# A PHASE 1 STUDY TO EVALUATE THE SAFETY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF ESCALATING DOSES AND TREATMENT INTENSIFICATION OF A VACCINE-BASED IMMUNOTHERAPY REGIMEN-2 (VBIR-2) (PF-06936308) FOR ADVANCED NON-SMALL CELL LUNG CANCER AND METASTATIC TRIPLE-NEGATIVE BREAST CANCER

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| **Investigational Product Number:** | PF-06936308 |
| **Investigational Product Name:** | Not Applicable (N/A) |
| **United States (US) Investigational New Drug (IND) Number:** | CCI [redacted] |
| **European Clinical Trials Database (EudraCT) Number:** | N/A |
| **Protocol Number:** | C3621001 |
| **Phase:** | 1 |

## Document History

| Document | Version Date | Summary of Changes and Rationale |
|---|---|---|
| Amendment 2 | 22 Dec 2020 | Overarching rationale for the C3621001 Protocol Amendment 2: Part 1 has been completed. Part 2 – Dose Expansion will evaluate the safety and preliminary anti-tumor activity of VBIR-2 at RP2D in participants with NSCLC. The entire protocol has been updated accordingly.<br><br>Rationale: Based on the following strategic reasons, the Sponsor has decided to focus on NSCLC and remove TNBC as a study population in Dose Expansion:<br><br>a. NSCLC is known to be immuno-responsive ("Hot" tumor) and may remain so in the relapsed setting;<br><br>b. More efficient use of resources in a population of significantly larger prevalence, hence greater unmet medical need.<br><br>• PF-06801591 was changed to sasanlimab throughout the document.<br><br>Rationale: Sasanlimab non-proprietary name was assigned to PF-06801591.<br><br>• Section SOA: Schedule of assessments for the treatment period, maintenance period and PK in Part 2 were added.<br><br>Rationale: Part 2 (Dose Expansion) was added to the study.<br><br>• Section SOA: PBMC collection during the maintenance period was updated.<br><br>Rationale: PBMC collection was updated to align with other blood collections.<br><br>• Section 1.2: Background, Section 1.3 VBIR2, Section 1.6 Dose Rationale, and Section 1.6: Clinical overview were updated. |

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| | | Rationale: New information has become available.<br>• Section 2. Part 1 Objectives and Endpoints were updated. Part 2 Objectives and Endpoints were added.<br>Rationale: Part 2 (Dose Expansion) of the study differ from Part 1.<br>• Section 4.1.2 New section: Part 2 Inclusion Criteria were added.<br>Rationale: Population in Part 2 is different from Part 1<br>• Section 4.2.2 New section: Part 2 Exclusion Criteria were added.<br>Rationale: Population in Part 2 is different from Part 1<br>• Section 5.4.5 Dose reductions was updated to include guidance for Part 2.<br>Rationale: Information from Part 1 was use to include guidance for dose reductions in Part 2.<br>C [redacted]<br>C<br>I<br>• Section 9.3 Sample size determination; Part 2 sample size added.<br>Rationale: The Part 2 sample size was determined non-quantitatively, based on typical sample sizes needed for accurate statistical prediction of Early Signals of Efficacy in the Expansion Cohort.<br>• Section 9.4 Efficacy analysis: Clinical Benefit Rate (CBR) endpoint added<br>Rationale: CBR is used in trials using immunotherapy.<br>• Appendix 4 irRECIST was removed.<br>Rationale: irRECIST criteria will no longer be used. |

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| | | • Appendix 7: New section: Alternative Measures During Public Emergencies<br><br>Rationale: Instructions to address COVID-19 related study issues. |
| Amendment 1 | 7 May 2020 | • Section 1.5 Clinical Overview added.<br><br>Rationale: New clinical information from the April 2020 PF-06936308 IB (VBIR-2: Adenovirus, plasmid DNA and anti-CTLA4 tremelimumab).<br><br>• Section 1.6.4.1 Updated PF-06801591 (anti-PD1) clinical information.<br><br>Rationale: New clinical information from the October 2019 PF-06801591 (anti-PD1) IB.<br><br>• Section 1.6.4.2 Updated VBIR PrCa PF-06753512 IB (VBIR PrCa: Adenovirus, plasmid DNA and anti-CTLA4 tremelimumab) and B7791001 clinical information, including risk of myocarditis.<br><br>Rationale: New clinical information from the January 2020 VBIR PF-06753512 IB (VBIR PrCa: Adenovirus, plasmid DNA and anti-CTLA4 tremelimumab) and safety reports has been incorporated.<br><br>• Cardiac troponin I testing was added at screening and during treatment (SOA and Section 7.1.9).<br><br>Rationale: Cardiac monitoring to mitigate the potential risk of myocarditis.<br><br>• Section 4.2 Exclusion Criteria 1 (brain metastases) and 8 (HIV+ participants) were updated.<br><br>Rationale: Incorporating language from the 17Sep2018 and 13May2019 Protocol Administrative Change Letters.<br><br>• Section 4.2 Exclusion criterion for COVID-19/SARS-CoV2 infection added. |

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| | | Rationale: Guidance regarding COVID-19/SARS-CoV2 infection was required.<br>• Section 5.4.3 Added recommendations for dose interruptions/delays due to Non-related Adverse Events.<br>Rationale: Dose interruptions due to reasons other than treatment-related toxicity include guidance for COVID-19/SARS-CoV2 infection.<br>• Section 5.4.3.3 Dose Modifications: Added treatment discontinuation for myocarditis of any grade and Grade ≥3 colitis or diarrhea.<br>Rationale: Based on emerging safety information, additional discontinuation criteria for potential new adverse events. |
| Original protocol | 16-March-2018 | Not applicable (N/A) |

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ ECs.

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## APPENDICES

## SCHEDULE OF ACTIVITIES

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the ASSESSMENTS section of the protocol for detailed information on each assessment required for compliance with the protocol.

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

## SCHEDULE OF ACTIVITIES FOR DOSE ESCALATION (PART 1)

| Protocol Activity | Screen[1] (£28 days) | Treatment Period | | | | | | | | | | | | | | Post Treatment | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cycle 1 | | | | | | | | | Cycle 2 | | | | | End of Treatment[33] | Follow- Up (Months after EOT visit) | | | | Survival Follow-up[35] |
| Study Day | | Day 1 | Day 8 | Day 15 | Day 22 | Day 29 | Day 43 | Day 57 | Day 71 | Day 85 | Day 113 | | | | | | Month 1[34] | Month 2 | Month 4 | Month 6 | Post 6-Month Follow-up |
| Cycle Day | | | | | | | | | | | Day 1 | Day 29 | Day 57 | Day 85 | Day 99 | | 28 to 35 days | | | | Every 3 Months |
| Visit Window (Days)* | | | ±1 | ±2 | ±2 | ±2 | ±4 | ±2 | ±4 | ±2 | ±2 | ±2 | ±2 | ±2 | ±4 | | | ±4 | ±4 | ±4 | ±10 |
| Informed consent[2] | X | | | | | | | | | | | | | | | | | | | | |
| Tumor history[3] | X | | | | | | | | | | | | | | | | | | | | |
| CCI [redacted] | [redacted] | | | | | | | | | | | | | | | | | | | | |
| [redacted] | | [redacted] | | | | | | | | | [redacted] | | | | | [redacted] | | | | | |
| Medical history[7] | X | | | | | | | | | | | | | | | | | | | | |
| Complete physical examination[8] | X | | | | | | | | | | | | | | | X | | | | | |
| Abbreviated physical examination[8] | | X | | X | | X | | X | | X | X | X | X | X | | | X | X | X | X | |
| Assessment of skin thickness at administration sites[9] | X | | | | | | | | | | | | | | | | | | | | |

| Protocol Activity | Screen [1] (£28 days) | Treatment Period | | | | | | | | | | | | | | Post Treatment | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cycle 1 | | | | | | | | | Cycle 2 | | | | | End of Treatment [33] | Follow- Up (Months after EOT visit) | | | | Survival Follow-up [35] |
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| **Cycle Day** | | | | | | | | | | | **Day 1** | **Day 29** | **Day 57** | **Day 85** | **Day 99** | | **28 to 35 days** | | | | **Every 3 Months** |
| **Visit Window (Days)*** | | | **±1** | **±2** | **±2** | **±2** | **±4** | **±2** | **±4** | **±2** | **±2** | **±2** | **±2** | **±2** | **±4** | | | **±4** | **±4** | **±4** | **±10** |
| Height | X | | | | | | | | | | | | | | | | | | | | |
| Weight | X | X | | | | | | | | | X | | | | | X | | | | | |
| Vital signs [10] | X | X | X | X | X | X | | X | | X | X | X | X | X | | X | X | X | X | X | |
| Performance status [11] | X | X | | | | X | | X | | X | X | X | X | X | | X | X | X | X | X | |
| **Laboratory** | | | | | | | | | | | | | | | | | | | | | |
| Unique Screening Labs [12] | X | | | | | | | | | | | | | | | | | | | | |
| Hematology [13] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Blood Chemistry [14] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Coagulation [15] | X | | | X | | X | | X | | X | | | | | | X | X | | | | |
| Cardiac Troponin-I (cTnI) [16] | X | | | | | X | | X | | X | | X | | | | | | | | | |
| Urinalysis [17] | X | | | X | | X | | X | | X | X | X | X | X | | X | X | | | | |
| Pregnancy Test or FSH Level (Serum) [18] | X | X | | | | X | | X | | X | X | X | X | X | | X | X | | | | |
| Contraception Check [19] | X | X | | | | X | | X | | X | X | X | X | X | | X | X | X | X | X | |
| (12 lead) ECG [20] | X | X | | | | X | | | | | X | | | X | | X | X | | | | |
| **Registration** | | | | | | | | | | | | | | | | | | | | | |
| Registration [21] | | X | | | | | | | | | | | | | | | | | | | |
| **Study Treatment** | | | | | | | | | | | | | | | | | | | | | |
| Adenovirus (AdC68) administration [22] | | Refer to Part 1 Schedule of Study Treatment, Pharmacokinetics and Immunogenicity Assessments | | | | | | | | | | | | | | | | | | | |
| Plasmid DNA (pDNA) administration [22] | | | | | | | | | | | | | | | | | | | | | |

| Protocol Activity | Screen[1] (£28 days) | Treatment Period | | | | | | | | | | | | | | Post Treatment | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cycle 1 | | | | | | | | | Cycle 2 | | | | | End of Treatment[33] | Follow- Up (Months after EOT visit) | | | | Survival Follow-up[35] |
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| **Cycle Day** | | | | | | | | | | | **Day 1** | **Day 29** | **Day 57** | **Day 85** | **Day 99** | | **28 to 35 days** | | | | **Every 3 Months** |
| **Visit Window (Days)*** | | | **±1** | **±2** | **±2** | **±2** | **±4** | **±2** | **±4** | **±2** | **±2** | **±2** | **±2** | **±2** | **±4** | | | **±4** | **±4** | **±4** | **±10** |
| Tremelimumab administration –For cohorts assigned to receive tremelimumab[22] | | | | | | | | | | | | | | | | | | | | | |
| Sasanlimab administration –For cohorts assigned to receive sasanlimab[22] | | | | | | | | | | | | | | | | | | | | | |
| **Tumor Assessment** | | | | | | | | | | | | | | | | | | | | | |
| CT scan, MRI scan or bone scan[23] | X | Performed every 8 weeks up to Week 32[23] | | | | | | | | | | | | | | | | | | | |
| **Other samplings** | | | | | | | | | | | | | | | | | | | | | |
| CCI [redacted] | | | | | | | | | | | | | | | | | | | | | |
| AChR antibody[25] | X | | | | | | | | | | | | | | | | | | | | |
| CCI [redacted] | | | | | | | | | | | | | | | | | | | | | |
| ER, PR, HER2 Status[30] | X | | | | | | | | | | | | | | | | | | | | |
| Pharmacokinetics and Tremelimumab ADA | | Refer to Part 1 Schedule of Study Treatment, Pharmacokinetics and Immunogenicity Assessments | | | | | | | | | | | | | | | | | | | |

| Protocol Activity | Screen [1] (£28 days) | Treatment Period | | | | | | | | | | | | | | Post Treatment | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cycle 1 | | | | | | | | | Cycle 2 | | | | | End of Treatment [33] | Follow- Up (Months after EOT visit) | | | | Survival Follow-up[35] |
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| Pharmacokinetics and SasanlimabADA | | | | | | | | | | | | | | | | | | | | | |
| **Other clinical assessments** | | | | | | | | | | | | | | | | | | | | | |
| Serious and non-serious adverse event monitoring[31] | X | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | |
| Concomitant medications and non-drug supportive interventions[32] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Survival Follow-up[35] | | | | | | | | | | | | | | | | | | | | | X |

* Visit windows during the treatment period are to be calculated based on the previous dosing visit.

**Abbreviations**: → = ongoing; AChR = acetylcholine receptor; ADA = anti-drug antibodies; AdC68= Adenovirus; AE = adverse events; CRP= C-Reactive Protein; CT = computed tomography; [redacted]; ECG = electrocardiogram; EOT = End of Treatment; ER = estrogen receptors; HER2 = human epidermal growth factor receptor 2; hsCRP=high sensitivity C-reactive protein; MRI = magnetic resonance imaging; MSLN = mesothelin; MUGA = multigated acquisition scan; PBMC = peripheral blood mononuclear cell; pDNA=plasmid deoxyribonucleic acid; PR = progesterone receptors; (X)=Optional

1. **Screening:** To be obtained within 28 days prior to study entry.
2. **Informed Consent**: Must be obtained prior to undergoing any study specific procedures. May be collected more than 28 days prior to study entry. As part of the consenting process, participants will be informed of the potential occurrence of immune related adverse events and will be provided with a Patient Information Card.
3. **Tumor History:** Will be collected within 28 days prior to study entry. Includes details of primary diagnosis and treatment history.

[redacted]

| Protocol Activity | Screen [1] (£28 days) | Treatment Period | | | | | | | | | | | | | | Post Treatment | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cycle 1 | | | | | | | | | Cycle 2 | | | | | End of Treatment [33] | Follow- Up (Months after EOT visit) | | | | Survival Follow-up[35] |
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| Cycle Day | | | | | | | | | | | Day 1 | Day 29 | Day 57 | Day 85 | Day 99 | | 28 to 35 days | | | | Every 3 Months |
| Visit Window (Days)* | | | ±1 | ±2 | ±2 | ±2 | ±4 | ±2 | ±4 | ±2 | ±2 | ±2 | ±2 | ±2 | ±4 | | | ±4 | ±4 | ±4 | ±10 |

CCI [redacted]

7. **Medical History**: Includes history of disease process other than NSCLC and TNBC (active or resolved), smoking history, and significant concurrent illness. Includes prior treatments and any current medical treatment for any condition.
8. **Complete and abbreviated physical examinations**: A neurologic examination must be conducted at Screening to look for potential signs of underlying autoimmune disorders. In addition, all abbreviated physical examinations conducted during Cycle 1 must include a neurologic examination.
9. **Assessment of the Skin and Subcutaneous Tissue Thickness:** Assessment of the skin and subcutaneous tissue thickness at the eligible administration sites will be performed at screening as described in the TDS-IM Instructions for Use. The assessment procedure does not need to be repeated during the course of the study unless the participant experiences a greater than 10% change in body mass relative to screening.
10. **Vital signs:** Includes temperature, pulse, and blood pressure (BP) to be recorded in the seated position after approximately 5 minutes of rest. Vitals signs, including temperature, pulse, and BP to be recorded 1-hour post-study drug administration during each cycle on days 1, 29, 57, and 85.
11. **Performance status**: Use Eastern Cooperative Oncology Group (ECOG) – see Appendix 2.
12. **Unique Screening Labs**: Active and clinically significant bacterial, fungal, or viral infection, including hepatitis B surface antigen, hepatitis B core antibody, hepatitis C antibody, known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness is exclusionary per Exclusion Criteria #8. In equivocal cases, subjects may be eligible if they have a negative viral load. Samples will be analyzed locally.

| Protocol Activity | Screen [1] (£28 days) | Treatment Period | | | | | | | | | | | | | | Post Treatment | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cycle 1 | | | | | | | | | Cycle 2 | | | | | End of Treatment [33] | Follow- Up (Months after EOT visit) | | | | Survival Follow-up [35] |
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| Cycle Day | | | | | | | | | | | Day 1 | Day 29 | Day 57 | Day 85 | Day 99 | | 28 to 35 days | | | | Every 3 Months |
| Visit Window (Days)* | | | ±1 | ±2 | ±2 | ±2 | ±4 | ±2 | ±4 | ±2 | ±2 | ±2 | ±2 | ±2 | ±4 | | | ±4 | ±4 | ±4 | ±10 |

13. **Hematology:** Complete blood count (CBC) to include hemoglobin, platelets, WBC, Absolute neutrophils, absolute lymphocytes, absolute monocytes,absolute eosinophils, and absolute basophils. If baseline assessment was performed within 72 hours of Cycle 1 Day 1, repeat is not required. Samples will be analyzed locally.
14. **Blood Chemistry**: Should include sodium, potassium, total chloride, bicarbonate or carbon dioxide, BUN (or urea), uric acid, creatinine, glucose (non-fasted), total calcium, magnesium, phosphorous and phosphate, albumin, total protein, aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT), alkaline phosphatase, total bilirubin, amylase, lipase, lactate dehydrogenase (LDH), and TSH + reflex free T4 and free T3. If baseline assessment was performed within 72 hours of Cycle 1 Day 1, repeat is not required. Samples will be analyzed locally.
15. **Coagulation**: Should include Prothrombin Time (PT) or International Normalized Ratio (INR) and Partial Thromboplastin Time (PTT). Samples will be analyzed locally.
16. **Cardiac Troponin**: For participants undergoing screening, circulating levels of cardiac Troponin-I (cTnI) must be measured and found to be within the normal reference range within 28 days before study entry, preferably using the central laboratory kits provided. See Section 7.1.8 for full details.
17. **Urinalysis:** Dipstick is acceptable. Microscopic analyses if dipstick abnormal. Samples will be analyzed locally.
18. **Pregnancy Test** or FSH Level (Serum): For female participants of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL and assayed in a certified laboratory, will be performed on 2 occasions prior to starting study therapy, once at the start of screening and once at the baseline visit immediately before investigational product administration. Pregnancy tests will also be routinely repeated at Day 1 of every treatment cycle during the active treatment period, at the End of Treatment visit, at the 28-day Follow-Up Visit, and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by institutional review board/ethics committee (IRB/ECs) or if required by local regulations. Participants with confrmed positive pregnanct test(s) should not be dosed. For female participants who achieved postmenopausal status and have not experienced their menses for at least 12 consecutive months, a serum FSH test must be conducted at screening only to confirm a FSH level within the laboratory's reference ranges.
19. **Contraception Check**: The contraception check is to confirm that contraception, if assigned, is used consistently and correctly. Male participants who are able to father children and female participants who are of childbearing potential will need to affirm that they meet the criteria for correct use of 2 of the selected methods of contraception. The investigator or his or her designee will discuss with the participant the need to use 2 highly effective contraception methods consistently and correctly and document such conversation in the participant's chart. In addition, the investigator or his or her designee will instruct the participant to call immediately if one or both selected contraception methods are discontinued, or if pregnancy is known or suspected in the participant or the participant's partner.
20. **12 leads ECGs**: A single ECG will be performed at Screening. At all other time points, three consecutive 12-lead ECGs will be performed approximately 2 minutes apart to determine mean QTcF interval. If the mean QTcF is prolonged (>500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation. Following the end of Cycle 2, triplicate ECGs will be performed at Month 12 Day 1, Month 18 Day 1, and may be performed as clinically indicated.
21. **Registration**: Participant number and dose level allocation operated by Pfizer Inc.
22. **Investigational Product Administration:** Treatment to be administered after all other assessments required on that day have been performed.

| Protocol Activity | Screen [1] (£28 days) | Treatment Period | | | | | | | | | | | | | | Post Treatment | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cycle 1 | | | | | | | | | Cycle 2 | | | | | End of Treatment [33] | Follow- Up (Months after EOT visit) | | | | Survival Follow-up [35] |
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| Visit Window (Days)* | | | ±1 | ±2 | ±2 | ±2 | ±4 | ±2 | ±4 | ±2 | ±2 | ±2 | ±2 | ±2 | ±4 | | | ±4 | ±4 | ±4 | ±10 |

23. **Tumor Assessments:** Tumor assessments will include all known or suspected disease sites. Screening images may be obtained within 5 weeks of registration. Imaging obtained as part of standard of care but within 28 days (-7 days) of registration may be used for screening assessment. Imaging may include chest, abdomen and pelvis CT or MRI scans, and bone scans. Bone scans will be performed at baseline if disease is suspected and on study as appropriate to follow disease. Baseline central nervous system (CNS) imaging MRI or CT Brain to be conducted only if clinically indicated based on the investigator's judgement. CT or MRI scans, as well as bone scans, when indicated, are to be done every 8 weeks (±5 days) with the first one to occur 8 weeks after C1D1 Repeat imaging will be completed every 8 weeks up to and including Week 32 or until disease progression that requires new treatment modality, permanent discontinuation, or death. Disease progression will be confirmed with two consecutive timepoints at least 4-8 weeks apart in the absence of rapid clinical deterioration. Tumor assessment should be repeated at the End of Treatment visit if more than 6 weeks have passed since the last evaluation.

CCI [redacted]

25. **Acetylcholine receptor (AChR) antibody:** Sample to be sent to the central laboratory for analysis. CCI [redacted] The evaluation for AChR antibodies is included to exclude participants who test positive at screening as agreed upon with the United States Food and Drug Administration (US FDA) and to confirm requirement for evaluation if myasthenia gravis is suspected.[99]

CCI [redacted]

30. **ER, PR and HER2 Status**: Inclusion Criteria 1 (Section 4.1) defines TNBC as HER2 negative by IHC, FISH or CISH, and ⩽10% ER/PR stain positive. Results required during Screening, prior to participant randomization.

31. **Serious and Non-serious Adverse Event Monitoring**: Adverse events should be documented and recorded at each visit using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTC AE) version 5.0. Participants must be followed for AEs for 6 months after the last study treatment administration or until all drug related toxicities have resolved, whichever is later; or earlier than 6 months should the participant commence another anticancer therapy in the meantime. 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 through and including 6 months after the last study treatment administration or until all drug related toxicities have resolved, whichever is later. If the participant begins a

| Protocol Activity | Screen [1] (£28 days) | Treatment Period | | | | | | | | | | | | | | Post Treatment | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cycle 1 | | | | | | | | | Cycle 2 | | | | | End of Treatment [33] | Follow- Up (Months after EOT visit) | | | | Survival Follow-up[35] |
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new anticancer therapy, the period for recording non-serious AEs on the CRF ends at the time the new treatment is started. However, any SAEs occurring during the active collection period must still be reported to Pfizer Safety and recorded on the CRF, irrespective of any intervening treatment.

32. **Concomitant Treatments**: All concomitant medications and non-drug supportive interventions should be recorded in the CRF.
33. **End of Treatment Visit**: The End of treatment visit will be completed at the time point when a decision is made to discontinue study treatment. This can occur during Cycles 1 or 2 or during the Maintenance Treatment Phase of the study. Obtain these assessments if not completed in the past two weeks (past 6 weeks for tumor assessments).
34. **Follow-up**: At least 28 days, and no more than 35 days after discontinuation of study treatment, participants will return to complete the required assessments. Participants will then return at Month 2, Month 4 and Month 6 to complete the required assessments.
35. **Survival:** After treatment discontinuation, participant survival status will be collected every 3 months until death, participant refusal, or lost to follow-up (telephone contact acceptable).

## SCHEDULE OF ACTIVITIES FOR MAINTENANCE TREATMENT PERIOD FOR DOSE ESCALATION (PART 1)

| **Protocol Activity** | | **Maintenance Treatment Period*** | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Month**** | **Month 9** | **Month 10** | **Month 11** | **Month 12** | **Month 13** | **Month 14** | **Month 15** | **Month 16** | **Month 17** | **Month 18** | **Month 19** | **Month 20** | **Month 21** | **Month 22 and every month thereafter** |
| **Visit Window (Days)** | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 |
| Abbreviated physical examination[1] | | X | | X | | X | | X | | X | | X | | X[1] |
| Weight | X | X | X | X | X | X | X | X | X | X | X | X | X | X[1] |
| Vital signs[2] | X | X | X | X | X | X | X | X | X | X | X | X | X | X[1] |
| Performance status[3] | X | X | X | X | X | X | X | X | X | X | X | X | X | X[1] |
| Laboratory | | | | | | | | | | | | | | |
| Hematology[4] | | X | | X | | X | | X | | X | | X | | X[1] |
| Blood Chemistry[5] | | X | | X | | X | | X | | X | | X | | X[1] |
| Coagulation[6] | | X | | | | X | | | | X | | | | X[11] |
| Cardiac Troponin-I (cTnI)[7] | X | | | X | | | | | | | | | | |
| Urinalysis[8] | | X | | | | X | | | | X | | | | X[11] |
| Pregnancy Test or FSH Level (Serum)[9] | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Contraception Check[10] | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| (12 lead) ECG[12] | | | | X | | | | | | X | | | | X* |
| **Study Treatment** | | | | | | | | | | | | | | |
| pDNA Administration[13] | | X | | X | | X | | X | | X | | X | | X[1] |
| Tremelimumab administration for cohorts assigned to receive tremelimumab[13] | | X | | X | | X | | X | | X | | X | | X[1] |
| Sasanlimab administration for cohorts assigned to receive sasanlimab[13] | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| **Tumor Assessment** | | | | | | | | | | | | | | |
| CT scan, MRI scan or bone scan[14] | | | | | | | | X[14] | | | | | | |
| **Other Samplings** | | | | | | | | | | | | | | |
| PK and Tremelimumab ADA | | X | | | | X | | | | X | | | | X[11] |
| PK and Sasanlimab ADA | | X | | | | X | | | | X | | | | X[11] |
| CCI | | | | | | | | | | | | | | |

| Protocol Activity | | Maintenance Treatment Period* | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Month**** | **Month 9** | **Month 10** | **Month 11** | **Month 12** | **Month 13** | **Month 14** | **Month 15** | **Month 16** | **Month 17** | **Month 18** | **Month 19** | **Month 20** | **Month 21** | **Month 22 and every month thereafter** |
| **Visit Window (Days)** | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 |
| CCI [redacted] | | [redacted] | | | | [redacted] | | | | [redacted] | | | | [redacted] |
| **Other clinical assessments** | | | | | | | | | | | | | | |
| Serious and non-serious adverse event monitoring[18] | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant medications and non-drug supportive interventions[19] | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

**Abbreviations:** → = ongoing; ADA = anti-drug antibodies; AdC68= Adenovirus; AE = adverse events; CT = computed tomography; ECG = electrocardiogram; EOT = End of Treatment; MRI = magnetic resonance imaging; PBMC = peripheral blood mononuclear cell; pDNA= plasmid deoxyribonucleic acid; SC = Subcutaneous(ly)

*** When a decision is made to discontinue study treatment during the Maintenance Treatment Period, the End of Treatment visit assessments should be performed. The participant will then enter the Post Treatment Period of the study.**

** Study visit is based on completion of two cycles in the treatment period. Visit window for the first maintenance treatment visit is to be calculated based on the Cycle 2 Day 85 dosing date. The first dose in the maintenance period should occur 28 days after the C2D85 dosing date. A month is defined as 28 days.

1. To be assessed every 2 months.
2. **Vital signs:** Includes temperature, pulse, and blood pressure (BP) to be recorded in the seated position after approximately 5 minutes of rest. Vitals signs, including temperature, pulse and BP to be recorded 1-hour post-study drug administration during each cycle on days 1, 29, 57, and 85.
3. **Performance status:** Use Eastern Cooperative Oncology Group (ECOG) – see Appendix 2.
4. **Hematology:** Complete blood count (CBC) to include hemoglobin, platelets, WBC, absolute neutrophils, absolute lymphocytes, absolute monocytes, absolute eosinophils, and absolute basophils. Samples will be analyzed locally.
5. **Blood Chemistry:** Should include sodium, potassium, total chloride, bicarbonate or carbon dioxide, BUN (or urea), uric acid, creatinine, glucose, total calcium, magnesium, phosphorous and phosphate, albumin, total protein, aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT), alkaline phosphatase, total bilirubin, amylase, lipase, lactate dehydrogenase (LDH) and TSH + reflex free T4 and free T3. Samples will be analyzed locally.
6. **Coagulation:** Should include Prothrombin Time (PT) or International Normalized Ratio (INR) and Partial Thromboplastin Time (PTT). Samples will be analyzed locally.
7. **Cardiac Troponin**: For participants undergoing screening, circulating levels of cardiac Troponin-I (cTnI) must be measured and found to be within the normal reference range within 28 days before study entry, preferably using the central laboratory kits provided. See Section 7.1.8 for full details.
8. **Urinalysis:** Dipstick is acceptable. Microscopic analyses if dipstick abnormal. Samples will be analyzed locally.
9. **Pregnancy Test** or FSH Level (Serum): For female participants of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL and assayed in a certified laboratory, will be performed on 2 occasions prior to starting study therapy, once at the start of screening and once at the baseline visit immediately before investigational product administration. Pregnancy tests will also be routinely repeated at Day 1 of every treatment cycle during the active treatment period, at the End of Treatment visit, at the 28-day Follow-Up Visit, and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional

| Protocol Activity | | Maintenance Treatment Period* | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study Month** | Month 9 | Month 10 | Month 11 | Month 12 | Month 13 | Month 14 | Month 15 | Month 16 | Month 17 | Month 18 | Month 19 | Month 20 | Month 21 | Month 22 and every month thereafter |
| Visit Window (Days) | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 |

pregnancy tests may also be undertaken if requested by institutional review board/ethics committee (IRB/ECs) or if required by local regulations. Participants with confrmed positive pregnanct test(s) should not be dosed. For female participants who achieved postmenopausal status and have not experienced their menses for at least 12 consecutive months, a serum FSH test must be conducted at screening only to confirm a FSH level within the laboratory's reference ranges.

10. **Contraception Check:** Male participants who are able to father children and female participants who are of childbearing potential will need to affirm that they meet the criteria for correct use of 2 of the selected methods of contraception. The investigator or his or her designee will discuss with the participant the need to use 2 highly effective contraception methods consistently and correctly and document such conversation in the participant's chart. In addition, the investigator or his or her designee will instruct the participant to call immediately if one or both selected contraception methods are discontinued, or if pregnancy is known or suspected in the participant or the participant's partner.
11. To be assessed every 4 months.
12. **Triplicate 12 leads ECGs:** At each time point, three consecutive 12 lead ECGs will be performed approximately 2 minutes apart to determine mean QTcF interval. If the mean QTcF is prolonged (>500 msec), the ECGs should be reevaluated by a qualified person at the institution for confirmation. Additional triplicate ECGs will be performed at Month 12 Day 1, Month 18 Day 1, or may be performed as clinically indicated.
13. **Investigational Product Administration:** Treatment to be administered after all other assessments required on that day have been performed, including pregnancy test. All participants will continue to receive the components to which they were assigned to receive during the treatment period. – note either the tremelimumab or the sasanlimab may be dose reduced or permanently discontinued after discussion with the Sponsor for participants assigned to receive these components.
14. **Tumor Assessments:** Tumor assessments will include all known or suspected disease sites. Imaging may include chest, abdomen and pelvis CT or MRI scans, and bone scans. CT or MRI scans, as well as bone scans, when indicated, are to be done every 12 weeks (±5 days) or when if clinically indicated until disease progression that requires new treatment modality, permanent discontinuation, or death. Disease progression will be confirmed with two consecutive timepoints at least 4-8 weeks apart in the absence of rapid clinical deterioration.

