NCT04916002

CMP-001-009

A MULTICENTER, OPEN-LABEL, PHASE 2 STUDY OF INTRATUMORAL VIDUTOLIMOD (CMP-001) IN COMBINATION WITH INTRAVENOUS CEMIPLIMAB IN SUBJECTS WITH SELECTED TYPES OF ADVANCED OR METASTATIC CANCER

Study Phase: Phase 2

IND Number: 16695

EU CT: 2023-507344-36-00

Issue Date: Original Protocol, 25 January 2021
Amendment 1, 26 April 2021
Amendment 2, 17 September 2021
Amendment 3, 06 December 2022
Amendment 4, 06 February 2023
Amendment 5 EU-1, 29 July 2023
Amendment 5 EU-2, 25 September 2023
Amendment 5 Global, *See appended electronic signature page*

AMENDMENT HISTORY

Overall Rationale for Amendment 5 Global

The primary purpose of this amendment is to add a new cohort (Cohort F), to study the combination of vidutolimod and cemiplimab in subjects with recurrent/metastatic (R/M) HPV-positive, PD-L1 with CPS ≥1 oropharynx squamous cell carcinoma (OPSCC) who have not received prior systemic therapy in the R/M setting. This global amendment also incorporates changes from two recent EU-specific amendments, and other minor clarifications of the protocol as described in the tables.

Description of Change	Brief Rationale	Section # and Name
Changes to study design & eligibility criteria		
Added a new cohort - Cohort F for PD-L1 CPS score ≥ 1, HPV-positive OPSCC	Preliminary clinical data suggest a signal for enhanced efficacy with the addition of TLR9 agonist to pembrolizumab in HPV-positive head and neck cancer	Synopsis Vidutolimod: Methodology, Diagnosis and main criteria for inclusion, and Statistical methods sections Section 1.3.3.4. Head and Neck (HPV-Positive) Section 3.1. Overall Study Design Section 3.5. Subject Inclusion Criterion #1 Section 8.1. Sample Size Justification
Clarified that subjects enrolled to Cohort D (BCC) are immunotherapy naïve	It has always been the explicit intent to enroll to Cohort D subjects who have not previously received systemic therapy in the R/M setting, (including both hedgehog pathway inhibitor therapy or prior anti-PD-1/PD-L1 therapy)	Synopsis Vidutolimod: Methodology and Diagnosis and main criteria for inclusion sections Section 3.1. Overall Study Design Section 3.5. Subject Inclusion Criterion #1
Revised Exclusion Criterion #3 to decrease the washout after systemic steroids to 15 days (from 30 days currently)	A shorter washout period would allow more subjects to meet the eligibility criteria. The proposed 15-day steroid washout period enables the clearance of steroids before initiating immunotherapy	Synopsis Vidutolimod: Diagnosis and main criteria for inclusion section Section 3.6. Subject Exclusion Criterion #3
Revised the language regarding the use of systemic steroids at enrollment and during study conduct	To align Section 3.8 with Exclusion Criterion #3 (discussing systemic steroids at enrollment) and to provide guidance for the use of steroids during study conduct	Section 3.8. Prohibited Treatments
Revised the language regarding the use of systemic anti-cancer therapy	Clarified that only systemic anti-cancer therapy agents are prohibited in this study	Section 3.8. Prohibited Treatments
Revised the language in dose modifications for vidutilomod	Deleted the reference to “Q3W” to allow skipped doses of vidutilomod during the 7 weekly dosing period.	Section 4.1.1.4 . Dose Modifications for Vidutilomod
Revised the dosing delay period from 12 weeks to 9 weeks	To synchronize with vidutilomod dosing schedule in 4.1.1.4.	Section 4.1.2.1 Treatment Modifications

Changes to the schedule of assessments		
Deleted W4D2	Removing this visit can simplify scheduling and potentially boost the accrual rate. Patient safety is not compromised by removing vitals, AE monitoring, and concurrent meds. This change did not impact the correlative objectives.	Table 1 Schedule of Assessments and Footnote "a"
Coagulation Tests added for Screening	Requirement for Coagulation tests completed at Screening.	Table 1 Schedule of Assessments
Other changes		
Added analysis of plasma ctDNA to identify the presence of tumor mutations to translational assessments	Evaluation of ctDNA will assist as an exploratory biomarker for monitoring early anti-tumor activity, including associations with change in tumor burden, PFS and OS.	Section 6.3.1 Collection of Blood for Translational Biomarker Analysis
Other minor edits for clarity	To improve readability or for clarification	Global

Overall Rationale for Amendment 5 EU-2

The primary purpose of this amendment is to implement modifications requested following Part 1 assessment of the Clinical Trial Application under the scope of the EU Regulation No 536/2014.

The following table outlines the changes made to the protocol, with a brief rationale, and the affected sections:

Description of Change	Brief Rationale	Section # and Name
Changes to eligibility criteria		
Amended study Cohort D (BCC) inclusion criteria to only include subjects who are not candidates for curative surgery or curative RT, have not received prior hedgehog pathway inhibitor therapy and who do not wish to receive or who are not candidates for a hedgehog inhibitor	Based on Health Authority (HA) request	Synopsis Vidutolimod: Methodology, and Diagnosis and Main Criteria for Inclusion Section 3.1Overall Study Design Section 3.5 Subject Inclusion Criteria, criterion #1
Amended study Cohort E (NSCLC) to indicate that it will not be conducted in Europe	Based on HA request	Synopsis Vidutolimod: Methodology, and Diagnosis and Main Criteria for Inclusion Section 3.1 Overall Study Design Section 3.5 Subject Inclusion Criteria, criterion #1
Other changes		
Added the REGN2810 name for cemiplimab	Based on HA request	Section 1.3.2 Cemiplimab (REGN2810)
Updated the language in ethical conduct of the study to align with current template language	The text was not applicable anymore since the EU regulation cited has been repealed.	Section 11.2 Ethical Conduct of the Study

Overall Rationale for Amendment 5 EU-1

The primary purpose of this amendment is to implement modifications requested following Part 1 assessment of the Clinical Trial Application under the scope of the EU Regulation No 536/2014.

