analyzed as specified above for Combination C. as
• **Combination C:** Confirmed soft tissue OR as determined by the investigator using RECIST v 1.1 (Appendix 9) with no evidence of confirmed bone disease progression on repeat bone scan at least 6 weeks later per PCWG3 criteria (Appendix 10)	• **Combination C:** Confirmed soft tissue OR will be analyzed as specified above for Combination B.
• **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 (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).	• **Combination C:** 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 at any assessment on treatment, and 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. 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 circulating tumor cells (CTC) count conversion rate and CTC0 rate will be calculated along with the 2-sided 95% CI using the Clopper-Pearson method.
• **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.	• **Combinations B and C:** Time to PSA progression (TTPSAP) is defined as the time from the date of first dose of study treatment to 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. Early rises (before week 12) should be ignored in determining progression. As such, for participants 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.

Endpoints	Statistical Analysis Methods
	• 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 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. TTPSAP will be analyzed using Kaplan-Meier methods. Kaplan-Meier estimates (product-limit estimates) will be presented together with a summary of associated statistics including the median TTPSAP with 2-sided 95% CIs. In addition, TTPSAP rates at different time points will be estimated with corresponding 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley and the 95% 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.

9.4.2. Safety Analyses

All safety analyses will be performed on the Safety Population.

Endpoint	Statistical Analysis Methods
Primary	DLT during the DLT evaluation period (Cycle 1). The dose finding in Phase 1b of the study will be guided by a Bayesian Logistic Regression Model (BLRM) of Cycle 1 DLTs in DLT-evaluable participants.[56] After each cohort of participants completes the DLT evaluation period, the posterior distribution for the risk of DLT for different dose combination doses of interest will be evaluated. The posterior distribution of DLT rate (posterior probabilities that DLT rate is in the intervals of underdosing (<0.16), target toxicity [0.16-0.33) and overdosing (≥0.33) at the end of Phase 1b will be provided.
Secondary	Simple summary statistics (descriptive) will be presented for participants with SAEs, AEs of special interest, lab abnormalities and other secondary safety endpoints during the on-treatment period (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) unless otherwise described in the SAP.

9.4.3. Analysis of Pharmacokinetics, Pharmacodynamics, and Biomarkers

PK, pharmacodynamic, CCI [redacted] will be described in the statistical analysis plan finalized before database lock. The population PK analysis and

pharmacodynamic analyses, CCI will be presented separately from the main clinical study report (CSR).

9.4.3.1. Analysis of Pharmacokinetics of Investigational Products

All analyses of Pharmacokinetic will be performed based on the Pharmacokinetic analysis set. Pharmacokinetic data analysis will include all PK samples collected for all investigational products (avelumab, bempegaldesleukin [NKTR-214], talazoparib and enzalutamide) as outlined in the SOA. Descriptive summary statistics of predose concentrations (C_{trough}) for avelumab, talazoparib and enzalutamide and end of infusion concentration (C_{EOI}) for avelumab and bempegaldesleukin (NKTR-214) will be calculated. Additional summary statistics will be presented for avelumab and bempegaldesleukin (NKTR-214) across all treatment groups by study phase as well as combined across study phases. Pharmacokinetic data of each investigational product will be compared to the historical data when each drug is administered alone to assess the effect of each drug on the PK of the other drugs.

9.4.3.2. Population Pharmacokinetic Analysis or Pharmacokinetic/Pharmacodynamic (PK/Pharmacodynamic) Modeling

Pharmacokinetic and pharmacodynamic data from this study may be analyzed using modeling approaches and may also be pooled with data from other studies investigating avelumab, bempegaldesleukin (NKTR-214), talazoparib and/or enzalutamide 1) to assess the effect of each drug on the PK of other drugs, and 2) explore any association between study drug exposure and biomarkers or significant safety endpoints. If performed, the details of these analyses will be outlined in a separate pharmacometric analysis plan (PMAP). The results of these analyses, if performed, may be reported separately.

9.4.3.3. Analysis of Biomarker Endpoints

All analyses of biomarkers will be performed based on the biomarker analysis set, separately by treatment combinations and pooled across treatment combinations. Biomarker data will include baseline and on-treatment/end of treatment levels of and changes in biomarkers. 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. Appropriate change from baseline measurements will be provided. For discrete measurement biomarkers (eg, tumor marker status), frequencies and percentages of categorical biomarker measures will be determined at baseline and on-treatment/post-treatment time points, as appropriate; shift tables may also be provided. Data from biomarker assays may be analyzed using graphical methods and statistics such as Fisher's exact test, Wilcoxon rank-sum test, Kaplan-Meier estimates, and linear regression as appropriate. The statistical approaches will explore the correlations of biomarker results with pharmacokinetic parameters and measures of efficacy, such as tumor response and progression free survival.

The correlation of anti-tumor activity with PD-L1 expression level in baseline tumor tissue will be calculated as follows: 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.

9.4.3.4. Analysis of Avelumab Immunogenicity Data

ADA/NAb data for avelumab will be listed and summarized.

The percentage of participants with positive ADA and NAbs will be summarized by combination and, if deemed appropriate, combined across all combinations. For participants with positive ADA, the magnitude (titer), time of onset, and duration of ADA response will also be described, if data permit. The effect of ADA on avelumab pharmacokinetics may be evaluated, if data permit.

9.4.3.5. Analysis of Bempegaldesleukin Immunogenicity Data

ADA/NAb data for bempegaldesleukin (NKTR-214) will be listed and summarized.