CCI [redacted]

18. **Serious and Non-serious Adverse Event Monitoring:** Adverse events should be documented and recorded at each visit using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTC AE) version 5.0. Participants must be followed for AEs for 6 months after the last study treatment administration or until all drug related toxicities have resolved, whichever is later; or earlier than 6 months should the participant commence another anticancer therapy in the meantime. 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 through and including 6 months after the last study treatment administration or until all drug related toxicities have resolved, whichever is later. If the participant begins a new anticancer therapy, the period for recording non-serious AEs on the CRF ends at the time the new treatment is started. However, any SAEs occurring during the active collection period must still be reported to Pfizer Safety and recorded on the CRF, irrespective of any intervening treatment.
19. **Concomitant Treatments:** All concomitant medications and non-drug supportive interventions should be recorded in the CRF.

## Schedule of Study Treatment, Pharmacokinetics, Tremelimumab and Sasanlimab Immunogenicity Assessments (Part 1)

| Protocol Activity | Screen (£28 days) | Treatment Period | | | | | | | | | | | | | | | Post Treatment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cycle 1 | | | | | | | | | | Cycle 2 | | | | | End of Treatment | Follow- Up (Months after EOT visit) | | | |
| **Study Day** | | **Day 1** | **Day 3 -6** | **Day 8** | **Day 15** | **Day 22** | **Day 29** | **Day 43** | **Day 57** | **Day 71** | **Day 85** | **Day 113** | | | | | | **M1** | **M2** | **M4** | **M6** |
| **Cycle Day** | | | | | | | | | | | | **Day 1** | **Day 29** | **Day 57** | **Day 85** | **Day 99** | | **28-35 days** | | | |
| **Visit Window (hours)** | | | | **±24 hr** | **±48 hr** | **±48 hr** | | | | | | | | | | | | | | | |
| **Visit Window (days)** | | | | | | | **±2** | **±4** | **±2** | **±4** | **±2** | **±2** | **±2** | **±2** | **±2** | **±4** | | | **±4** | **±4** | **±4** |
| **Study Treatment** | | | | | | | | | | | | | | | | | | | | | |
| AdC68[1] – all participants | | X | | | | | | | | | | X | | | | | | | | | |
| pDNA[2] – all participants | | | | | | | X | | X | | X | | X | X | X | | | | | | |
| Tremelimumab[3] – for cohorts assigned to receive tremelimumab | | X | | | | | X | | X | | X | X | X | X | X | | | | | | |
| Sasanlimab [4] – for cohorts assigned to receive sasanlimab | | X | | | | | X | | X | | X | X | X | X | X | | | | | | |
| **Pharmacokinetics Immunogenicity** | | | | | | | | | | | | | | | | | | | | | |
| PK for tremelimumab[5] | | X | X[6] | X[6] | X[6] | X[6] | X | | X | | X | X | X | | | | X | | X | X | X |
| ADA for tremelimumab[5] | | X | | | | | X | | | | X | | X | | | | X | | X | X | X |
| PK for sasanlimab[6] | | X | X[8] | X[8] | X[8] | X[8] | X | | X | | X | X | X | | | | X | | X | X | X |
| ADA forsasanlimab[7] | | X | | | | | X | | | | X | | X | | | | X | | X | X | X |

| Protocol Activity | Screen (£28 days) | Treatment Period | | | | | | | | | | | | | | | Post Treatment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cycle 1 | | | | | | | | | | Cycle 2 | | | | | End of Treatment | Follow- Up (Months after EOT visit) | | | |
| Study Day | | Day 1 | Day 3 -6 | Day 8 | Day 15 | Day 22 | Day 29 | Day 43 | Day 57 | Day 71 | Day 85 | Day 113 | | | | | | M1 | M2 | M4 | M6 |
| Cycle Day | | | | | | | | | | | | Day 1 | Day 29 | Day 57 | Day 85 | Day 99 | | 28-35 days | | | |
| Visit Window (hours) | | | | ±24 hr | ±48 hr | ±48 hr | | | | | | | | | | | | | | | |
| Visit Window (days) | | | | | | | ±2 | ±4 | ±2 | ±4 | ±2 | ±2 | ±2 | ±2 | ±2 | ±4 | | | ±4 | ±4 | ±4 |
| Study Treatment | | | | | | | | | | | | | | | | | | | | | |

Abbreviations: ADA = Anti-drug antibody; Adenovirus (AdC68); EOT = End of Treatment; pDNA = Plasmid deoxyribonucleic acid, PK = Pharmacokinetics

1. Adenovirus (AdC68) will be administered intramuscularly on Cycle 1 Day 1 and Cycle 2 Day 1. Tremelimumab and sasanlimab will be administered after the adenovirus for participants assigned to receive these components.
2. Plasmid DNA (pDNA) vaccinations will be administered intramuscularly using an electroporation device on Day 29, Day 57 and Day 85 of each cycle. Tremelimumab and sasanlimab will be administered after the pDNA for participants assigned to receive these components. All pDNA vaccinations should be administered prior to administering the tremelimumab and sasanlimab.
3. Tremelimumab will be administered subcutaneously in close proximity to the vaccine injected muscle and vaccine draining lymph nodes on Day 1, Day 29, Day 57 and Day 85 of each cycle. Tremelimumab will be administered after the adenovirus or pDNA and, for participants assigned to receive sasanlimab, before the sasanlimab. Both tremelimumab injections should be administered prior to administering the sasanlimab.
4. Sasanlimab will be administered subcutaneously in close proximity to the vaccine injected muscle and vaccine draining lymph nodes on Day 1, Day 29, Day 57 and Day 85 of each cycle. Sasanlimab will be administered after the adenovirus or pDNA and after the tremelimumab.
5. Blood samples for determination of tremelimumab drug concentrations and for detection of ADA/NAb against tremelimumab will be collected as outlined in the schedule of activities. Samples to be collected on dosing days are to be obtained within 6 hours prior to tremelimumab dosing.
6. For participants assigned to Cohorts 3A, 6A, and 7A only.
7. Blood samples for determination of sasanlimab drug concentrations and for detection of ADA/NAb against sasanlimab will be collected as outlined in the schedule of activities. Samples to be collected on dosing days are to be obtained within 6 hours prior to sasanlimab dosing.
8. For participants assigned to Cohorts 4A and 5A only.

## SCHEDULE OF ACTIVITIES FOR DOSE EXPANSION (PART 2)

| Protocol Activity | Screen [1] (≤28 days) | Treatment Period | | | | | | | | | | | | | | Post Treatment | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cycle 1 | | | | | | | | | Cycle 2 | | | | | End of Treatment [32] | Follow- Up (Months after EOT visit) | | | | Survival Follow-up [34] |
| Study Day | | Day 1 | Day 8 | Day 15 | Day 22 | Day 29 | Day 43 | Day 57 | Day 71 | Day 85 | Day 113 | | | | | | Month 1 [33] | Month 2 | Month 4 | Month 6 | Post 6-Month Follow-up |
| Cycle Day | | | | | | | | | | | Day 1 | Day 29 | Day 57 | Day 85 | Day 99 | | 28 to 35 days | | | | Every 3 Months |
| Visit Window (Days)* | | | ±1 | ±2 | ±2 | ±2 | ±4 | ±2 | ±4 | ±2 | ±2 | ±2 | ±2 | ±2 | ±4 | | | ±4 | ±4 | ±4 | ±10 |
| Informed consent [2] | X | | | | | | | | | | | | | | | | | | | | |
| Tumor history [3] | X | | | | | | | | | | | | | | | | | | | | |
| CCI [redacted] | [redacted] | | | | | | | | | | | | | | | | | | | | |
| | | [redacted] | | | | | | | | | [redacted] | | | | | [redacted] | | | | | |
| Medical history [7] | X | | | | | | | | | | | | | | | | | | | | |
| Complete physical examination [8] | X | | | | | | | | | | | | | | | X | | | | | |
| Abbreviated physical examination [8] | | X | | X | | X | | X | | X | X | X | X | X | | | X | X | X | X | |
| Assessment of skin thickness at administration sites [9] | X | | | | | | | | | | | | | | | | | | | | |
| Height | X | | | | | | | | | | | | | | | | | | | | |
| Weight | X | X | | | | | | | | | X | | | | | X | | | | | |
| Vital signs [10] | X | X | X | X | X | X | | X | | X | X | X | X | X | | X | X | X | X | X | |
| Performance status [11] | X | X | | | | X | | X | | X | X | X | X | X | | X | X | X | X | X | |
| **Laboratory** | | | | | | | | | | | | | | | | | | | | | |
| Unique Screening Labs [12] | X | | | | | | | | | | | | | | | | | | | | |
| Hematology [13] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Blood Chemistry [14] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Coagulation [15] | X | | | X | | X | | X | | X | | | | | | X | X | | | | |

| Protocol Activity | Screen [1] (≤28 days) | Treatment Period | | | | | | | | | | | | | | Post Treatment | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cycle 1 | | | | | | | | | Cycle 2 | | | | | End of Treatment [32] | Follow- Up (Months after EOT visit) | | | | Survival Follow-up [34] |
| Study Day | | Day 1 | Day 8 | Day 15 | Day 22 | Day 29 | Day 43 | Day 57 | Day 71 | Day 85 | Day 113 | | | | | | Month 1 [33] | Month 2 | Month 4 | Month 6 | Post 6-Month Follow-up |
| Cycle Day | | | | | | | | | | | Day 1 | Day 29 | Day 57 | Day 85 | Day 99 | | 28 to 35 days | | | | Every 3 Months |
| Visit Window (Days)* | | | ±1 | ±2 | ±2 | ±2 | ±4 | ±2 | ±4 | ±2 | ±2 | ±2 | ±2 | ±2 | ±4 | | | ±4 | ±4 | ±4 | ±10 |
| Cardiac Troponin-I (cTnI) [16] | X | | | | | X | | X | | X | | X | | | | | | | | | |
| Urinalysis [17] | X | | | X | | X | | X | | X | X | X | X | X | | X | X | | | | |
| Pregnancy Test or FSH Level (Serum) [18] | X | X | | | | X | | X | | X | X | X | X | X | | X | X | | | | |
| Contraception Check [19] | X | X | | | | X | | X | | X | X | X | X | X | | X | X | X | X | X | |
| (12 lead) ECG [20] | X | X | | | | X | | | | | X | | | X | | X | X | | | | |
| **Registration** | | | | | | | | | | | | | | | | | | | | | |
| Registration [21] | | X | | | | | | | | | | | | | | | | | | | |
| **Study Treatment** | | | | | | | | | | | | | | | | | | | | | |
| Adenovirus (AdC68) administration [22] | | Refer to Part 2 Schedule of Study Treatment, Pharmacokinetics and Immunogenicity Assessments | | | | | | | | | | | | | | | | | | | |
| Plasmid DNA (pDNA) administration [22] | | | | | | | | | | | | | | | | | | | | | |
| Tremelimumab administration [22] | | | | | | | | | | | | | | | | | | | | | |
| Sasanlimab administration [22] | | | | | | | | | | | | | | | | | | | | | |
| **Tumor Assessment** | | | | | | | | | | | | | | | | | | | | | |
| CT scan, MRI scan or bone scan [23] | X | Performed every 8 weeks up to Week 32 [23] | | | | | | | | | | | | | | | | | | | (X) |
| **Other samplings** | | | | | | | | | | | | | | | | | | | | | |
| CCI [redacted] | | [redacted] | | | | | [redacted] | | | | [redacted] | | | | | [redacted] | | | | | |
| AChR antibody [25] | X | | | | | | | | | | | | | | | | | | | | |

| Protocol Activity | Screen [1] (≤28 days) | Treatment Period | | | | | | | | | | | | | | Post Treatment | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cycle 1 | | | | | | | | | Cycle 2 | | | | | End of Treatment [32] | Follow- Up (Months after EOT visit) | | | | Survival Follow-up [34] |
| **Study Day** | | **Day 1** | **Day 8** | **Day 15** | **Day 22** | **Day 29** | **Day 43** | **Day 57** | **Day 71** | **Day 85** | **Day 113** | | | | | | **Month 1 [33]** | **Month 2** | **Month 4** | **Month 6** | **Post 6-Month Follow-up** |
| **Cycle Day** | | | | | | | | | | | **Day 1** | **Day 29** | **Day 57** | **Day 85** | **Day 99** | | **28 to 35 days** | | | | **Every 3 Months** |
| **Visit Window (Days)*** | | | **±1** | **±2** | **±2** | **±2** | **±4** | **±2** | **±4** | **±2** | **±2** | **±2** | **±2** | **±2** | **±4** | | | **±4** | **±4** | **±4** | **±10** |
| CCI [redacted] | | | | | | | | | | | | | | | | | | | | | |
| Pharmacokinetics and Tremelimumab ADA | | Refer to Part 2 Schedule of Study Treatment, Pharmacokinetics and Immunogenicity Assessments | | | | | | | | | | | | | | | | | | | |
| Pharmacokinetics and Sasanlimab ADA | | | | | | | | | | | | | | | | | | | | | |
| **Other clinical assessments** | | | | | | | | | | | | | | | | | | | | | |
| Serious and non-serious adverse event monitoring [30] | X | → | | | | | | | | | | | | | | | | | | | |
| Concomitant medications and non-drug supportive interventions [31] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Survival Follow-up [34] | | | | | | | | | | | | | | | | | | | | | X |

* Visit windows during the treatment period are to be calculated based on the previous dosing visit.

**Abbreviations**: → = ongoing; AChR = acetylcholine receptor; ADA = anti-drug antibodies; AdC68= Adenovirus; AE = adverse events; CRP= C-Reactive Protein; CT = computed tomography; CCI [redacted] ECG = electrocardiogram; EOT = End of Treatment; ER = estrogen receptors; HER2 = human epidermal growth factor receptor 2; hsCRP=high sensitivity C-reactive protein; MRI = magnetic resonance imaging; MSLN = mesothelin; MUGA = multigated acquisition scan; PBMC = peripheral blood mononuclear cell; pDNA=plasmid deoxyribonucleic acid; PR = progesterone receptors; (X)=Optional

| Protocol Activity | Screen [1] (≤28 days) | Treatment Period | | | | | | | | | | | | | | Post Treatment | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cycle 1 | | | | | | | | | Cycle 2 | | | | | End of Treatment [32] | Follow- Up (Months after EOT visit) | | | | Survival Follow-up [34] |
| Study Day | | Day 1 | Day 8 | Day 15 | Day 22 | Day 29 | Day 43 | Day 57 | Day 71 | Day 85 | Day 113 | | | | | | Month 1 [33] | Month 2 | Month 4 | Month 6 | Post 6-Month Follow-up |
| Cycle Day | | | | | | | | | | | Day 1 | Day 29 | Day 57 | Day 85 | Day 99 | | 28 to 35 days | | | | Every 3 Months |
| Visit Window (Days)* | | | ±1 | ±2 | ±2 | ±2 | ±4 | ±2 | ±4 | ±2 | ±2 | ±2 | ±2 | ±2 | ±4 | | | ±4 | ±4 | ±4 | ±10 |

1. **Screening:** To be obtained within 28 days prior to study entry.
2. **Informed Consent**: Must be obtained prior to undergoing any study specific procedures. May be collected more than 28 days prior to study entry. As part of the consenting process, participants will be informed of the potential occurrence of immune related adverse events and will be provided with a Patient Information Card.
3. **Tumor History:** Will be collected within 28 days prior to study entry. Includes details of primary diagnosis and treatment history.

[redacted]

7. **Medical History**: Includes history of disease process other than NSCLC (active or resolved), smoking history, and significant concurrent illness. Includes prior treatments and any current medical treatment for any condition.
8. **Complete and abbreviated physical examinations**: A neurologic examination must be conducted at Screening to look for potential signs of underlying autoimmune disorders. In addition, all abbreviated physical examinations conducted during Cycle 1 must include a neurologic examination.
9. **Assessment of the Skin and Subcutaneous Tissue Thickness:** Assessment of the skin and subcutaneous tissue thickness at the eligible administration sites will be performed at screening as described in the TDS-IM Instructions for Use. The assessment procedure does not need to be repeated during the course of the study unless the participant experiences a greater than 10% change in body mass relative to screening.
10. **Vital signs:** Includes temperature, pulse, and blood pressure (BP) to be recorded in the seated position after approximately 5 minutes of rest. Vitals signs, including temperature, pulse, and BP to be recorded 1-hour post-study drug administration during each cycle on Days 1, 29, 57, and 85.

| Protocol Activity | Screen [1] (≤28 days) | Treatment Period | | | | | | | | | | | | | | Post Treatment | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cycle 1 | | | | | | | | | Cycle 2 | | | | | End of Treatment [32] | Follow- Up (Months after EOT visit) | | | | Survival Follow-up [34] |
| Study Day | | Day 1 | Day 8 | Day 15 | Day 22 | Day 29 | Day 43 | Day 57 | Day 71 | Day 85 | Day 113 | | | | | | Month 1 [33] | Month 2 | Month 4 | Month 6 | Post 6-Month Follow-up |
| Cycle Day | | | | | | | | | | | Day 1 | Day 29 | Day 57 | Day 85 | Day 99 | | 28 to 35 days | | | | Every 3 Months |
| Visit Window (Days)* | | | ±1 | ±2 | ±2 | ±2 | ±4 | ±2 | ±4 | ±2 | ±2 | ±2 | ±2 | ±2 | ±4 | | | ±4 | ±4 | ±4 | ±10 |

11. **Performance status**: Use Eastern Cooperative Oncology Group (ECOG) – see Appendix 2.
12. **Unique Screening Labs**: Active and clinically significant bacterial, fungal, or viral infection, including hepatitis B surface antigen, hepatitis B core antibody, hepatitis C antibody, known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness is exclusionary per Exclusion Criteria #9. In equivocal cases, subjects may be eligible if they have a negative viral load. Samples will be analyzed locally.
13. **Hematology:** Complete blood count (CBC) to include hemoglobin, platelets, WBC, Absolute neutrophils, absolute lymphocytes, absolute monocytes,absolute eosinophils, and absolute basophils. If baseline assessment was performed within 72 hours of Cycle 1 Day 1, repeat is not required. Samples will be analyzed locally.
14. **Blood Chemistry**: Should include sodium, potassium, total chloride, bicarbonate or carbon dioxide, BUN (or urea), uric acid, creatinine, glucose (non-fasted), total calcium, magnesium, phosphorous and phosphate, albumin, total protein, aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT), alkaline phosphatase, total bilirubin, amylase, lipase, lactate dehydrogenase (LDH), and TSH + reflex free T4 and free T3. If baseline assessment was performed within 72 hours of Cycle 1 Day 1, repeat is not required. Samples will be analyzed locally.
15. **Coagulation**: Should include Prothrombin Time (PT) or International Normalized Ratio (INR) and Partial Thromboplastin Time (PTT). Samples will be analyzed locally.
16. **Cardiac Troponin**: For participants undergoing screening, circulating levels of cardiac Troponin-I (cTnI) must be measured and found to be within the normal reference range within 28 days before study entry, preferably using the central laboratory kits provided. See Section 7.1.8 for full details.
17. **Urinalysis:** Dipstick is acceptable. Microscopic analyses if dipstick abnormal. Samples will be analyzed locally.
18. **Pregnancy Test** or FSH Level (Serum): For female participants of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL and assayed in a certified laboratory, will be performed on 2 occasions prior to starting study therapy, once at the start of screening and once at the baseline visit immediately before investigational product administration. Pregnancy tests will also be routinely repeated at Day 1 of every treatment cycle during the active treatment period, at the End of Treatment visit, at the 28-day Follow-Up Visit, and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by institutional review board/ethics committee (IRB/ECs) or if required by local regulations. Participants with confirmed positive pregnancytest(s) should not be dosed. For female participants who achieved postmenopausal status and have not experienced their menses for at least 12 consecutive months, a serum FSH test must be conducted at screening only to confirm a FSH level within the laboratory's reference ranges.
19. **Contraception Check**: The contraception check is to confirm that contraception, if assigned, is used consistently and correctly. Male participants who are able to father children and female participants who are of childbearing potential will need to affirm that they meet the criteria for correct use of 2 of the selected methods of contraception. The investigator or his or her designee will discuss with the participant the need to use 2 highly effective contraception methods consistently and correctly and document such conversation in the participant's chart. In addition, the investigator or his or her designee will instruct the participant to call immediately if one or both selected contraception methods are discontinued, or if pregnancy is known or suspected in the participant or the participant's partner.
20. **12 leads ECGs**: A single ECG will be performed at Screening. At all other time points, 3 consecutive 12-lead ECGs will be performed approximately 2 minutes apart to determine mean QTcF interval. If the mean QTcF is prolonged (>500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation.

| Protocol Activity | Screen [1] (≤28 days) | Treatment Period | | | | | | | | | | | | | | Post Treatment | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cycle 1 | | | | | | | | | Cycle 2 | | | | | End of Treatment [32] | Follow- Up (Months after EOT visit) | | | | Survival Follow-up [34] |
| Study Day | | Day 1 | Day 8 | Day 15 | Day 22 | Day 29 | Day 43 | Day 57 | Day 71 | Day 85 | Day 113 | | | | | | Month 1 [33] | Month 2 | Month 4 | Month 6 | Post 6-Month Follow-up |
| Cycle Day | | | | | | | | | | | Day 1 | Day 29 | Day 57 | Day 85 | Day 99 | | 28 to 35 days | | | | Every 3 Months |
| Visit Window (Days)* | | | ±1 | ±2 | ±2 | ±2 | ±4 | ±2 | ±4 | ±2 | ±2 | ±2 | ±2 | ±2 | ±4 | | | ±4 | ±4 | ±4 | ±10 |

21. **Registration**: Participant number and dose level allocation operated by Pfizer Inc.

22. **Investigational Product Administration:** Treatment to be administered after all other assessments required on that day have been performed.

23. **Tumor Assessments:** Tumor assessments will include all known or suspected disease sites. Screening images may be obtained within 5 weeks of registration. Imaging obtained as part of standard of care but within 28 days (-7 days) of registration may be used for screening assessment. Imaging may include chest, abdomen and pelvis CT or MRI scans, and bone scans. Bone scans will be performed at baseline if disease is suspected and on study as appropriate to follow disease. Baseline central nervous system (CNS) imaging MRI or CT Brain to be conducted only if clinically indicated based on the investigator's judgement. CT or MRI scans, as well as bone scans, when indicated, are to be done every 8 weeks (±5 days) with the first one to occur 8 weeks after C1D1 Repeat imaging will be completed every 8 weeks up to and including Month 8 (Week 32) or until disease progression that requires new treatment modality, permanent discontinuation, or death. Disease progression will be confirmed with 2 consecutive timepoints at least 4-8 weeks apart in the absence of rapid clinical deterioration. Tumor assessment should be repeated at the End of Treatment visit if more than 6 weeks have passed since the last evaluation.

CCI [redacted]

25. **Acetylcholine receptor (AChR) antibody:** Sample to be sent to the central laboratory for analysis. CCI [redacted] The evaluation for AChR antibodies is included to exclude participants who test positive at screening as agreed upon with the United States Food and Drug Administration (US FDA) and to confirm requirement for evaluation if myasthenia gravis is suspected.[99]

CCI [redacted]

30. **Serious and Non-serious Adverse Event Monitoring**: Adverse events should be documented and recorded at each visit using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTC AE) version 5.0. Participants must be followed for AEs for 6 months after the last study treatment administration or until all drug related toxicities have resolved, whichever is later; or earlier than 6 months should the participant commence another anticancer therapy in the meantime. 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 through and including 6 months after the last study treatment administration or until all drug related toxicities have resolved, whichever is later. If the participant begins a

| Protocol Activity | Screen [1] (≤28 days) | Treatment Period | | | | | | | | | | | | | | Post Treatment | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cycle 1 | | | | | | | | | Cycle 2 | | | | | End of Treatment [32] | Follow- Up (Months after EOT visit) | | | | Survival Follow-up[34] |
| Study Day | | Day 1 | Day 8 | Day 15 | Day 22 | Day 29 | Day 43 | Day 57 | Day 71 | Day 85 | Day 113 | | | | | | Month 1[33] | Month 2 | Month 4 | Month 6 | Post 6-Month Follow-up |
| Cycle Day | | | | | | | | | | | Day 1 | Day 29 | Day 57 | Day 85 | Day 99 | | 28 to 35 days | | | | Every 3 Months |
| Visit Window (Days)* | | | ±1 | ±2 | ±2 | ±2 | ±4 | ±2 | ±4 | ±2 | ±2 | ±2 | ±2 | ±2 | ±4 | | | ±4 | ±4 | ±4 | ±10 |

new anticancer therapy, the period for recording non-serious AEs on the CRF ends at the time the new treatment is started. However, any SAEs occurring during the active collection period must still be reported to Pfizer Safety and recorded on the CRF, irrespective of any intervening treatment.

31. **Concomitant Treatments**: All concomitant medications and non-drug supportive interventions should be recorded in the CRF.
32. **End of Treatment Visit**: The End of treatment visit will be completed at the time point when a decision is made to discontinue study treatment. This can occur during Cycles 1 or 2 or during the Maintenance Treatment Phase of the study. Obtain these assessments if not completed in the past 2 weeks (past 6 weeks for tumor assessments).
33. **Follow up**: At least 28 days, and no more than 35 days after discontinuation of study treatment, participants will return to complete the required assessments. Participants will then return at Month 2, Month 4 and Month 6 to complete the required assessments.
34. **Survival:** After treatment discontinuation, participant survival status will be collected every 3 months until death, participant refusal, or lost to follow-up (telephone contact acceptable).

CCI [redacted]

## SCHEDULE OF ACTIVITIES FOR MAINTENANCE TREATMENT PERIOD FOR DOSE EXPANSION (PART 2)

| **Protocol Activity** | | **Maintenance Treatment Period*** | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Month**** | **Month 9** | **Month 10** | **Month 11** | **Month 12** | **Month 13** | **Month 14** | **Month 15** | **Month 16** | **Month 17** | **Month 18** | **Month 19** | **Month 20** | **Month 21** | **Month 22 and every month thereafter** |
| **Visit Window (Days)** | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 |
| Abbreviated physical examination[1] | | X | | X | | X | | X | | X | | X | | X[1] |
| Weight | X | X | X | X | X | X | X | X | X | X | X | X | X | X[1] |
| Vital signs[2] | X | X | X | X | X | X | X | X | X | X | X | X | X | X[1] |
| Performance status[3] | X | X | X | X | X | X | X | X | X | X | X | X | X | X[1] |
| Laboratory | | | | | | | | | | | | | | |
| Hematology[4] | | X | | X | | X | | X | | X | | X | | X[1] |
| Blood Chemistry[5] | | X | | X | | X | | X | | X | | X | | X[1] |
| Coagulation[6] | | X | | | | X | | | | X | | | | X[11] |
| Cardiac Troponin-I (cTnI)[7] | X | | | X | | | | | | | | | | |
| Urinalysis[8] | | X | | | | X | | | | X | | | | X[11] |
| Pregnancy Test or FSH Level (Serum)[9] | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Contraception Check[10] | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| (12 lead) ECG[12] | | | | X | | | | | | X | | | | X* |
| **Study Treatment** | | | | | | | | | | | | | | |
| pDNA Administration[13] | | X | | X | | X | | X | | X | | X | | X[1] |
| Tremelimumab administration[13] | | X | | X | | X | | X | | X | | X | | X[1] |
| Sasanlimab administration[13] | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| **Tumor Assessment** | | | | | | | | | | | | | | |
| CT scan, MRI scan or bone scan[14] | | X[14] | | | | | | | | | | | | |
| **Other Samplings** | | | | | | | | | | | | | | |
| PK and Tremelimumab ADA | | Refer to Part 2 Schedule of Study Treatment, Pharmacokinetics and Immunogenicity Assessments | | | | | | | | | | | | |
| PK and Sasanlimab ADA | | | | | | | | | | | | | | |
| CCI [redacted] | | [redacted] | | | | [redacted] | | | | [redacted] | | [redacted] | | [redacted] |
| **Other clinical assessments** | | | | | | | | | | | | | | |
| Serious and non-serious adverse event monitoring[18] | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

| Protocol Activity | | Maintenance Treatment Period* | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Month**** | **Month 9** | **Month 10** | **Month 11** | **Month 12** | **Month 13** | **Month 14** | **Month 15** | **Month 16** | **Month 17** | **Month 18** | **Month 19** | **Month 20** | **Month 21** | **Month 22 and every month thereafter** |
| **Visit Window (Days)** | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 |
| Concomitant medications and non-drug supportive interventions[19] | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

**Abbreviations:** → = ongoing; ADA = anti-drug antibodies; AdC68= Adenovirus; AE = adverse events; CT = computed tomography; ECG = electrocardiogram; EOT = End of Treatment; MRI = magnetic resonance imaging; PBMC = peripheral blood mononuclear cell; pDNA= plasmid deoxyribonucleic acid; SC = Subcutaneous(ly)

*** When a decision is made to discontinue study treatment during the Maintenance Treatment Period, the End of Treatment visit assessments should be performed. The participant will then enter the Post Treatment Period of the study.**

** Study visit is based on completion of 2 cycles in the treatment period. Visit window for the first maintenance treatment visit is to be calculated based on the Cycle 2 Day 85 dosing date. The first dose in the maintenance period should occur 28 days after the C2D85 dosing date. A month is defined as 28 days.