The following table outlines the changes made to the protocol, with a brief rationale, and the affected sections:

Description of Change	Brief Rationale	Section # and Name
Changes to eligibility criteria		
Amended Inclusion Criteria 1 to: - Allow enrollment in Cohort A1 to subjects with metastatic or locally and/or regionally advanced unresectable CSCC and who are not eligible for curative radiation - Allow enrollment in Cohorts C1 and C2 to subjects who have previously received treatment with sacituzumab govitecan (all TNBC patients), with trastuzumab deruxtecan (HER2-low patients) and with PARP inhibitor (for BRCA) - Specify that enrollment in Cohort E will be based on prior PD-L1 result and will be limited to subjects who do not wish to receive chemotherapy	Based on HA request	Synopsis Vidutolimod: Methodology, and Diagnosis and Main Criteria for Inclusion Sections Section 3.1 Overall Study Design Section 3.5 Subject Inclusion Criteria, criterion #1
Added exclusion criterion to exclude from enrollment subjects who had major surgeries (including complete oncologic resection) within last 4 weeks prior to enrollment, and/or have not recovered adequately from the toxicities and/or complications from the intervention. Minor surgeries (including routine resections of early stage CSCCs and BCCs that may be due to field cancerization) require a 7-day washout	Based on HA request	Synopsis Vidutolimod: Methodology, and Diagnosis and Main Criteria for Inclusion Sections Section 3.6 Subject Exclusion Criteria, criterion #26 (new)
Changes to the schedule of assessments		
Modified time points for physical examination to implement targeted physical examination at every vidutolimod injection visit (to be performed before vidutolimod administration)	Based on HA request	Table 1 Schedule of Assessments and Footnote h

Description of Change	Brief Rationale	Section # and Name
Other changes		
Revised management of adverse events associated with cemiplimab in line with Libtayo SmPC and cemiplimab Investigator's Brochure	Based on HA request	Table 5 Recommended Dosage Modifications for Adverse Reactions
Revised tumor selection for vidutolimod injections to implement systematic support from interventional radiology in case of intratumoral injections to visceral lesions	Based on HA request	Section 4.1.1.3.1 Tumor Selection
Minor updates throughout document	To improve readability or for clarification	Global

Overall Rationale for Amendment 4

The primary purpose of this amendment is to fix administrative errors, and to revise Exclusion criterion 7 to severe uncontrolled medical disease within 12 months of screening (previously, within 6 months of screening). In addition, the cemiplimab dose modification table has been updated to reflect the current risks associated with cemiplimab.

Overall Rationale for Amendment 3

The primary purpose of this amendment is to add 2 new cohorts to investigate the combination of vidutolimod and cemiplimab in first line advanced basal cell carcinoma (BCC) patients (Cohort D) and first line advanced non-small cell lung cancer (NSCLC) whose tumors have high PD-L1 expression (Cohort E). Additionally, the size of several cohorts has been reduced. Other changes are described in the table below.

Description of Change	Brief Rationale	Section # and Name
Changes to study design		
Added 2 new cohorts Cohort D (BCC) and Cohort E (NSCLC).	Vidutolimod merits study in BCC because it is a tumor type that is responsive to interferon-alpha. Vidutolimod in combination with standard cemiplimab also warrants further development and evaluation in NSCLC in the population of newly diagnosed advanced NSCLC subjects with high PD-L1 expression (≥50%), with disease that is amenable to IT injections.	Synopsis Vidutolimod: Methodology, Diagnosis and main criteria for inclusion, statistical method section Section 1.1 Background Section 1.3.3.1 Non-Melanoma Skin Cancer (Basal Cell Carcinoma) Section 1.3.3.3 Non-small cell lung cancer Section 1.3.3.3 Non-Small Cell Lung Cancer (NSCLC) Section 3.1 Overall Study Design Section 3.5 Subject Inclusion Criteria, criterion #1
Updated the sample size	Number of subjects being enrolled changed with the addition of 2 new cohorts: Sample size per cohort reduced because it is possible to detect potentially meaningful efficacy with the reduced sample size	Synopsis Vidutolimod: Number of subjects (planned), sample size calculation, statistical analysis methods Section 8.1 Sample Size Justification

Description of Change	Brief Rationale	Section # and Name
Removed the secondary endpoint evaluation of iORR, iDOR and iPFS based on immunotherapy Response Evaluation Criteria in Solid Tumors (iRECIST)	iRECIST after PD can create confusion at sites. Revised protocol provides clear guidance on treatment past progression, and collects post-PD response data to account for unconventional responses	Synopsis Vidutolimod: Secondary Endpoints, Methodology, Criteria for evaluation (efficacy), Statistical analysis methods Table 1 Schedule of Assessments Section 2.2.2 Secondary Endpoints Section 3.1 Overall Study Design Section 3.2 Treatment Discontinuation Section 6.2 Disease Assessments Section 6.2.5 Treatment and Disease Assessment Beyond Progressive Disease Section 7.2.6 Confirmation of Response (removed) Section 8.6.1 Confirmed Objective Response Rate Section 8.6.3 Progression-Free Survival Section 8.6.5 Post-progression Disease Response (removed)
Removed the exploratory endpoint evaluation of response per intratumoral Response Evaluation Criteria in Solid Tumors (itRECIST)	Ongoing immuno-oncology trials are using RECIST 1.1 for tumor assessments. itRECIST is not a standard approach and investigators may not be familiar with it.	Synopsis Vidutolimod: Exploratory Endpoints, Statistical analysis methods Section 2.2.3 Exploratory endpoints Section 6.2 Disease Assessments Section 6.2.1 Radiographic Imaging Section 8.6.1 Confirmed Objective Response Rate Section 8.6.6 Exploratory Efficacy Analysis (removed)
Revised the exploratory objective and endpoints for pharmacodynamics	Change made to interrogate pharmacodynamic activity in peripheral blood and tumor tissue and improve understanding about Vidutolimod mechanism of action across tumor types being evaluated.	Section 2.1.3 Exploratory Objectives Section 2.2.3 Exploratory Endpoints
Removed autoimmune laboratory panel from the schedule of assessments	The immune panel does not help in subject selection beyond the protocol specified inclusion/exclusion criteria	Table 1 Schedule of Assessments Section 6.1.12 Clinical Laboratory Assessments Table 7 Clinical Laboratory Assessments

Description of Change	Brief Rationale	Section # and Name
Revised inclusion criterion # 1 to remove the requirement that PD-1 blocking must have been the most recent therapy received	Per SITC resistance criteria (Maus, 2020), subjects who received intercurrent treatment, should still be included in the current definitions of PD-L1 resistance	Synopsis Vidutolimod: Diagnosis and main criteria for inclusion Section 3.5 Subject Inclusion Criteria, criterion #1
Revised exclusion criteria to exclude subjects with emphysema who require imaging-guided administration of IT vidutolimod, and have FEV1 ≤ 50 % of normal	To select subjects with adequate respiratory function due to risk of pneumothorax associated with IT lung injections	Synopsis (Vidutolimod): Key Exclusion Criteria Section 3.6 Exclusion Criteria, criterion #7
Added a new section on treatment beyond progression	To account for the possibility of pseudoprogression and to allow subjects who derive clinical benefit to continue treatment	Section 3.2.1 Treatment beyond progression (new section)
Other changes		
Revised Tumor Selection section to add CT detectable cutaneous, SC, and/or nodal tumors to the definition of acceptable tumors for IT injections (previous definition restricted to visible/palpable or US detectable cutaneous, SC, and/or nodal tumors)	For clarity and to align with the Procedure Manual for the image-guided injection of lymph nodes.	Section 4.1.1.3.1 Tumor Selection
Guidance for COVID-19 vaccination was revised to include the booster dose:	Guidance has been updated regarding when subjects may be vaccinated and receive a booster dose while enrolled in this study to support global vaccination activities during the COVID-19 pandemic.	Section 3.8.1 Vaccinations
An additional pregnancy test must be conducted at the end of the relevant systemic exposure, i.e., 16-18 weeks after last study dose treatment. A urine test conducted at home and communicated to the investigator by phone would be acceptable.	Based upon health authority requests in other studies.	Table 1 Schedule of Assessments footnote “m” Section 6.1.13 Pregnancy Testing
Changes to the protocol to comply with EU CTR		
Added the definition for end of study	To comply with EU CTR guidance	Synopsis (Vidutolimod): end of study Section 3.4 End of Clinical Trial