The percentage of participants with positive ADA and NAbs will be summarized by treatment combination and, if deemed appropriate, combined across all treatment combinations. For participants with positive ADA, the magnitude (titer), time of onset, and duration of ADA response will also be described, if data permit. The effect of ADA on bempegaldesleukin (NKTR-214) pharmacokinetics may be evaluated, if data permit.

9.5. Interim Analyses

No formal interim analysis will be conducted in this study. However, as this is an open-label Phase 1b/2 study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose-finding decisions, facilitating PK/Pharmacodynamic modeling, or to support clinical development.

9.5.1. Data Monitoring Committee (DMC)

This study will not use a data monitoring committee (DMC).

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

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

- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations, including applicable privacy laws.

- The protocol, protocol amendments, ICD, Investigator Brochure, and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.
- In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.
- In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative (applicable for subjects only where locally acceptable) and answer all questions regarding the study.

- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The investigator must ensure that each study participant or his or her legally authorized representative is fully informed about the nature and objectives of the study, the sharing of data related to the study and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The investigator further must ensure that each study participant or his or her legally authorized representative is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.
- Participants must be re-consented to the most current version of the ICD(s) during their participation in the study.
- A copy of the ICD(s) must be provided to the participant or the participant's legally authorized representative.

The ICD will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.

10.1.4. Data Protection

- All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.
- Participants' personal data will be stored at the study site in encrypted electronic form and will be password protected to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.
- To protect the rights and freedoms of natural persons with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or datasets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the Clinical Study Agreement and applicable privacy laws.

10.1.5. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its standard operating procedures (SOPs).

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in participants) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. US Basic Results are generally submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

PCD is defined as the date that the final participant was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the PCD for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

www.pfizer.com

Pfizer posts public disclosure synopses (Clinical Study Report [CSR] synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the European Medicines Agency (EMA) website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to participant-level data or full CSRs for the purposes of "bona-fide scientific research" that contribute to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Participant-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory

data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic form and are password protected to prevent access by unauthorized third parties.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the study monitoring plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for so long as they are maintained.
- When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.
- The investigator(s) will notify sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with sponsor or its agents to prepare the investigator site for the inspection and will allow sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's

medical records. The investigator will promptly provide copies of the inspection findings to sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.7. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the study monitoring plan.

10.1.8. Study and Site Closure

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

The investigator may initiate study-site closure at any time upon notification to the contract research organization (CRO) if requested to do so by the responsible IRB/IEC or if such termination is required to protect the health of study participants.

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

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

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol the contract will control as to termination rights.

10.1.9. Publication Policy

- The results of this study may be published or presented at scientific meetings by the Investigator after publication of the overall study results or one year after end of the study (or study termination), whichever comes first.

- The investigator agrees to refer to the primary publication in any subsequent publications such as secondary manuscripts, and submit all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor to protect proprietary information and to provide comments and the Investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer intervention-related information necessary to the appropriate scientific presentation or understanding of the study results.
- For all publications relating to the study, the Investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.
- The sponsor will comply with the requirements for publication of the overall study results covering all Investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.
- If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.1.10. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the study portal.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, participant study numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. For sites other than a Pfizer clinical research unit (CRU), the contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 1 will be performed by the local laboratory.

Samples for all laboratory assessments in Table 1 will be drawn at the time points indicated in the Schedule of Activities and when clinically indicated. Laboratory tests may be performed up to 3 days prior to the scheduled clinic visit. All safety laboratory analyses will be performed by the local laboratory(ies) for each study center**.**

- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations. If labs were conducted within 3 days of C1D1, they do not need to be repeated.

- Prior to study drug administration on Days 1 and 15 of each treatment cycle, hematology (ie, hemoglobin, platelets, and white blood cells) and chemistry (ie, ALT, AST, alkaline phosphatase, total bilirubin, blood urea nitrogen, creatinine, sodium, potassium, lipase, amylase, and glucose) tests must be performed and results reviewed by the treating physician prior to study drug administration. When applicable, results from pregnancy tests must also be available for review prior to dosing.

- There is a 7-day window allowed for PSA labs from C1D1.

Pregnancy Testing

Pregnancy testing (urine or serum as required by local regulations) should be conducted at monthly intervals (eg Day 1 of each cycle) during intervention as per SoA. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will then be required at the baseline visit on C1D1 before the participant may receive the study treatment. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

- Pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of relevant systemic exposure plus an additional 30 days.

- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

Table 1. Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count Hemoglobin	White blood cell (WBC) count with Differential: Neutrophils (absolute) Lymphocytes (absolute) Monocytes (absolute) Eosinophils (absolute) Basophils (absolute)		
Coagulation	aPTT (in seconds) INR and/or PT			
Clinical Chemistry[1]	ALP ALT AST Albumin Amylase	BUN or Urea Chloride Creatinine CRP Glucose (non-fasted)	GGT LDH Lipase Magnesium Phosphorus/Phosphate Potassium	Sodium Total Bilirubin Total Calcium Total Protein Uric Acid
Routine Urinalysis[2]	• Specific gravity • pH, glucose, protein, blood, ketones, (bilirubin, urobilinogen, nitrite, leukocyte esterase) by dipstick • Microscopic examination (Only if urine dipstick is positive for blood, protein, nitrites, or leukocyte esterase).			
Pregnancy Test	Serum or urine human chorionic gonadotropin (hCG) pregnancy test with a sensitivity of at least 25 IU/mL (as needed for women of childbearing potential)[2]			
Hepatitis B and C	Hepatitis B Surface antigen	Hepatitis C Virus AB HCV RNA (if Hepatitis C Ag tests positive)		
Thyroid function and ACTH	TSH, Free T4, ACTH			