1. **Abbreviated Physical Examination**: To be assessed every 2 months.
2. **Vital signs:** Includes temperature, pulse, and blood pressure (BP) to be recorded in the seated position after approximately 5 minutes of rest. On days of study drug administration, vitals signs, including temperature, pulse and BP are to be recorded 1-hour post-study drug administration.
3. **Performance status:** Use Eastern Cooperative Oncology Group (ECOG) – see Appendix 2.
4. **Hematology:** Complete blood count (CBC) to include hemoglobin, platelets, WBC, absolute neutrophils, absolute lymphocytes, absolute monocytes, absolute eosinophils, and absolute basophils. Samples will be analyzed locally.
5. **Blood Chemistry:** Should include sodium, potassium, total chloride, bicarbonate or carbon dioxide, BUN (or urea), uric acid, creatinine, glucose ( non-fasted), total calcium, magnesium, phosphorous and phosphate, albumin, total protein, aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT), alkaline phosphatase, total bilirubin, amylase, lipase, lactate dehydrogenase (LDH) and TSH + reflex free T4 and free T3. Samples will be analyzed locally.
6. **Coagulation:** Should include Prothrombin Time (PT) or International Normalized Ratio (INR) and Partial Thromboplastin Time (PTT). Samples will be analyzed locally.
7. **Cardiac Troponin**: For participants undergoing screening, circulating levels of cardiac Troponin-I (cTnI) must be measured and found to be within the normal reference range within 10 days of Month 9 and Month 12. See Section 7.1.8 for full details.
8. **Urinalysis:** Dipstick is acceptable. Microscopic analyses if dipstick abnormal. Samples will be analyzed locally.
9. **Pregnancy Test** or FSH Level (Serum): For female participants of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL and assayed in a certified laboratory, will be performed on 2 occasions prior to starting study therapy, once at the start of screening and once at the baseline visit immediately before investigational product administration. Pregnancy tests will also be repeated monthly during the Maintenance Treatment Period. Additional pregnancy tests may also be undertaken if requested by institutional review board/ethics committee (IRB/ECs) or if required by local regulations. Participants with confirmed positive pregnancy test(s) should not be dosed. For female participants who achieved postmenopausal status and have not experienced their menses for at least 12 consecutive months, a serum FSH test must be conducted at screening only to confirm a FSH level within the laboratory's reference ranges.
10. **Contraception Check:** Male participants who are able to father children and female participants who are of childbearing potential will need to affirm that they meet the criteria for correct use of 2 of the selected methods of contraception. The investigator or his or her designee will discuss with the participant the need to use 2 highly effective contraception methods consistently and correctly and document such conversation in the participant's chart. In addition, the investigator or his or her designee will instruct

| Protocol Activity | | Maintenance Treatment Period* | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study Month** | Month 9 | Month 10 | Month 11 | Month 12 | Month 13 | Month 14 | Month 15 | Month 16 | Month 17 | Month 18 | Month 19 | Month 20 | Month 21 | Month 22 and every month thereafter |
| Visit Window (Days) | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 |

the participant to call immediately if one or both selected contraception methods are discontinued, or if pregnancy is known or suspected in the participant or the participant's partner.

11. To be assessed every 4 months.
12. **Triplicate 12 leads ECGs:** At each time point, three consecutive 12 lead ECGs will be performed approximately 2 minutes apart to determine mean QTcF interval. If the mean QTcF is prolonged (>500 msec), the ECGs should be reevaluated by a qualified person at the institution for confirmation. Additional triplicate ECGs will be performed at Month 12 Day 1, Month 18 Day 1, or may be performed as clinically indicated.
13. **Investigational Product Administration:** Treatment to be administered after all other assessments required on that day have been performed, including pregnancy test. All participants will continue to receive the components to which they were assigned to receive during the treatment period. – note either the tremelimumab or the sasanlimab may be dose reduced or permanently discontinued after discussion with the Sponsor for participants assigned to receive these components.
14. **Tumor Assessments:** Tumor assessments will include all known or suspected disease sites. Imaging may include chest, abdomen and pelvis CT or MRI scans, and bone scans. CT or MRI scans, as well as bone scans, when indicated, are to be done every 12 weeks (±5 days) or when if clinically indicated until disease progression that requires new treatment modality, permanent discontinuation, or death. Disease progression will be confirmed with 2 consecutive timepoints at least 4-8 weeks apart in the absence of rapid clinical deterioration.

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18. **Serious and Non-serious Adverse Event Monitoring:** Adverse events should be documented and recorded at each visit using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTC AE) version 5.0. Participants must be followed for AEs for 6 months after the last study treatment administration or until all drug related toxicities have resolved, whichever is later; or earlier than 6 months should the participant commence another anticancer therapy in the meantime. 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 through and including 6 months after the last study treatment administration or until all drug related toxicities have resolved, whichever is later. If the participant begins a new anticancer therapy, the period for recording non-serious AEs on the CRF ends at the time the new treatment is started. However, any SAEs occurring during the active collection period must still be reported to Pfizer Safety and recorded on the CRF, irrespective of any intervening treatment.
19. **Concomitant Treatments:** All concomitant medications and non-drug supportive interventions should be recorded in the CRF.

## Schedule of Study Treatment, Pharmacokinetics, Tremelimumab and Sasanlimab Immunogenicity Assessments (Part 2)

| Protocol Activity | Screen (≤28 days) | Treatment Period | | | | | | | | Maintenance | End of Treatment | Post Treatment | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cycle 1 | | | | Cycle 2 | | | | Every 4 months starting at Month 10 | End of Treatment | Follow- Up (Months after EOT visit) | | | |
| **Study Day** | | **Day 1** | **Day 29** | **Day 57** | **Day 85** | **Day 113** | | | | | | **M1** | **M2** | **M4** | **M6** |
| **Cycle Day** | | | | | | **Day 1** | **Day 29** | **Day 57** | **Day 85** | | | **28-35 days** | | | |
| **Visit Window (days)** | | | **±2** | **±2** | **±2** | **±2** | **±2** | ±2 | **±2** | | | | **±4** | **±4** | **±4** |
| **Study Treatment** | | | | | | | | | | | | | | | |
| AdC68[1] | | X | | | | X | | | | | | | | | |
| pDNA[2] | | | X | X | X | | X | X | X | X[2] | | | | | |
| Tremelimumab[3] | | X | X | X | X | X | X | X | X | X[3] | | | | | |
| Sasanlimab[4] | | X | X | X | X | X | X | X | X | X[4] | | | | | |
| **Pharmacokinetics Immunogenicity** | | | | | | | | | | | | | | | |
| PK for tremelimumab[5] | | X | X | X | X | X | X | | | X | X | | X | X | X |
| ADA/NAb for tremelimumab[5] | | X | X | | X | | X | | | X | X | | X | X | X |
| PK for Sasanlimab[6] | | X | X | X | X | X | X | | | X | X | | X | X | X |
| ADA/NAb for Sasanlimab[6] | | X | X | | X | | X | | | X | X | | X | X | X |

Abbreviations: ADA = Anti-drug antibody; Adenovirus (AdC68); EOT = End of Treatment; pDNA = Plasmid deoxyribonucleic acid, PK = Pharmacokinetics

1. Adenovirus (AdC68) will be administered intramuscularly on Cycle 1 Day 1 and Cycle 2 Day 1. Tremelimumab and sasanlimab will be administered after the adenovirus for participants assigned to receive these components.
2. Plasmid DNA (pDNA) vaccinations will be administered intramuscularly using an electroporation device on Day 29, Day 57 and Day 85 of each cycle. During the Maintenance period, pDNA vaccinations will be administered every 2 months. All pDNA vaccinations should be administered prior to administering the tremelimumab and sasanlimab.
3. Tremelimumab will be administered subcutaneously in close proximity to the vaccine injected muscle and vaccine draining lymph nodes on Day 1, Day 29, Day 57 and Day 85 of each cycle. During the Maintenance period, tremelimumab will be administered every 2 months. Tremelimumab (both injections) will be administered after the adenovirus or pDNA and before the sasanlimab.

| Protocol Activity | Screen (≤28 days) | Treatment Period | | | | | | | | Maintenance | End of Treatment | Post Treatment | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cycle 1 | | | | Cycle 2 | | | | Every 4 months starting at Month 10 | End of Treatment | Follow- Up (Months after EOT visit) | | | |
| **Study Day** | | **Day 1** | **Day 29** | **Day 57** | **Day 85** | **Day 113** | | | | | | **M1** | **M2** | **M4** | **M6** |
| **Cycle Day** | | | | | | **Day 1** | **Day 29** | **Day 57** | **Day 85** | | | **28-35 days** | | | |
| **Visit Window (days)** | | | **±2** | **±2** | **±2** | **±2** | **±2** | ±2 | **±2** | | | | **±4** | **±4** | **±4** |
| **Study Treatment** | | | | | | | | | | | | | | | |

4. Sasanlimab will be administered subcutaneously in close proximity to the vaccine injected muscle and vaccine draining lymph nodes on Day 1, Day 29, Day 57 and Day 85 of each cycle. During the Maintenance period, sasanlimab will be administered each month. Sasanlimab will be administered after the adenovirus or pDNA and after the tremelimumab.
5. Blood samples for determination of tremelimumab drug concentrations and for detection of ADA/NAb against tremelimumab will be collected as outlined in the schedule of activities. Samples to be collected on dosing days are to be obtained within 6 hours prior to tremelimumab dosing.
6. Blood samples for determination of sasanlimab drug concentrations and for detection of ADA/NAb against sasanlimab will be collected as outlined in the schedule of activities. Samples to be collected on dosing days are to be obtained within 6 hours prior to sasanlimab dosing.

# 1. INTRODUCTION

## 1.1. Mechanism of Action/Indication

PF-06936308 is a vaccine-based immunotherapy regimen-2 (VBIR-2) that is currently being investigated in participants with advanced non-small cell lung cancer (NSCLC) and metastatic triple-negative breast cancer (mTNBC).

## 1.2. Background and Rationale

Lung cancer is the second most common cancer in both men and women, it accounts for approximately 160,000 deaths each year in the United States (US). About 80-85% of lung cancers are histologically classified as Non-Small Cell Lung Cancer (NSCLC), which includes 2 major sub-types: 1) Non-squamous carcinoma (including adenocarcinoma, large-cell carcinoma (rare), and other cell types), and 2) Squamous cell (epidermoid) carcinoma.[1] The 5-year survival rate of metastatic NSCLC is 4%.[16]

Triple-negative breast cancer accounts for 15% to 20% of breast cancers and is histologically defined by a lack of estrogen receptor (ER) and progesterone receptor (PR) expression as well as absence of human epidermal growth factor 2 (HER2) overexpression and/or amplification.[4,6] Following neoadjuvant and/or adjuvant chemotherapy,[7,8,9,10] patients with TNBC have a higher incidence of early visceral recurrence, with a subsequent median survival of approximately 1 year.[2,3,11]

Given these extraordinarily low survival rates, there is a need for new therapies with acceptable side-effect profiles to provide long-term disease control in these patient populations.

Recent advances in understanding methods to increase immune surveillance and to reduce native immune tolerance have yielded encouraging therapeutic advances in a variety of tumor types, including NSCLC.[12,13,14,15] Unfortunately, these current approaches generally encompass the use of single-agent immunotherapy, in which only a sub-group of patients respond, or show a long-term survival benefit.

In contrast, PF-06936308 is a multi-agent, combination approach to the immune treatment of NSCLC. The multi-agent regimen consists of a series of priming and booster vaccinations containing three antigens, along with 2 immune checkpoint inhibitors, delivered in support of the vaccinations. It is hoped that this multi-agent approach will more thoroughly induce, expand, and maintain the pool of T-cells providing the anti-tumor responses at the sites of metastatic NSCLC. As NSCLC is known to express the tumor antigens encoded and expressed by the vaccine, (see below), and as NSCLC is associated with a so-called "inflamed" tumor microenvironment (indicating a an intrinsic level of anti-tumor T-cell infiltration), it is hope this regimen will induce clinically significant responses in participants with metastatic NSCLC that will reduce tumor burden, delay disease progression, and ultimately lead to prolonged overall survival.

**VBIR-2 Regimen**

The VBIR-2 (PF-06936308) regimen consists of 4 components:

(1) PF-06871923 (AdC68), a replication incompetent chimpanzee adenovirus, delivered as a priming vaccination intramuscularly. AdC68 contains the 3 selected non-small cell lung cancer-associated antigens mucin 1 (MUC1), mesothelin (MSLN) and telomerase reverse transcriptase (TERT);

(2) PF-06871925, a plasmid DNA (pDNA) construct that encodes the same 3 tumor antigens as in the AdC68 viral vector. The pDNA is also delivered intramuscularly, and is used as a boost vaccination at pre-specified intervals after the viral vector is delivered;

(3) PF-06753388 (tremelimumab), an anti-cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) monoclonal antibody given subcutaneously (SC) in conjunction with each vaccination.

(4) PF-06801591 (sasanlimab), an anti-programmed death-1 (PD-1) monoclonal antibody also given SC in conjunction with each vaccination.

### 1.2.1. Non-Small Cell Lung Cancer Treatment Overview

**Limitations of Treating Activating Genetic Mutations**

Numerous genetic changes have been associated with lung cancer that may serve as activators of the malignant process. Epidermal growth factor receptor (EGFR) is expressed or overexpressed in the majority of NSCLC tumors.[17,18,19] Agents targeting EGFR include tyrosine kinase inhibitors (TKIs), such as gefitinib,[17] erlotinib,[18] and afatinib.[19] In metastatic NSCLC harboring activating EGFR mutations, these treatments may result in some patients obtaining response rates exceeding 60%, accompanied by median Overall Survival exceeding 2 years. Unfortunately, most patients progress in about 9 months, which in 50% of cases is due to a secondary, T790M mutation in exon 20. In addition to EGFR mutations, abnormalities in the anaplastic lymphoma kinase (ALK) gene have been identified in a subset of NSCLC patients. These gene rearrangements, which appear mutually exclusive with both EGFR and KRAS (Proto-Oncogene) gene mutations, render cancers highly responsive to ALK inhibitors including crizotinib[20] and ceritinib.[21]

For the majority of patients diagnosed with advanced-stage NSCLC without targetable driver gene mutations, platinum-based doublet chemotherapy (ChTx) has been the standard of care (SOC) for over 30 years. With the exception of bevacizumab,[22,23] and despite extensive study of multiple targeted and cytotoxic agents, addition of a third agent to platinum-doublet chemotherapy has not been shown to improve progression-free survival (PFS) or overall survival (OS) over platinum-doublet chemotherapy.[24] Targeting driver mutations responsible for tumor progression (EGFR receptor and the echinoderm microtubule-associated protein-like 4 (EML4)-anaplastic lymphoma kinase (ALK) EML4-ALK receptor) is modestly effective; however resistance to these therapies inevitably ensues.[25,26,27]

**Advantages of Immunotherapy Regimens with Checkpoint Inhibitors**

Checkpoint inhibitors, tumor vaccines, and cellular therapies induce formation of specific tumor-directed cytotoxic T cells capable of destroying cancer cells. This process may involve T-cell memory and longer-term, ongoing anti-tumor effects, which may possibly provide longer overall survival benefits compared to current therapies, as described below.

Checkpoint inhibitors, including anti-PD-1 and anti-CTLA-4, have recently been tested for efficacy in NSCLC, and shown success in the immunotherapy-naïve setting.[28,29,30] Initial use of the checkpoint inhibitors ipilimumab (anti-CTLA-4) and nivolumab (anti-PD-1) for the treatment of NSCLC demonstrated encouraging clinical results, especially in patients with program death-ligand 1 (PD-L1) expression in >50% of their tumor cells.[35] In first-line NSCLC, patients with PD-L1+ >50% were treated with nivolumab 3 mg/kg every 2 weeks (Q2W) plus ipilimumab 1 mg/kg every 12 weeks (Q12W), or every 6 weeks (Q6W). The ORR was 47% for the ipi/nivo combination versus 23% for nivolumab alone. Median duration of response was not reached with median follow-up times of 12.8 months.[37] Participants had a tolerable safety profile, although Grade 3 or Grade 4 treatment-related adverse events (TRAEs) were observed in 37% of patients, including increased lipase, pneumonitis, adrenal insufficiency and colitis.

More recently, in 2018, new standards of care have emerged in treatment-naïve, NSCLC without sensitizing EGFR or ALK mutations, using regimens consisting of PD-axis inhibitors combined with a variety of chemotherapy or other novel agents. In KEYNOTE 189, pemetrexed and platinum-based chemotherapy, along with pembrolizumab, was administered in a Phase 3 trial, and compared to patients receiving the same regimen without pembrolizumab.[147] Those patients receiving pembrolizumab in addition to the pemetrexed and platinum-based chemotherapy achieved a superior 12-month OS of 69.2 % versus 49.4%, HR = 0.49 and a mPFS of 8.8 months versus 4.9 months. Both groups had the same safety profile of 65 – 67 % Grade 3 AEs. Similarly, in IMpower150, patients with non-squamous, treatment-naïve NSCLC without EGFR or ALK driver mutations were treated with bevacizumab plus carboplatin plus paclitaxel (BCP), or atezolizumab plus BCP (ABCP) every 3 weeks for 4 or 6 cycles, followed by maintenance therapy with atezolizumab, bevacizumab, or both. Patients treated with ABCP achieved an improved mPFS (8.3 versus 6.8 months, HR = 0.62) and mOS (19.2 versus 14.7 months, HR = 0.78).[148]

**Triple-Negative Breast Cancer**

Triple-negative breast cancer accounts for 15% to 20% of breast cancers and is histologically defined by a lack of estrogen receptor and progesterone receptor expression and the absence of HER2 overexpression and/or amplification.[4,6] Triple-negative breast cancer is a heterogeneous disease, not only on the molecular level, but also on the pathologic and clinical levels. The majority of patients with TNBC respond with high sensitivity to chemotherapies including anthracyclines and taxanes in the neoadjuvant or adjuvant settings. Responses to chemotherapy occur, but are often short lived and are frequently accompanied by considerable toxicity.[39,40,41,42,43] After neoadjuvant and/or adjuvant chemotherapy, patients with TNBC have a higher incidence of early visceral recurrence,[7,8,9,10] with a

subsequent median survival of approximately 1 year.[11] The lack of ER, PR and HER2 expression precludes the use of targeted therapies, and the only approved systemic treatment option is chemotherapy. Various chemotherapy regimens (single agent taxane, capecitabine or combinations paclitaxel + gemcitabine, platinum + gemcitabine) are used in first-line therapy for mTNBC; they are associated with an ORR of 25-35%, a modest PFS (median PFS of less than 6 months) and a median OS of less than 12 months.[46] Given the suboptimal outcomes with chemotherapy, new therapies for mTNBC are urgently needed.

**Classification of Immunoresponsiveness of Tumors**

Tumors can be broadly categorized as inflamed or noninflamed.[47,48,49]

Representative images of tumor CD8 Immunohistochemistry (IHC) shows three patterns T cells. Tumors with preexisting immunity are represented by an abundance of tumor infiltrating lymphocytes (TILs), dense functional $CD8^+$ T-cell infiltration reflected by interferon gamma (IFNɤ) signaling, expression of checkpoint markers including PD-L1, and high mutational burden. These characteristics reflect highly inflamed tumors. The collective clinical evidence to date suggests that checkpoint inhibitors largely act by reinvigorating preexisting antitumor T-cell responses and are most effective in inflamed tumors.[50,68,69,70] In a study investigating the relationship between TILs at diagnosis and clinical outcome after anthracycline-based chemotherapy, the results reported significant prognostic association for TNBC but not for luminal breast cancers. Patients with TNBC with at least 50% TILs (10.5% of patients) had a 5-year disease-free survival of 89% compared with 62% in luminal breast cancers ($p = 0.018$, hazard ratio 0.29, 95% confidence interval 0.11–0.81).[71]

PD-1/PD-L1 expression has been studied by various methods in different cancer subtypes.[72] PD-1 and PD-L1 expression in various breast cancer subtypes are summarized in Table 1 below. Triple-negative breast cancer is frequently (70%–100%) infiltrated with PD-1+ TILs. Recent clinical trials have demonstrated that blocking of the PD-1/PD-L1 pathway induces an objective and durable remission in patients with advanced solid tumors.[12,15,73,74,75] The efficacy of these agents has been primarily linked to the expression of PD-L1 in the tumor cells and PD-1 on activated T lymphocytes.[76,77,78,79]

**Table 1. PD-1 and PD-L1 expression in breast cancers, according to the molecular subtype[79]**

| Breast cancer subtypes ($n = 116$) | PD-1 expression/hpf (TILs; % and range) | PD-L1 (tumor cells; %) | Concurrent PD-1 and PD-L1 expression (%) |
|---|---|---|---|
| Luminal tumors ($n = 58$) | | | |
| Luminal A ($n = 33$) | 25% (1–>10) | 33% | 13% |
| Luminal B ($n = 25$) | 44% (1–20) | 33% | 17% |
| HER2 positive ($n = 5$) | 60% (1–9) | 20% | 20% |
| Triple-negative ($n = 53$) | 70% (1–20)[a] | 59%[a] | 45%[a] |

Abbreviation: hpf, high-power fields.
[a]Significantly higher than in luminal tumors.

Immune checkpoint inhibitors in breast cancer: Cytotoxic T-lymphocyte-associated protein 4 is an inhibitory receptor found on $CD8^+$ and $CD4^+$ T cells, and is constitutively expressed on regulatory T cells (Treg cells).[80] CTLA-4 functions to attenuate co-stimulatory signaling by competing with the stimulatory receptor CD28 expressed by T cells for the ligands CD80 and CD86 presented by antigen-presenting cells.[81] The United States (US) Food and Drug Administration (FDA) approved the use of combination of nivolumab and ipilimumab in treatment for patients with unresectable or metastatic melanoma without a proto-oncogene protein B-raf (BRAF) mutation. Very promising Phase I and II trials have been reported on increased activity of the combined blockade of CTLA4 and PD-1, nivolumab and ipilimumab,[82] durvalumab and tremelimumab[83] and pembrolizumab and ipilimumab[84] in NSCLC, with an ORR up to 40% across all the studies.[85] Hence combination therapy with anti-CTLA-4 and anti-PD-1 therapy may also have application in TNBC patients. Several lines of evidence indicate that a greater number of TILs in the tumor stroma is associated with a higher probability of cure in patients with early stage TNBC.[86]

In KEYNOTE-012,[44] a multicenter, nonrandomized Phase 1b trial, the safety and antitumor activity of PD-1 inhibitor pembrolizumab was assessed in patients with heavily pretreated, advanced TNBC. In this trial of 111 TNBC patients whose tumor samples were screened for PD-L1 expression, 58.6% had PD-L1-positive tumors and 32 women were enrolled; single-agent pembrolizumab was given intravenously at 10 mg/kg every 2 weeks to patients with advanced PD-L1–positive tumors. Common toxicities were mild (eg, arthralgia, fatigue, myalgia, and nausea). Among the 27 patients who were evaluable for antitumor activity, the overall response rate was 18.5%.[44]

Part 1 (dose escalation) included participants with advanced NSCLC and mTNBC for whom no standard therapy is available. TNBC will not be included in Part 2 (dose expansion).

## 1.3. VBIR-2

### 1.3.1. Rationale for the Components of VBIR-2

**General Background of T-Cell Activity in Cancer Therapy**

High titers of tumor antigen-specific T cells can be induced by a variety of methods including checkpoint inhibition, genetic modification (chimeric antigen receptor T cells), and ex-vivo stimulation or incubation with antigen and anti-gen presenting cells[51]. Each of these methods has demonstrated the ability to reduce tumor burden in a variety of cancers. In addition to these approaches, a cancer vaccine will also induce large numbers of polyclonal, tumor antigen-associated T cells. It has been shown that using a viral vector carrying tumor-associated antigens, increases in circulating, vaccine-induced T-cells increase after each vaccination, but require multiple boost vaccinations with additional tumor-specific antigens before high T-cell titers can be reached.

Vaccine-induced T cells are expected to be of lower avidity of normal tissues, due to thymic deletion of high-avidity T cells that are specific for self-antigens. The slower induction of T cells by vaccines, along with thymic deletion of high avidity T cells, might explain the good safety profile observed to date in patients treated with cancer vaccines.

**Hypothesis of Increased Anti-tumor Activity with VBIR-2**

To date, anti-tumor activity with current clinical trial vaccines have been encouraging but not yet significantly superior to other clinical immunotherapy trials. We expect VBIR-2 to overcome previous vaccine shortcomings (poor target choice, ineffective vaccine technology, immunosuppressive tumor microenvironment) based on the following design improvements:

(a) Instead of selecting single antigens and in most cases single epitopes as tumor associated antigens (TAAs), VBIR-2 applied a stringent selection and validation process of indication-specific tumor associated antigens (TAAs) (Section 1.3.2). To avert tumor escape and target a broader major histocompatibility complex (MHC) restriction-independent patient population, VBIR-2 encodes three TAA proteins instead of only single-antigen protein or peptides;

(b) To maximize the TAA-specific immunogenicity, a potent heterologous AdC68 prime/pDNA boost vaccination regimen combined with concomitant tremelimumab administration was selected to boost an enhanced induction and expansion of TAA-specific T cells;

(c) To maintain the functionality of TAA-specific T cells in an immunosuppressive tumor microenvironment, sasanlimab injections are given with every vaccine administration. The combination of all four components (vaccine prime, pDNA boost, anti-CTLA-4 tremelimumab, anti-PD-1 sasanlimab) may allow for the induction and maintenance of high titers of durable and functional TAA-specific immune responses.

### 1.3.2. Selection of Vaccine Antigens (MUC1, MSLN, TERT)

A multi-antigen, multi-indication VBIR-2 offers the potential benefit of mitigating the risk of immune escape by the tumor while increasing the likelihood of activating tumor-specific immune responses in a broad patient population. The 3 TAAs (MUC1, MSLN, and TERT) were selected based on the following 2 criteria: 1) Over expression in NSCLC and TNBC tumors in comparison to surrounding healthy tissues (Pfizer Internal Report VR-VTR-10375: Evaluation of MUC1, MSLN and TERT Antigen Expression in Human Tumor Tissues via Immunohistochemical Analysis), and 2) Evidence that cellular and/or humoral immune responses to the selected antigens correlate with clinical activity with acceptable safety profile in the clinic.[37,88,89]

Evidence for selecting the 3 antigens, based on the above criteria, is a follows. Human tumor tissues from different stages of NSCLC (n=100) and TNBC (n=32) and five additional solid tumors spanning different stages including some metastatic tissues were evaluated by IHC. According to the H-score classification using an antigen-specific semi-quantitative IHC assay, positive anti-MUC1 and anti-TERT staining was detected in the majority of NSCLC and TNBC cancer tissues evaluated (94% and 100% of TNBC and 79% and 91% of NSCLC, respectively). Additionally anti-MSLN-staining was detected in 56% of TNBC and 30% of NSCLC tumor tissues analyzed. Consistent with literature, the results confirmed good coverage of the different stages of TNBC and NSCLC by the three antigens.[90] Consequently,

MUC1, MSLN, and TERT were selected as vaccine antigens of VBIR-2. High level expression of these antigens were also found in ovarian and pancreatic cancers suggesting these cancer types as additional promising target indications.

**Antigen Descriptions**

**MUC1 (mucin 1, cell surface associated):** MUC1 is a heavily glycosylated transmembrane protein generally expressed on the epithelial surface of a variety of organs, where it serves a protective function against toxin or pathogen infiltration into internal tissues. MUC1 has been used as a safe vaccine target antigen, and clinical trial results have shown direct correlation between MUC1-specific immunogenicity and clinical activity.[93]

In a Phase 2b part of a randomized, double-blind, placebo-controlled, Phase 2b/3 trial, n = 222 previously untreated patients were enrolled with stage IV NSCLC without a known activating EGFR mutation and with MUC1 expression in at least 50% of tumor cells. Patients were randomized 1:1 to TG4010 vaccine, which delivers full-length human MUC1 and human IL-2 by a recombinant vaccinia virus (n = 111) or placebo (n= 111) from the beginning of chemotherapy every week for 6 weeks and then every 3 weeks up to progression or discontinuation due to toxicity. The median overall survival (mOS) for non-squamous (non-sq) NSCLC was 14.6 months in the vaccine + chemotherapy arm versus 10.8 months in the placebo + chemotherapy arm. No Grade 3 or 4 or serious adverse events were deemed to be related to TG4010 only.

**TERT (telomerase reverse transcriptase):** Human TERT is the catalytic subunit of the telomerase enzyme which functions to increase the number of telomere DNA repeats protecting chromosome ends, extending the replicative capacity of the DNA. In healthy tissues, TERT activity is minimal, ensuring that cells are able to replicate only for a fixed number of times. A few human cell types with increased replication requirements, such as stem cells or germline cells, or activated lymphocytes, show increased TERT expression.[95,96] TERT overexpression is extremely prevalent in almost all cancer types.

In general terms, elevated TERT levels are present in over 85% of tumors where increased cellular life span has been observed.[97] In a clinical trial with canine B cell lymphosarcoma animals, animals that received ChTx plus the canine TERT vaccine demonstrated induction of TERT-specific cellular responses and almost tripled the mOS compared to the ChTx-only control arm.[89] Moreover, in a phase I/II trial with 22 previously treated stage III-IV NSCLC patients, patients showing an increased immune response to the Vx-001 TERT-specific vaccine showed a significantly increased mTTP and mOS.[98] The correlation of anti-TERT immune responses and increased survival, manageable safety profile as well as the expression of TERT on almost all cancers, make TERT an attractive cancer vaccine target. More specifically related to NSCLC, TERT is overexpressed in more than 85% of NSCLC and is associated with poor prognosis.[98] In a recent Phase I/II trial with 22 previously treated stage III-IV NSCLC patients, subjects showing an immune response to the Vx-001 TERT-specific vaccine showed an increased median time to progression (mTTP) and median overall survival (mOS) relative to those with no evidence of T cell response.[37] TERT572 specific T-cell responders had a mTTP of 4.2 months (immune responders, n=16) versus

2.1 months (non-responders, n=5); p=0.046 and a mOS of 30 months (immune responders, n = 16) versus 4.1 months (non-immune responders, n=5); p=0.012.[37] The subcutaneously administered TERT572 peptide vaccine + Montanide was well tolerated with the main toxicity being local skin reactions seen in n=8 (36.4%)of subjects.

**MSLN (mesothelin):** Human MSLN is a glycophosphatidylinositol (GPI)-anchored glycoprotein present on the surface of cells lining the pleura, peritoneum and pericardium, and is involved in cellular recognition and/or adhesion[145]. The MSLN gene encodes a 71-kilodalton (kDa) precursor protein that is processed to a 40-kDa Mesothelin membrane-bound protein and a 31-kDa secreted megakaryocyte potentiating factor (MPF) protein.[90] MSLN is overexpressed in several human tumors including NSCLC (reference IHC Pfizer internal study report VR-VTR-10375), mesothelioma, ovarian, pancreatic adenocarcinoma, and triple-negative breast cancer.[90] In two phase II trials with pancreatic cancer patients, the cancer vaccine (GVAX) pancreatic vaccine induced MSLN-specific cellular responses; the increased response magnitude/or correlated with increased disease-free survival and/or overall survival, making it an attractive cancer vaccine candidate.[88,89] In terms of the amount of MSLN within NSCLC, human tumor tissues from different stages of NSCLC have been evaluated by IHC.[90] According to the H-score classification using an antigen-specific semi-quantitative IHC assay, anti-MSLN-staining was detected in 30% of NSCLC tumors. From the standpoint of clinical utility, a live-attenuated Listeria monocytogene (LM) engineered to express MSLN (CRS-207) was used in a Phase 1 trial, to vaccinate 17 treatment refractory patients (3 with NSCLC) in a dose escalation of up to 4 intravenous doses at 21 day intervals. CRS-207 was well tolerated with 37% of the patient population surviving for >15 months including 2/3 with NSCLC.[146] MSLN specific immune responses recorded and SD reported in 1 NSCLC patient.