Description of Change	Brief Rationale	Section # and Name
Recruitment strategy, data protection, subject confidentiality and clinical study data transparency sections added	To comply with EU CTR guidance	Section 10.4.1 Recruitment Strategy (new section) Section 10.4.2 Data Protection (new section) Section 11.4 Subjects Confidentiality and Data Protection (new section) Section 11.5 Clinical Study Data Transparency (new section)
Changes to the protocol based on alignment with the Regeneron protocol template		
Added a new section on risk/benefit	As this protocol will be submitted globally, added this new section as required by health authorities (HA)	Section 1.4 Risk-Benefit (new section)
Added relevant sections pertaining to information related to cemiplimab	Change made to reflect the Regeneron template	Section 1.3.2 Cemiplimab (new section) Section 1.3.4.2 Rationale for PD-1 Blocking Antibody Dose Section 4.2 Management of Acute Reactions for Cemiplimab (new section)
Changed inclusion/exclusion criteria for women of childbearing potential	Change made to reflect the Regeneron template and to align with feedback received from HA	Section 3.5 Subject Inclusion Criteria, criterion 8 (removed) Section 3.6 Subject Exclusion Criteria, criterion #25 (added) Section 4.3 Women of Childbearing Potential (removed)
Added new section for replacement of subjects,	To align with Regeneron template	Section 3.7 Replacement of Subjects (new)
Revised Study Treatment Materials and Management section	To align with Regeneron template	Section 5.2 Study Treatment Packaging and Labeling Section 5.3 Study Treatment Handling, Storage, and Accountability

Description of Change	Brief Rationale	Section # and Name
Revised safety sections	To align with Regeneron template	Section 8.1.3 Definition of a Treatment Emergent Adverse Event (removed) Section 7.1.3 Adverse Events of Special Interest (new section) Section 7.2.2 Relationship to Study Drug Section 7.3 Procedures for Recording and Reporting Adverse Events Section 7.3.1 Individual Case Safety Reporting (ICSR) (new section) Section 7.3.4 Events that Require Expedited Reporting to Sponsor (new section) Section 7.3.5 Notifying Health Authorities, IRB/Ethics Committees, and Investigators (new section)
New appendix on RECIST added	To comply with Regeneron standards	Appendix B Response Evaluation Criteria in Solid Tumors (new)
Revised CMP-001 to Vidutolimod and PD-1 blocking antibody to cemiplimab	To begin using the INN	Title page and global
Replaced medical monitor information	To change the medical monitoring responsibility from IQVIA to Regeneron	Procedures in Case of Emergency Page
Typographical and editorial changes	To improve readability and for clarifications	Global

INVESTIGATOR'S AGREEMENT

A MULTICENTER, OPEN-LABEL, PHASE 2 STUDY OF INTRATUMORAL VIDUTOLIMOD (CMP-001) IN COMBINATION WITH INTRAVENOUS CEMIPLIMAB IN SUBJECTS WITH SELECTED TYPES OF ADVANCED OR METASTATIC CANCER

Protocol Number: CMP-001-009

I have read this protocol and agree to the following:

- I am thoroughly familiar with the appropriate use of the investigational drug, as described in this protocol, and any other information provided by the Sponsor including, but not limited to, the current Investigator's Brochure (IB) provided by the Sponsor.
- I will conduct the study in compliance with this protocol, with any future amendments, and with any other written study conduct procedures provided, reviewed, and approved by the Sponsor or its representatives.
- I will conduct the study in accordance with the current United States (US) Food and Drug Administration (FDA)/applicable local regulations; International Council for Harmonisation (ICH) guidelines and any other applicable regulatory requirements; as well as Good Clinical Practice (GCP) standards (CPMP/ICH/135/95); the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the principles of GCP; all local ethical and legal requirements; and will complete the study within the time designated.
- I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure they are fully informed regarding the drug and the conduct of the study.
- I agree that the Sponsor or its representatives shall have access to any source documents from which electronic case report form (eCRF) information may have been generated.

_____

Printed Name of Investigator

_____ _____

Signature of Investigator Date

SPONSOR PROTOCOL APPROVAL

I have read this protocol and approve the design of this study:

_____ _____

[redacted]

Date

Regeneron Pharmaceuticals, Inc

PROCEDURES IN CASE OF EMERGENCY

Emergency Contact Information:

Name	Role in Study	Address and Telephone Number
[redacted]	Medical Monitor	777 Old Saw Mill River Road Tarrytown, NY 10581

Serious adverse events (SAEs) should be recorded on an SAE Report Form and completed and submitted within 24 hours of awareness. Information including a detailed description of the event; date and time (24-hour clock) of event onset and resolution.

SYNOPSIS VIDUTOLIMOD

Name of Sponsor/Company: Regeneron Pharmaceuticals, Inc.

Name of Investigational Product: Vidutolimod (CMP-001), Cemiplimab (R2810);

Name of Active Ingredient: Vidutolimod is a Toll-like receptor 9 (TLR9) agonist composed of G10, a CpG-A oligodeoxynucleotide with a native DNA backbone that is encapsulated in a virus-like particle formed by a capsid protein derived from bacteriophage Qbeta.

Title of Study: A multicenter, open-label, Phase 2 study of intratumoral vidutolimod in combination with intravenous cemiplimab in subjects with selected types of advanced or metastatic cancer

Study center(s): This study will be conducted at clinical sites in regions including (but not limited to) North America and EU.