Abbreviations: ACTH=adrenocorticotropic hormone, ALP=alkaline phosphatase; ALT=alanine aminotransferase, AST=aspartate aminotransferase, BUN=blood urea nitrogen, CRP=C-reactive protein; GGT= gamma-glutamyl transferase;HBV=hepatitis B virus, HCV=hepatitis C virus, INR=international normalized ratio, LDH=lactate dehydrogenase, PT=prothrombin time, PTT=partial thromboplastin time, RNA=ribonucleic acid, TSH=thyroid-stimulating hormone, WBC=white blood cell.

NOTES:

Table 1. Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters

1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1.1 and Appendix 6. All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis). For potential Hy's Law cases, in addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma glutamyl transferase, prothrombin time (PT)/INR, alkaline phosphatase, total bile acids and acetaminophen drug and/or protein adduct levels. Refer to Appendix 6 for further details.
2. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

Investigators must document their review of each laboratory safety report. The results of each test must be entered in the CRF.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a participant or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. • Worsening of signs and symptoms of the malignancy under study should be recorded as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

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

and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

- Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the active collection period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the active collection period, then the event leading to death must be recorded as an AE on the CRF, and as an SAE with Common Terminology Criteria for Adverse Events (CTCAE) Grade 5 (see the Severity Assessment section).

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

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) non-serious adverse events (AEs); and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Non-serious AE	All	None

Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	**None**	All (And exposure during pregnancy [EDP] supplemental form for EDP)

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the Pfizer Safety /AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

GRADE	Clinical Description of Severity
1	MILD adverse event
2	MODERATE adverse event
3	SEVERE adverse event
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH RELATED TO adverse event

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and

each occurrence of each AE/SAE.

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Pfizer Safety. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** Pfizer Safety**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor" and "In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Pfizer Safety to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • New or updated information will be recorded in the originally completed CRF. • The investigator will submit any updated SAE data to the Pfizer Safety within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone. • Contacts for SAE reporting can be found in the Investigator Site File.

SAE Reporting to Pfizer Safety via Paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to Pfizer Safety. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in the Investigator Site File.

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

Definitions:

Woman of Childbearing Potential (WOCBP)
A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:

    - Documented hysterectomy;
    - Documented bilateral salpingectomy;
    - Documented bilateral oophorectomy.

    For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

    NOTE: Documentation for any of the above conditions can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

3. Postmenopausal female
    - A postmenopausal state is defined as age 60 or older or no menses for 12 months without an alternative medical cause.
        - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT).
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance:

The contraception check is an opportunity to confirm that contraception, if assigned, is used consistently and correctly. Also, for studies enrolling adult participants, it is the opportunity to assess changing potential to father/bear children and allows for altering contraception if new disease contraindicates a selected method of contraception or if nonchildbearing status is achieved.

Male Participants

Male participants with the ability to father a child are eligible to participate if they agree to the following during the intervention period and for at least 30 days after the last dose of avelumab, at least 3 months after the last dose of enzalutamide or bempegaldesleukin (NKTR-214); (azospermic males are exempt from contraceptive requirements for bempegaldesleukin [NKTR-214]), and at least 4 months after the last dose of talazoparib. In addition, male participants MUST:

- Refrain from donating sperm
- PLUS either:
    - Be abstinent from intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

      OR

    - Use an additional highly effective contraceptive method with a failure rate of <1% per year as described for a female partner of childbearing potential. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.
- Must agree to use contraception/barrier as detailed below:
    - Agree to use a male condom when engaging in any activity that allows passage of ejaculate to another person.

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Bilateral tubal occlusion
• Vasectomized partner o Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.
Highly Effective Methods[b] That Are User Dependent
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] o oral o intravaginal o transdermal o injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[c] o oral o injectable
• Sexual abstinence o *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*

a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

b) Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure with friction)

Collection of Pregnancy Information:

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy (EDP) occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product.

- An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

- A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a participant or participant's partner becomes or is found to be pregnant during the participant's treatment with the investigational product, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a participant reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

10.5. Appendix 5: Genetics

Use/Analysis of DNA:

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Therefore, where local regulations and IRB/IEC allow, blood samples will be collected for DNA analysis.
- Genetic research may consist of the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to study interventions of this class, treatments for the disease(s) under study or the disease(s) themselves.
- The results of genetic analyses may be reported in the clinical study report (CSR) or in a separate study summary, or may be used for internal decision-making without being included in a study report.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained as indicated:
    - Samples for specified genetic analysis (refer to Section 8.7.1) will be stored for up to 15 years or other period as per local requirements beyond the completion of this study (eg, Clinical Study Report finalization).
    - Samples for banking (refer to Section 8.7.2) will be stored for up to 15 years or other period as per local requirements beyond the completion of this study (eg, Clinical Study Report finalization).

- [redacted]

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

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

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (TBili) elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same lab sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

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

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.
- For participants with baseline AST OR ALT OR TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

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

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

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy’s law case should be reviewed with the sponsor. The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory

tests, detailed history, and physical assessment. The possibility of hepatic neoplasia (primary or secondary) should be considered.