**Summary of Components of VBIR-2**

VBIR-2 (PF-06936308) for advanced NSCLC and mTNBC consists of the following components:

1. A priming immunization administered IM with a replication-deficient adenovirus vector derived from chimpanzee that expresses three tumor-associated antigens – MUC1, MSLN, and TERT (AdC68, PF-06871923);

2. Boost vaccinations with plasmid deoxyribonucleic acid (PF-06871925, pDNA), encoding the same three antigens administered IM with an electroporation device [intramuscular TriGrid Delivery System Version 2.0 (TDS-IM) V 2.0];

3. An anti-CTLA4 monoclonal antibody tremelimumab (PF-06753388) given SC in conjunction with each vaccination; and

4. An anti-PD-1 monoclonal antibody sasanlimab (PF-06801591) also given SC in conjunction with each vaccination.

- Part 1 of C3621001 evaluated the safety and tolerability of the vaccine components (AdC68 and pDNA) alone and in combination with increasing doses of tremelimumab and sasanlimab.

- Part 2 (Expansion) of the study will utilize the following doses: AdC68 $6 \times 10^{11}$ VP, 5 mg of pDNA, 80 mg of tremelimumab and 300 mg of sasanlimab.

Tremelimumab will be given locally by SC injection with the priming and boost vaccinations. This monoclonal antibody has been shown to increase responder frequency and enhance the breadth and magnitude of the T-cell response to the selected cancer vaccine antigens.

Sasanlimab, is a humanized, hinge region-stabilized IgG4 monoclonal antibody (mAb) specific for human PD-1 that can selectively and reversibly bind to human PD-1, thereby blocking the interaction between PD-1 and PD-L1/programmed death-ligand 2 (PD-L2). It will be injected subcutaneously at an anatomic location close to the injection sites of the vaccine vector and tremelimumab. The objective of using sasanlimab is to help maintain the activity of VBIR-induced T cells during the activation, expansion, and the intra-turmoral effector phase of antigen-specific T cell responses.

## 1.4. Nonclinical Safety

### 1.4.1. Nonclinical Toxicity Study for VBIR-2

The local and systemic toxicity of AdC68/pDNA+tremelimumab was assessed with and without sasanlimab in sexually mature cynomolgus monkeys. AdC68 ($6 \times 10^{11}$ viral particles (VP)/animal) plus tremelimumab (150 mg/animal) with and without sasanlimab (20 mg/kg) were administered on Day 1 (prime), followed by 2 boost doses of pDNA (5 mg/animal) plus tremelimumab (150 mg/animal) with and without sasanlimab (20 mg/kg) administered 28 and 56 days later. The number of doses is supported by data indicating that the TAA-specific CD8 and CD4 IFNγ T-cell titers reached a plateau following one AdC68 priming dose and two pDNA boosts. Necropsy was conducted 8 and 29 days following the last boost dose administered. The toxicokinetics of sasanlimab and tremelimumab and the immunogenicity of sasanlimab, tremelimumab, TERT, MUC1, and MSLN were evaluated.

The systemic exposure of tremelimumab was higher (~2.6x) in females compared to males, at the fixed dose of 150 mg. The male body weights were ~2.3x those of females (6.9 to 8.8 kg for males and 3.0 to 3.9 kg for females). Therefore, the observed difference in exposure between males and females was attributed to differences in body weight. The systemic exposure of sasanlimab (dose adjusted for body weight; 20 mg/kg) was similar in male and female animals. For tremelimumab, exposure was similar in cynomolgus monkeys administered AdC68/pDNA+tremelimumab alone or with sasanlimab. In general, exposures for both tremelimumab and sasanlimab were lower on Days 29 and 57 compared with Day 1, due to anti-drug antibodies (ADA). The incidence of ADA (on Day 57) to tremelimumab was 60% in cynomolgus monkeys administered AdC68/pDNA+tremelimumab and 90%

when co-administered with sasanlimab. The incidence of ADA to sasanlimab when co-administered with tremelimumab was 100%.

Administration of AdC68/pDNA+tremelimumab alone or with sasanlimab was not associated with any effects on clinical signs, body weights or body weight changes, food consumption, ophthalmology, electrocardiology, body temperature, urinalysis, gross pathology, or organ weights. Injection site reactions were observed on Days 29 and 57 in cynomolgus monkeys administered AdC68/pDNA+tremelimumab alone or with sasanlimab. Following the first dose (Days 3-8) and at the end of the dosing phase, administration of AdC68/pDNA+tremelimumab alone or with sasanlimab was associated with transient, nonadverse changes in clinical pathology parameters including increased lymphocytes, monocytes, basophils, large unstained cells, fibrinogen, globulins, and C-reactive protein compared to control values that were interpreted to be in response to immune stimulation following vaccine administration.

Administration of AdC68/pDNA+tremelimumab alone or with sasanlimab to cynomolgus monkeys was not associated with any macroscopic observations or organ weight changes at the end of the dosing or recovery phases of the study (Days 65 and 86, respectively). Microscopically, AdC68/pDNA+tremelimumab- and/or AdC68/pDNA+tremelimumab+ sasanlimab-related increases in mononuclear cell infiltrates in the pituitary gland, pancreas, heart, urinary bladder, sciatic nerve, and injection sites were observed. This finding was adverse in the pituitary gland of one female treated with AdC68/pDNA+tremelimumab + sasanlimab at the end of the dosing phase due to increased severity and the widespread infiltrative nature of the mononuclear cells; however, no mononuclear cell infiltrates were present in any monkeys treated with AdC68/pDNA+tremelimumab + sasanlimab at the end of the recovery phase (Day 86). Minimal treatment-related nonadverse pituitary gland infiltrates were present in AdC68/pDNA+tremelimumab-treated males at both the end of dosing and end of recovery phase. The female animal noted previously with mononuclear cell infiltrates in the pituitary gland also had nonadverse scattered multifocal perivascular infiltrates of lymphocytes and plasma cells in the pancreas. This female also had the highest exposure to tremelimumab on Days 29 and 57 of the ten animals in the dose group (eg, Area Under the Curve (AUC)= 74,400 µg·h/mL for this female on Day 57, compared with a mean AUC of 20,700 µg·h/mL for the remaining 4 animals in the group), and did not have detectable ADA to tremelimumab at the completion of the dosing period. Exposure to tremelimumab and other anti-CTLA4 or anti-PD-1 inhibitors has been previously associated with pituitary mononuclear cell infiltrates in monkeys and hypophysitis in humans.[52,53] In the heart and urinary bladder, treatment-related mononuclear cell infiltrates were interpreted to reflect an exacerbation of background findings and were fully recovered by the end of the recovery phase on Day 86. The chronic active inflammation observed at the injection sites was reversible and a typical finding related to IM and SC injections.[54,55,56,57,58,59,60,61] Infiltrates in and around the sciatic nerve were minimal and were fully reversed in AdC68/pDNA+tremelimumab -treated monkeys and partially reversed in monkeys treated with AdC68/pDNA+tremelimumab + sasanlimab.

A robust increase in IFN-γ cellular responses to each of the vaccine antigens (MSLN, MUC1 and TERT) and a robust serum immunoglobulin G (IgG) antibody response to both MUC1 and MSLN were seen in all animals in both the AdC68/pDNA+tremelimumab alone or with sasanlimab dose groups post-vaccination.

In summary, administration of a repeat dose (once per 28 days) of AdC68/pDNA+tremelimumab alone or with sasanlimab in sexually mature cynomolgus monkeys was generally well tolerated.

### 1.5. Clinical Overview

Part 1 will enroll up to 40 participants at escalating doses of the VBIR-2 regimen.


The clinical experience with PF-06936308 support the safety and design of Protocol C3621001 and the continuation of the clinical development of PF-06936308 in participants with NSCLC.

### 1.6. Dose Rationale

Below are listed the rationales for the doses of the various components:

#### 1.6.1. Clinical AdC68 (PF-06871923) Dosing

Anticipated efficacy and safety were considered when selecting the AdC68 dose range for clinical testing. The dose ranges of 1 x $10^9$ to 5 x $10^{11}$ VP of a modified adenovirus antigen delivery system have shown a tolerable safety profile in participants with colorectal cancer as well as dose-dependent immune responses to a self-antigen.[62] Previously, high doses of different adenovirus vectors were evaluated preclinically. The absence of germ line transmission was demonstrated in mice and baboons.[63,64] In a separate study in nonhuman primates (NHPs), a dose of 5 x $10^{12}$ VP/kg was found to be well tolerated.[65] Importantly, repeated administration did not appear to alter the toxicity/tolerability profile.[66] It is also important to note that these animals were dosed IV per kg body weight, making the total dose substantially higher than the highest dose planned in this study (6 x $10^{11}$ VP IM total dose).

Furthermore, since the administration in this study is IM, the systemic safety profile is anticipated to be more favorable.[63] Higher doses of adenovirus, up to 2 x $10^{11}$ VP/kg (total dose in excess of 1 x $10^{13}$ VP), when administered directly into the hepatic artery are tolerated in participants with partial ornithine transcarbamylase deficiency.[67]

In the VBIR-2 nonclinical toxicity study (AdC68, pDNA, tremelimumab and sasanlimab ) in monkeys, the safety and VBIR-2 antigen-specific T-cell responses were evaluated following administration of AdC68 at 6 x $10^{11}$ VP using the same dosing frequency as planned for the VBIR-2 Phase 1 study. As described in Section 1.4, findings were limited to the injection sites and the draining lymph nodes, as well as mononuclear cell infiltrates in a number of tissues, consistent with those observed with other anti-CTLA4 or anti-PD-1 inhibitors. Administration of AdC68 at 6 x $10^{11}$ VP with tremelimumab and sasanlimab led to substantial and sustained increases in MUC1-, MSLN-, and TERT-specific IFN-γ T-cell responses, which were further boosted by the pDNA with tremelimumab and sasanlimab treatment. Thus, the AdC68 dose at 6 x $10^{11}$ VP was generally safe and efficacious in inducing immune responses in monkeys.

Based on the above pre-clinical safety and VBIR-2 antigen-specific immune response data in NHPs, and the clinical safety data from the ongoing Prostate Cancer VBIR study (PrCa VBIR)[99] (also using 6 x $10^{11}$ VP administered IM), a dose of 2 x $10^{11}$ VP administered IM has been selected as the starting dose for AdC68 in Part 1 of the study. The highest dose of AdC68 planned to be elevated in this study is 6 x $10^{11}$ VP.

### 1.6.2. Clinical pDNA (PF-0681925) Dosing

Efficacy and safety were factors considered to select the pDNA dose for clinical testing. DNA doses of 0.2 to 8 mg have been reportedly delivered in clinical trials by other sponsors using the Ichor Intramuscular TriGrid Delivery System (TDS-IM) electroporation device. In NHPs, the data collected to date demonstrated that electroporation of a DNA dose of 5 mg can effectively and reproducibly boost AdC68 vector primed IFN-γ CD8 T-cell responses to a self-antigen in the presence of tremelimumab. A pDNA dose of 10 mg was well tolerated but no significant benefit on the magnitude or responder frequency of the IFN-γ CD8 T-cell response was observed (the results are from PrCaVBIR NHP studies; VR-VTR-10228; The Impact of pDNA Dose on Vaccine-Specific Immune Responses at Boost Vaccinations).

Thus, a dose of 5 mg is selected for the pDNA for clinical testing.

### 1.6.3. Clinical Tremelimumab (PF-06753388) Dosing

More than 1000 participants with cancer have been treated with tremelimumab as single-agent or in combination with another anti-cancer treatment. Clinical safety data for tremelimumab, at intravenous (IV) doses ranging from 0.01 to 15 mg/kg, indicate an acceptable safety profile in participants with cancer. The established maximum tolerated dose (MTD) for single-agent therapy is 15 mg/kg IV every 12 weeks, a dose level that has been extensively studied in a Phase 3 trial in participants with melanoma.[101] Diarrhea, pruritus, and rash were the most common treatment-related adverse events (AEs) associated

with tremelimumab. Another important event observed related to tremelimumab was hypopituitarism.

Monthly dosing, as planned for this study, was tested in the clinic in participants with melanoma, where administration of up to 10 mg/kg IV monthly,[102] was tolerated with no dose-limiting toxicity observed. The most frequent treatment-related AEs being diarrhea, rash, and pruritus. Frequency of Grade 3/4 AEs was 27% in the participants dosed with 10 mg/kg tremelimumab alone, compared to 16.3 % in participants treated with nivolumab alone, and 27.3 % of participants treated with ipilimumab alone. Treatment-related adverse events leading to therapy discontinuation occurred in 36.4, 7.7, and 14.8 % of participants, respectively (most commonly diarrhea, fatigue, and pruritus).

### 1.6.4. Clinical Sasanlimab Dosing

Binding of the programmed cell death protein-1 ligands, PD-L1 and PD-L2, to the programmed cell death protein-1 (PD-1) receptor found on T cells inhibits T-cell proliferation, cytokine production, and its cytotoxic functions. Upregulation of PD-1 ligands occurs in certain tumor types, and signaling through this pathway can contribute to the inhibition of active T-cell immune surveillance of tumors.[103] In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth. Approval of nivolumab/Opdivo® (a fully human immunoglobulin G4 [IgG4] anti-PD-1 antibody [Ab]), pembrolizumab/Keytruda® (a humanized IgG4 anti-PD-1 Ab), Atezolizumab/Tecentriq® (a humanized IgG1 anti-PD-L1 Ab), durvalumab/Imfizi® (a humanize IgG1 anti-PD-1 antibody), and avelumab/Bavencio® (a fully human IgG1 anti-PD-L1 Ab) for the treatment of multiple tumor indications provide compelling evidence that blockage of the PD-1 pathway is a validated immunotherapeutic approach (Opdivo® United States Package Insert (USPI), 2020; Tecentriq® USPI, 2019; Keytruda® USPI, 2020; Imfinzi™ USPI, 2020; Bavencio® USPI, 2019).[104,105,106,107,108]

#### 1.6.4.1. Sasanlimab Clinical Experience B8011001 (NCT02573259)

B8011001 is an ongoing Phase 1, open-label, multi-center, multiple-dose, dose escalation and expansion, safety, PK, and PD study of sasanlimab. The primary purpose of this study is to evaluate safety and early signs of efficacy. This clinical study was divided into a dose escalation (Part A) phase and a dose expansion (Part B) phase. One hundred forty-six participants have been dosed on the study. No dose limiting toxicity was observed and there was no maximum tolerated dose identified.

Part A Dose Escalation evaluated 4 pre-specified IV dose levels (0.5, 1, 3, and 10 mg/kg administered every 3 weeks [Q3W]), and 1 subcutaneous (SC) dose level (300 mg administered every 4 weeks [Q4W]) in adult participants with locally advanced or metastatic melanoma, squamous cell cancer of head and neck, ovarian cancer, sarcoma, small cell lung cancer, adenocarcinoma of salivary gland, endometrial adenocarcinoma, malignant peritoneal neoplasm, esophageal adenocarcinoma or renal cell carcinoma. Participants had progressive disease on ≥1 prior line of therapy for locally advanced or metastatic disease or refused standard of care therapy; were not previously treated with an anti-PD-1/PD-L1 agent; and

had adequate renal, bone marrow, liver, and cardiac function, with Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1. Forty participants were enrolled into Part A with 25 participants total enrolled into the IV dose cohorts and 15 participants enrolled into the SC dose cohort.

Part B Dose Expansion evaluated the 300 mg SC dose in a population of 106 participants. This included 68 participants with locally advanced or metastatic non-small cell lung cancer (NSCLC) and 38 participants with locally advanced or metastatic urothelial carcinoma who were anti-PD-1 or anti-PD-L1 treatment-naïve and who had progressive disease on or were intolerant to systemic therapy or for whom standard of care systemic therapy was refused or unavailable. Participants with NSCLC could have received up to 1 line of prior systemic therapy for locally advanced or metastatic disease and if they had known epidermal growth factor receptor (EGFR) activating mutation or an anaplastic lymphoma kinase (ALK) rearrangement were required to have, in addition, at least 1 targeted therapy for their disease. Participants with UC could have received up to 2 lines of prior systemic therapies for locally advanced or metastatic disease. The selected participants had adequate renal, bone marrow, liver, and cardiac function, with ECOG performance status 0 or 1. All participants received 300 mg of sasanlimab SC every 4 weeks.

### 1.6.4.2. Sasanlimab Clinical Experience in B7791001 (NCT#02616185)

B7791001 is a study of a similar vaccine-based immunotherapy regimen in prostate cancer using prostate directed antigens (VBIR PrCA). CCI

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### 1.6.5. Combination of CTLA-4 and PD-1 Monoclonal Antibodies: Safety Findings

Available data suggest that, in both metastatic NSCLC, small-cell lung cancer (SCLC) and melanoma, combined PD-1 and CTLA-4 blockade produce a higher tumor response rate and longer disease control than PD-1 or CTLA-4 blockade alone. Unfortunately, these improved results are associated with an increased rate of toxicity.

In the pretreated NSCLC population, pembrolizumab given iv at 2 or 10 mg/kg every 3 weeks combined with ipilimumab iv either at 1 or 3 mg/kg every 3 weeks for four doses was associated with 49% serious treatment-related adverse event rate, compared to 10% with pembrolizumab monotherapy. The most frequent serious adverse events were diarrhea in 6% and pneumonitis in 8% of participants. The recommended dosage for future trials was pembrolizumab 2 mg/kg plus ipilimumab 1 mg/kg both given every 3 weeks intravenously.[116]

Similarly a combination of nivolumab (anti-PD-1) plus ipilimumab has been tested.[35] Serious treatment-related adverse events were observed in 48% of participants; grade 3–4 adverse events were seen in 55% of participants (most commonly diarrhea, fatigue, and pruritus) compared to 16.3% in participants treated with nivolumab alone, and 27.3 % of participants treated with ipilimumab alone. Combined therapy resulted in 35% of participants discontinuing treatment as compared to 7.7% and 14.8% of participants treated with nivolumab and ipilimumab, respectively.

In a Phase 1b study of durvalumab (anti-PD-1) and tremelimumab, there was an increased rate of serious adverse events of 42%, compared to 8% with durvalumab monotherapy. Durvalumab 20 mg/kg given iv every 4 weeks plus tremelimumab 3 mg/kg iv was more toxic, with an increased rate of diarrhea and colitis, without improved efficacy relative to tremelimumab 1 mg/kg. In participants with tremelimumab 1 mg/kg, most adverse events

were manageable and did not require treatment discontinuation. Overall, treatment-related adverse events and grade 3 or 4 adverse events were more frequent with the regimen of durvalumab 10 mg/kg every 2 weeks plus tremelimumab 1 mg/kg, compared to the regimen with durvalumab 20 mg/kg every 4 weeks plus tremelimumab at 1 mg/kg. Given the above, durvalumab 20 mg/kg every 4 weeks plus tremelimumab 1 mg/kg regimen has been selected for assessment in phase 3 studies.[117,118]

In a study of nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032),[119] two (2) schedules of administration were compared: nivolumab 1 mg/kg plus ipilimumab 3 mg/kg versus nivolumab 3 mg/kg plus ipilimumab 1 mg/kg. The percentage of grade 3 / 4 toxicities was 30% with 3mg/kg ipilimumab and 19% with 1 mg/kg ipilimumab.

Considering the data reported in the literature about the combination anti-PD-1 (or PD-L1) and anti CTLA-4 inhibitors, the dose and frequency of anti CTLA4 appears to be the major determinant of toxicity, compared to dose levels of PD-1 or PD-L1.

### 1.6.6. Clinical Dosing VBIR-2

The proposed VBIR-2 (PF-06936308) clinical dosage, dosage form, route of administration, and dosing regimen are outlined in Table 2. There are 2 treatment phases in VBIR-2:

(a) Active Treatment Phase:

Each VBIR-2 cycle will be initiated with an intramuscular AdC68 priming vaccination accompanied by subcutaneous administrations of tremelimumab and sasanlimab. Three monthly intramuscular pDNA boost vaccinations by electroporation, along with concomitant administrations of tremelimumab and sasanlimab subcutaneously will follow the AdC68 vaccination. The single AdC68 priming vaccination followed by 3pDNA boost vaccinations (each given monthly) concludes 1 treatment cycle of 4 months duration. The second treatment cycle will be initiated with another priming of intramuscular AdC68 vaccination, with later boost vaccinations of pDNA, along with a subcutaneous administration of tremelimumab and sasanlimab, as noted for Cycle 1. The second treatment cycle will follow the same injection schedule as outlined for the first cycle. The activities during the Active Treatment Phase are outlined in the Schedule of Activities for Active Treatment.

(b) Maintenance Treatment Phase:

Following the second treatment cycle the participants enter a “Maintenance Phase”, consisting of monthly doses of sasanlimab with pDNA and tremelimumab, given at every-other-month intervals. A description of this Maintenance Phase is outlined in the Schedule of Activities for maintenance phase.

**Table 2. Expansion Phase Components, Dosage, Dosage Form, Route of Administration, and Dosing Regimen of the Vaccine-Based Immunotherapy Regimen for NSCLC (See Section 5 for detailed Study Treatment instructions.)**

| Component | Dosage Form | Dose | Route of Administration | Dosing Regimen |
|---|---|---|---|---|
| **AdC68** | Liquid | 6e11 VP | Bilateral IM injection | Priming dose (administered on Cycle 1 Day 1) |
| **pDNA*** | Liquid | 5 mg | Bilateral IM injection with electroporation | Every 4 weeks after AdC68 dose for a total of 3 doses |
| **Tremelimumab*** | Liquid | 80 mg | Bilateral SC injection | Every 4 weeks for a total of 4 doses per cycle given on the day of AdC68 or pDNA administration |
| **Sasanlimab**** | Liquid | 300 mg | Bilateral SC injection | Every 4 weeks for a total of 4 doses given on the day of AdC68 or pDNA administration |

**Abbreviations:** AdC68 = Adenovirus C68; IM = Intramuscular; SC = Subcutaneous.
*Maintenance Treatment Schedule for pDNA and tremelimumab after Month 8 will be administered every other month starting with Month 10.
**Maintenance Treatment Schedule for sasanlimab starting at Month 9 will continue to be administered monthly. Treatment will be continued until disease progression, unacceptable toxicity, death, or participant's or investigator's decision.

### (1) Single Reference Safety Document for VBIR-2

Additional information for VBIR-2 may be found in the single reference safety document (SRSD), which for this study is the PF-06936308 Investigator Brochure for: AdC68 (PF-06871923), plasmid DNA (PF-06871925), sasanlimab (PF-06801591) and tremelimumab (PF-06753388).

### (2) Single Reference Safety Document for Intramuscular TriGrid Electroporation Delivery System

The SRSD for the Ichor Intramuscular TriGrid Delivery System electroporation device is the Trigrid™ Delivery System Version 2.0 Investigator Brochure.

Additional reference information can be found in the individual tremelimumab IB and the sasanlimab IB.

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## 2. STUDY OBJECTIVES AND ENDPOINTS

### 2.1. Part 1: Dose Escalation Objectives and Endpoints

| Primary Objective(s): Part 1 | Primary Endpoint(s): Part 1 |
|---|---|
| • To assess safety and tolerability of increasing dose levels of VBIR-2.<br>• To characterize the dose limiting toxicities (DLTs) and overall safety profile of escalated doses of VBIR-2.<br>• To assess safety and tolerability at increasing dose levels of VBIR-2 components in successive cohorts of participants s in order to estimate the Maximum Tolerated Dose (MTD) and select the Recommended Phase 2 Dose (RP2D)/schedule. | • Incidence and grade of treatment-emergent adverse events including DLTs (following the 28-day DLT observation period).<br>• Adverse Events as characterized by type, frequency, severity, timing, seriousness, and relationship to study therapy.<br>• Laboratory abnormalities as characterized by type, frequency, severity, and timing. |
| **Secondary Objective(s):** | **Secondary Endpoint(s):** |
| • To evaluate the PK of tremelimumab and of sasanlimab after SC administration.<br>• To evaluate the anti-drug antibody (ADA) response of tremelimumab and sasanlimab after SC administration with the other components. | • Tremelimumab and sasanlimab single-dose PK parameters, including the maximum concentration ($C_{max}$), time to maximum concentration ($T_{max}$), and if data permit, area under the concentration-time curve (AUC) from time zero extrapolated to infinity (AUC0-∞); and trough concentrations after multiple dosing ($C_{trough}$).<br>• Incidence and titers of ADA and neutralizing antibodies against tremelimumab and against sasanlimab. |

| | |
|---|---|
| • To document any preliminary evidence of anti-tumor activity. | • Objective tumor response, as assessed using the Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1 by calculating the Objective Response Rate (ORR) and Progression-Free Survival (PFS). |

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## 2.2. Part 2: Dose Expansion Objectives and Endpoints

| **Primary Objective(s): Part 2** | **Primary Endpoint(s): Part 2** |
|---|---|
| • To document preliminary evidence of anti-tumor activity using the Clinical Benefit rate (CBR) in participants with NSCLC. | • CBR (proportion of participants who achieve Complete Response, Partial Response or Stable Disease for > 6 months) using the Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1 (Appendix 3). |
| • To assess safety and tolerability of VBIR-2 in participants with NSCLC. | • Adverse Events as characterized by type, frequency, severity, timing, seriousness, and relationship to study therapy.<br>• Laboratory abnormalities as characterized by type, frequency, severity, and timing. |
| **Secondary Objective(s):** | **Secondary Endpoint(s):** |
| • To document preliminary evidence of anti-tumor activity in participants with NSCLC. | • Objective Response Rate (ORR), Duration of Response (DOR) and Progression-Free Survival (PFS) using RECIST version 1.1 (Appendix 3). |
| • To evaluate the PK of tremelimumab and of sasanlimab after SC administration. | • Overall survival (OS).<br>• Tremelimumab and sasanlimab trough concentrations after multiple dosing ($C_{trough}$) at various time points. |
| • To evaluate the anti-drug antibody (ADA) response of tremelimumab and sasanlimab after SC administration with the other components. | • Incidence and titers of ADA and neutralizing antibodies against tremelimumab and against sasanlimab. |

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## 3. STUDY DESIGN

### 3.1. Study Overview

This is a Phase 1, open label, multi-center, multiple dose, safety, PK, PD and immunogenicity study evaluating the components of VBIR-2 (PF-06936308), now solely in participants with advanced or metastatic NSCLC or TNBC.

The study is divided into two parts, Dose Escalation (Part 1) in participants with NSCLC and TNBC without acceptable alternative treatment options, followed by Dose Expansion (Part 2) in participants with NSCLC who have progressed on or after treatment with platinum-based chemotherapy and treatment with ≤1 immune checkpoint inhibitor, given concurrently or sequentially with chemotherapy.

**Dose Escalation (Part 1)**

The Dose Escalation (Part 1) completed its determination of MTD after 6 cohorts. It enrolled 36 participants in Part 1. It included participants for whom no standard therapy was available for advanced or metastatic NSCLC or TNBC, without restrictions as to the prior number of lines of immunotherapy or chemotherapy.

Six dose escalation cohorts were investigated:

- AdC68 2 x $10^{11}$ VP +5 mg pDNA.
- AdC68 6 x $10^{11}$ VP +5 mg pDNA:
  - If needed – dose reduction of the AdC68 dose to 2 x $10^{11}$ VP is allowed.
- AdC68 6 x $10^{11}$ VP +5 mg pDNA +40 mg tremelimumab.*
- AdC68 6 x $10^{11}$ VP +5 mg pDNA +40 mg tremelimumab +130 mg sasanlimab*:
- AdC68 6 x $10^{11}$ VP +5 mg pDNA +40 mg tremelimumab +300 mg sasanlimab;

- AdC68 6 x $10^{11}$ VP +5 mg pDNA +80 mg tremelimumab +300 mg sasanlimab.*

  * If needed – dose reduction of the tremelimumab or sasanlimab dose is allowed.

### 3.1.1. Criteria for Dose Escalation

The principles of modified toxicity probability interval (mTPI) design,[140] will be utilized for the dose escalation portion of the study.

An mTPI design, targeting a DLT rate of 27.5% and an acceptable DLT equivalence interval (22.5% to 32.5%), will be utilized in the dose escalation phase.

The dose levels to be evaluated are given in Figure 1. If a high DLT rate is observed at the starting dose, the study may explore a lower dose or may be stopped.

Each cohort would enroll 2 to 4 DLT evaluable participants and at least 6 and up to 12 participants would be enrolled at a dose level that is predicted to be the MTD as per the mTPI method. Dose cohorts with an acceptable safety profile may be expanded up to N=12 to further assess safety, CCI pharmacokinetics, CCI. Decisions to enroll additional participants at dose levels already cleared for safety will be based on clinical judgment.

The mTPI method relies upon a statistical probability algorithm, calculated using all participants treated in the current dose level to determine one of the following dose-finding decisions: the subsequent dose should be escalated, maintained at the current dose, or de-escalated in the next cohort of 2 to 4 participants, or the trial should be terminated. It is currently envisaged that AdC68 6 x $10^{11}$ VP +5 mg pDNA +150 mg tremelimumab +300 mg ANTI-PD-1 (PF-06801591) will potentially be the highest dose level.

**Table 3. Decision Rules**

Number of participants treated at current dose

| #DLTs | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 | E | E | E | E | E | E | E | E | E | E | E | E |
| 1 | D | S | S | S | E | E | E | E | E | E | E | E |
| 2 | | U | D | S | S | S | S | S | S | S | E | E |
| 3 | | | U | U | D | D | S | S | S | S | S | S |
| 4 | | | | U | U | U | U | D | S | S | S | S |
| 5 | | | | | U | U | U | U | U | D | S | S |
| 6 | | | | | | U | U | U | U | U | U | U |

- Columns indicate number of participants in the cohort and rows indicate number of participants with DLTs
- E= Escalate to the next higher dose; S: Stay at the same dose; D: De-escalate to the previous lower dose; U: De-escalate to the previous lower dose and the current dose will never be used again in the trial

If a participant discontinues close to Day 28 for reasons other than toxicity and due to an evident non drug-related event, the participant may be deemed evaluable for safety if safety assessments have been unremarkable and the investigator and sponsor's medical monitor both agree that the participant is evaluable for DLT safety observation.

The dose escalation Part 1 of the study will stop if any of the following criteria is met:

The maximum sample size has been achieved (approximately 36 participants in total as per the current dosing schedule);

6 to 12 participants have been enrolled at a dose level that is predicted to be the MTD according to Table 3;

All dose levels explored appear to be overly toxic, and the MTD cannot be determined;

All candidate dose levels have been tested and deemed safe.

As an example, if the total number of participants (cumulative in the study) treated at the current dose is 4, the following dosing rules are applied:

0-1 DLT -> escalate;

1 DLT -> remain at the same dose;

2 DLTs -> De-escalate to the previous or intermediate lower dose;

3-4 DLTs -> De-escalate and consider current dose as intolerable.

Activation of each cohort will occur no sooner than 28 days after the first 2-4 participants receive the first AdC68 vaccination, but may occur later if the sponsor and investigators determine additional safety data is needed. The Pfizer clinical team and investigators will review all available safety data from the previous and current cohorts prior to making a decision to dose escalate. If no safety issues that would prohibit dose escalating are observed, the next cohort of participants would be open for accrual.

If dose escalation continues up to a predefined Maximum Feasible Dose (MFD), the escalation is halted without a maximum tolerated dose (MTD) estimate. In those circumstances, the MFD may be the recommended Phase 2 dose (RP2D).