Phase of development: Phase 2

Objectives:

Primary:

- To determine confirmed objective response rate (ORR) with vidutolimod in combination with cemiplimab per RECIST 1.1 by investigator

Secondary:

- To evaluate the safety and tolerability of vidutolimod administered by intratumoral (IT) injection in combination with cemiplimab
- To evaluate the efficacy of vidutolimod in combination with cemiplimab

Study Endpoints:

Primary Endpoint:

- ORR, defined as the proportion of subjects with a confirmed objective response of complete response (CR) or partial response (PR) based on Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) by investigator assessment

Secondary Endpoints:

- Adverse events (AEs), serious adverse events (SAEs), and AEs leading to discontinuation or death, and severity of AEs as assessed by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE v5.0)
- Duration of response (DOR), defined as the time from date of first documented response (CR or PR) to date of documented progressive disease (PD), based on RECIST v1.1, per investigator
- Progression free survival (PFS), defined as the time from date of first dose of study treatment to date of documented PD based on RECIST v1.1 or death, whichever occurs first
- Response in injected and noninjected target lesions per RECIST v1.1
- Overall survival (OS), defined as the time from date of first dose of study treatment to date of death

Methodology:

This is a multicenter, open-label, Phase 2 clinical study of vidutolimod administered by IT injection in combination with intravenous (IV) cemiplimab in subjects with selected types of advanced or metastatic cancer with or without prior PD-1–blocking antibody treatment, as follows:

- Cohorts A1 and A2: Subjects with metastatic or locally and/or regionally advanced unresectable cutaneous squamous cell carcinoma (CSCC):
    - Cohort A1: Subjects who had not received prior systemic therapy for CSCC and who are not eligible for curative radiation
    - Cohort A2: Subjects who have progressed while receiving a PD-1–blocking antibody or within 12 weeks of discontinuation
- Cohorts B1 and B2: Subjects with metastatic or locally and/or regionally advanced unresectable Merkel cell carcinoma (MCC):
    - Cohort B1: Subjects who had not received prior systemic therapy for MCC
    - Cohort B2: Subjects who have progressed while receiving a PD-1–blocking antibody or within 12 weeks of discontinuation
- Cohorts C1 and C2: Previously treated subjects with advanced or metastatic triple-negative breast cancer (TNBC). Subjects must have previously received treatment with sacituzumab govitecan (all TNBC patients), with trastuzumab deruxtecan (HER2-low subjects) and with PARP inhibitor (for BRCA) subjects:
    - Cohort C1: Subjects who had not received prior therapy with immune checkpoint inhibitors (iCPIs)
    - Cohort C2: Subjects who have progressed while receiving a PD-1–blocking antibody or within 12 weeks of discontinuation
- Cohort D: Subjects with metastatic or locally and/or regionally advanced unresectable basal cell carcinoma (BCC) who have not received prior hedgehog pathway inhibitor therapy or prior anti-PD-1/PD-L1 therapy and who do not wish to receive or who are not candidates for a hedgehog inhibitor.
- Cohort E (not conducted in Europe): Advanced non-small cell lung cancer (NSCLC) subjects (locally advanced who are not candidates for surgical resection or definitive chemoradiation or metastatic) whose tumors have high PD-L1 expression (Tumor Proportion Score [TPS] ≥50%) based on a prior PD-L1 result as determined by College of American Pathologists (CAP)/Clinical Laboratory Improvement Amendments (CLIA) (or equivalently licensed) lab, with no EGFR, ALK or ROS1 aberrations, and who have not received prior anti-PD-1/PD-L1 therapy and are amenable to IT therapy and do not wish to receive chemotherapy.
- Cohort F: Recurrent/metastatic (R/M) Oropharynx Squamous Cell Carcinoma (OPSCC) subjects with PD-L1 combined positive score (CPS) ≥ 1, human papillomavirus (HPV)-positive disease who have not received prior systemic therapy for R/M disease. Human papillomavirus-positive status, based on a prior result, must be established in a surgical specimen or a core biopsy specimen from any site of OPSCC (primary site, nodal site, and/or distant metastatic site, either at time of diagnosis or later) in a CAP/CLIA (or equivalently licensed) lab. PD-L1 expression (CPS ≥ 1) is based on a prior PD-L1 result as determined by CAP/CLIA (or equivalently licensed) lab.

All enrolled subjects will receive vidutolimod IT and cemiplimab IV infusion (cemiplimab 350 mg Q3W) according to the treatment schedule for up to 2 years or until a reason for treatment discontinuation is reached.

Disease status will be assessed by computed tomography (CT) or magnetic resonance imaging (MRI) and other appropriate measures beginning predose at baseline and Week 10 Day 1 (W10D1) and will be repeated every 9 weeks (e.g. W19D1, W28D1, etc.) while the subject is on treatment. All scans should be performed at least 2 weeks after the previous vidutolimod IT injection to prevent detection of injection-related pseudoprogression. Imaging should not be delayed for delays in treatment.

Objective responses will be assessed by the Investigator according to RECIST v1.1.

Number of subjects (planned):

The planned enrollment for this study is approximately 225 subjects.

Diagnosis and main criteria for inclusion:

Key Inclusion Criteria:

Subjects enrolled in the study must meet all of the following inclusion criteria to be eligible.

- Histopathologically-confirmed diagnosis of cancer that is metastatic or unresectable at Screening.
  - Subjects with metastatic or locally and/or regionally advanced unresectable CSCC.

  Note 1: CSCC subjects without radiographically measurable disease are not excluded if there is at least 1 lesion ≥ 10 mm in at least 1 dimension documented by color photography.

  Note 2: Subjects with tumors that arise in the setting of chronic inflammation (Marjolin's ulcer) such as chronic wounds and/or scars are excluded.

  Cohort A1: Subjects who have not received prior systemic therapy for CSCC and who are not eligible curative radiation.

  Cohort A2: Subjects who have progressed while receiving a PD-1–blocking antibody or within 12 weeks of discontinuation and who are not eligible for radiotherapy. PD-1–blocking antibody treatment may have been administered in the adjuvant and/or neoadjuvant and/or locally advanced or metastatic setting.

  - Subjects with metastatic or locally and/or regionally advanced unresectable MCC.

  Note: MCC subjects without radiographically measurable disease are not excluded if there is at least 1 lesion ≥ 10 mm in at least 1 dimension documented by color photography.

  Cohort B1: Subjects who had not received prior systemic therapy for MCC.

  Cohort B2: Subjects who have progressed while receiving a PD-1-blocking antibody or within 12 weeks of discontinuation. PD-1-blocking antibody treatment may have been administered in the adjuvant and/or neoadjuvant and/or locally advanced or metastatic setting.

  - Previously treated subjects with advanced or metastatic TNBC must have disease that is HER2-negative, estrogen and progesterone receptor-negative, or < 5% expression based on American Society of Clinical Oncology/College of American Pathologists guidelines. Subjects with disease recurrence or progression following neoadjuvant or adjuvant therapy are eligible. Subjects with advanced or metastatic disease may have up to 5 lines of systemic therapy. Subjects must have previously received treatment with sacituzumab govitecan (all TNBC subjects), with trastuzumab deruxtecan (HER2-low subjects) and with PARP inhibitor (for BRCA) subjects.

  Cohort C1: Subjects who had not received prior therapy with iCPIs for TNBC.