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

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the liver function test (LFT) abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

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

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

ECG Findings That <u>May</u> Qualify as Adverse Events (AEs)

- Marked sinus bradycardia (rate <40 bpm) lasting minutes.
- New PR interval prolongation >280 msec.
- New prolongation of QTcF to >480 msec (absolute) or by ≥60 msec from baseline.
- New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm.
- New-onset type I second-degree (Wenckebach) AV block of >30 seconds' duration.
- Frequent premature ventricular complexes (PVCs), triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.

ECG Findings That <u>May</u> Qualify as Serious Adverse Events (SAEs)

- QTcF prolongation >500 msec.
- New ST-T changes suggestive of myocardial ischemia.
- New-onset left bundle branch block (QRS >120 msec).
- New-onset right bundle branch block (QRS >120 msec).
- Symptomatic bradycardia.
- Asystole:
  - In awake, symptom-free participants in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node.
  - In awake, symptom-free participants with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer.
  - Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 beats per minute (bpm).
- Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).
- Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (rate <40 bpm), accelerated idioventricular rhythm (40< x <100), and monomorphic/polymorphic ventricular tachycardia >100 bpm (such as torsades de

pointes).

- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as Serious Adverse Events

- Change in pattern suggestive of new myocardial infarction.
- Sustained ventricular tachyarrhythmias (>30 seconds' duration).
- Second- or third-degree AV block requiring pacemaker placement.
- Asystolic pauses requiring pacemaker placement.
- Atrial flutter or fibrillation with rapid ventricular response requiring cardioversion.
- Ventricular fibrillation/flutter.
- At the discretion of the investigator, any arrhythmia classified as an adverse experience.

The enumerated list of major events of potential clinical concern are recommended as "alerts" or notifications from the core ECG laboratory to the investigator and Pfizer study team, and not to be considered as all inclusive of what to be reported as AEs/SAEs.

10.8. Appendix 8: ECOG Performance Status

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

From Oken, NM et al (1982)[57]

10.9. Appendix 9: Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 Guidelines

Adapted from E.A. Eisenhauer, et al (2009).[58]

Categorizing Lesions at Baseline

Measurable Lesions

- Lesions that can be accurately measured in at least one dimension.
- Lesions with longest diameter twice the slice thickness and at least 10 mm or greater when assessed by CT or MRI (slice thickness 5-8 mm).
- Lesions with longest diameter at least 20 mm when assessed by chest X-ray.
- Superficial lesions with longest diameter 10 mm or greater when assessed by caliper.
- Malignant lymph nodes with the short axis 15 mm or greater when assessed by CT.

NOTE: The shortest axis is used as the diameter for malignant lymph nodes, longest axis for all other measurable lesions.

Non-measurable disease

Non-measurable disease includes lesions too small to be considered measurable (including nodes with short axis between 10 and <15 mm) and truly non-measurable disease such as pleural or pericardial effusions, ascites, inflammatory breast disease, leptomeningeal disease, lymphangitic involvement of skin or lung, clinical lesions that cannot be accurately measured with calipers, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques.

- Bone disease: Bone disease is non-measurable with the exception of soft tissue components that can be evaluated by CT or MRI and meet the definition of measurability at baseline.
- Previous local treatment: A previously irradiated lesion (or lesion subjected to other local treatment) is non-measurable unless it has progressed since completion of treatment.

Normal sites

- Cystic lesions: Simple cysts should not be considered as malignant lesions and should not be recorded either as target or non-target disease. Cystic lesions thought to represent cystic metastases can be measurable lesions, if they meet the specific

definition above. If non-cystic lesions are also present, these are preferred as target lesions.

- Normal nodes: Nodes with short axis <10 mm are considered normal and should not be recorded or followed either as measurable or non-measurable disease.

RECORDING TUMOR ASSESSMENTS

All sites of disease must be assessed at baseline. Baseline assessments should be done as close as possible prior to study start. For an adequate baseline assessment, all required scans must be done within 28 days prior to treatment and all disease must be documented appropriately. If baseline assessment is inadequate, subsequent statuses generally should be inevaluable.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ, 5 lesions in total, representative of all involved organs, should be identified as target lesions at baseline. Target lesions should be selected on the basis of size (longest lesions) and suitability for accurate repeated measurements. Record the longest diameter for each lesion, except in the case of pathological lymph nodes for which the short axis should be recorded. The sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions at baseline will be the basis for comparison to assessments performed post-baseline.

- If two target lesions coalesce the measurement of the coalesced mass is used. If a large target lesion splits, the sum of the parts is used.

- Measurements for target lesions that become small should continue to be recorded. If the lesion is considered to have disappeared, 0 mm should be recorded; otherwise if a lesion is determined to be present but too small to measure, the lesion status will indicate “too small to measure and judged to be less than 10 mm” and 5 mm will be used in the calculation of the sum of the diameters.

NOTE: When nodal lesions decrease to <10 mm (normal), the actual measurement should still be recorded.

Non-target Disease

- All non-measurable disease is non-target. All measurable lesions not identified as target lesions are also included as non-target disease. Measurements are not required but rather assessments will be expressed as ABSENT, INEVALUABLE, PRESENT WITHOUT UNEQUIVOCAL PROGRESSION, UNEQUIVOCAL PROGRESSION. Multiple non-target lesions in one organ may be recorded as a single item on the case report form (eg, ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

Objective response status at each evaluation

Disease sites must be assessed using the same technique as baseline, including consistent administration of contrast and timing of scanning. If a change needs to be made the case should be discussed with the radiologist and the sponsor to determine if substitution is possible. If not, subsequent objective statuses are not evaluable.