### 3.1.2. Dose Expansion (Part 2)

The Expansion Phase will enroll participants in 1 cohort of participants with metastatic or locally-advanced NSCLC who have previously received treatment with a platinum-based chemotherapy regimen and not more than one treatment with an immune checkpoint inhibitor regimen either concurrently or sequentially with the chemotherapy.

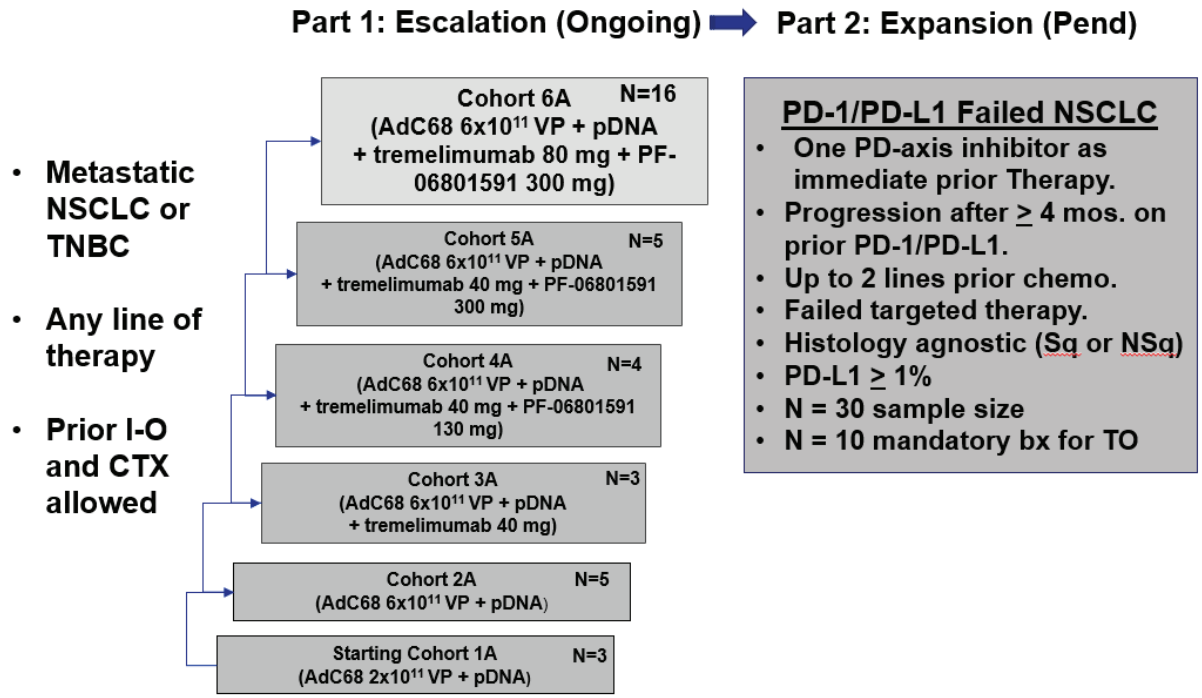
Participants will participate in the active treatment period of the study for approximately 9 months. This includes a 28 day screening period followed by 2 cycles of vaccine treatment, totaling 8 months in duration. After completion of the active treatment phase (vaccine prime, pDNA boosts, checkpoint inhibitor support), participants will then enter the maintenance phase of the study (pDNA boosts only with checkpoint inhibitor support).

Treatment will continue until: disease progression, unacceptable toxicity, death or participant's or investigator's decision occurs. Since the treatment effect of cancer immunotherapy can often be delayed, participants will be encouraged to continue on study treatment for at least 24 weeks before an investigator considers removing the participant due to disease progression, as long as (a) Participant and investigator agree; (b) Participant continues to meet all other study protocol eligibility criteria; (c) Toxicity remains acceptable; and (d) No deterioration of participant performance status. Disease progression will be confirmed with 2 consecutive timepoints at least 4-8 weeks apart in the absence of rapid clinical deterioration.

Participants who demonstrate clinical benefit with manageable toxicity and who are willing to continue receiving study treatment will be given the opportunity to continue treatment upon agreement between the investigator and sponsor. When the participant discontinues treatment, they will then enter a 6 month post-dose follow-up period to assess safety CCI [redacted] The end of the study is the last participant last visit.

The overall design is presented in Figure 1 below:

**Figure 1. Study Design**



### 3.2. DLT Definition

Severity of adverse events (AEs) will be graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. For the purpose of dose escalation, any of the following AEs occurring in the first 28 days following the first AdC68 vaccination that are considered possibly related to study treatment and are not considered related to disease/progression will be classified as DLTs:

Hematologic:

- Grade ≥3 neutropenia lasting >7 days.
- Febrile neutropenia (febrile neutropenia is defined as an absolute neutrophil count $<1.0 \times 10^9$/L with a single temperature of >38.3°C, or 101°F, or a sustained temperature of ≥38°C, or 100.4°F, for more than one hour).
- Grade ≥3 neutropenic infection.
- Grade ≥3 thrombocytopenia with ≥ Grade 2 clinically significant bleeding (for bleeding events with no grading available, clinically significant bleeding is defined as requiring hospitalization or urgent medical intervention).
- Grade ≥3 anemia lasting more than 7 days.
- Grade ≥3 lymphopenia lasting more than 14 days.

Nonhematologic:

- Grade ≥3 AEs that are considered non-hematologic, non-hepatic major organ toxicity (excluding alopecia of any grade; Grade 3 nausea/vomiting or diarrhea <72 hours with adequate antiemetic and other supportive care; ≥ Grade 3 electrolyte abnormality that lasts <24 to 72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical interventions).
- Grade 3 flu-like symptoms lasting greater than 3 days with adequate treatment.
- Fever of >40.0°C, or 104.0°F, lasting for more than 3 days with adequate treatment.
- Concurrent aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3x upper limit of normal (ULN) and total bilirubin >2x ULN (potential Hy's law case).
- Nonhematologic laboratory abnormalities: Grade ≥3 laboratory abnormalities either associated with symptoms or associated with worsening of an existing condition or that suggests a new disease process or that requires additional active management (eg, discontinuation of the drug, close observation, more frequent follow-up

assessments, further diagnostic investigation or specific treatment).In addition, clinically important or persistent toxicities that are not included in the above criteria may be considered a DLT following review by Pfizer and the investigators. All DLTs need to represent a clinically significant shift from baseline.

The following AEs will not be adjudicated as DLTs:

- Isolated Grade 3 laboratory abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of onset.

### 3.3. MTD Definition

The MTD is defined as the highest dose with true toxicity probabilities in the equivalence interval (EI) where the EI is defined as (22.5%, 32.5%).

Even though the mTPI model may select an MTD with an incidence of DLTs that is higher than 32.5% since mTPI decision rules are based on unit probability mass (UPM) and not on point estimates of the DLT rate (see Section 9.2.1), doses with an incidence of DLT >32.5% (eg, 3 out of 9) cannot be declared as the MTD. In practice, model recommendations may be overridden by clinical judgment, and MTD with an incidence of DLTs that is higher than 32.5% will not be considered acceptable to be selected as MTD.

### 3.4. Toxicities Observed in the Expansion Phase

Adverse events that meet the same grading criteria as the DLT criteria listed above will be discussed promptly by Pfizer and Investigators during the next available Safety meeting. At the meeting, the details of the toxicity will be presented, and actions to be taken (if any) will be discussed, which may involve individual participants, or the Expansion Cohort as a whole.

### 3.5. Recommended Part 2 Expansion Dose Definition

The RP2D is the dose chosen for further investigation based on Phase 1 study results. If the MTD proves to be clinically feasible for long-term administration in a reasonable number of participants, then this dose usually becomes the RP2D. Further experience with the MTD may result in a RP2D dose lower than the MTD.

The Expansion Dose recommended for Part 2 is: AdC68 $6 \times 10^{11}$ VP, 5 mg of pDNA, 80 mg of tremelimumab and 300 mg of sasanlimab.

## 4. PARTICIPANT ELIGIBILITY CRITERIA

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 particular participant is suitable for this protocol.

## 4.1. Inclusion Criteria

Participant eligibility should be reviewed and documented by an appropriate member of the investigator's study team before participants are included in the study.

Participants, for each assigned part, must meet all of the following inclusion criteria to be eligible for enrollment in the study:

### 4.1.1. Part 1 Inclusion Criteria

1. Histological or cytological diagnosis of advanced NSCLC or metastatic TNBC (defined as HER2 negative by IHC, fluorescence in situ hybridization (FISH) or chromogenic in situ hybridization (CISH) and ≤10% ER/PR stain positive by IHC) with progressive disease that is resistant to standard therapy or for which no standard therapy is available or is refused by the participant.

2. A mandatory archived formalinfixed paraffin embedded (FFPE) tumor tissue block (preferred) must be provided. If an FFPE tumor tissue block cannot be provided, sites should contact sponsor for approval to submit slides. For Part 1, if an archived FFPE tissue is not available, a de novo (ie, fresh) tumor sample can substitute and should be obtained in accordance with local institutional practice for tumor biopsies.

3. Females and/or male participants age ≥18 years.

4. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0 or 1.

5. Measurable disease as per RECIST v. 1.1.

6. Adequate Bone Marrow Function, including:

    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.

7. Adequate Renal Function, including:

    a. Estimated creatinine clearance ≥60 mL/min as calculated using the method standard for the institution. In unequivocal cases, a 24 hour urine can be collected and used to estimate the creatinine clearance more accurately.

8. Adequate Liver Function, including:

    a. Total serum bilirubin ≤1.5 x ULN unless the participant has documented Gilbert syndrome;

b. Aspartate and Alanine aminotransferase (AST and ALT) ≤2.5 x ULN; ≤5.0 x ULN if there is liver involvement by the tumor;

c. Alkaline phosphatase ≤2.5 x ULN (≤5 x ULN in case of bone metastasis).

9. Resolved acute effects of any prior therapy to baseline severity or National Cancer Institute (NCI) CTCAE V5.0 Grade ≤1 except for adverse events (AEs) not constituting a safety risk by investigator judgment.

10. Serum or urine pregnancy test (for females of childbearing potential) negative at screening.

11. Female participants of nonchildbearing potential must meet at least 1 of the following criteria:

- Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed with a serum follicle-stimulating hormone (FSH) level confirming the postmenopausal state;
- Have undergone a documented hysterectomy and/or bilateral oophorectomy;
- Have medically confirmed ovarian failure.

All other female participants (including female participants with tubal ligations) are considered to be of childbearing potential.

12. Evidence of a personally signed and dated informed consent document indicating that the participant [or a legally acceptable representative/parent(s)/legal guardian] has been informed of all pertinent aspects of the study].

13. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other procedures.

### 4.1.2. Part 2 Inclusion Criteria

1. Histological or cytological diagnosis of locally advanced or metastatic NSCLC (squamous or non-squamous histology) meeting the following criteria:

a. Receipt of at least 1, but not more than 2, prior treatment regimens in the advanced disease setting. In addition to participants with established metastatic or recurrent disease, the advanced disease setting also includes participants with platinum-based adjuvant, neoadjuvant, or definitive chemoradiation therapy given for locally advanced disease followed by recurrent or metastatic disease within 6 months of completing therapy.

b. Prior treatment must have included an anti-PD-1/PD-L1 and a platinum-based chemotherapy, which may have been given in combination, or sequentially;

c. Prior treatment must have included an appropriate TKI if activating mutations are present, eg, EGFR/ALK/ROS1/BRAF/RET/TRK;

d. Most recent treatment must have included anti-PD-1/PD-L1 for at least 4 months, without radiographic disease progression, followed by confirmed radiographic disease progression on or within 12 weeks of the last dose;

e. No more than 1 prior anti-PD-1/PD-L1 treatment regimen may have been given;

f. Prior anti-PD-1/PD-L1 may not have been discontinued permanently for toxicity.

g. No prior treatment may have been given with any immunologic therapy other than anti PD-1 or PD-L1.

2. A mandatory archived formalinfixed paraffin embedded (FFPE) tumor tissue block (preferred) must be provided. If an FFPE tumor tissue block cannot be provided, sites should contact sponsor for approval to submit slides. If an archived FFPE tissue is not available, a de novo (ie, fresh) tumor sample can substitute and should be obtained in accordance with local institutional practice for tumor biopsies.

3. Females and/or male participants age ≥18 years.

4. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0 or 1.

5. Measurable disease as per RECIST v. 1.1.

6. Adequate Bone Marrow Function, including:

   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.

7. Adequate Renal Function, including:

   a. Estimated creatinine clearance ≥60 mL/min as calculated using the method standard for the institution. In unequivocal cases, a 24 hour urine can be collected and used to estimate the creatinine clearance more accurately.

8. Adequate Liver Function, including:

   a. Total serum bilirubin ≤1.5 x ULN unless the participant has documented Gilbert syndrome;

b. Aspartate and Alanine aminotransferase (AST and ALT) ≤2.5 x ULN; ≤5.0 x ULN if there is liver involvement by the tumor;

c. Alkaline phosphatase ≤2.5 x ULN (≤5 x ULN in case of bone metastasis).

9. Resolved acute effects of any prior therapy to baseline severity or National Cancer Institute (NCI) CTCAE V5.0 Grade ≤1 except for adverse events (AEs) not constituting a safety risk by investigator judgment. Participants with hypothyroidism or hypopituitarism resulting from immunotherapy who are stable on chronic hormone replacement therapy are eligibile, as are participants with adrenal insufficiency receiving doses <15mg/day or prednisone.

10. Serum or urine pregnancy test (for females of childbearing potential) negative at screening.

11. Female participants of nonchildbearing potential must meet at least 1 of the following criteria:

    - Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed with a serum follicle-stimulating hormone (FSH) level confirming the postmenopausal state;
    - Have undergone a documented hysterectomy and/or bilateral oophorectomy;
    - Have medically confirmed ovarian failure.

    All other female participants (including female participants with tubal ligations) are considered to be of childbearing potential.

12. Evidence of a personally signed and dated informed consent document indicating that the participant or a legally acceptable representative has been informed of all pertinent aspects of the study].

13. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other procedures.

### 4.2. Part 1 Exclusion Criteria

Participants, for each assigned part, with any of the following characteristics/conditions will not be included in the study:

#### 4.2.1. Part 1 Exclusion Criteria

1. Participants with known symptomatic brain metastases, with the following two exceptions:

a. Participants with previously diagnosed brain metastases are eligible if they have completed their treatment and have recovered from the acute effects of radiation therapy or surgery prior to study entry, have discontinued corticosteroid treatment for these metastases for at least 4 weeks and are neurologically stable for 3 months (confirmed by MRI)

b. Participants with newly diagnosed brain metastases identified by a screening brain MRI who are clinically asymptomatic are eligible if the Investigator deems their clinical status acceptable for participation in the trial and all other inclusion and exclusion criteria are satisfied, including being neurologically stable for 3 months since the screening brain MRI. A baseline MRI at screening is to be conducted only if clinically indicated based on the treating Investigator's judgement

2. History of prior malignancy other than the disease under study within the past 3 years excluding successfully resected treated basal cell carcinoma or squamous cell carcinoma of the skin or adequately treated carcinoma in situ.

3. Participants with intolerance to or who have had (Grade ≥3) allergic or anaphylactic reaction to antibodies or infused therapeutic proteins.

4. Major surgery within 4 weeks prior to study entry.

5. Radiation therapy within 4 weeks prior to study entry.

6. Systemic anticancer therapy within 4 weeks prior to study entry.

7. Participant has AE(s) due to cancer therapeutics administered >4 weeks earlier, which have not recovered to CTCAE Grade ≤1 (except alopecia, and except for AEs not constituting a safety risk by investigator judgment).

8. Active and clinically significant bacterial, fungal, or viral infection, including hepatitis B virus (HBV), hepatitis C virus (HCV), known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)related illness.

   HIV seropositive participants, who are healthy and low-risk for AIDS-related outcomes,[143] may qualify for inclusion in the study after discussion with the Sponsor.

   The following criteria for immune status and HIV ongoing therapy must be met for a HIV seropositive participant to be eligible for the study:

   a. Immune status criteria:

      - $CD4^+$ T-cell counts ≥350 cells/μL at the study start;
      - No history of AIDS-defining opportunistic infections;

- Only remote AIDS-defining opportunistic infections in the past and none in one year prior to study start.

b. Ongoing HIV therapy criteria:

- Must be receiving recommended concurrent ART treatment according to NIH guidelines;[144]

- Began ART treatment >4 weeks prior to study start (to ensure ART is tolerated and toxicities are not confused with study drug toxicities);

- HIV viral load <400 copies/mL for >4 weeks prior to study start (to ensure ART is tolerated and HIV controlled).

Anti-retroviral medications should be listed as concomitant medication.

Equivocal cases of viral hepatitis may be eligible if they have a negative viral load.

9. Receipt of an immunosuppressive dose of corticosteroids (ie, 10 mg prednisone daily or equivalent) or other immunosuppressive medication (eg, methotrexate, rapamycin) within 2 weeks of registration. Note: Participants with adrenal insufficiency may take 5 mg of prednisone or equivalent daily. Topical applications, inhaled sprays, eye drops or local injections of corticosteroids are allowed. Low dose corticosteroids for a short duration [5 mg once daily (QD) prednisone for 2 weeks] as symptomatic treatment and upon with discussion with the sponsor is allowed.

10. History of or active autoimmune disorders (including but not limited to: myasthenia gravis, thyroiditis, pneumonitis, rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, scleroderma) and other conditions that disorganize or alter the immune system. Active inflammatory gastrointestinal disease, Crohn's disease, ulcerative colitis, and primary sclerosing cholangitis are excluded, however, gastroesophageal reflux disease under treatment with protonpump inhibitors is allowed (assuming no drug interaction potential).

11. Acetylcholine receptor binding antibody ≥0.5 nmol/L.

12. Abnormal neurologic examination at screening indicating possible underlying autoimmune disorder(s).

13. Any of the following in the previous 12 months or currently: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident, transient ischemic attack or symptomatic pulmonary embolism, as well as ongoing cardiac dysrhythmias of NCI CTCAE Grade ≥2, atrial fibrillation or any grade, or QTc interval >470 msec at screening.

14. Individuals in whom a skin-fold measurement of the cutaneous and subcutaneous tissue for two or more eligible injection sites exceeds 50 millimeters (mm).

15. Bleeding diathesis or condition associated with prolonged bleeding time that would contraindicate IM injection.

16. Current use of any implanted electronic stimulation device, such as cardiac demand pacemakers, automatic implantable cardiac defibrillator, nerve stimulators, or deep brain stimulators.

17. Presence of any surgical or traumatic metal implants at the site of administration (medial deltoid muscles or overlying skin or vastus lateralis muscle).

18. Hypertension that cannot be controlled by medications (>150/100 mmHg despite optimal medical therapy).

19. Participation in other studies involving investigational drug(s) within 4 weeks prior to study entry.

20. Known or suspected hypersensitivity to any of the VBIR-2 components.

21. 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.

22. COVID-19/SARS-CoV2: SARS-CoV2 testing is not mandated for entry into this protocol. However, testing should follow local clinical practice standards and requirements. A positive result on an approved test, even if the participant is asymptomatic, excludes a participant from this trial.

23. 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.

*24.* Fertile male participants and female participants of childbearing potential who are unwilling or unable to use 2 highly effective methods of contraception as outlined in this protocol for the duration of the study and for at least 5 months after the last dose of investigational product *[per Section 4.3 below]*.

### 4.2.2. Part 2 Exclusion Criteria

Participants with any of the following characteristics/conditions will not be included in the study:

1. Participants with known symptomatic brain metastases, with the following 2 exceptions:

    a. Previously Diagnosed Brain Metastases: Participants with previously diagnosed brain metastases are eligible if (a) they have completed their treatment and have recovered from the acute effects of radiation therapy or surgery prior to study entry, (b) have discontinued corticosteroid treatment for these metastases for at least 4 weeks and are neurologically stable for 3 months (confirmed by MRI).

    b. Screening-Detected Brain Metastases: Participants with newly diagnosed brain metastases identified by a screening brain MRI who are clinically asymptomatic are eligible if (a) the Investigator deems their clinical status acceptable for participation in the trial and (b) all other inclusion and exclusion criteria are satisfied, including being neurologically stable for 3 months since the screening brain MRI. A baseline MRI at screening is to be conducted only if clinically indicated, based on the treating Investigator's judgement.

2. History of prior malignancy other than the disease under study within the past 3 years excluding successfully resected treated basal cell carcinoma or squamous cell carcinoma of the skin or adequately treated carcinoma in situ.

3. Participants with high-volume or visceral spread of disease, or those who are symptomatic from their disease, such that they are at risk for life threatening complications in the short term. Examples include participants with uncontrolled pleural, pericardial, or peritoneal effusions; pulmonary lymphangitis; and over 50% liver involvement. Note: Participants with indwelling catheter(s) for drainage, or requirement for intermittent drainage no more frequently than monthly, will be considered eligible.

4. Participants with intolerance to or who have had (Grade ≥3) allergic or anaphylactic reaction to antibodies or infused therapeutic proteins.

5. Major surgery within 4 weeks prior to first dose.

6. External beam radiation therapy to large areas of the thorax or other sites within 4 weeks prior to first dose; focal, palliative radiation within 2 weeks of first dose.

7. Systemic anticancer therapy within 2 weeks prior to first dose.

8. Participant has AE(s) due to cancer therapeutics administered >4 weeks earlier, which have not recovered to CTCAE Grade ≤1 (except alopecia, and except for AEs not constituting a safety risk by investigator judgment).

9. Active and clinically significant bacterial, fungal, or viral infection, including hepatitis B virus (HBV), hepatitis C virus (HCV), known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS) related illness.

   HIV seropositive participants, who are healthy and low-risk for AIDS-related outcomes,[143] may qualify for inclusion in the study after discussion with the Sponsor.

   The following criteria for immune status and HIV ongoing therapy must be met for a HIV seropositive participant to be eligible for the study:

   a. Immune status criteria:

      - $CD4^+$ T-cell counts ≥350 cells/μL at the study start;
      - No history of AIDS-defining opportunistic infections;
      - Only remote AIDS-defining opportunistic infections in the past and none in 1 year prior to study start.

   b. Ongoing HIV therapy criteria:

      - Must be receiving recommended concurrent ART treatment according to NIH guidelines;[144]
      - Began ART treatment >4 weeks prior to study start (to ensure ART is tolerated and toxicities are not confused with study drug toxicities);
      - HIV viral load <400 copies/mL for >4 weeks prior to study start (to ensure ART is tolerated and HIV controlled).

   Anti-retroviral medications should be listed as concomitant medication.

   Equivocal cases of viral hepatitis may be eligible if they have a negative viral load.

10. Receipt of an immunosuppressive dose of corticosteroids (ie, 10 mg prednisone daily or equivalent) or other immunosuppressive medication (eg, methotrexate, rapamycin) within 2 weeks of registration. Note: Participants with adrenal insufficiency may take 5 mg of prednisone or equivalent daily. Topical applications, inhaled sprays, eye drops or local injections of corticosteroids are allowed. Low dose corticosteroids for a short duration [5 mg once daily (QD) prednisone for 2 weeks] as symptomatic treatment and upon with discussion with the sponsor is allowed.

11. History of or active autoimmune disorders (including but not limited to: myasthenia gravis, thyroiditis, pneumonitis, rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, scleroderma) and other conditions that alter the immune system. Active inflammatory gastrointestinal disease, Crohn's disease, ulcerative colitis, and

primary sclerosing cholangitis are excluded; however, non-immune mediated gastroesophageal reflux disease (esophagitis/gastritis) under treatment with proton pump inhibitors is allowed (assuming no drug interaction potential).

12. Acetylcholine receptor binding antibody ≥0.5 nmol/L.

13. Abnormal neurologic examination at screening indicating possible underlying autoimmune disorder(s).

14. Any of the following in the previous 12 months or currently: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident, transient ischemic attack or symptomatic pulmonary embolism, as well as ongoing cardiac dysrhythmias of NCI CTCAE Grade ≥2, atrial fibrillation of any grade, or QTc interval >470 msec at screening.

15. Cardiac Troponin-I (cTnI) must be measured and found to be within the normal reference range before the administration of the first dose. Abnormal circulating levels of cTnI are exclusionary.

16. Individuals in whom a skin-fold measurement of the cutaneous and subcutaneous tissue for 2 or more eligible injection sites exceeds 50 millimeters (mm).

17. Bleeding diathesis or condition associated with prolonged bleeding time that would contraindicate IM injection.

18. Current use of any implanted electronic stimulation device, such as cardiac demand pacemakers, automatic implantable cardiac defibrillator, nerve stimulators, or deep brain stimulators.

19. Presence of any surgical or traumatic metal implants at the site of administration (medial deltoid muscles or overlying skin or vastus lateralis muscle).

20. Hypertension that cannot be controlled by medications (>150/100 mmHg despite optimal medical therapy).

25. Severely symptomatic Chronic Obstructive Pulmonary Disease (eg, requiring ambulatory oxygen).

21. Participation in other studies involving investigational drug(s) within 4 weeks prior to study entry.

22. Known or suspected hypersensitivity to any of the VBIR-2 components.

23. 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.

24. COVID-19/SARS-CoV2: SARS-CoV2 testing is not mandated for entry into this protocol. However, testing should follow local clinical practice standards and requirements. A positive result on an approved test, even if the participant is asymptomatic, excludes a participant from this trial.

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.

26. Fertile male participants and female participants of childbearing potential who are unwilling or unable to use 2 highly effective methods of contraception as outlined in this protocol for the duration of the study and for at least 5 months after the last dose of investigational product *[per* Section 4.3 *below]*.

### 4.3. Lifestyle Requirements (Part 1 and Part 2)

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 (see list below) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the Schedule of Activities, the investigator or designee will inform the participant of the need to use 2 highly effective methods of contraception consistently and correctly and document the conversation, and the participant's affirmation, in the participant's chart. In addition, the investigator or designee will instruct the participant to call immediately if 1 or both of the selected contraception methods is discontinued or if pregnancy is known or suspected in the participant or partner.

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.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include:

1. Correctly placed copper-containing intrauterine device (IUD).

2. Male condom or female condom used WITH a spermicide (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.

3. Male sterilization with absence of sperm in the postvasectomy ejaculate.

4. Bilateral tubal ligation/ bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

    a. All sexually active male participants must agree to prevent potential transfer to and exposure of partner(s) to drug through ejaculate by using a condom consistently and correctly, beginning with the first dose of investigational product and continuing for; at least 5 months after the last dose of [investigational product OR comedication].

### 4.4. 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 supporting Study Manual and in the team SharePoint Site.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with an Emergency Contact Card (ECC). The ECC contains, at a minimum, (a) Protocol and investigational product identifiers; (b) Participant study numbers; (c) At least 2 emergency phone numbers, active 24 hours/day, 7 days/week, all holidays and weekends, providing a method to contact both the Principal Investigator and the Research Site; and (d) a Pfizer Call Center number.

The ECC is to be used only by outside medical personnel, not involved in the research study, primarily as a means of contacting the Principal Investigator or Research Site related to the care of a study participant. The Pfizer Call Center information is to be used only in the event that, after calling the phone numbers of both the Principal Investigator and Research Site Staff, neither could not be reached in case of an Emergency.

The ECC should be used only in the event that the established communication pathways between the Principal Investigator, the Research site, and the Study Team are not available. Importantly, the ECC is intended to augment, and not to replace, the established communication pathways between the Principal Investigator, the Research site, and the Study Team for advice on medical issues arising during the study. The ECC is not intended for use by the participant directly; if a participant calls the Pfizer Call Center directly, the participant will be directed back to the Principal Investigator or Research site.

## 5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonisation (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference/comparator in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

For this study, the investigational product VBIR-2 (PF-06936308) consists of:

| Reagent | PF # |
|---|---|
| AdC68, an adenovirus prime vaccination | PF-06871923 |
| pDNA, aPlasmid DNA boost vaccination | PF-06871925 |
| Tremelimumab, an CTLA4 monoclonal antibody | PF-06753388 |
| Sasanlimab, an anti-PD-1 monoclonal antibody | PF-06801591 |

### 5.1. Allocation to Treatment

Eligible participants will be enrolled to receive components of VBIR-2 in an open-labeled, unblinded manner. In Part 1, participants will be successively assigned to the next available treatment slot at a dose level decided on after the previous cohort's safety evaluation and ongoing observations of earlier enrolled participants.

Dose level allocation will be performed by the sponsor after participants have given their written informed consent and have completed the necessary baseline assessments. The site staff will email a completed Registration Form to the designated sponsor study team member. The sponsor will assign a participant identification number documenting participant enrollment.

No participant shall receive investigational product until the investigator or designee has received the following information in writing from the sponsor:

- Confirmation of the participant's enrollment;
- Specification of the dose level for that participant;
- Permission to proceed with dosing the participant.

The sponsor or designee will notify the other sites of the inclusion of a new participant, and will inform study sites about the next possible enrollment date.

### 5.2. Participant Compliance

All doses of adenovirus, pDNA, tremelimumab and sasanlimab will be administered by the appropriately designated study staff at the investigational site. 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.

Participants who fail to comply with the study requirements may be withdrawn from the study.

## 5.3. Investigational Product Supplies

All components of VBIR-2 will be supplied by Pfizer. VBIR-2 consists of the following components: Adenovirus (AdC68), plasmid DNA (pDNA), tremelimumab and sasanlimab. Sites will be provided with the following supplies:

- PF-06871923 AdC68 Solution for Injection 3 x $10^{11}$ VP/mL;
- PF-06871925 pDNA Solution for Injection 2.5 mg/mL;
- PF-06753388 Tremelimumab Solution for Injection 100 mg/mL;
- TDS-IM V 2.0 electroporation device and associated supplies (eg, cartridges) for pDNA administration;
- PF-06801591 Sasanlimab Solution for Injection 50 mg/mL.

Study centers will receive a supply of clinical trial materials upon site activation with instructions on how to confirm drug receipt. Resupplies will be made during the course of the study based on need. Study centers will supply commonly available sterile syringes and needs for IM and SC administration. The details on drug supply will be provided in the Investigational Product Manual (IP Manual). The study monitor should be contacted for any issues related to drug supplies.

### 5.3.1. Dosage Form(s) and Packaging

PF-06871923 AdC68 Solution for Injection is presented as a sterile solution for intramuscular administration. Each vial contains AdC68 at 3 x $10^{11}$ VP/mL in an aqueous buffered solution. Each vial is filled with an adequate volume to eject a minimum 1.0 mL from a syringe with an IM needle attached. The vial is sealed with a stopper and an overseal and labeled according to local regulatory requirements. Two vials will be dispensed per participant, regardless of dose, to facilitate bilateral injection.

PF-06871925 pDNA Solution for Injection, 2.5 mg/mL, is presented as a sterile solution for intramuscular administration. Each glass prefilled syringe (PFS) contains pDNA at 2.5 mg/mL in aqueous buffered solution. The PFS is filled with an adequate volume to eject 1.0 mL when administered using the TDS-IM V 2.0 electroporation device. The PFS is sealed with a plunger stopper and a tip cap and labeled according to local regulatory requirements. Two (2) prefilled syringes will be dispensed per participant.