Cohort C2: Subjects who have progressed while receiving a PD-1-blocking antibody or within 12 weeks of discontinuation.

Cohort D: Advanced BCC subjects (metastatic or locally advanced) who are not candidates for curative surgery and have not received prior therapy with a hedgehog pathway inhibitor (vismodegib or sonidegib) or prior anti-PD-1/PD-L1 therapy and who do not wish to receive or who are not candidates for a hedgehog inhibitor.

Cohort E (not conducted in Europe): Advanced NSCLC subjects (locally advanced who are not candidates for surgical resection or definitive chemoradiation or metastatic) whose tumors have high PD-L1 expression (TPS ≥50%) based on a prior PD-L1 result as determined by CAP/CLIA (or equivalently licensed) lab, with no EGFR, ALK or ROS1 aberrations, and who have not received prior anti-PD-1/PD-L1 therapy and are amenable to IT therapy and do not wish to receive chemotherapy.

Cohort F: R/M Oropharyngeal squamous cell carcinoma (OPSCC) subjects with PD-L1 CPS score ≥ 1, HPV-positive disease who have not received prior systemic therapy for R/M disease. HPV-positive status, based on a prior result, must be established in a surgical specimen or a core biopsy specimen from any site of OPSCC (primary site, nodal site, and/or distant metastatic site, either at time of diagnosis or later) in a CAP/CLIA (or equivalently licensed) lab, as follows:

For subjects with documented history of oropharynx primary disease, either of the following will be accepted as evidence of HPV-positive OPSCC: positive p16 immunohistochemistry (IHC) or positive HPV DNA or RNA in situ hybridization (ISH).

For subjects with HNSCC of unknown primary, positive HPV DNA or RNA ISH is required as evidence of HPV-positive disease.

PD-L1 expression (CPS ≥ 1) is based on a prior PD-L1 result as determined by CAP/CLIA (or equivalently licensed) lab.

- Measurable disease, as defined by RECIST v1.1 and all of the following:
    a. At least 1 accessible lesion amenable to repeated IT injection.
    b. A previously irradiated lesion may be used as a target lesion if subsequent disease progression in that lesion (at least 20% increase in dimensions with a 5 mm absolute increase) was documented.

Key Exclusion Criteria:

Subjects presenting with any of the following will not qualify for entry into the study:

- Received radiation therapy (or other nonsystemic therapy) within 2 weeks before first dose of study treatment on W1D1. Subjects should have recovered (i.e. Grade ≤ 1 or at baseline) from radiation-related toxicities.
- Had major surgeries (including complete oncologic resection) within last 4 weeks prior to enrollment, and/or have not recovered adequately from the toxicities and/or complications from the intervention. Minor surgeries (including routine resections of early stage CSCCs and BCCs that may be due to field cancerization) require a 7-day washout.
- Received systemic pharmacologic doses of corticosteroids > 10 mg/day prednisone within 15 days before first dose of study treatment on W1D1.
    – Subjects who are currently receiving steroids at a prednisone-equivalent dose of ≤ 10 mg/day do not need to discontinue steroids prior to enrollment.

  - Replacement doses, topical, ophthalmologic, and inhalational steroids are permitted.
  - Stress-dose corticosteroids will be required in subjects with adrenal insufficiency (see Section 4.1.1.1.1).
- History of immune-mediated AE leading to permanent discontinuation due to prior PD-1–blocking antibody.
- Not fully recovered from AEs due to prior treatment (to Grade 1 or less, per CTCAE), with the exception of persistent vitiligo, alopecia, hypothyroidism, diabetes mellitus, and adrenal and/or pituitary insufficiency.
- NOTE: Subjects previously treated with a CTLA-4–blocking antibody, subjects receiving corticosteroids with daily doses > 5 mg and ≤ 10 mg of prednisone equivalent for > 2 weeks, and subjects with clinical symptoms and/or laboratory findings suggesting risk for adrenal insufficiency should undergo diagnostic tests for adrenal insufficiency via local laboratory.
- Active pneumonitis or history of noninfectious pneumonitis that required steroids.
- Severe uncontrolled medical disease within 12 months of Screening, including but not limited to poorly controlled hypertension, unstable angina, myocardial infarction, congestive heart failure (New York Heart Association Class II or greater), pericarditis, cerebrovascular accident, or implanted or continuous use of a pacemaker or defibrillator, or emphysema with FEV1 ≤ 50% predicted.
- Known history of immunodeficiency.
- Known additional malignancy that is progressing or required active treatment within the past 3 years. Exceptions include cancers that have undergone potentially curative therapy, e.g. basal cell carcinoma of the skin, squamous cell carcinoma of the skin, localized prostate cancer with prostate-specific antigen level below 4.0 ng/mL, in situ cervical cancer on biopsy or a squamous intraepithelial lesion on Papanicolaou smear, and thyroid cancer (except anaplastic), in situ breast cancer, and adjuvant hormonal therapy for breast cancer > 3 years from curative-intent surgical resection.
- Active autoimmune disease that required systemic treatment in past 2 years; replacement therapy is not considered a form of systemic treatment.
- Untreated, symptomatic, or enlarging central nervous system metastases or carcinomatous meningitis (including leptomeningeal metastases from solid tumors).

Investigational product, dosage, and mode of administration:

Subjects will receive vidutolimod and cemiplimab, as follows:

1. Vidutolimod IT 10 mg weekly for 7 doses (W1D1 to W7D1), after which vidutolimod will be administered every 3 weeks (Q3W) (W10D1, W13D1, etc.). The first dose of vidutolimod may be administered subcutaneously or by IT injection at the discretion of the Investigator; all subsequent doses are planned to be administered by IT injection. The initial 7 doses of vidutolimod delivered on a weekly dosing schedule, must be completed before starting the Q3W vidutolimod dosing schedule.
2. Cemiplimab 350 mg IV infusion over 30 minutes (± 10 minutes) Q3W for the duration of the study (up to 2 years).

On visits where both study drugs are administered (W1D1 and Q3W thereafter), vidutolimod should be administered before cemiplimab.

Duration of treatment:

Subjects will continue study treatment until they reach a reason for treatment or study discontinuation. Clinically stable subjects may continue study treatment beyond RECIST v1.1 progression based upon Investigator judgment of potential benefit. Study treatment may not continue beyond 2 years from initial dose of study treatment.

If a subject achieves and maintains a confirmed CR, treatment with vidutolimod or the combination of vidutolimod and cemiplimab may be discontinued at the Investigator's discretion once they meet both of the following criteria:

- Subject has been treated with both study treatments for at least 24 weeks.
- Subject has received at least 3 doses of both study treatments beyond the date of the initial CR

Subjects who discontinue vidutolimod or both vidutolimod and cemiplimab may not be retreated on this study with the previously discontinued treatment(s).