Target Disease

- Complete Response (CR): Complete disappearance of all target lesions with the exception of nodal disease. All target nodes must decrease to normal size (short axis <10 mm). All target lesions must be assessed.

- Partial Response (PR): Greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. All target lesions must be assessed.

- Stable Disease (SD): Does not qualify for CR, PR or Progression. All target lesions must be assessed. Stable can follow PR only in the rare case that the sum increases by less than 20% from the nadir (smallest sum of diameters consider baseline and all assessments prior to the time point under evaluation), but enough that a previously documented 30% decrease no longer holds.

- Objective Progression (PD): 20% increase in the sum of diameters of target measurable lesions above the smallest sum observed (over baseline if no decrease in the sum is observed during therapy), with a minimum absolute increase of 5 mm.

- Not evaluable (NE): Progression has not been documented, and

    - one or more target lesions have not been assessed; or

    - assessment methods used were inconsistent with those used at baseline; or

    - one or more target lesions cannot be measured accurately (eg, poorly visible unless due to being too small to measure); or

    - one or more target lesions were excised or irradiated and have not reappeared or increased.

Non-target Disease

- CR: Disappearance of all non-target lesions and normalization of tumor marker levels (if being followed). All lymph nodes must be 'normal' in size (<10 mm short axis).

- Non-CR/Non-PD: Persistence of any non-target lesions and/or tumor marker level (if being followed) above the normal limits.

- PD: Unequivocal progression of pre-existing lesions. Generally, the overall tumor burden must increase sufficiently to merit discontinuation of therapy. In the presence

of SD or PR in target disease, progression due to unequivocal increase in non-target disease should be rare.

- Not evaluable (NE): Progression has not been determined and one or more non-target lesion sites have not been assessed or assessment methods used were inconsistent with those used at baseline or one or more non-target lesions cannot be assessed (eg, poorly visible or unclear images) or one or more non-target lesions were excised or irradiated and have not reappeared or increased.

New Lesions

The appearance of any new unequivocal malignant lesion indicates PD. If a new lesion is equivocal, for example due to its small size, continued assessment will clarify the etiology. If repeat assessments confirm the lesion, then progression should be recorded on the date of the initial assessment. A lesion identified in an area not previously scanned will be considered a new lesion.

Supplemental Investigations

- If CR determination depends on a residual lesion that decreased in size but did not disappear completely, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate. If no disease is identified, objective status is CR.

- If progression determination depends on a lesion with an increase possibly due to necrosis, the lesion may be investigated with biopsy or fine needle aspirate to clarify status.

Subjective Progression

Participants requiring discontinuation of treatment without objective evidence of disease progression should not be reported as PD on tumor assessment CRFs. This should be indicated on the end of treatment CRF as off treatment due to Global Deterioration of Health Status. Every effort should be made to document PD even after discontinuation of study treatment.

Determination of Tumor Response by RECIST

When both target and non-target lesions are present, individual assessments will be recorded separately. New lesions will also be recorded separately. Determination of tumor response at each assessment based on target, non-target and new lesions is summarized in the following table.

Objective Response Status at Each Assessment for Participants with Measurable Disease at Baseline

Target Lesions	Non-target Lesions	New Lesions	Objective status
CR	CR	No	CR
CR	Non-CR/Non-PD or not all evaluated	No	PR
PR	Non-PD* or not all evaluated	No	PR
SD	Non-PD* or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes**	PD

*Non PD includes CR and Non CR/Non PD
** New lesions must be unequivocal

Determination of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest sum on study). For CR and PR, the participant's best response assignment will depend on the achievement of both measurement and confirmation criteria. CR and PR must be confirmed by 2 measurements at least 4 weeks apart. In the case of SD, follow up measurements must have met the SD criteria at least once after start of the treatment at a minimum interval of 6 weeks.

10.10. Appendix 10: Assessment of Radiographic Response and Progression in Participants with mCRPC

Radiographic imaging for participants with CRPC is categorized as soft tissue or bone. Soft tissue imaging may include CT scans of the chest, abdomen and pelvis or MRIs of the abdomen and pelvis). Bone imaging must be whole body radionuclide bone scan (scintigraphy).

The investigator will assess response of soft tissue disease by RECIST v1.1 (refer to Appendix 9). However, bone disease will not be considered as non-target lesions assessed by RECIST v1.1. An objective response is defined as a best overall response of CR or PR per RECIST v1.1 and must be confirmed on repeated imaging at least 4 weeks after initial documentation.

Bone disease will be assessed for progressive disease only by PCWG3.[59] The documentation required for the determination of radiographic progression is shown in the table below.

Criteria for Evidence of Radiographic Progression

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 (after week 52 on study treatment)	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).

Disease progression in bone disease must be confirmed at least 6 weeks later, as per PCWG3. Refer to the following table for the timing of confirmatory imaging requirements.

Confirmatory Imaging Requirements for Participants with mCRPC Based on RECIST v1.1 and PCWG3

Disease Site	Response	Progression[a]
Soft tissue	Must be confirmed at least 4 weeks later	No confirmation required
Bone	Not applicable	Must be confirmed at least 6 weeks later

a To inform permanent treatment discontinuation.