Each TDS-IM V 2.0 6mm Application cartridge, for unique use, for intramuscular administration of the pDNA solution will be supplied in a sterile tray (one cartridge/tray) labeled according to local regulatory requirements.

PF-06753388 Tremelimumab Solution for Injection is presented as a sterile solution. Each vial contains tremelimumab at 100 mg/mL in aqueous buffered solution. The vial is filled with an adequate volume to eject a minimum 0.75 mL from a syringe with a SC needle

attached. The vial is sealed with a stopper and an overseal and labeled according to local regulatory requirements. Two vials will be dispensed per participant, regardless of dose, to facilitate bilateral injection.

PF-06801591 Sasanlimab Solution for Injection 50 mg/mL is presented as a sterile solution. Each vial contains 100 mg of sasanlimab in 2 mL of aqueous buffered solution, and contains a sufficient amount to ensure an extractable volume of 2 mL. Each vial is sealed with a stopper and an overseal, and labeled according to local regulatory requirements.

### 5.3.2. Preparation and Dispensing

AdC68, tremelimumab and sasanlimab are provided as single use vials; pDNA is provided as a single use prefilled syringe. They will be packaged and dispensed in cartons with tamper evident seals. The cartons should not be opened until the drug is to be administered. For the adenovirus, pDNA, tremelimumab and sasanlimab, see the Investigational Product (IP) manual and the TDS-IM V 2.0 Instructions for Use for instructions on how to prepare the investigational products for administration.

The TDS-IM v2.0 6mm Application cartridges for the administration of the plasmid are provided for single use, and will be packaged and dispensed in cartons with tamper evident seals. The cartons should not be opened until the time of administration.

Investigational product should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance.

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

## 5.4. Administration

All AdC68 intramuscular injections are given bilaterally. AdC68 will be administered on Day 1 of Cycles 1 and 2. Please refer to the IP manual for full instructions on the dosage and administration.

Plasmid DNA intramuscular injections are given bilaterally. pDNA will be administered beginning on Day 29 of Cycles 1 and 2 and will then be given at 4 week intervals. After Cycle 2, pDNA will continue to be administered every 2 months in the Maintenance Treatment Period. Please refer to the IP manual for full instructions on the dosage and administration of the pDNA and to the TDS-IM V 2.0 Instructions for Use document for the set up and use of the electroporation device. The TDS-IM device should be operated by clinical personnel that have completed the necessary training on device operation.

All IM injections (AdC68 and pDNA) will be given bilaterally in the deltoid muscles or in the vastus lateralis muscles of the quadriceps. Preference should be given to the vastus lateralis muscles when possible.

Tremelimumab will be administered bilaterally subcutaneously at 4 week intervals during Cycles 1 and 2 on the same day as the AdC68 or pDNA dosing as described in the SCHEDULE OF ACTIVITIES. After Cycle 2, tremelimumab will continue to be administered every 2 months in the Maintenance Treatment Period. Both AdC68 and pDNA injections should be given prior to tremelimumab administration. Please refer to the IP manual for full instructions on the dosage and administration of tremelimumab. Tremelimumab is to be administered in close proximity to the vaccination site. If the vaccination is administered in the vastus lateralis, the tremelimumab is to be administered SC in either the lower quadrants of the abdomen or the quadriceps. If the vaccination is administered in the deltoid, the tremelimumab is to be administered SC bilaterally in the outer triceps.

Sasanlimab will be administered bilaterally subcutaneously at 4 week intervals on the same day as the AdC68 or pDNA and tremelimumab during Cycles 1 and 2 as described in the SCHEDULE OF ACTIVITIES. The AdC68 or pDNA as well as the tremelimumab doses should be given prior to sasanlimab administration. During the Maintenance Treatment Period, participants will continue to be dosed with sasanlimab at monthly intervals until confirmed disease progression per RECIST. Please refer to the IP manual for full instructions on the dosage and administration of sasanlimab. Sasanlimab is to be administered in close proximity to the vaccination site. If the vaccination is administered in the vastus lateralis, the sasanlimab is to be administered SC bilaterally in the lower quadrants of the abdomen. If the vaccination is administered in the deltoid, the sasanlimab is to be administered SC bilaterally in the outer triceps.

### 5.4.1. Recommended Dose Modifications

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

In the event of significant toxicity, dosing may be delayed and/or reduced as described below. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed. Participants are to be instructed to notify investigators at the first occurrence of any adverse symptom.

Dose modifications may occur in one of three ways:

- Within a cycle: dosing interruption until adequate recovery and dose reduction, if required, during a given treatment cycle;
- Between cycles: next cycle administration may be delayed due to persisting toxicity when a new cycle is due to start;

- In the next cycle: dose reduction may be required in a subsequent cycle based on toxicity experienced in the previous cycle.

### 5.4.2. Dosing Interruptions/Delays due to Treatment Related Toxicity

Participants experiencing Grade 3 or 4 potentially treatment related toxicity or intolerable Grade 2 toxicity despite supportive care should have their treatment with all of the components interrupted/delayed. Appropriate follow-up assessments should be done until adequate recovery occurs as assessed by the investigator.

Re-treatment following treatment interruption for treatment related toxicity or at the start of any new cycle may not occur until all of the following parameters have been met:

- ANC ≥1,000/$mm^3$.
- Platelets count ≥50,000/$mm^3$.
- Non-hematologic toxicities have returned to baseline or Grade ≤1 severity (or, at the investigator discretion, Grade ≤2 if not considered a safety risk for the participant).

If a treatment delay results from worsening of hematologic or biochemical parameters, the frequency of relevant blood tests should be increased as clinically indicated.

### 5.4.3. If these conditions are met within 2 weeks of treatment interruption or cycle delay, investigational product(s) may be resumed. Refer to section Dosing Interruptions/Delays due to Non-Related Events

If participants require treatment interruption for reasons other than treatment-related toxicity (eg, surgery) lasting >4weeks, treatment resumption should be decided in consultation with the Sponsor.

In the event of active SARS-CoV2 infection confirmed (positive by regulatory authority-approved test) or presumed (test pending/clinical suspicion), the following criteria apply:

- For symptomatic participants with active SARS-CoV2 infection, investigational treatment should be delayed for at least 14 days from start of symptoms.
- This delay is intended to allow resolution of symptoms of SARS-CoV2 infection.
- Prior to restarting treatment, the participants should be afebrile for 72 hours and SARS-CoV2-related symptoms should have recovered to ≤ Grade 1 for a minimum of 72 hours.
- Discuss with the Sponsor prior to restarting treatment.
- Consider potential drug-drug interactions (as described per study protocol) for any concomitant medication administered for treatment of SARS-CoV2 infection.

Dose Reductions for adverse events requiring dose reduction at the time of treatment resumption.

If these conditions are not met, treatment resumption must be delayed up to a maximum of 2 weeks. If these parameters have not been met after 2 weeks of dosing interruption or 2 weeks of new cycle delay, permanent discontinuation of treatment should be considered. Treatment resumption for participants recovering from treatment-related toxicity after >2 weeks of treatment interruption or cycle delay may be considered only if the participant is deemed to be deriving obvious clinical benefit per the investigator's best medical judgment and needs to be agreed between the investigator and the sponsor.

### 5.4.4. Dosing Interruptions/Delays due to Non-Related Events

If participants require treatment interruption for reasons other than treatment-related toxicity (eg, surgery) lasting >4weeks, treatment resumption should be decided in consultation with the Sponsor.

In the event of active SARS-CoV2 infection confirmed (positive by regulatory authority-approved test) or presumed (test pending/clinical suspicion), the following criteria apply:

- For symptomatic participants with active SARS-CoV2 infection, investigational treatment should be delayed for at least 14 days from start of symptoms.
- This delay is intended to allow resolution of symptoms of SARS-CoV2 infection.
- Prior to restarting treatment, the participants should be afebrile for 72 hours and SARS-CoV2-related symptoms should have recovered to ≤ Grade 1 for a minimum of 72 hours.
- Discuss with the Sponsor prior to restarting treatment.
- Consider potential drug-drug interactions (as described per study protocol) for any concomitant medication administered for treatment of SARS-CoV2 infection.

### 5.4.5. Dose Reductions

Following dose interruption or cycle delay due to toxicity, the investigational product(s) may need to be reduced when treatment is resumed.

No specific dose adjustments are recommended for Grade 1/2 treatment-related toxicity, unless otherwise specified. However, investigators should always manage their participants according to their medical judgment based on the particular clinical circumstances.

### 5.4.5.1. AdC68 Dose Reductions

Changes in the dose levels for AdC68 will be discussed with the sponsor. Dose reduction of adenovirus by 1 dose level may be allowed in Part 1 depending on the type and severity of toxicity encountered. No dose level reduction is allowed in Part 2. All dose modifications/adjustments must be clearly documented in the participant's source notes and CRF.

Once a dose has been reduced for a given participant, all subsequent cycles should be administered at that dose level for that participant, unless further dose reduction is required. Dose re-escalation for adenovirus is not allowed.

**Table 4. AdC68 Available Dose Levels (Part 1)**

| Dose Level | AdC68* |
|---|---|
| +1 | $6 \times 10^{11}$ VP |
| Starting | $2 \times 10^{11}$ VP |

**Table 5. AdC68 Available Dose Levels (Part 2)**

| Dose Level | AdC68* |
|---|---|
| Starting | $6 \times 10^{11}$ VP |
| -1 | $2 \times 10^{11}$ VP |

**Table 6. Dose Modifications for AdC68 Related Toxicity**

| Toxicity | Grade ½ | Grade 3 | Grade 4 |
|---|---|---|---|
| Non-hematologic (other than irAE management described in Appendix 5) | Continue at the same dose level. | Withhold dose until toxicity is Grade ≤1, or has returned to baseline, then resume treatment at the same dose level or reduce the dose by 1 level at the discretion of the investigator*. | Discontinue treatment. |
| Hematologic | Continue at the same dose level. | Withhold dose until toxicity is Grade ≤2, or has returned to baseline, then resume treatment at the same dose level. | Discontinue treatment. |

* Nausea, vomiting, or diarrhea must persist at Grade 3 despite maximal medical therapy to require dose modification.

### 5.4.5.2. Tremelimumab Dose Reductions

Changes in the dose levels for tremelimumab will be discussed with the sponsor. A dose reduction of tremelimumab by 1 dose level (from 80 mg to 40 mg) may be allowed depending on the type and severity of toxicity encountered. In addition, an intermediate dose may be considered. Participants requiring a dose level lower than 40 mg will be discontinued from treatment and enter into the follow-up phase unless otherwise agreed between the investigator and sponsor. Algorithms for the management of suspected pulmonary,

gastrointestinal (GI), liver, endocrine, skin, neurological and renal toxicities have been developed (See Appendix 5). All dose modifications/adjustments must be clearly documented in the participant's source notes and case report form (CRF).

Once a dose has been reduced for a given participant, all subsequent cycles should be administered at that dose level, unless further dose reduction is required. Dose re-escalation for tremelimumab is not allowed.

**Table 7. Tremelimumab Available Dose Levels (Part 1)**

| Dose Level | Tremelimumab |
|---|---|
| Starting | 40 mg |
| +1 | 80 mg |

**Table 8. Tremelimumab Available Dose Levels (Part 2)**

| Dose Level | Tremelimumab |
|---|---|
| Starting | 80 mg |
| -1 | 40 mg |

**Table 9. Dose Modifications for Tremelimumab Related Toxicity When Given in Combination with AdC68 and pDNA**

| Toxicity | Grade ½ | Grade 3 | Grade 4 |
|---|---|---|---|
| Non-hematologic | Continue at the same dose level. | Withhold dose until toxicity is Grade ≤1, or has returned to baseline, then resume treatment at the same dose level or reduce the dose by 1 level at the discretion of the investigator.* | Discontinue treatment. |
| Hematologic | Continue at the same dose level. | Withhold dose until toxicity is Grade ≤2, or has returned to baseline, then resume treatment at the same dose level. | Discontinue treatment. |

* Nausea, vomiting, or diarrhea must persist at Grade 3 despite maximal medical therapy to require dose modification.

### 5.4.5.3. Sasanlimab Dose Reductions

Events including, but not limited to, pneumonitis, colitis, creatinine and liver function test (LFT) elevation should be monitored carefully with this class of agents. Dose reductions may be required for sasanlimab, tremelimumab or potentially both compounds depending on the event and the severity of the toxicity. Dose reductions of sasanlimab from 300 mg to 130 mg may be allowed. In addition an intermediate dose may be considered. All dose modifications/adjustments must be clearly documented in the participant's source notes and CRF.

**Table 10. Sasanlimab Available Dose Levels (Part 1)**

| Dose Level | Sasanlimab |
|---|---|
| Starting | 130 mg |
| +1 | 300 mg |

**Table 11. Sasanlimab Available Dose Levels (Part 2)**

| Dose Level | Sasanlimab |
|---|---|
| Starting | 300 mg |
| -1 | 130 mg |

Algorithms for the management of suspected pulmonary, GI, liver, endocrine, skin, neurological and renal toxicities have been developed (See Appendix 5).

Participants requiring >4 weeks of dose interruption should be considered for discontinuation of treatment with sasanlimab. Participants may be allowed to resume dosing with the AdC68, pDNA and tremelimumab without sasanlimab for one dose with plans to resume sasanlimab at the next dosing time point if agreed upon by the investigator and sponsor. Participants who discontinue sasanlimab due to toxicity will be allowed to remain in the study and continue treatment with the other components.

The following serves as demonstrating general rules. Action may differ in specific cases based on evaluation by the investigator and the sponsor.

**Table 12. Dose Modifications for Sasanlimab and/or Tremelimumab Related Toxicity**

| Toxicity | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Non-hematologic | Continue at the same dose level. | For pneumonitis, endocrinopathy, colitis, creatinine, AST, ALT, or total bilirubin elevations, withhold dose until toxicity is Grade ≤1, or has returned to baseline, then resume at the same dose level or reduce by 1 level (considering each compound separately) at the discretion of the investigator.<br><br>For all other events, continue at the same dose level. | For pneumonitis, colitis, endocrinopathy, creatinine, AST, ALT or total bilirubin elevations, or pruritus discontinue treatment.**<br><br>For all other events withhold dose until toxicity is Grade ≤1, or has returned to baseline, then resume treatment at the same dose level or reduce the dose by 1 level (considering each compound separately) at the discretion of the investigator.*<br>Treatment may resume with VBIR-2 with an interruption of sasanlimab for one dose at the discretion of the investigator. | Discontinue treatment.** |
| Hematologic | Continue at the same dose level. | Continue at the same dose level. | Withhold dose until toxicity is Grade ≤2, or has returned to baseline, then resume treatment at the same dose level. | Discontinue treatment.** |

* Nausea, vomiting, or diarrhea must persist at Grade 3 despite maximal medical therapy to require dose modification.

** For Grade ≥3 colitis or pneumonitis, discontinue treatment permanently. For any grade of myocarditis discontinue treatment permanently. For all other conditions participants may be allowed to remain in the study to receive the VBIR-2 2 after the toxicity is Grade ≤1 or returned to baseline, and only if agreed upon by the Investigator and Sponsor.

## 5.5. Investigational Product Storage

The investigator, or an approved representative, eg, pharmacist will ensure that all investigational products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational products should be stored in their original containers and in accordance with the labels.

Upon receipt at the site, all drug product should be immediately transferred, in its original container, to the appropriate monitored storage area. Current storage conditions for

AdC68 vials are frozen (-20°C±5°C). The current storage conditions for the pDNA, tremelimumab and sasanlimab are refrigerated (2-8°C).

Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the product label. Please see the Instructions for Use for details on storage of the TDS-IM device.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room-temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous monitoring systems, a log or site procedure that ensures active evaluation for excursions should be available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no excursion occurred since the last evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all nonworking days upon return to normal operations. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure they are maintained in working order.

Any excursions from the product label storage conditions should be reported to Pfizer upon discovery. The site should actively pursue options for returning the product to the storage conditions described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer.

Once an excursion is identified, the investigational product must be quarantined and not used until Pfizer provides permission to use the investigational product. It will not be considered a protocol deviation if Pfizer approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to Pfizer approval will be considered a protocol deviation. Specific details regarding information the site should report for each excursion will be provided to the site.

### 5.6. Investigational Product Accountability

The investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All investigational products will be accounted for using a drug accountability form/record.

#### 5.6.1. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused investigational product (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.

## 5.7. Concomitant Treatment(s)

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

All concomitant treatments, blood products, as well as nondrug interventions received by participants from screening until the end of study visit will be recorded on the CRF.

### 5.7.1. Prohibited Concomitant Vaccines

No vaccines (licensed or investigational) other than study vaccine, influenza, COVID-19 and pneumococcal vaccines should be given during the study within 30 days prior to or after dosing. Other vaccines may be administered only if medically necessary (eg, tetanus post exposure prophylaxis).

For participants who receive tremelimumab, live attenuated vaccines should not be administered within 30 days prior to or after dosing with tremelimumab. The administration of inactivated vaccines are allowed.

### 5.7.2. Other Anti-tumor/Anti-Cancer or Experimental Drugs

No additional anti-tumor treatment will be permitted while participants are receiving study treatment. Additionally, the concurrent use of select vitamins or herbal supplements is not permitted

### 5.7.3. Supportive Care

Palliative and supportive care for disease related symptoms may be administered at the investigator's discretion and according to any available American Society of Clinical Oncology (ASCO) guidelines.

Participants currently being treated with denosumab or bisphosphonates (eg, zoledronate) for bone disease may continue treatment while participating in this study. However, initiation of treatment with these types of compounds should be avoided while participating in the study.

Palliative radiotherapy on study is permitted for the treatment of painful bony lesions providing the lesions were known at the time of study entry and the investigator clearly indicates that the need for palliative radiotherapy is not indicative of disease progression.

Participants currently being treated with a gonadotropin-releasing hormone agonist (GnRH agonist) may continue treatment while on clinical study C3621001 as long as the GnRH agonist treatment has been well tolerated for at least 3 months prior to study entry.

### 5.7.4. Hematopoietic Growth Factors

Primary prophylactic use of granulocyte-colony stimulating factors is not permitted during Cycle 1, but they may be used to treat treatment emergent neutropenia as indicated by the current American Society of Clinical Oncology guidelines.[2]

Erythropoietin may be used at the investigator's discretion for the supportive treatment of anemia.

### 5.7.5. Anti-Diarrheal, Anti-Emetic Therapy

Primary prophylaxis of diarrhea, nausea and vomiting is not permitted prior to the first dose of AdC68, tremelimumab and/or sasanlimab. Primary prophylaxis on subsequent dosing days is at the investigator's discretion. The choice of the prophylactic drug is up to the investigator with sponsor approval and assuming the drug is not prohibited as specified in Section 5.7, as well as the duration of treatment assuming there is no known or expected drug-drug interaction. If so, then it must be approved by the sponsor.

### 5.7.6. Anti-Inflammatory Therapy

Anti-inflammatory or narcotic analgesic may be offered as needed assuming there is no known or expected drug-drug interaction and assuming the drug is not included in the Concomitant Treatment(s) Section 5.7.

### 5.7.7. Corticosteroids

Chronic, systemic corticosteroid use for palliative or supportive purpose is not permitted. The short term use of corticosteroids (eg, 5 mg q.d. of prednisone for 2 weeks) as symptomatic treatment on an individual basis and upon discussion with the sponsor is allowed. Acute emergency administration, topical applications, inhaled sprays, eye drops, or local injections of corticosteroids are allowed.

### 5.7.8. Surgery

Caution is advised on theoretical grounds for any surgical procedures during the study. The appropriate interval of time between surgery and administration of VBIR-2 required to minimize the risk of impaired wound healing and bleeding has not been determined. Stopping all components of VBIR-2 is recommended at least 7 days prior to surgery. Postoperatively, the decision to reinitiate treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery.

## 6. STUDY PROCEDURES

### 6.1. Screening

For screening procedures see the Schedule of Activities and ASSESSMENTS sections.

### 6.2. Study Period

For the treatment period procedures, see the Schedule of Activities and ASSESSMENTS sections.

### 6.3. End of Treatment

The End of treatment visit will be completed at the time point when a decision is made to discontinue study treatment. This can occur during Cycles 1 or 2 or during the Maintenance

Treatment Phase of the study. Obtain the specified EOT assessments (see Schedule of Activities) if not completed in the past two weeks (past 6 weeks for tumor assessments).

### 6.4. Follow-up

For follow-up procedures see the Schedule of Activities and ASSESSMENTS sections.

### 6.5. Survival Follow-up

After treatment discontinuation, participant survival status will be collected every 3 months until death, participant refusal, or lost to follow-up (telephone contact acceptable).

### 6.6. Participant Withdrawal

**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 them 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; this information should be entered on the appropriate CRF page. In the event that survival status (whether the participant is alive or dead) is being measured, and if publicly available information is part of the origin of this data, it is important that collecting this information should be carried out only as appropriately directed in accordance with local law.

**Lost to follow-up:**

All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant as noted above. "Lost to Follow-up" is defined by the inability to reach the participant after a minimum of 2 documented phone calls, faxes, or e-mails as well as lack of response by the participant to 1 letter sent by registered mail. All attempts should be documented in the participant's medical records. If it is determined that the participant has died, the site will use locally-permissible methods to obtain the cause and the date of death. If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the participant's informed consent, then the Investigator may use a sponsor-retained third-party representative to assist site staff with obtaining the participant's contact information or other public survival status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the participant remains lost to follow-up, then the last-known-alive date

as determined by the Investigator should be reported and documented in the participant's medical records.

Participants may withdraw from treatment at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety (see also the Withdrawal From the Study Due to Adverse Events (see also the Participant Withdrawal Section) or behavioral reasons, or the inability of the participant to comply with the protocol-required schedule of study visits or procedures at a given investigator site.

Reasons for withdrawal of study treatment may include:

- Objective disease progression;
- Global deterioration of health status requiring discontinuation;
- Unacceptable toxicity;
- Pregnancy;
- Significant protocol violation;
- Lost to follow-up;
- Participant refused further treatment;
- Study terminated by sponsor;
- Death.

Reasons for withdrawal from study follow-up may include:

- Completed study follow-up;
- Study terminated by sponsor;
- Lost to follow-up;
- Refused further follow-up;
- Death.

If a participant does not return for a scheduled visit, every effort should be made to contact the participant. All attempts to contact the participant and information received during contact attempts should be documented in the participant's medical record. Regardless of the 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.

If the participant refuses further visits, the participant should continue to be followed for survival (if survival is a secondary endpoint) 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.

## 7. ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that occasionally there may be circumstances outside of 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 this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely manner.

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

### 7.1. Safety Assessment

Safety assessments will include collection of AEs, serious adverse events (SAEs), vital signs and physical examination, electrocardiogram (ECG [12-lead]), laboratory assessments, including pregnancy tests and verification of concomitant treatments.

#### 7.1.1. Pregnancy Testing

All pregnancy tests used in this study, either urine or serum, must have a sensitivity of at least 25 mIU/mL and must be performed by a certified laboratory. For female participants of childbearing potential, 2 negative pregnancy tests are required before receiving study treatment(s) (1 negative pregnancy test at screening and 1 at the baseline visit immediately before study treatment administration). Following a negative pregnancy test result at screening, appropriate contraception must be commenced and the second negative pregnancy test result will then be required at the baseline visit and within 5 days after the first day of the menstrual period (counting the first day of the menstrual period as Day 1) before the participant may receive the study treatment. In the absence of regular menstrual bleeding, the study candidate should have used 2 forms of contraception for at least 1 month before the second pregnancy test. Pregnancy tests will also be routinely repeated at (pre-dose) every cycle (Days 1, 29, 57, and 85) during the active treatment period, at the end of study treatment, at the 28-day Follow-Up visit to confirm that the participant has not become pregnant during the study. Pregnancy tests will also be done whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected, and may be repeated if requested

by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations. In the case of a positive confirmed pregnancy, the participant will be withdrawn from administration of investigational product, but may remain in the study.

For female participants who achieved postmenopausal status and have not experienced their menses since at least 12 consecutive month, a serum FSH test must be conducted at screening only, in order to confirm a FSH level within the laboratory's reference ranges for post menopause.

### 7.1.2. Adverse Events

Assessment of adverse events will include the type, incidence, severity (graded by the NCI CTCAE version 5.0) timing, seriousness, and relatedness.

### 7.1.3. Laboratory Safety Assessment

Hematology and blood chemistry will be drawn at the time points described in the Schedule of Activities and analyzed at local laboratories.

**Table 13. Safety Laboratory Tests**

| Hematology | Chemistry | Coagulation | Urinalysis | Pregnancy Test |
|---|---|---|---|---|
| Hemoglobin | ALT | PT or INR | Urine dipstick for urine protein: If positive collect 24-hr and microscopic (Reflex Testing) | For female participants of childbearing potential, serum or urine (see Section 7.1.1) |
| Platelets | AST | PTT | | |
| WBC | Alk Phos | | | |
| Absolute Neutrophils | Sodium | | | |
| Absolute Lymphocytes | Potassium | | | |
| Absolute Monocytes | Magnesium | | Urine dipstick for urine blood: If positive collect a microscopic (Reflex Testing) | |
| Absolute Eosinophils | Total Chloride | | | |
| Absolute Basophils | Total calcium | | | |
| | Total bilirubin[1] | | | |
| | BUN or Urea | | | |
| | Creatinine | | Viral Tests[2] (at Screening) | |
| | Uric Acid | | Hepatitis B surface antigen[2] | |
| | Glucose (nonfasted) | | Hepatitis B core antibody[2] | |
| | Albumin | | Hepatitis C antibody[2] | |
| | Phosphorous or Phosphate | | Human immunodefiency virus (HIV)[2] | |
| | Lactate dehydrogenase | | | |
| | Lipase | | | |
| | Amylase | | | |
| | Bicarbonate or carbon dioxide | | | |
| | Total protein | | | |
| | TSH + reflex free T4 and free T3 | | | |

**Table 13. Safety Laboratory Tests**

| Hematology | Chemistry | Coagulation | Urinalysis | Pregnancy Test |
|---|---|---|---|---|

1. 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.
2. Hepatitis B surface antigen, hepatitis B core antibody, hepatitis C antibody, and human immunodeficiency virus (HIV). Samples will be analyzed locally.

### 7.1.4. Vital Signs and Physical Examination

Participants will have a physical examination to include weight, vital signs, assessment of ECOG performance status and height; height will be measured at screening only.

A complete physical examination (PE) will be performed at Screening and at the End of Treatment visit for each participant and will include an assessment of all body systems. A neurologic examination must be conducted at Screening to look for potential signs of underlying autoimmune disorders. Findings of all physical examinations should be recorded in the source documents, and any change from baseline considered by the investigator to be clinically significant should be recorded as an adverse event in the CRF.

Abbreviated PEs should be performed as appropriate per the Schedule of Activities (SOA), and on an as needed basis for assessment of adverse events. Abbreviated exams should be targeted to specific symptoms or complaints and be consistent with local standard of care. However, a neurologic examination must be performed during each exam conducted during Cycle 1.

Weight and body surface area (BSA) do not need to be performed at each visit; however participants should be monitored throughout the study for significant weight change.

Vital signs should include measurements of blood pressure, pulse, and temperature (oral, temporal, tympanic or axillary). On dosing days, vital signs should be measured prior to administration of any of the study treatments. Sitting blood pressure (BP) and pulse after approximately 5 minutes rest should be measured with the participant's arm supported at the level of the heart and recorded to the nearest mmHg. The same arm shouldbe used throughout the trial. A properly-sized and calibrated blood pressure cuff should be used to measure blood pressure. The use of automated devices for measuring BP is acceptable. Vitals signs, including temperature, pulse, and BP to be recorded 1-hour post-study drug administration during each Cycle on Days 1, 29, 57, and 85.

Assessment of the skin and subcutaneous tissue thickness at the eligible administration sites will be performed at screening as described in the TDS-IM V 2.0 Instructions for Use. The assessment procedure does not need to be repeated during the course of the study unless the participant experiences a greater than 10% change in body mass relative to screening.

### 7.1.5. (12-Lead) Electrocardiogram

Electrocardiogram machines to be utilized in this study will be supplied by a third party vendor.

At screening, a single 12-lead ECG tracing (with a 10-second rhythm strip) will be obtained. For Cycle 1 Day 1 and all subsequent specified time points (see Schedule of Activities), triplicate 12-lead ECG tracings (with a 10-second rhythm strip) will be obtained.

Generally, baseline and all corresponding time point ECGs should not be collected within 3 hours after food or beverage consumption and should be performed after the participant has rested quietly for at least 10 minutes in a supine position. All 12 lead ECGs should be confirmed by a qualified person at the institution and will be reviewed by a central laboratory.

At each time point, (see the Schedule of Activities), three consecutive ECGs will be performed at approximately 2 minutes apart to determine the mean QTcF interval. If the mean QTcF is prolonged (value of >500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation. If manual reading verifies a QTcF of >500 msec, immediate correction for reversible causes (including electrolyte abnormalities, hypoxia and concomitant medications for drugs with the potential to prolong the QTcF interval) should be performed. In addition, repeat ECGs should be immediately performed hourly for at least 3 hours until the QTcF interval falls below 500 msec. If QTcF interval reverts to less than 500 msec, and in the judgment of the investigator(s) and sponsor it is determined to be due to cause(s) other than investigational product, treatment may be continued with regular ECG monitoring. If in that timeframe the QTcF intervals rise above 500 msec the investigational product will be held until the QTcF interval decreases to 500 msec. Participants will then re-start the investigational product at the next lowest dose level. If the QTcF interval has still not decreased to 500 msec after 2-weeks, or if at any time a participant has a QTcF interval >515 msec or becomes symptomatic, the participant will be removed from the study. Additional triplicate ECGs may be performed as clinically indicated.

Prior to concluding that an episode of prolongation of the QTcF interval is due to investigational product, thorough consideration should be given to potential precipitating factors (eg, change in participant clinical condition, effect of concurrent medication, electrolyte disturbance) and possible evaluation by specialist.

If the participant experiences a cardiac or neurologic AE (specifically syncope, dizziness, seizures, or stroke), an ECG (triplicate) should be obtained at the time of the event.

Prior to concluding that an episode of prolongation of the QTcF interval is due to investigational product, thorough consideration should be given to potential precipitating factors (eg, change in participant clinical condition, effect of concurrent medication, electrolyte disturbance) and possible evaluation by specialist.

When matched with PK sampling, the ECG must be carried out before each PK sample drawing such that the PK sample is collected at the nominal time (ie, the timing of the PK collections over rides the timing of the ECG collections).