End of Study

The definition for End of Study (Trial) is the date of global last subject's last visit (100 days ±7 days after the last dose of study drug: vidutolimod or cemiplimab), or the date of withdrawal from the study, or lost to follow-up (ie, the study subject can no longer be contacted by the investigator) whichever comes first. The sponsor has the right to terminate the study at any time.

Reference therapy, dosage and mode of administration:

Not applicable.

Criteria for evaluation:

Efficacy:

Disease status will be assessed by CT or MRI and other appropriate measures according to the Schedule of Assessments. Calipers and photographs containing a ruler may be used to facilitate measurement of superficial cutaneous tumors. Objective responses will be assessed by the Investigator according to RECIST v1.1. Other endpoints include PFS, DOR, best overall response, and OS.

Translational Assessments:

- Quantification of the concentration of selected cytokines and chemokines from blood of subjects obtained at time points specified in the Schedule of Assessments.
- Analysis of $CD3^+$ and $CD8^+$ T cell infiltrates or other multi-parameter assessment of the tumor microenvironment in tumor tissue obtained via fresh biopsy or from archival tumor tissue, and correlation with antitumor activity.
- Intra-subject changes in immune status from pretreatment to posttreatment may be evaluated by technologies such as RNA profiling, gene expression, tumor mutation analysis, flow cytometry, and/or immunohistochemistry using tumor biopsies of injected or noninjected target lesions, collected prior to treatment and during treatment.

Safety:

Safety and tolerability will be assessed by evaluating the following:

- Treatment-emergent adverse events, which will be evaluated and assigned a grade using CTCAE v5.0.
- Vital signs (oral temperature, respiratory rate, pulse, systolic and diastolic blood pressure) and physical examination (including weight and body mass index).

- Clinical laboratory parameters (chemistry, hematology, urinalysis, coagulation, and thyroid function tests).
- 12-lead electrocardiograms.

Statistical methods:

Sample size calculation:

The study is conducted as an exploratory trial. Each cohort of A1, A2, B1, B2, C1, C2, D, E and F will enroll approximately 25 subjects. The total number of subjects to be enrolled into this study is approximately 225. Based on historical data, the ORR of available treatment for each disease in Cohort is listed in Table 12. If the observed ORRs in Cohorts A1, A2, B1, B2, C1, C2, D, E and F are as listed in Table 12, then the lower bound of 90% confidence interval of ORR is also listed in Table 12.

Statistical analysis methods:

This section provides the basis for the statistical analysis plan (SAP) for the study. The SAP will be revised prior to the end of the study, to accommodate amendments to the clinical study protocol and to make changes to adapt to unexpected issues in study execution and data that may affect the planned analyses. The final SAP will be issued before the first database lock. Statistical analyses will be performed using SAS® software version 9.4 or higher.

All primary efficacy and safety analyses will be based on the population of all enrolled subjects who received at least 1 dose of study treatment (Safety Analysis Set).

The primary efficacy analysis of confirmed ORR will be assessed according to RECIST v1.1 for the Safety Analysis Set in each of the cohort. The hypothesis testing for the ORR will be based on the exact binomial distribution. Point estimate and 2-sided 95% confidence interval (CI) of ORR will be provided.

Secondary efficacy analyses will include DOR and PFS for the Safety Analysis Set, and treatment response in injected and noninjected target lesions based on RECIST v1.1,

Safety and tolerability will be monitored through continuous reporting of AEs and SAEs, laboratory abnormalities, and incidence of subjects experiencing dose modifications, dose interruptions, and/or premature discontinuation of study drug. AEs, physical examinations (including vital sign measurements), clinical laboratory information, and concomitant medications/procedures will be tabulated. All AEs will be summarized by frequency, severity grade based on the NCI CTCAE (Version 5.0) and relationship to treatment. AEs will be coded according to the Medical Dictionary for Regulatory Activities and will be summarized by system organ class and preferred term. SAEs, events of interest, and events leading to discontinuation or death will be listed separately.

Exploratory pharmacodynamics analyses include descriptive summaries of concentrations CXCL10 and other chemokine or cytokine biomarkers. Tumor biopsy obtained at baseline and specified time points during the study may be analyzed for protein, RNA, DNA, or other biomarkers related to TLR9, immune checkpoints, and potential markers of resistance or response to immunotherapy.

Table 1: Schedule of Assessments

Procedure or Assessment	**Screening (Day -30 to Day -1)**	**W1D1**	**W2D1**	**W3D1**	**W4D1**	**W5D1**	**W6D1**	**W7D1**	**Q3W (W10, W13, etc.)**	**End of Treatment (EOT)** [b]	**100-Day Follow-up (100DFU)** [c]	**Posttreatment Follow-up (PTFU) (Q3mo)** [d]	**Long-term Survival Follow-up (LTSFU) (Q3mo)** [e]
Visit Windows	**n/a**	**n/a**	**±2d**	**±2d**	**±2d**	**±2d**	**±2d**	**±2d**	**±3d**	**±7d**	**±7d**	**±2 weeks**	**±4 weeks**
Vidutolimod injection (Dose number) [f]		1 SC/IT	2	3	4	5	6	7	8+				
Cemiplimab dosing (Dose number) [g]		1			2			3	4+				
Informed Consent[s]	X												
Eligibility Criteria Assessment	X												
Demographics	X												
Medical History	X												
Cancer History	X												
Prior Cancer Treatment	X												
Physical Examination [h]	X	X	X	X	X	X	X	X	X	X			
Vital Signs[i]	X	X	X	X	X	X	X	X	X	X			
ECOG Performance Status	X	X		X				X	X	X			
Adverse Event Monitoring [j]	X	X	X	X	X	X	X	X	X	X	X		
Concomitant Medications [k]	X	X	X	X	X	X	X	X	X	X	X		

Table 1: Schedule of Assessments (Continued)

Procedure or Assessment	Screening (Day -30 to Day -1)	W1D1	W2D1	W3D1	W4D1	W5D1	W6D1	W7D1	Q3W (W10, W13, etc.)	End of Treatment (EOT) [b]	100-Day Follow-up (100DFU) [c]	Posttreatment Follow-up (PTFU) [d] (Q3mo)	Long-term Survival Follow-up (LTSFU) [e] (Q3mo)
Visit Windows	**n/a**	**n/a**	**± 2d**	**± 2d**	**± 2d**	**±2d**	**±2d**	**±2d**	**± 3d**	**+7d**	**+7d**	**± 2 weeks**	**± 4 weeks**
12-Lead ECG [l]	X	X		X				X		X			
Clinical Laboratory Tests (hematology, serum chemistry, urinalysis) [m]	X	X	X	X	X	X	X	X	X	X			
Coagulation Tests [m]	X	X						X	X	X			
Thyroid Function Tests [m]	X			X				X	X	X			
Pregnancy Test and Follicle Stimulating Hormone [m]	X	X			X			X	X	X			
Biomarkers													
Serum for Cytokine analysis [n]		X		X	X			X		X			
Serum for exploratory biomarkers (eg, anti-Qb Ab) [n]		X			X			X		X			
Plasma for ctDNA		X		X		X		X		X			
Archived tumor tissue [p]	X												
Blood DNA sample (germline control for mutational analysis)[t]	X												
Blood DNA sample for Pharmacogenomics (Optional)[u]	X												