Radiographic PFS is defined as the time from enrollment to documentation of radiographic progression in soft tissue by investigator' assessment according to RECIST v1.1, in bone by investigator's assessment according to PCWG3, or death, whichever occurs first.

10.11. Appendix 11: 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 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): $\text{logit}\big(\pi_1(d_1)\big) = \log(\alpha_1) + \beta_1 \log(d_1/d_1^*)$

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

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:

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

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:

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

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

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 $\big(\log(\alpha^*), \log(\beta^*)\big)$ 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:

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

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

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

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

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 as presented in Table 1 are used to derive the priors of the single agent logistic parameters for bempegaldesleukin (NKTR-214).[4] The Q3W schedule was mapped to the Q2W assuming linear relationship between PK with accumulation for bempegaldesleukin (NKTR-214) based on clinical-pharmacology assessment.

Table 1. 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.

The prior distributions for the model used for deriving the MAP priors are specified in Table 2.

Table 2. 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 as presented in Table 3 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. [1]

Table 3. 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.

The prior distributions for the model used for deriving the MAP priors are specified in Table 4.

Table 4. 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 5. Table 6 illustrates the resulting prior distribution of DLT rate derived from the priors given in Table 5. 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 5. Prior Distribution for the Model Parameters

Parameter	Mean	Standard deviations	Correlation
Bempegaldesleukin (NKTR-214) single agent parameters: BVN MAP Prior			
$\left(\log(\alpha_1), \log(\beta_1)\right)$	-2.612, 0.946	0.932, 1.153	0.056
Avelumab single agent parameters: BVN MAP Prior			
$\left(\log(\alpha_2), \log(\beta_2)\right)$	-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 6. 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 7 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 7. 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)	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 8). 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 8. Combination A: Dose Limiting Toxicity Rate Scenarios (Fixed Avelumab Dose 10 mg/kg every 2 Weeks)

Scenarios	Bempegaldesleukin (NKTR-214) mg/kg Q2W IV	
	0.003	**0.006**
1. Prior means	0.115	0.186
2. 25% more toxic	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($0.16 \leq \pi_{\tilde{d}} < 0.33$)≥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 9. 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 9. Combination A: Operating Characteristics

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	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.

10.12. Appendix 12: BLRM Design for Talazoparib Triplet - Combination B

This appendix provides the details of the statistical model, the derivation of prior distributions 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 between talazoparib, bempegaldesleukin (NKTR-214) and avelumab

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

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

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

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 11.

Single Agent Talazoparib

Dose-DLT data from study PRP-001 (C3441007)[60] presented in Table 1 are used to derive the prior of the single agent logistic parameters for talazoparib.

Table 1. Historical Dose Limiting Toxicity data from study NCT01286987

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 2. 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).

Summary of Prior Distributions

The prior distributions of the model parameters are provided in Table 3.

Table 3. 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 avelumab and talazoparib;
η_{23}: Two-way interaction between bempegaldesleukin (NKTR-214) and avelumab;
η_{123}: Three-way interaction between avelumab, bempegaldesleukin (NKTR-214) and talazoparib.
Abbreviations: BVN=bivariate normal; MAP=meta-analytic-predictive.

From Table 4, in absence of the B9991025 avelumab + talazoparib doublet data and the on-trial avelumab + bempegaldesleukin (NKTR-214) data, 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 4. Summary of Prior Distribution of DLT Rates for the Triplet Combination of Avelumab 10 mg/kg) 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 5 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, the starting dose can be avelumab= 10 mg/kg, bempegaldesleukin (NKTR-214) = 0.006 mg/kg and talazoparib= 0.5 mg (Scenario 2) 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 5. Combination B: Clinically Meaningful Starting Dose Given Hypothetical Data from the Doublet Combination, and the Interval Probability of Target Toxicity and Overdosing at Starting Dose.

	Doublet Dose			D/N*	Triplet starting dose (SD)			Pr(TT) at SD	Pr(OD) at SD
Scenario	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 6 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 6. Combination B: 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)	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 7). 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 7. 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		
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($0.16 \leq \pi_{\tilde{d}} < 0.33$)≥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 8. 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 8. Combination B: Operating Characteristics

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	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.

10.13. Appendix 13: BLRM Design for Enzalutamide Triplet – Combination C

This appendix provides the details of the statistical model, the derivation of prior distributions 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 avelumab +bempegaldesleukin (NKTR-214) + enzalutamide 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 between avelumab, bempegaldesleukin (NKTR-214) and enzalutamide

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

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

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

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 12).

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 11.

Single Agent Enzalutamide

Dose-DLT data from Study S-3100-1-01 (for ENZA) presented in Table 1 are used to derive the prior of the single agent logistic parameters for enzalutamide.[61]

Table 1. 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 2. 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).

Summary of Prior Distributions

The prior distributions of the model parameters provided in Table 3.

Table 3. 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 4, 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 4 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 5 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 5. 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.

	Doublet Dose			D/N*	Triplet Starting Dose (SD)			Pr(TT) at ND	Pr (OD) at ND
Scenarios	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 6 shows data scenarios for Combination C and the corresponding recommendations for the next dose. The recommended next doses are adequate for all considered scenarios (Scenarios 1-7).

Table 6. 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 7). 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 7. 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		
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.