### 7.1.6. Monitoring for Potential Immune Mediated Endocrinopathies

Participants will be monitored for clinical signs and symptoms of hypophysitis, adrenal insufficiency (including Addisonian crisis), and hyper- or hypothyroidism. Laboratory evaluation will be performed as clinically indicated based on symptoms. For example, the development of symptoms of adrenal insufficiency, such as unexplained nausea, vomiting and hypotension, would trigger prompt evaluation (Cosyntropin Stimulation Testing) and treatment (systemic glucocorticoids). Symptoms suggestive of an inflammatory pituitary process with mass effect, such as diplopia, visual field abnormalities and severe headache, call for urgent pituitary imaging and evaluation for hypopituitarism, with specific attention to the pituitary-adrenal axis. Symptoms of disordered thyroid metabolism, such as changes in bowel frequency, fatigue, unexplained weight loss or gain should prompt evaluation of thyroid function tests, with a focus on free thyroid hormone levels (T3 and T4) given the possibility that thyroid stimulating hormone levels may be unreliable due to immune-mediated pituitary dysfunction.

### 7.1.7. Acetylcholine Receptor Testing

A blood sample will be collected at screening for central evaluation of acetylcholine receptor (AChR) antibodies. CCI [redacted] reatment decisions will be made based on the clinical diagnosis. The evaluation for AChR antibodies is included to exclude participants who test positive at screening as agreed upon with the US FDA and to confirm requirement for evaluation if myasthenia gravis is suspected.[99]

### 7.1.8. Cardiac Safety Monitoring

The algorithm for cardiac Safety Monitoring is shown in Figure 2 below.

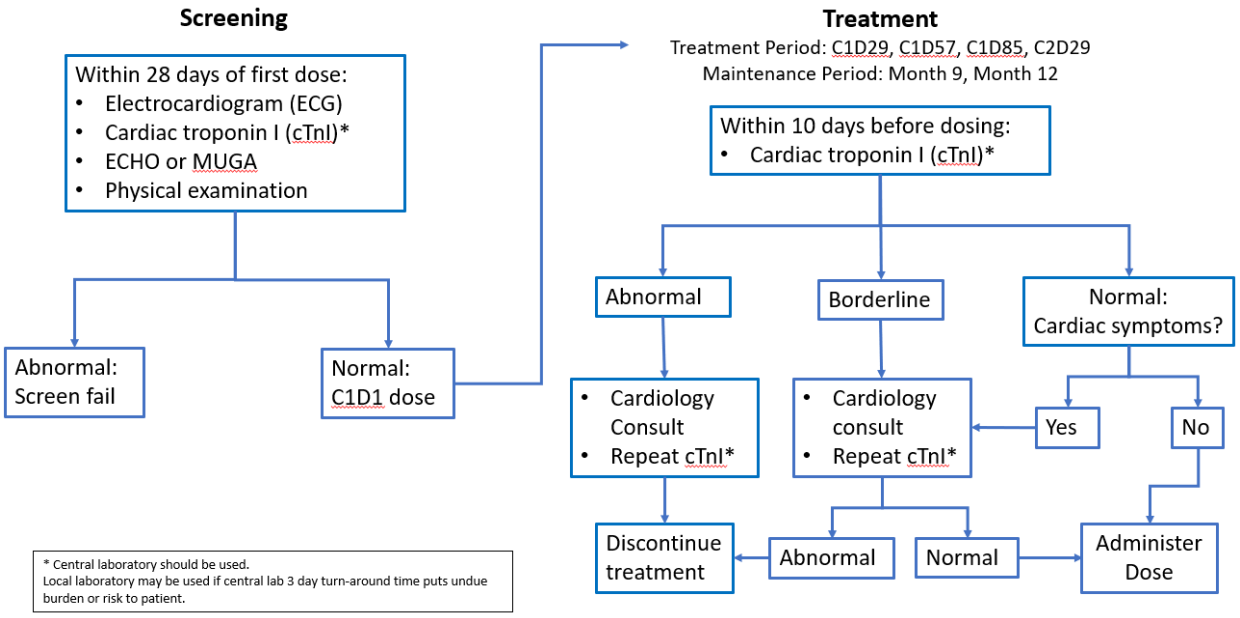
For participants undergoing screening, circulating levels of cardiac Troponin-I (cTnI) must be measured and found to be within the normal reference range within 28 days before study entry, preferably using the central laboratory kits provided. Dosing should not proceed until results within the normal reference range have been received by the Investigator. For any results above of the normal reference range (even if borderline), the participant should be referred to a cardiologist by the Investigator for complete cardiac workup and repeat cardiac troponin. The participant can only enter the study after cardiac evaluation, troponin findings within the normal reference range, cardiac clearance, and the Sponsor's approval.

For participants ongoing in the study, circulating levels of cardiac Troponin-I (cTnI) must be measured within 10 days of dosing on the days shown in the SOA (ie, C1D29, C1D57, C1D85, C2D29, month 9 and month 12) and found to within the normal reference range. No dosing of participants can occur unless the cTnI is within the normal reference range. For any results above the normal reference range (even if borderline) the participant must be referred by the Investigator to a cardiologist for complete work-up and repeat cTnI. Dosing

can only occur after cardiac evaluation, cTnI findings within the normal reference range, cardiac clearance, and the Sponsor's approval.

While central laboratory testing for cTnI is preferred, it requires a minimum of 3 days to return results. Therefore, local laboratory testing of cTnI may be used, but only if the timing of measuring cTnI by the central laboratory test (minimum 3 day turnaround time) puts an undue burden or risk on the participant. The use of cardiac troponin-T is strongly discouraged, but could be used in place of cTnI if the central laboratory test puts an undue burden or risk on the participant.

**Figure 2. Cardiac Safety Monitoring Algorithm**




## 7.2. Pharmacokinetics Assessments

### 7.2.1. Serum for Assessment of Tremelimumab Pharmacokinetics

Blood samples (approximately 3 mL whole blood) to provide a minimum of 1 mL of serum for measurement of serum tremelimumab concentrations will be collected from participants receiving tremelimumab. The samples will be collected into appropriately labeled tubes at time points outlined in the Schedule of Activities. The PK sampling schedule may be modified based on emerging PK data, but the total number of PK samples will remain the same.

In addition to samples collected at the scheduled times, an additional blood sample for determination of serum tremelimumab concentration should be collected from participants experiencing unexpected and/or serious AEs and the date and time of blood sample collection and of last dosing prior to PK collection documented on the CRF.

Where noted in the Schedule of Activities, blood samples for tremelimumab concentrations will be collected at approximately the same time as other assessments such as PD samples and ECGs (first ECG then PK collection), wherever possible.

All efforts will be made to obtain the PK samples at the scheduled nominal time relative to dosing. However, samples obtained within the protocol specified time window will be considered compliant with the protocol, and the exact time of the sample collection will always be noted on the CRF. If a scheduled blood sample collection cannot be completed for any reason, the missed sample time may be re-scheduled with agreement of the clinical investigator, participant, and sponsor.

PK samples will be assayed for tremelimumab using a validated analytical method at a central laboratory in compliance with Pfizer standard operating procedures (SOPs).

The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK 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. Any deviation from the specified sample handling procedure resulting in compromised sample integrity will be considered a protocol deviation.

As part of understanding the PK of the investigational product, samples may be used for evaluation of the bioanalytical method, CCI [redacted]
These data will not be included in the Clinical Study Report (CSR).

### 7.2.2. Serum for Assessment of Sasanlimab Pharmacokinetics

Blood samples (approximately 5 mL whole blood) to provide a minimum of 2 mL of serum for measurement of serum sasanlimab concentrations will be collected from participants receiving sasanlimab. The samples will be collected into appropriately labeled tubes at time points outlined in the Schedule of Activities. The PK sampling schedule may be modified based on emerging PK data, but the total number of PK samples will remain the same.

In addition to samples collected at the scheduled times, an additional blood sample for determination of serum sasanlimab concentration should be collected from participants experiencing unexpected and/or serious AEs and the date and time of blood sample collection and of last dosing prior to PK collection documented on the CRF.

Where noted in the Schedule of Activities, blood samples for sasanlimab concentrations will be collected at approximately the same time as other assessments such as CCI [redacted]
ECGs (first ECG then PK collection), wherever possible.

All efforts will be made to obtain the PK samples at the scheduled nominal time relative to dosing. However, samples obtained within the protocol specified time window will be considered compliant with the protocol, and the exact time of the sample collection will always be noted on the CRF. If a scheduled blood sample collection cannot be completed for

any reason, the missed sample time may be re-scheduled with agreement of the clinical investigator, participant, and sponsor.

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

The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK 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. Any deviation from the specified sample handling procedure resulting in compromised sample integrity will be considered a protocol deviation.

As part of understanding the PK of the investigational product, samples may be used for evaluation of the bioanalytical method, CCI
These data will not be included in the Clinical Study Report (CSR).

CCI

CCI

[redacted]

CCI

[redacted]

### 7.4. Tumor Response Assessments

Tumor assessments will include all known or suspected sites of disease. Screening images may be obtained within 5 weeks of registration. Imaging obtained as part of standard of care that are performed within 28 days (-7 days) of registration may be used for screening assessment. Imaging will include (a) CT scan (computerized tomography) of the chest, abdomen and pelvis, or magnetic resonance imaging (MRI) of these same areas, and (b) bone scan, for participants with known or suspected bone metastases. Baseline brain imaging (CT or MRI) is not required, except in the case of symptomatic participants to rule out brain metastases (see Section 4).

The same imaging technique (CT scan or MRI) used to characterize lesions identified at baseline should be employed when performing on-study tumor assessments. As the intention of administration of VBIR-2 is to activate an anti-tumor immune response in the vaccine draining lymph nodes, the inguinal (limb) and axillary (arm) lymph nodes should not be used as target lesions, since injections of antigens may be given in the upper arm or thigh. It is possible that lymph nodes draining the upper arm or thigh may become enlarged following administration of the VBIR-2, and may not accurately reflect the status of underlying disease.

Anti-tumor activity will be assessed through radiological tumor assessments conducted at baseline; during treatment as specified in the SOA; whenever disease progression is suspected (eg, symptomatic deterioration); and at the time of withdrawal from treatment (if not done in the previous 6 weeks).

Assessment of response will be made using RECIST version 1.1 (Appendix 3).

All participants' files and radiologic images must be available for source verification and for potential peer review. In addition, historical images (collected up to one year prior to study entry) may be requested for potential peer review.

### 7.5. Tremelimumab and Sasanlimab Immunogenicity Assessments

In participants receiving tremelimumab, blood samples (approximately 5 mL, to provide at least 2 mL of serum) will be collected to detect anti-drug antibodies (ADA) and neutralizing antibody (NAb) against tremelimumab (~1 mL each of ADA and NAb). Similarly, in participants receiving sasanlimab, blood samples (approximately 5 mL, to provide at least 2 mL of serum) will be collected to detect ADA and NAb against sasanlimab (~1 mL each of ADA and NAb). The sampling schedule is specified in the SOA.

Samples will be analyzed using a validated analytical method in compliance with Pfizer SOPs. The ADA sample analysis will follow a tiered approach of screening, confirmation, and titer determination. Only those samples tested positive for ADA will be further tested for NAb.

The immunogenicity samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the immunogenicity 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. Any deviation from the specified sample handling procedure resulting in compromised sample integrity will be considered a protocol deviation.

As part of understanding the immunogenicity of the investigational product, samples may be used for evaluation of the bioanalytical method. CCI [redacted]

CCI

[redacted]

CCI

[redacted]

### 7.7. Other Assessments

#### 7.7.1. Tumor and Medical History

History of the participant's disease under study including details of the primary diagnosis and treatment history will be collected within 28 before the start of treatment. In addition, a history of disease process other than the cancer under study (active or resolved) and concurrent illnesses will be collected. This will also include prior treatments and any current medical treatments for any condition.

## 8. ADVERSE EVENT REPORTING

### 8.1. Requirements

The Table 14 below summarizes the requirements for recording safety events on the CRF and for reporting safety 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.

**Table 14. Requirements for Recording Safety Events on the Case Report Form (CRF) and Reporting Safety Events on the Clinical Trial Serious Adverse Events Form**

| 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 | All (regardless of whether associated with an AE), **except occupational exposure** | Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE) |

All observed or volunteered events regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following paragraphs.

Events listed in the table above that require reporting to Pfizer Safety on the CT SAE Report Form within 24 hours of awareness of the event by the investigator **are to be reported regardless of whether the event is determined by the investigator to be related to an investigational product under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available event information. This time frame also applies to additional new (follow-up) information on previously forwarded reports. In the rare situation that the investigator does not become immediately aware of the occurrence of an event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the Serious Adverse Events section below). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this 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. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

As part of ongoing safety reviews conducted by the sponsor, any non-serious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

### 8.1.1. Additional Details On Recording Adverse Events on the CRF

All events detailed in the table above will be recorded on the AE page(s) of the CRF. 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.

### 8.1.2. Eliciting Adverse Event Information

The investigator is to record on the CRF all directly observed AEs and all AEs spontaneously reported by the study participant or legally acceptable representative. In addition, each study participant/legally acceptable representative will be questioned about the occurrence of AEs in a non-leading manner.

### 8.1.3. Withdrawal From the Study Due to Adverse Events (see also the Participant Withdrawal Section)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted below, and recorded on the CRF.

When a participant withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the CT SAE Report Form, in accordance with the Requirements section above.

### 8.1.4. Time Period for Collecting AE/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 6 months; except as indicated below after the last administration of the investigational product.

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

#### 8.1.4.1. 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.

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.

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.

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.

#### 8.1.4.2. 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.

Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

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.

### 8.1.5. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship on the CRF, and report such an assessment in accordance with the SAE reporting requirements, if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. 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. If the investigator's causality assessment is "unknown but not related" to investigational product, this should be clearly documented on study records.

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.

### 8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions will be carried out in accordance with applicable local regulations.

## 8.2. Definitions

### 8.2.1. Adverse Events

An AE is any untoward medical occurrence in a study participant administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include, but are not limited to:

- Abnormal test findings;
- Clinically significant signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Drug abuse;
- Drug dependency.

Additionally, AEs may include signs and symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

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.

### 8.2.2. Abnormal Test Findings

Abnormal objective test findings should be recorded as AEs when any of the following conditions are met:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE.

### 8.2.3. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inparticipant hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Or that is considered to be:

- An important medical event.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the participant or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are 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).

Medical device complaints may meet the SAE reporting requirement criteria (see the Medical Device Complaint Reporting Requirements section). An incident is any malfunction (ie, the failure of a device to meet its performance specifications or to perform as intended; performance specifications include all claims made in the labeling for the device) that, directly or indirectly, might lead to or might have led to the death of a participant, or user, or of other persons, or to a serious deterioration in their state of health.

A serious injury that can cause a serious deterioration in state of health can include:

- A life-threatening illness, even if temporary in nature;
- A permanent impairment of a body function or permanent damage to a body structure;
- A condition necessitating medical or surgical intervention to prevent the above 2 bulleted items;

  Examples: clinically relevant increase in the duration of a surgical procedure; a condition that requires hospitalization or significant prolongation of existing hospitalization;
- Any indirect harm as a consequence of an incorrect diagnostic or in vitro diagnostic device test results when used within the manufacturer's instructions for use;
- Fetal distress, fetal death, or any congenital abnormality or birth defects.

### 8.2.4. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility, or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit is assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;

- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of a persistent pretreatment laboratory abnormality);
- Social admission (eg, participant has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual participant;
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as SAEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an SAE. For example, an acute appendicitis that begins during the reporting period should be reported if the SAE requirements are met, and the resulting appendectomy should be recorded as treatment of the AE.

## 8.3. Severity Assessment

**Table 15. Clinical Description of Severity**

| GRADE | Clinical Description of Severity |
|---|---|
| 0 | No change from normal or reference range (This grade is not included in the Version 5.0 CTCAE document but may be used in certain circumstances). |
| 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 |

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the participant's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

## 8.4. Special Situations

### 8.4.1. Potential Cases of Drug-Induced Liver Injury

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, 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, alkaline phosphatase and acetaminophen drug and/or protein adduct levels. 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) 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 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.

### 8.4.2. Exposure to the Investigational Product 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.

#### 8.4.2.1. Exposure During Pregnancy (EDP)

For both unapproved/unlicensed products and for marketed products, an 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.

#### 8.4.2.2. 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.

#### 8.4.2.3. 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.

### 8.4.3. Medication Errors

Other exposures to the investigational product under study may occur in clinical trial settings, such as medication errors. (see Table 16).

**Table 16. Medication Errors Reporting on the Clinical Trial Serious Adverse Event Form**

| 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 |

#### 8.4.3.1. 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 based on the investigational product administration, such as inadvertent exposure, or at the wrong dosage strength.

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.

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 medication dosing error, the sponsor should be notified within 24 hours.

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**.

### 8.5. Medical Device Complaint Reporting Requirements

All medical device complaints, regardless of whether the medical device complaint is associated with an AE, will be recorded on the applicable pages within the CRF. This includes potential incidents or malfunctions associated with the use of a medical device

product. An incident or malfunction is an event that might have led to death or serious deterioration in health, or if it occurred again might lead to death or serious deterioration in health.

Pfizer is to be notified of all medical device complaints within 24 hours of the investigator's awareness of the event.

## 9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

### 9.1. Analysis Sets

For safety evaluation, participants should have received at least one of the regimen components. For efficacy CCI [redacted] evaluation, participants should have received at least one dose of all components administered on Cycle 1 Day 1. See Section 9.4 for definitions related to efficacy.

Participants who receive the designated investigational product of interest and have at least one post-dose drug concentration measurement will be included in the PK data analysis.

1. **Safety analysis set.**

   The safety analysis set includes all enrolled participants who receive at least one dose of one of the components of the regimen.

2. **Full analysis set.**

   The full analysis set includes all enrolled participants.

3. **Per protocol analysis set**.

   The per protocol (PP) analysis set includes all enrolled participants who receive at least one dose of all regimen components administered on Cycle 1 Day 1 of study medication and who do not have major protocol deviations during the 28 days after the first vaccination.

4. **Modified Intention-to-Treat analysis set.**

   CCI [redacted] modified Intention-to-Treat (mITT), which is defined as all enrolled participants who received at least one dose of all regimen components administered on Cycle 1 Day 1. CCI [redacted] a participant

must have at least 1 valid and determinate assay result related to the proposed analysis. Participants who have no valid and determinate assay result related to any proposed analysis will be excluded from the mITT analysis set.

CCI [redacted]

5. **PK analysis set.**

   The PK parameter analysis population is defined as all enrolled participants treated who have sufficient information to estimate at least 1 of the PK parameters of interest and who have no major protocol deviations influencing the PK assessment.

6. **Immunogenicity analysis set.**

   The immunogenicity analysis set includes all enrolled participants who receive at least one dose of the VBIR-2 component that is the subject of the immunogenicity assessment (tremelimumab or sasanlimab).

## 9.2. Statistical Methods and Properties

### 9.2.1. Statistical Methods for Dose Escalation/De-Escalation

Many alternative designs have been proposed to the standard 3+3 design for Phase 1 dose escalation studies that improve its accuracy, efficiency and statistical validity. This study will utilize the mTPI design (Ji et al., 2010).[140]

The mTPI design (Ji et al., 2010)[140] uses a Bayesian statistics framework and a beta/binomial hierarchical model to compute the posterior probability of 3 dosing intervals that reflect the relative difference between the toxicity rate of each dose level to the target rate (pT = 0.275). If the toxicity rate of the currently used dose level is far smaller than pT, the mTPI will recommend escalating the dose level; if it is close to target probability (pT), the mTPI will recommend continuing at the current dose; if it is far greater than pT, the mTPI will recommend de-escalating the dose level. These rules are conceptually similar to those used by the 3+3 design, except the decisions of a mTP design are based on posterior probabilities calculated under a coherent probability model.

Being a model-based design, mTPI automatically and appropriately tailors dose-escalation and de-escalation decisions for different studies with different toxicity parameters. More importantly, all the dose-escalation decisions for a given study can be pre-calculated under the mTPI design and presented in a two-way table (Table 3). It is currently envisaged that AdC68 6 x $10^{11}$ VP + 5 mg pDNA + 150 mg tremelimumab + 300 mg sasanlimab will potentially be the highest dose level.

Thus, compared to other advanced model-based designs published in the literature, the mTPI design is logistically less complicated and easier to implement.

Decision rules are based on calculating posterior probabilities of 3 dosing i intervals corresponding to under, proper, and over dosing in terms of toxicity. Specifically, the underdosing interval is defined as (0; pT-$e_1$), the over-dosing interval (pT+$e_2$, 1), and the proper-dosing interval (pT- $e_1$, pT+ $e_2$), where $e_1$ and $e_2$ are small fractions. In this study, $e_1$ is selected as 0.05 and $e_2$ is selected as 0.05, therefore, the target interval for the DLT rate is (0.225, 0.325). The 27.5% target, the symmetry of the Equivalence Interval, and its upper limit were chosen based on safety considerations. The prior distribution of DLT is set as a beta (0.5, 0.5), and the threshold probability for early termination and dose exclusion is set to 0.95. Even though the upper limit of the mTPI is higher than 27.5%, doses with an incidence of DLT >27.5% (eg, 3 out of 9) cannot be declared as the MTD.

The 3 dosing intervals are associated with 3 different dose-escalation decisions. The underdosing interval corresponds to a dose-escalation I, overdosing corresponds to a dose de-escalation (D/U), and proper dosing corresponds to remaining at the current dose (S).

### 9.2.2. Statistical Method for Estimating the MTD

As previously described, the estimated MTD is the highest tested dose level with a DLT rate ≤32.5% in at least 6 DLT-evaluable participants. It is assumed that higher doses result in higher toxicity rates. But, due to the relatively low number of participants that may be potentially allocated to any dose combination, this assumption may be incorrect, allowing for higher dose levels to be tested.

Clinical judgment will be exercised in taking forward doses to the expansion cohort(s), in case no clear choice exists between more than 1 competing MTD. This decision will be based upon the combination of data related to safety, anti-tumor activity, and clinical judgment of the investigators and the sponsor.

## 9.3. Sample Size Determination

It is anticipated that each of the cohorts will aim to enroll 2-4 participants, with the exception of the cohort with the anticipated MTD dose that will aim to enroll up to 12 participants. Due to the dynamic nature of the Bayesian allocation procedure, the sample size of the mTPI approach cannot be determined in advance. It is estimated approximately 36 DLT evaluable participants may be enrolled in the dose escalation stage in order to have a reliable and accurate estimate of the MTD. The actual sample size for the dose escalation may be smaller, depending on the underlying dose toxicity profile.

At least 6 and up to 12 participants should be enrolled at a dose level that is predicted to be the MTD as per the mTPI method. Dose cohorts with an acceptable safety profile may be expanded up to N=12 to further assess safety, CCI [redacted] pharmacokinetics, CCI [redacted] Decisions to enroll additional participants at dose levels already cleared for safety will be based on clinical judgment of the investigators and the sponsor considering all evaluable safety, CCI [redacted] data.

The expansion phase of the study (Part 2) will consist of 1 cohort of participants with metastatic or locally-advanced NSCLC. Approximately 30 participants will be enrolled for

the dose expansion. A Bayesian approach will be used to estimate the objective response rate (ORR) and clinical benefit rate (CBR) in the study indications. As an example of this approach related to ORR, assuming a non informative prior (ie, Jeffrey's prior), if 14 out of 30 participants (46.7%) achieve a CR or PR, this would translate into a posterior probability (Beta Binomial) of 77% that the true ORR/clinical benefit rate is not inferior to 20%. (See Definitions of ORR and CBR in Section 9.4).

### 9.4. Efficacy Analysis

In this First-In-Patient study anti-tumor activity is a secondary [redacted] objective. The main analysis populations will be based on mITT and EP (see Section Analysis Sets).

Disease response will be presented in the form of participant data listings that include, but are not limited to starting dose, disease response at each visit, and best overall response. In addition, progression date, death date, date of first response and last disease assessment date, and date of last contact will be listed.

Summary of objective response rates (ORR) and clinical benefit rate (CBR) will be provided by descriptive statistics.

**Progression -free survival (PFS)** is the time from start date to date of first documentation of progression, or death due to any cause. Progression is defined as the appearance of local, regional or distant disease of the same type after complete response or progression of pre-existing lesions. It does not include second primary malignancies of unrelated types.

**Overall survival (OS)** is the time from start date to date of death due to any cause.

**Duration of Response (DOR)** is defined as the duration of overall response measured from the time measurement criteria are met for complete response (CR) or partial response (PR) (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

**Duration of Stable Disease (DOSD)** is defined as stable disease measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

**Clinical Benefit Rate (CBR)** is defined as the proportion of participants who achieved anti-tumor responses of Complete Response (CR), Partial Response (PR), or Stable Disease for > 6 months (SD).

The Kaplan--Meier methods will be used to analyze all time to event endpoints. Details of these endpoint analyses methods will be included in the Statistical Analysis Plan.

## 9.5. Safety Analysis

The main analyses of DLTs will be based on the Per Protocol analysis set. Participants not meeting the criteria for inclusion in the Per Protocol Analysis set (ie, not evaluable for assessment of DLTs) will be replaced. Summaries and analyses of other safety parameters will include all participants in the Safety Analysis Set (see Section Analysis Sets).

### 9.5.1. Analysis of Primary Endpoint

Dose Limiting Toxicity (DLT) is the primary endpoint of Part 1 of the study. The occurrence of DLTs observed in the dosing cohorts will govern the dose escalation as described in Section 3.1. If a participant is withdrawn from study for any reason other than a DLT prior to completion of the 28-day safety observation period, a replacement participant will be assigned for the same dose as the replaced participant. The properties of the statistical methods for the analyses of DLTs are described in section Statistical Methods and Properties. Adverse Events constituting DLTs will be listed per dose level. Adverse Events (AEs) will be graded by the investigator according to the CTCAE version 5.0 and coded using the Medical Dictionary for Regulatory Activities (MedDRA). The focus of AE summaries will be on Treatment Emergent-Emergent Adverse Events, those with initial onset or increasing in severity after the first dose of study treatment. The number and percentage of participants who experienced any AE, SAE, treatment related AE, and treatment related SAE will be summarized according to worst toxicity grades. The summaries will present AEs both on the entire study period by dose and by cycle.

### 9.5.2. Analysis of Secondary Endpoints

**Laboratory Tests Abnormalities**

The number and percentage of participants who experienced laboratory test abnormalities will be summarized according to worst toxicity grade observed for each lab assay. The analyses will summarize laboratory tests both on the entire study period and by cycle (Cycle 1 and Cycles beyond 1). Shift tables will be provided to examine the distribution of laboratory toxicities.

For laboratory tests without CTCAE grade definitions, results will be categorized as normal, abnormal or not done.

### 9.5.3. ECG

The analysis of ECG results will be based on participants in the safety analysis set with baseline and on-treatment ECG data. Baseline is defined as the pre-dose ECG collected before the first dose of any component of the study treatment.

ECG measurements (an average of the triplicate measurements) will be used for the statistical analysis and all data presentations. Any data obtained from ECGs repeated for safety reasons after the nominal time-points will not be averaged along with the preceding triplicates. Interval measurements from repeated ECGs will be included in the outlier analysis (categorical analysis) as individual values obtained at unscheduled time points.

QT intervals will be corrected for heart rate (QTc) using standard correction factors (ie, Frederica's). Data will be summarized and listed for QT, HR, PR interval, QRS, and QTcF by cohort. Individual QT intervals will be listed by time and cohort. Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be used to summarize the absolute corrected QT interval and changes from baseline in corrected QT after treatment by cohort and time point. For each participant and by treatment, the maximum change from baseline will be calculated as well as the maximum post-baseline interval across time-points. Categorical analysis will be conducted for the maximum change from baseline in corrected QT and the maximum post-baseline QT interval.

Shift tables will be provided for baseline versus worst on treatment corrected QT using Maximum CTC AE Grade. Shift tables will also be provided for ECG abnormality at baseline versus on treatment (yes, no, not done: (n, %)). Participants experiencing clinically -relevant morphological ECG changes will be summarized (including frequency and percentage).

If applicable, the effect of relevant drug concentrations on corrected QT change from baseline will be explored graphically. Additional concentration -corrected QT analyses may be performed. Data may be pooled with other study results and/or explored further with PK/PD models.

## 9.6. Analysis of Pharmacokinetics CCI [redacted]

### 9.6.1. Analysis of Pharmacokinetics

#### 9.6.1.1. Tremelimumab Pharmacokinetic Analysis

The concentration -time data for tremelimumab will be summarized descriptively (n, mean, standard deviation, coefficient of variation (CV), median, minimum, maximum, geometric mean and its associated CV) by dose, and nominal time for both Part 1 and Part 2.

For participants assigned to Cohorts 3A and 6A , the concentration -time data of tremelimumab after the first dose will be analyzed individually by noncompartmental methods to determine PK parameters. The PK parameters to be estimated will include the maximum plasma concentration ($C_{max}$), time to maximum plasma concentration ($T_{max}$), and area under the plasma concentration versus time curve following the first dose from time 0 to the last time point prior to the second tremelimumab dose ($AUC_{last}$) and if data permit or if considered appropriate, area under the plasma concentration versus time curve from time 0 extrapolated to infinity ($AUC_{inf}$), terminal elimination half-life- ($t_{1/2}$), apparent serum clearance (CL/F), apparent volume of distribution ($V_z$/F). The PK parameters will be summarized descriptively (n, mean, standard deviation, coefficient of variation (CV), median, minimum, maximum, geometric mean and its associated CV) by dose.

Individual participant and median profiles of the concentration time data, after the first tremelimumab dose, will be plotted by dose, using nominal times. Individual and median profiles will be presented on both linear-linear and log-linear scales.

### 9.6.1.2. Sasanlimab Pharmacokinetic Analysis

The concentration -time data for sasanlimab will be summarized descriptively (n, mean, standard deviation, CV, median, minimum, maximum, geometric mean and its associated CV) by dose, and nominal time for both Part 1 and Part 2.

For participants assigned to Cohorts 4A and 5A, the concentration -time data of sasanlimab after the first dose will be analyzed individually by noncompartmental methods to determine PK parameters. The PK parameters to be estimated will include the following: (a) the maximum plasma concentration ($C_{max}$), (b) time to maximum plasma concentration ($T_{max}$), and (c) area under the plasma concentration versus time curve following the first dose from time 0 to the last time point prior to the second sasanlimab dose ($AUC_{last}$). If data permit or if considered appropriate, other analyses may include: (a) area under the plasma concentration versus time curve from time 0 extrapolated to infinity ($AUC_{inf}$), (b) terminal elimination half-life ($t_{1/2}$), (c) apparent serum clearance (CL/F), and (d) apparent volume of distribution ($V_z$/F). The PK parameters will be summarized descriptively (n, mean, standard deviation, coefficient of variation (CV), median, minimum, maximum, geometric mean and its associated CV) by dose).

Individual participant and median profiles of the concentration-time data after the first sasanlimab dose will be plotted by dose using nominal times. Individual and median profiles will be presented on both linear-linear and log-linear scales.

CCI

[redacted]

### 9.6.3. Analysis of Immunogenicity Data

The percentage of participants with positive tremelimumab ADA and NAb will be summarized by each cohort. For participants with positive ADA or NAb, the magnitude (titer), time of onset, and duration of ADA or NAb response will also be described, if data permit.

The percentage of participants with positive sasanlimab ADA and NAb will be summarized by cohort. For participants with positive ADA or NAb, and if data permits, the magnitude (titer), time of onset, and duration of ADA or NAb response will be described.