Table 1: Schedule of Assessments (Continued)

Procedure or Assessment	Screening (Day -30 to Day -1)	W1D1	W2D1	W3D1	W4D1	W5D1	W6D1	W7D1	Q3W (W10, W13, etc.)	End of Treatment (EOT) [b]	100-Day Follow-up (100DFU) [c]	Posttreatment Follow-up (PTFU) [d] (Q3mo)	Long-term Survival Follow-up (LTSFU) [e] (Q3mo)
Visit Windows	**n/a**	**n/a**	**± 2d**	**± 2d**	**± 2d**	**±2d**	**±2d**	**±2d**	**± 3d**	**±7d**	**±7d**	**± 2 weeks**	**± 4 weeks**
Fresh Tumor Biopsy [o]	X				X								
Disease Assessment (radiographic imaging) [q]	X [r]								W10[q]; Q9W	X[q]		X	
Disease Assessment (CNS Imaging) [q]	X [r]								W10[r]; Q9W	X[q]		X	
Disease Assessment (photographic imaging) [q]	X [r]	X							X	X[q]		X	
100-day Follow-up (Office or Phone Call)											X		
Long-Term Survival Follow-up Phone Call													X

Abbreviations: 100DFU = 100-Day Follow-up; ACTH = adrenocorticotropic hormone; AE = adverse event; BMI = body mass index; CNS = central nervous system; d = day; CR = complete response; CRS = cytokine release syndrome; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FSH = follicle-stimulating hormone; INR = international normalized ratio; IT = intratumorally; LTSFU = long-term survival follow-up; MRI = magnetic resonance imaging; n/a = not applicable; PD = progressive disease; PD-1 = programmed cell death protein 1; PD-L1 = programmed death-ligand 1; PE = physical examination; PR = partial response; PT = prothrombin time; PTFU = posttreatment follow-up; PTT = partial thromboplastin time; Q3W = every 3 weeks; Q3mo = every 3 months; Qb = Qbeta; QTc = QT corrected; RECIST = Response Evaluation Criteria in Solid Tumors; SC = subcutaneously; W = week; WOCBP = women of childbearing potential.

a. ~~The W4D2 visit is mandatory but may be waived under certain circumstances. The site must contact the medical monitor for a waiver.~~ (Note: Footnote "a" is not applicable from Protocol Amendment 5)

b. End of Treatment assessments are to be performed within 30 days (±7 days) after subject discontinuation from last study treatment. Subjects who discontinue vidutolimod but continue on treatment with cemiplimab will have separate EOT visits for both vidutolimod and cemiplimab. Removal of a subject from vidutolimod treatment is defined as the time in which the Investigator decides to discontinue study treatment. If a subject has vidutolimod dosing withheld for more than 3 consecutive doses for any reason during the Q3W dosing period, resumption of treatment must be discussed with the Medical Monitor; otherwise, the subject will be discontinued from study treatment and will have all EOT assessments performed.

c. AEs and concomitant medications data will be collected until 100 days (±7 days) after the last dose of study drug (vidutolimod or cemiplimab) or until an alternative anticancer treatment is initiated, or until overall End of Clinical Trial (Section 3.4), whichever occurs first. The 100DFU should occur 100 days (±7 days) from the last study treatment (vidutolimod or cemiplimab) and may be conducted at the study site or via phone.
d. Posttreatment follow-up (PTFU) will be conducted Q3mo (±2 weeks) for all subjects who discontinue study treatment but have not met criteria for study discontinuation. These subjects should remain on study and receive disease assessments Q3mo, until disease progression or discontinuation of PTFU for any reason. For an individual subject, the maximum duration of PTFU is 18 months. After completing PTFU, subjects go to LTSFU.
e. LTSFU will be conducted Q3mo (± 4 weeks) after the EOT visit or the last disease assessment date in PTFU and may occur via phone. LTSFU may continue until overall End of Clinical Trial (Section 3.4).
f. Vidutolimod dosing will begin on W1D1. A window of ±2 days is permitted for vidutolimod weekly dosing from W1D1 to W7D1. The first dose of vidutolimod may be administered SC or IT, at the discretion of the Investigator; all subsequent doses are planned to be administered IT until no injectable lesions remain. Subjects must complete all 7 weekly vidutolimod doses before moving to the Q3W dosing schedule. Q3W dosing (W10D1+): A window of ±3 days is permitted for vidutolimod dosing from W10D1 throughout the study. When cemiplimab treatment is permanently discontinued, vidutolimod must also be permanently discontinued. Refer to Section 4.3 for treatment compliance.
g. Treatment with cemiplimab will begin on W1D1 and continue Q3W throughout the study. When vidutolimod injection and cemiplimab dosing fall on the same day, vidutolimod injection will be given before cemiplimab. Refer to Section 4.1.2 for details of cemiplimab dosing.
h. A full PE will be conducted at Screening and EOT. If the Screening full PE is performed >72 hours before the W1D1 visit, then a brief (symptom directed) PE must be performed within 72 hours before the first injection of vidutolimod. Brief PEs focused on areas of disease or AEs must be performed at every vidutolimod injection visit (before vidutolimod administration), and at any other time as clinically indicated. Height will be obtained at Screening only and weight at all PE assessments.
i. Vital signs include measurement of blood pressure (systolic and diastolic blood pressure), respiratory rate, heart rate, and body temperature. Blood pressure and heart rate should be taken in the seated position following ≥3 minutes of rest. For the first 6 vidutolimod dosing visits (W1D1 to W6D1), vital signs must be collected prior to the vidutolimod injection (±10 minutes) and at 30-minute (±15 minutes) intervals for 4 hours after vidutolimod injection. Starting at W7D1, observation periods may be reduced to a minimum of 1 hour following vidutolimod injection at the Investigator's discretion based on the AE profile of the individual subject. When vital signs are scheduled at the same time as collection of a blood sample, the vital sign measurements should be obtained before the scheduled phlebotomy. If a study visit occurs where only cemiplimab is administered, vital signs must be collected before the start of cemiplimab infusion.
   NOTE: Oxygen saturation is not a required parameter to be collected. Sites are to capture oxygen saturation every time an AE of hypoxia or CRS is reported for a subject.
j. AEs will be assessed from time of consent through 100 days after the last dose of study treatment or until an alternative anticancer treatment is initiated, whichever occurs first. Subjects who discontinue vidutolimod but remain on treatment with cemiplimab will continue to have AEs collected according to this schedule until 100 days after the last dose of cemiplimab or until an alternative anticancer treatment is initiated, whichever occurs first. Any SAEs related to IP will continue to be assessed.
k. Concomitant medications will be assessed continually from 30 days before the first dose of study treatment through 100 days after the last dose of study treatment or until an alternative anticancer treatment is initiated, whichever occurs first. Treatment medications for study-related AEs that occur through 100 days after the last dose of study treatment will be collected during the 100DFU period.
l. 12-lead ECGs will be obtained at Screening, before the W1D1, W3D1, and W7D1 vidutolimod injections, and at EOT. ECG parameters will include heart rate and PR interval, QRS, QT, and QTc intervals. ECGs will be performed after the subject has been resting in supine or semi-supine position for at least 5 minutes. When an ECG is scheduled at the same time as a blood sampling, the ECG reading should be obtained before the scheduled blood sampling.
m. Clinical laboratory assessments may be performed up to 72 hours before vidutolimod injection. When clinical laboratory assessments are done the same day as vidutolimod injection, vital signs should be performed prior to collection of clinical laboratory tests. Refer to Section 6.1.12 for Clinical Laboratory Assessments.