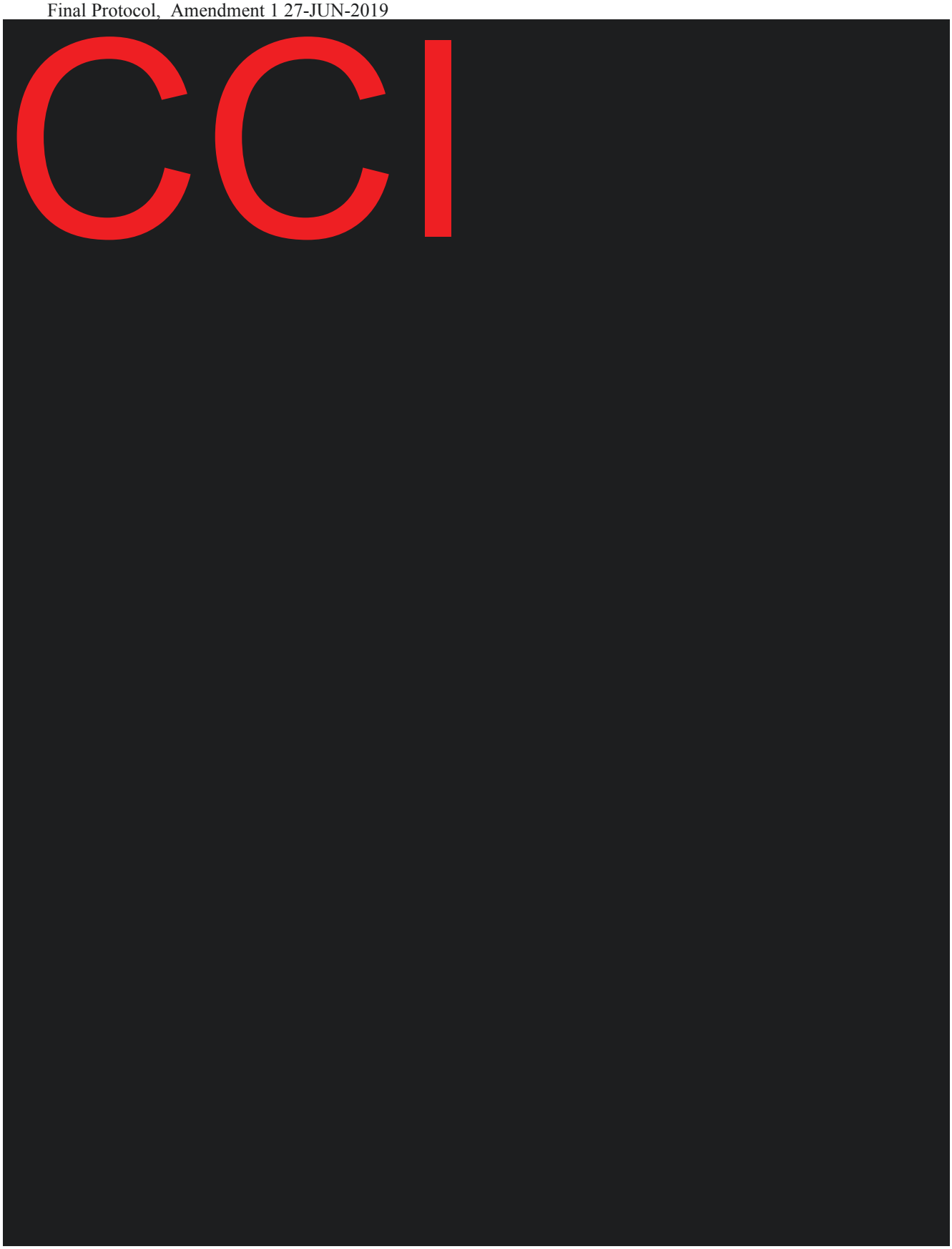
Simulation Results

Operating characteristics for Combination C are presented in Table 8. 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 8. Combination C: Operating Characteristics

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	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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10.17. Appendix 17: Abbreviations

ACTH	Adrenocorticotropic Hormone
ADA	Anti-Drug Antibody
ADP	Adenosine Diphosphate
ADT	Androgen-deprived therapy
AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine Aminotransferase
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
AR	Androgen receptor
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
BCRP	Breast Cancer Resistance Protein
BID	Twice daily
BLRM	Bayesian Logistic Regression Model
BNP	B-type natriuretic peptide
BP	Blood Pressure
BPM	Beats per Minute
BRAF	B-Raf proto-oncogene serine/threonine-protein kinase
BRCA	Breast Cancer Susceptibility Gene
BRCA 1/2	Breast Cancer Susceptibility Gene 1/2
BUN	Blood Urea Nitrogen
BVN	Bivariate Normal
C1D1	Cycle 1 Day 1

CAP	College of American Pathologists
C_{EOI}	Concentration at End of Infusion
CFR	Code of Federal Regulations
CI	Confidence Interval
CK	Creatine Kinase
CL	Clearance
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	Maximum Plasma Concentration
CPS	Combined Positive Score
CR	Complete Response
CRC	Colorectal Cancer
CR_{CL}	Creatinine Clearance
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-Reactive Protein
CRPC	Castration Resistant Prostate Cancer
CRU	Clinical Research Unit
CSR	Clinical Study Report
CT	Computed Tomography
CTC	Circulating Tumor Cell
CTCAE	Common Terminology Criteria for Adverse Events
CCI	[redacted]
CTLA-4	Cytotoxic T-Lymphocyte Associated Protein 4
C_{trough}	Trough Concentration
CV	Coefficient of Variation