### 9.6.4. Population Pharmacokinetic Analysis or Pharmacokinetic/[redacted] (PK[redacted]) Modeling

PK[redacted] data from this study may be analyzed using modeling approaches and may also be pooled with data from other studies to investigate any association between tremelimumab or sasanlimab exposure[redacted] or significant safety and/or efficacy endpoints. The results of these analyses, if performed, may be reported separately.

### 9.7. Data Monitoring Committee

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

## 10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the investigator site may be subject to review by the IRB/EC, and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the investigator site for the inspection and will allow Pfizer 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 Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

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.

## 11. DATA HANDLING AND RECORD KEEPING

### 11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included participant. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to

third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator shall ensure that the CRFs are securely stored at the study site in [encrypted electronic and/or paper] form and will be [password protected or secured in a locked room] to prevent access by unauthorized third parties.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital or the physician's chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

### 11.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating participants (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

# 12. ETHICS

## 12.1. Institutional Review Board/Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the participants. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

## 12.2. Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, legal and regulatory requirements and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), ICH Guideline for Good Clinical Practice, and the Declaration of Helsinki.

## 12.3. Participant Information and Consent

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant personal data. Such measures will include omitting participant names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable law.

The personal data will be stored at the study site in [encrypted electronic and/or paper] form and will be [password protected or secured in a locked room] 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, when study data are compiled for transfer to Pfizer and other authorized parties, participant names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, subject-specific code. The investigator 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, Pfizer will maintain high standards of confidentiality and protection of participants' personal data consistent with the Clinical Study Agreement and applicable privacy laws.

The informed consent documents and any participant recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process and any participant recruitment materials must be reviewed and approved by Pfizer, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study participant or his or her legally acceptable representative is fully informed about the nature and objectives of the study, the sharing of data relating to the study and possible risks associated with participation, including the risks associated with the processing of the participant's personal data. The investigator further must ensure that each study participant[, or his or her legally acceptable representative, or parent(s) or legal guardian if a minor,] 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.

Whenever consent is obtained from a participant's legally acceptable representative, the participant's assent (affirmative agreement) must subsequently be obtained when the participant has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a participant's decisional capacity is so limited he or she cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the participant's assent may be waived with source documentation of the reason assent was not obtained. If the study participant does not provide his or her own consent, the source documents must record why the participant did not provide consent (eg, minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the participant's legally acceptable representative, the consent signer's relationship to the study participant (eg, parent, spouse), and that the participant's assent was obtained or waived. If assent is obtained verbally, it must be documented in the source documents.

The investigator, or a person designated by the investigator, will obtain written informed consent from each participant or the participant's legally acceptable representative before any study-specific activity is performed unless a waiver of informed consent has been granted by an IRB/EC. The investigator will retain the original of each participant's signed consent document.

### 12.4. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

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.

## 13. DEFINITION OF END OF TRIAL

### 13.1. End of Trial in All Participating Countries

### 13.2. End of trial is Defined as Last Subject Last Visit (LSLV).

## 14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of VBIR-2 at any time.

If a study is prematurely terminated, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating participants and the hospital pharmacy (if applicable) within an acceptable time period per the institutional policy and IRB/EC following receipt of notification. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

## 15. IN THE CASE OF PREMATURE TERMINATION (EG, THE SPONSOR DISCONTINUES DEVELOPMENT), THE STUDY WILL BE CLOSED NO LATER THAN 2 YEARS FROM THE FIRST DOSE OF THE LAST SUBJECT.PUBLICATION OF STUDY RESULTS

### 15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting of the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and or www.pfizer.com, along with other public registries in accordance with applicable local laws and regulations.

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 Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are 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 (CSR synopses in which any data that could be used to identify individual participants has 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.

### 15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by the Principal Investigator (PI) of the results of the study based on information collected or generated by the PI, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer with an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before it is submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all investigator sites, and that any subsequent publications by the PI will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II — "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for

Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study participants, and the CSA will control as to all other issues.

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## Appendix 1. Abbreviations

The following is a list of abbreviations that may be used in the protocol.

| Abbreviation | Term |
|---|---|
| Ab | anti-body |
| ABCP | atezolizumab plus BCP |
| AChR | acetylcholine receptor |
| ACRIN | American College of Radiology Imaging Network |
| ADA | anti-drug antibodies |
| AdC68 | a chimpanzee adenovirus 68 |
| AE | adverse event |
| AIDS | acquired immunodeficiency syndrome |
| ALK WT | Anaplastic lymphoma kinase wild-type |
| ALT | alanine aminotransferase |
| ANC | absolute neutrophil count |
| ANOVA | analysis of variance |
| ART | antiretroviral therapy |
| ASCO | American Society of Clinical Oncology |
| AST | aspartate aminotransferase |
| AUC | area under the curve |
| $AUC_{inf}$ | area under the curve plasma concentration versus time curve from time 0 extrapolated to infinity |
| $AUC_{last}$ | area under the curve plasma concentration following the first dose from time 0 to last time point |
| CCI | [redacted] |
| BCP | bevacizumab plus carboplatin plus paclitaxel |
| BCT | blood collection tube |
| BID | twice daily |
| BP | blood pressure |
| BRAF | proto-oncogene protein B-raf |
| BSA | body surface area |
| BUN | blood urea nitrogen |
| C | Cycle |
| CAR | chimeric antigen receptor |
| CBR | clinical benefit rate |
| CL/F | apparent serum clearance |
| $C_{max}$ | maximum plasma concentration |
| C1D1 | cycle 1 day 1 |
| CHF | congestive heart failure |
| cHL | classical Hodgkin lymphoma |
| ChTx | chemotherapy treatment |
| CI | confidence interval |

| Abbreviation | Term |
|---|---|
| CISH | chromogenic in situ hybridization |
| CK | creatine kinase |
| CL | Clearance |
| CLL | chronic lymphocytic leukemia |
| CNS | central nervous system |
| COVID-19 | coronavirus disease of 2019 |
| CR | complete response |
| CRF | case report form |
| CRM | Continual Reassessment Method |
| CSA | clinical study agreement |
| CSF | cerebrospinal fluid |
| CSR | clinical study report |
| CT | computed tomography |
| CT | clinical trial |
| CTA | clinical trial application |
| CCI | [redacted] |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTLA4 | Anti-cytotoxic T Lymphocyte-associated antigen 4 |
| cTnI | cardiac troponin-I |
| CV | coefficient of variation |
| DILI | drug-induced liver injury |
| DLI | donor lymphocyte infusion |
| DLT | dose-limiting toxicity |
| DMC | data monitoring committee |
| DNA | deoxyribonucleic acid |
| DR | duration of Response |
| DU | dispensable unit |
| D/U | dose de-escalation |
| DOR | duration of response |
| DOSD | duration of stable disease |
| EC | ethics committee |
| ECC | emergency contact card |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| E-DMC | external data monitoring committee |
| EDP | exposure during pregnancy |
| EDTA | ethylenediaminetetraacetic acid |
| EFS | event-free survival |
| Eg | for example |
| EGFR | epidermal growth factor receptor |
| EI | equivalence interval |

| Abbreviation | Term |
|---|---|
| EML4 | echinoderm microtubule-associated protein-like 4 |
| EP | evaluable population |
| ER | estrogen receptor |
| Etc | 'and other things' or 'and so forth' |
| EU | European Union |
| EudraCT | European Clinical Trials Database |
| FDA | Food and Drug Administration (United States) |
| FFPE | formalin-fixed paraffin-embedded |
| FIP | first in patient |
| FISH | fluorescence in situ hybridization |
| FSH | follicle-stimulating hormone |
| GCP | Good Clinical Practice |
| GGT | gamma-glutamyl transferase |
| GI | gastrointestinal |
| GnRH | gonadotropin-releasing hormone agonist |
| GPI | glycophosphatidylinositol |
| GVAX | cancer vaccine |
| GVHD | graft versus host disease |
| HBV | hepatitis B virus |
| HCC | hepatocellular carcinoma |
| HCV | hepatitis C virus |
| HER2 | human epidermal growth factor 2 |
| Hgb | Hemoglobin |
| HIV | human immunodeficiency virus |
| HR | heart rate / hazard ratio |
| IB | investigator's brochure |
| ICH | International Conference on Harmonisation |
| ICOS | inducible T-cell costimulatory |
| ID | Identification |
| Ie | that is |
| IFN | Interferon |
| Ig | Immunoglobulin |
| IgG4 | immunoglobulin G4 |
| IHC | immunohistochemistry |
| IM | intramuscular |
| IP | investigational product |
| IND | investigational new drug application |
| INR | international normalized ratio |
| IP manual | Investigational Product manual |
| IRB | institutional review board |
| IRC | internal review committee |

| Abbreviation | Term |
|---|---|
| irCR | immune related – complete response |
| irPD | immune related – progressive disease |
| irPR | immune related – partial response |
| irSD | immune related – stable disease |
| IRT | interactive response technology |
| ISR | injection site reaction |
| IUD | intrauterine device |
| IV | intravenous |
| IWR | interactive Web-based response |
| CCI [redacted] | [redacted] |
| kDa | kilodalton |
| KRAS | proto-oncogene |
| LAG3 | lymphocyte activation gene 3 |
| LDH | lactate dehydrogenase |
| LFT | liver function test |
| LM | listeria monocytogene |
| LSLV | last subject last visit |
| LVEF | left ventricular ejection fraction |
| mAb | monoclonal antibody |
| MCC | Merkel cell carcinoma |
| MD | multiple dose |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MFD | maximum feasible dose |
| MG | myasthenia gravis |
| MHC | major histocompatibility complex |
| mITT | modified intend to treat |
| mNSCLC | metastatic non-small cell lung cancer |
| mOS | median overall survival |
| MPF | megakaryocyte potentiating factor |
| mPFS | median progression-free survival |
| MRI | magnetic resonance imaging |
| MSLN | mesothelin |
| MTD | maximum tolerated dose |
| mTNBC | metastatic triple negative breast cancer |
| mTPI | modified toxicity probability interval |
| mTTP | median time to progression |
| MUC1 | mucin 1, cell surface associated |
| N/A | not applicable |
| NAb | neutralizing antibody |
| NCI | National Cancer Institute |

| Abbreviation | Term |
|---|---|
| NCI CTCAE | National Cancer Institute Common Terminology Criteria for Adverse Events |
| NHPs | nonhuman primates |
| NK | natural killer |
| NSCLC | non-small cell lung cancer |
| OBD | optimal biological dose |
| OR | Objective Response or Overall Response |
| ORR | objective response rate |
| OS | overall survival |
| CCI | [redacted] |
| PCD | primary completion date |
| PD | pharmacodynamics |
| PD | progressive disease |
| PD-1 | programmed death – 1 |
| PD-L1 | programmed death – ligand 1 |
| pDNA | Plasmid deoxyribonucleic acid |
| PET | positron emission tomography |
| PFS | Progression-Free Survival |
| PFS | prefilled syringe |
| PI | principal investigator |
| PK | Pharmacokinetic |
| PGx | pharmacogenomics |
| PP | per protocol |
| PR | partial response |
| PR | progesterone receptor |
| PrCa | prostate cancer |
| PrCaVBIR | Prostate Cancer Vaccine-based Immunotherapy Regimen |
| PS | performance status |
| PSA | Prostate specific antigen |
| PSCA | Prostate stem cell antigen |
| PSMA | Prostate specific membrance antigen |
| pT | Target probability |
| PT | prothrombin time |
| PTT | partial thromboplastin time |
| QD | every day |
| QT | time between the start of the Q wave and the end of the T wave |
| QTcF | QT interval with Fridericia's correction |
| QxW | Every x# of Weeks, ie, Q2W, Q4W, Q6W, Q12W) |
| RCC | renal cell carcinoma |
| RD | Response/Remission Duration |
| RECIST | Response Evaluation Criteria in Solid Tumors |

| Abbreviation | Term |
|---|---|
| RET | rearranged during transfection |
| RFS | Relapse-Free Survival |
| CCI [redacted] | [redacted] |
| ROS1 | ROS proto-oncogene 1, receptor tyrosine kinase |
| RP2D | recommended Phase 2 dose |
| RR | response rate |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SARS-CoV2 | severe acute respiratory syndrome coronavirus 2 |
| SC | Subcutaneous |
| SCCHN | squamous cell carcinoma of the head and neck |
| SCLC | small cell lung cancer |
| SD | single dose / stable disease |
| SGOT | serum glutamic-oxaloacetic transaminase |
| SGPT | serum glutamic-pyruvic transaminase |
| SOA | Schedule of Activities |
| SOP | standard operating procedure |
| SRSD | single reference safety document |
| $T_{1/2}$ | terminal elimination half-life |
| $T_{max}$ | time to maximum plasma concentration |
| Tbili | total bilirubin |
| TAAs | tumor associated antigens |
| TBR | tumor background ratio |
| CCI [redacted] | [redacted] |
| TERT | telomerase reverse transcriptase |
| TILs | tumor infiltrating lymphocytes |
| TKIs | tyrosine kinase inhibitors |
| TDS-IM | (Ichor) Intramuscular TriGrid Delivery System |
| TNBC | triple negative breast cancer |
| TRAEs | treatment-related adverse events |
| TRK | tyrosine receptor kinase |
| TSH | thyroid stimulating hormone |
| TTP | time to progression |
| ULN | upper limit of normal |
| UPM | unit probability mass |
| US | United States |
| USPI | United States Package Insert |
| UVB | ultraviolet B |
| VBIR-2 | Vaccine-based immunotherapy regimen - 2 |
| VP | viral particles |
| Vz/F | volume of distribution |

| Abbreviation | Term |
|---|---|
| WBC | white blood cell |
| WHO | World Health Organization |
| WT | wild-type |

## Appendix 2. ECOG Performance Status

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

*As published in Am J Clin Oncol 5:649 655, 1982

## Appendix 3. RECIST (Response Evaluation Criteria In Solid Tumors) version 1.1 Guidelines

*Adapted from E.A. Eisenhauer, et al: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer 45 (2009) 228–247.*

### 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 14.9 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 indeterminate.

**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 on study.

- 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 a target lesion becomes too small to measure, 0 mm should be recorded if the lesion is considered to have disappeared; otherwise a default value of 5 mm should be recorded.

**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, INDETERMINATE, PRESENT/NOT INCREASED, INCREASED. 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 must be discussed with the radiologist to determine if substitution is possible. If not, subsequent objective statuses are indeterminate.

### 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. The short diameter is used in the sum for target nodes, while the longest diameter is used in the sum for all other target lesions. All target lesions must be assessed.

- Stable: 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, 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.

- Indeterminate. Progression has not been documented, and

- one or more target measurable 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. 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 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 stable disease (SD) or PR in target disease, progression due to unequivocal increase in non-target disease should be rare.

- Indeterminate: Progression has not been determined and one or more non-target sites were not assessed or assessment methods were inconsistent with those used at baseline.

**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 objective progression even after discontinuation of treatment.

**Table 17. Objective Response Status at each Evaluation**

| Target Lesions | Non-target Disease | New Lesions | Objective status |
|---|---|---|---|
| CR | CR | No | CR |
| CR | Non-CR/Non-PD | No | PR |
| CR | Indeterminate or Missing | No | PR |
| PR | Non-CR/Non-PD, Indeterminate, or Missing | No | PR |
| SD | Non-CR/Non-PD, Indeterminate, or Missing | No | Stable |
| Indeterminate or Missing | Non-PD | No | Indeterminate |
| PD | Any | Yes or No | PD |
| Any | PD | Yes or No | PD |
| Any | Any | Yes | PD |

**Table 18. Objective Response Status at each Evaluation for Participants with Non-Target Disease Only**

| Non-target Disease | New Lesions | Objective status |
|---|---|---|
| CR | No | CR |
| Non-CR/Non-PD | No | Non-CR/Non-PD |
| Indeterminate | No | Indeterminate |
| Unequivocal progression | Yes or No | PD |
| Any | Yes | PD |

## Appendix 4. National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)

The NCI CTCAE (Version 5.0 dated November 27, 2017) has been placed in the Study Manual for this protocol. Alternatively, the NCI CTCAE may be reviewed on-line at the following NCI website:
https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm

## Appendix 5. Management of Immune-related Adverse Events (irAEs)

| Management of irAEs including Myasthenia Gravis | | |
|---|---|---|
| **Gastrointestinal irAEs** | | |
| **Severity of Diarrhea/Colitis (NCI-CTCAE v5.0)** | **Initial Management** | **Follow-up Management** |
| **Grade 1**<br><br>Diarrhea: <4 stools/day over Baseline<br><br>Colitis: asymptomatic | -Continue study treatment.<br><br>-Symptomatic treatment (eg, loperamide). | -Close monitoring for worsening symptoms.<br><br>-Educate patient to report worsening immediately.<br><br>-If worsens:<br><br>Treat as Grade 2, 3 or 4. |
| **Grade 2**<br><br>Diarrhea: 4 to 6 stools per day over Baseline; IV fluids indicated <24 hours; not interfering with ADL<br><br>Colitis: abdominal pain; blood in stool | -Withhold study treatment.<br><br>-Symptomatic treatment. | -If improves to Grade ≤1: Resume study treatment.<br><br>-If persists >5-7 days or recurs: Treat as Grade 3 or 4. |
| **Grade 3 to 4**<br><br>Diarrhea (Grade 3): ≥7 stools per day over Baseline; incontinence; IV fluids ≥24 h; interfering with ADL<br><br>Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs<br><br>Grade 4: life-threatening, perforation | -Withhold for Grade 3.<br><br>-Permanently discontinue study treatment for Grade 4 or recurrent Grade 3.<br><br>-1.0 to 2.0 mg/kg/day prednisone IV or equivalent.<br><br>-Add prophylactic antibiotics for opportunistic infections.<br><br>-Consider lower endoscopy. | -If improves:<br><br>-Continue steroids until Grade ≤1, then taper over at least 1 month; resume study treatment following steroids taper (for initial Grade 3).<br><br>-If worsens, persists >3 to 5 days, or recurs after improvement:<br><br>-Add infliximab 5mg/kg (if no contraindication).<br><br>-Note: infliximab should not be used in cases of perforation or sepsis. |

| Dermatological irAEs | | |
|---|---|---|
| **Grade of Rash (NCI-CTCAE v5.0)** | **Initial Management** | **Follow-up Management** |
| **Grade 1 to 2**<br><br>Covering ≤30% body surface area | -Continue study treatment.<br><br>-Symptomatic therapy (for example, antihistamines, topical steroids). | -If persists >1 to 2 weeks or recurs:<br><br>-Withhold study treatment;<br><br>-Consider skin biopsy.<br><br>-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.<br><br>-If worsens: Treat as Grade 3 to 4. |
| **Grade 3 to 4**<br><br>Grade 3: Covering >30% body surface area;<br><br>Grade 4: Life threatening consequences | -Withhold study treatment for Grade 3.<br><br>-Permanently discontinue for Grade 4 or recurrent Grade 3.<br><br>-Consider skin biopsy.<br><br>-Dermatology consult.<br><br>-1.0 to 2.0 mg/kg/day prednisone or equivalent.<br><br>-Add prophylactic antibiotics for opportunistic infections. | -If improves to Grade ≤1:<br><br>-Taper steroids over at least 1 month; resume study treatment following steroids taper (for initial Grade 3). |

| Pulmonary irAEs | | |
|---|---|---|
| **Grade of Pneumonitis (NCI-CTCAE v5.0)** | **Initial Management** | **Follow-up Management** |
| **Grade 1**<br>Radiographic changes only | -Consider withholding study treatment.<br>-Monitor for symptoms every 2 to 3 days.<br>-Consider Pulmonary and Infectious Disease consults. | -Re-assess at least every 3 weeks.<br>-If worsens: Treat as Grade 2 or Grade 3 to 4. |
| **Grade 2**<br>Mild to moderate new symptoms | -Withhold study treatment.<br>-Pulmonary and Infectious Disease consults.<br>-Monitor symptoms daily; consider hospitalization.<br>-1.0 to 2.0 mg/kg/day prednisone or equivalent.<br>-Add prophylactic antibiotics for opportunistic infections.<br>-Consider bronchoscopy, lung biopsy. | -Re-assess every 1 to 3 days If improves:<br>-When symptoms return to Grade ≤1, taper steroids over at least 1 month, and then resume study treatment following steroids taper.<br>-If not improving after 2 weeks or worsening: Treat as Grade 3 to 4. |
| **Grade 3 to 4**<br>Grade 3: Severe new symptoms; New/worsening hypoxia;<br>Grade 4: Life-threatening | -Permanently discontinue study treatment.<br>-Hospitalize.<br>-Pulmonary and Infectious Disease consults.<br>-1.0 to 2.0 mg/kg/day prednisone or equivalent.<br>-Add prophylactic antibiotics for opportunistic infections.<br>-Consider bronchoscopy, lung biopsy. | If improves to Grade ≤1:<br>-Taper steroids over at least 1 month.<br>-If not improving after 48 hours or worsening: Add additional immunosuppression (for example, infliximab, cyclophosphamide, IV.<br>-immunoglobulin, or mycophenolate mofetil). |

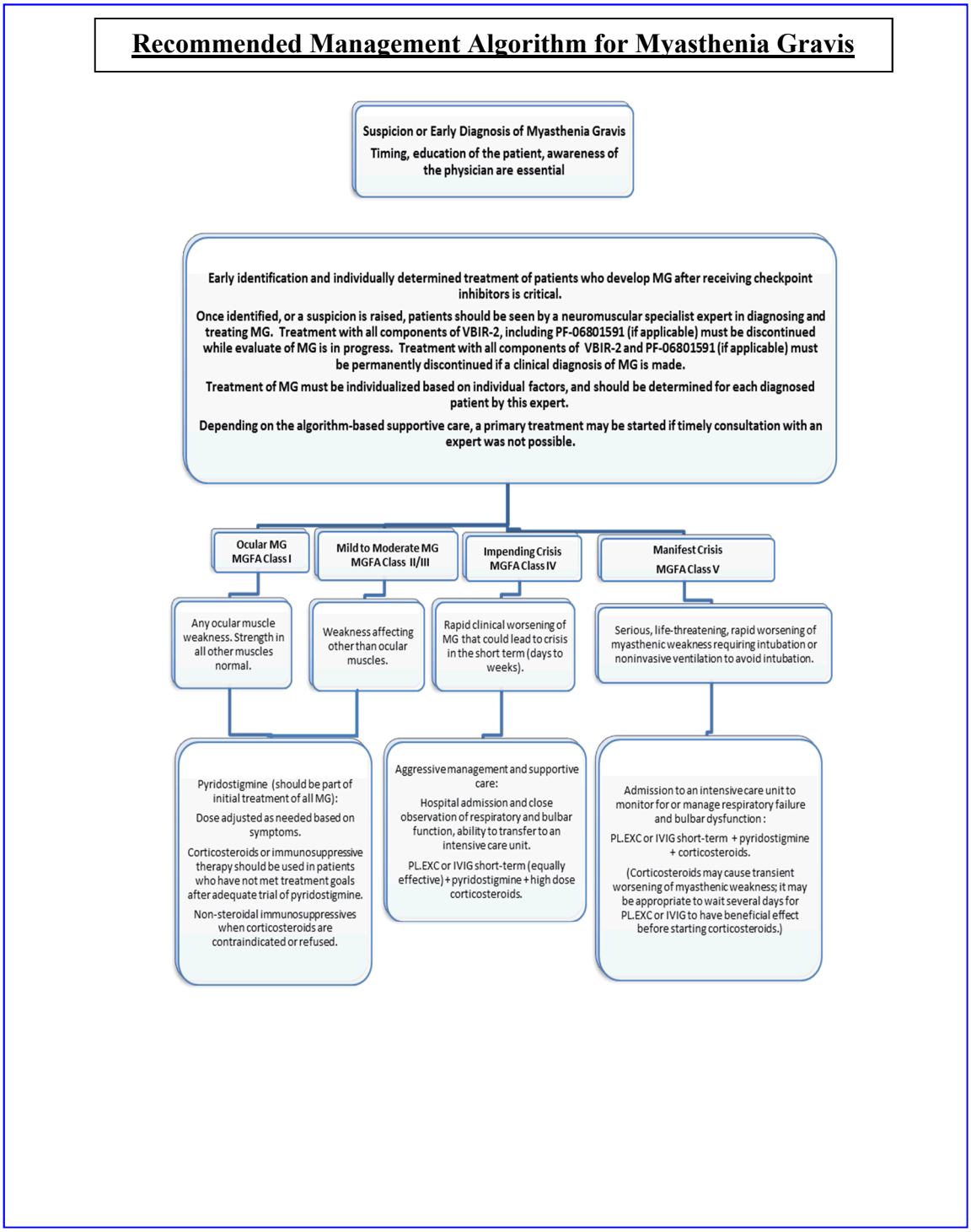
| Hepatic irAEs | | |
|---|---|---|
| **Grade of Liver Test Elevation (NCI-CTCAE v5.0)** | **Initial Management** | **Follow-up Management** |
| **Grade 1**<br>Grade 1 AST or ALT > ULN to 3.0 x ULN and/or Total bilirubin > ULN to<br>1.5 x ULN | -Continue study treatment. | -Continue liver function monitoring.<br>-If worsens: Treat as Grade 2 or 3 - 4. |
| **Grade 2**<br>AST or ALT >3.0 to ≤ 5 x ULN and/or total bilirubin >1.5 to ≤ 3 x ULN | -Withhold study treatment.<br>-Increase frequency of monitoring to every 3 days. | -If returns to Grade ≤1:<br>-Resume routine monitoring; resume study treatment.<br>-If elevation persists >5 to 7 days or worsens:<br>-Treat as Grade 3 to 4. |
| **Grade 3 to 4**<br>AST or ALT >5 x ULN and/or total bilirubin >3 x ULN | -Permanently discontinue study treatment.<br>-Increase frequency of monitoring to every 1 to 2 days.<br>-1.0 to 2.0 mg/kg/day prednisone or equivalent.<br>-Add prophylactic antibiotics for opportunistic infections.<br>-Consult gastroenterologist/hepatologist.<br>-Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted. | -If returns to Grade ≤1:<br>-Taper steroids over at least 1 month.<br>-If does not improve in >3 to 5 days, worsens or rebounds:<br>-Add mycophenolate mofetil 1 gram (g) twice daily.<br>-If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines. |

| Renal irAEs | | |
|---|---|---|
| **Grade of Creatinine Increased (NCI-CTCAE v5.0)** | **Initial Management** | **Follow-up Management** |
| **Grade 1**<br>Creatinine increased > ULN to 1.5 x ULN | -Continue study treatment. | -Continue renal function monitoring<br>-If worsens: Treat as Grade 2 to 3 or 4. |
| **Grade 2 to 3**<br>Creatinine increased >1.5 and ≤6 x ULN | -Withhold study treatment.<br>-Increase frequency of monitoring to every 3 days.<br>-1.0 to 2.0 mg/kg/day prednisone or equivalent.<br>-Add prophylactic antibiotics for opportunistic infections.<br>-Consider renal biopsy. | -If returns to Grade ≤1:<br>-Taper steroids over at least 1 month, and resume study treatment following steroids taper.<br>-If worsens:<br>-Treat as Grade 4. |
| **Grade 4**<br>Creatinine increased >6 x ULN | -Permanently discontinue study treatment.<br>-Monitor creatinine daily.<br>-1.0 to 2.0 mg/kg/day prednisone or equivalent.<br>-Add prophylactic antibiotics for opportunistic infections Consider renal biopsy.<br>-Nephrology consult. | -If returns to Grade ≤1:<br>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 study treatment.<br>-Hospitalize.<br>-In the presence of life threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management.<br>-Consult cardiologist to establish etiology and rule-out immune-mediated myocarditis.<br>-Guideline based supportive treatment as per cardiology consult.*<br>-Consider myocardial biopsy if recommended per cardiology consult. | -If symptoms improve and immune-mediated etiology is ruled out, re-start study treatment.<br>-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 study treatment.<br>-Guideline based supportive treatment as appropriate as per cardiology consult.*<br>1.0 to 2.0 mg/kg/day prednisone or equivalent.<br>-Add prophylactic antibiotics for opportunistic infections. | Once improving, taper steroids over at least 1 month.<br>If no improvement or worsening, consider additional immunosuppressants (eg, azathioprine, cyclosporine A). |

*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/UCM_316885_Guidelines-Statements.jsp.

## Appendix 6. Recommended Management Algorithm for Myasthenia Gravis



## Appendix 7. Alternative Measures During Public Emergencies

The alternative study measures described in this section are to be followed during public emergencies, including the COVID-19 pandemic. This appendix applies for the duration of the COVID-19 pandemic and will become effective for other public emergencies only upon written notification from Pfizer.

Use of these alternative study measures are expected to cease upon the return of business as usual circumstances (including the lifting of any quarantines and travel bans/advisories).

### Eligibility

While SARS-CoV2 testing is not mandated for this study, local clinical practice standards for testing should be followed. A participant should be excluded if he/she has a positive test result for SARS-CoV2 infection, is known to have asymptomatic infection, or is suspected of having SARS-CoV2. Participants with active infections are excluded from study participation as per exclusion criterion #9 (Part 2): Active and clinically significant bacterial, fungal or viral infection. When the infection resolves, the participant may be considered for re-screening.

### Alternative Facilities for Safety Assessments

#### Laboratory Testing

If a study participant is unable to visit the site for protocol-specified safety laboratory evaluations, testing may be conducted at a local laboratory if permitted by local regulations. The local laboratory may be a standalone institution or within a hospital. The safety laboratory evaluations included in Section 7.1.3 may be performed at a local laboratory.

If a local laboratory is used, qualified study site personnel must order, receive, and review results prior to dosing. Site staff must collect the local laboratory reference ranges and certifications/accreditations for filing at the site. Laboratory test results are to be provided to the site staff as soon as possible. The local laboratory reports should be filed in the participant's source documents/medical records. Relevant data from the local laboratory report should be recorded on the CRF.

### Study Intervention

If the safety of a trial participant is at risk because they cannot complete required evaluations or adhere to critical mitigation steps, then discontinuing that participant from study intervention must be considered.

The following is recommended for the continued administration of the investigational products for participants who have active confirmed (positive by regulatory authority-approved test) or presumed (test pending/clinical suspicion) SARS-CoV2 infection:

- For symptomatic participants with active SARS-CoV2 infection, study intervention should be delayed for at least 14 days from the start of symptoms. This delay is intended to allow the resolution of symptoms of SARS-CoV2 infection.

- Prior to restarting treatment, the participant should be afebrile for 72 hours, and SARS-CoV2-related symptoms should have recovered to ≤ Grade 1 for a minimum of 72 hours. Notify the study team when treatment is restarted.

- Continue to consider potential drug-drug interactions as described in Section 5.7 for any concomitant medication administered for treatment of SARS-CoV2 infection.

**Adverse Events and Serious Adverse Events**

If a participant has COVID-19 during the study, this should be reported as an AE or SAE and appropriate medical intervention provided. Temporary discontinuation of the study intervention may be medically appropriate until the participant has recovered from COVID-19.

It is recommended that the investigator discuss temporary or permanent discontinuation of study intervention with the study medical monitor.