DCs	Dendritic cells
DCR	Disease Control Rate
DDI	Drug-Drug Interaction
DDR	DNA Damage Repair
DILI	Drug-Induced Liver Injury
DLT	Dose-Limiting Toxicity
DNA	Deoxyribonucleic Acid
DR	Duration of Response
DU	Dispensable Unit
E	Escalation/ Re-Escalation
EC	Ethics Committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EDP	Exposure During Pregnancy
CCI	[redacted]
EOT	End of Treatment
EWOC	Escalation With Overdose Control
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FDA	Food and Drug Administration
FFPE	Formalin-Fixed Paraffin-Embedded
FSFV	First Subject First Visit
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice

GGT	Gamma-Glutamyl Transferase
GnRH	Gonadotropin-Releasing Hormone
GMP	Good Manufacturing Practice
HBV	Hepatitis B Virus
hCG	Human Chorionic Gonadotropin
HCV	Hepatitis C Virus
H&E	Hematoxylin and Eosin
HER2	Human Epidermal Growth Factor Receptor 2
HIV	Human Immunodeficiency Virus
HNSCC	Squamous Cell Carcinoma of the Head and Neck
HR	Heart rate
HRD	Homologous recombination defects
IB	Investigator's Brochure
ICH	International Council for Harmonisation
ID	Identification
IEC	Independent Ethics Committee
IERC	Independent Endpoint Review Committee
Ig	Immunoglobulin
IgF	Immunoglobulin F
IgG1	Immunoglobulin G1
IL-2	Interleukin-2
IL-2Rβγ	Interleukin-2 receptor beta gamma
IND	Investigational New Drug
INR	International Normalized Ratio
IP	Investigational Product

irAE	Immune-Related Adverse Event
IRB	Institutional Review Board
IRR	Infusion-Related Reaction
IRT	Interactive Response Technology
IUD	Intra-Uterine Device
IUS	Intra-Uterine System
IV	Intravenous
JAGS	Just Another Gibbs Sampler
K_2EDTA	Dipotassium Ethylenediaminetetraacetic Acid
K_3EDTA	Tripotassium Ethylenediaminetetraacetic Acid
1L SCCHN	Locally recurrent squamous cell carcinoma of the head and neck
L/A SCCHN	Locally Advanced squamous cell carcinoma of the head and neck
LDH	Lactate Dehydrogenase
LFT	Liver Function Test
LLQ	Lower Limit of Quantitation
LVEF	Left Ventricular Ejection Fraction
mAb	Monoclonal Antibody
MAP	Meta-Analytic-Predictive
MCMC	Markov Chain Monte Carlo
mCRPC	Metastatic castration-resistant prostate cancer
MDSC	Myeloid-derived suppressor cells
MedDRA	Medical Dictionary for Regulatory Activities
MFS	Metastatic-free survival
mHSPC	Hormone-sensitive metastatic prostate cancer
MRI	Magnetic Resonance Imaging

MSKCC	Memorial Sloan Kettering Cancer Center
MTD	Maximum Tolerated Dose
MUGA	Multigated Acquisition
N/A	Not Applicable
NAb	Neutralizing Antibody
NCI	National Cancer Institute
NE	Not Evaluable
NHT	Novel hormone therapy
NGS	Next-generation sequencing
NK	Natural Killer
NM CRPC	Non-metastatic castration-resistant prostate cancer
NSAIDs	Nonsteroidal Anti-inflammatory Drugs
NSCLC	Non-Small Cell Lung Cancer
NTI	Narrow Therapeutic Index
OR	Objective Response
ORR	Objective Response Rate
OS	Overall Survival
PARP	Poly (ADP-Ribose) Polymerase
PARPi	Poly (ADP Ribose) Polymerase inhibitor
PCD	Primary Completion Date
PCWG3	Prostate cancer working group 3
PD	Progressive Disease
PD-1	Programmed Death Receptor 1
PD-L1	Programmed Death-Ligand 1
PD-L2	Programmed Death-Ligand 2

PEG	Polyethylene Glycol
PFS	Progression-Free Survival
P-gp	P-glycoprotein
PK	Pharmacokinetics
PMAP	Pharmacometric analysis plan
PO	Orally
PR	Partial Response
PS	Performance Status
PSA	Prostate-specific antigen
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
Q2W	Every 2 Weeks
Q3W	Every 3 Weeks
QD	Once Daily
RANKL	Nuclear Factor Kappa-B Ligand
RCC	Renal Cell Carcinoma
RECIST v1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
R/M SCCHN	Recurrent/metastatic squamous cell carcinoma of the head and neck
RNA	Ribonucleic Acid
rPFS	Radiographic progression-free survival
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCLC	Small Cell Lung Cancer
S_{CR}	Serum Creatinine

SD	Stable Disease
SOA	Schedule of Assessments
SOC	Standard of Care
SOPs	Standard Operating Procedures
SRSD	Single Reference Safety Document
STING	Stimulation of Interferon Genes
TBili	Total Bilirubin
CCI	[redacted]
TEAE	Treatment Emergent Adverse Event
T_{max}	Time to Maximum Plasma Concentration
TNBC	Triple-Negative Breast Cancer
TO	Target Occupancy
TSH	Thyroid Stimulating Hormone
TTPSAP	Time to PSA Progression
TTR	Time-to-Tumor Response
UC	Urothelial Cancer
ULN	Upper Limit of Normal
US	United States
V/F	Apparent Volume of Distribution
WBC	White Blood Cell
WDC	Withdrawal of Consent
WHO	World Health Organization

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