Note: For WOCBP, a serum pregnancy test and FSH are completed at Screening and W1D1. WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin) within 24 hours prior to the start of study treatment. An extension up to 72 hours prior to the start of study treatment is permissible in situations where results cannot be obtained within the standard 24-hour window. Serum **or** urine pregnancy tests are also to be completed prior to vidutolimod injection on W4D1, W7D1, and Q3W thereafter and EOT. Refer to Section 6.1.13 for pregnancy testing. An additional pregnancy test must be conducted at the end of the relevant systemic exposure, ie, 16-18 weeks after last study dose treatment. A urine test conducted at home and communicated to the investigator by phone would be acceptable. Pregnancy testing should be performed in women having a bilateral tubal ligation. A follicle stimulating hormone test is required to confirm menopause in women with less than 12 months of amenorrhea. If fertility is unclear and a menstrual cycle cannot be confirmed before the first dose of study treatment (W1D1), subject should be considered of childbearing potential and applicable pregnancy tests completed.

Note: Coagulation samples (PT, INR, and PTT) are to be collected prior to the W1D1 visit. Subsequent results are to be reviewed before every vidutolimod injection beginning at W7D1 and continuing Q3W thereafter.

Note: At Screening, subjects assessed as at risk for adrenal insufficiency should undergo diagnostic tests for ACTH and morning cortisol, and/or high-dose ACTH stimulation test (preferred testing method), if clinically indicated, via local laboratory.

n. Serum samples are to be collected at the following time points:
   - Within 2 hours before vidutolimod injection on W1D1, W3D1, W4D1,W7D1
   - 4 hours (±30 minutes) after the start time of the vidutolimod injection on W1D1, W4D1, W7D1
   - 2 hours (±30 minutes) after the start time of the vidutolimod injection on W3D1

Refer to Section 6.3.1. Collection of Blood for Translational Biomarker Analyses.

o. Fresh tumor biopsy samples are mandatory, if safe and medically feasible, at Screening (before W1D1) and at W4D1 3 to 4 hours after vidutolimod IT injection . If the Investigator believes it is unsafe to perform a biopsy, the subject may be considered eligible after discussion with the Medical Monitor. . Refer to Section 6.3.2 for tumor biopsies.

p. Archival tumor biopsy samples should be collected during Screening, if available. If archived FFPE slides (instead of archived block) are provided, the slides must be ≤5 months old after being cut from the tissue block.

q. Disease Assessment methods include radiographic (contrast-enhanced CT or MRI), photographic, and CNS imaging by contrast enhanced CT or MRI (per site local standards). The same modality used at Screening must be used throughout the study. Disease assessments will be performed at screening and predose beginning at W10D1 (-7 days) and repeated every 9 weeks (-7 days) (eg, W19D1, W28D1, etc). Digital photographs of visible vidutolimod injected and noninjected skin lesions should be taken at baseline and if a clinically relevant change occurs. Disease assessments will continue every 9 weeks after the confirmatory scans. All scans should be performed at least 2 weeks after the previous vidutolimod IT injection to prevent injection-related pseudoprogression. Disease assessments may be performed every 12 weeks for subjects with a response continuing more than 1 year. Refer to Section 6.2 for disease assessments. NOTE: Imaging at the EOT visit is not required if the subject has had imaging within 60 days of the visit according to the modality by which the subject's disease was being monitored (CT, MRI, and/or photography) or if the subject has had disease progression. Imaging to confirm progression is encouraged but not mandatory.

r. Baseline brain imaging by contrast-enhanced CT or MRI (per site local standards, brain MRI preferred) should be provided at Screening for subjects with known or suspected brain metastases. On-study brain imaging is only required for subjects with current or prior history of brain metastases or clinical signs or symptoms of CNS disease. Photographic and/or radiographic images demonstrating disease progression on prior PD-1–blocking antibody treatment will be collected whenever available.

s. Informed consent must be provided before the initiation of screening procedures and must be obtained within 45 days prior to W1D1. All screening assessments must be performed within 30 days prior to W1D1. Assessments performed as part of standard of care that fall within the screening window, but before informed consent is obtained, may be used for screening and need not be repeated for enrollment eligibility. Subjects who fail screening may be screened one additional time and an ICF will need to be signed at the re-screen. Some procedures may not need to be repeated if they were previously completed within 30 days prior to W1D1 vidutolimod injection.

t. The mandatory blood sample for germline genomic control of tumor sequencing analysis should be collected during the screening period. However, if it is not obtained during the screening period, the sample may be collected at any time during the study.

u. The optional blood sample for genomic testing should be collected during the screening period. However, if it is not obtained during the screening period, the sample may be collected at any time during the study.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 2: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Definition
ACTH	adrenocorticotropic hormone
AE	adverse event
ATC	Anatomical Therapeutic Chemical
BCC	Basal cell carcinoma
BMI	body mass index
BOR	best overall response
CFR	Code of Federal Regulations
CPS	Combined positive score
CNS	central nervous system
CpG-A	cytosine linked to a guanine by a phosphate bond, Class A
CR	complete response
CRA	Clinical Research Associate
CRS	cytokine release syndrome
CSCC	cutaneous squamous cell carcinoma
CT	computed tomography
CTCAE v5.0	Common Terminology Criteria for Adverse Events Version 5.0
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
CXCL	C-X-C motif chemokine
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
eCRF	electronic case report form
EOT	end of treatment
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
GCP	Good Clinical Practice
HHI	Hedgehog inhibitor
IB	Investigator's Brochure

Abbreviation or Specialist Term	Definition
ICF	Informed Consent Form
ICH	International Council for Harmonisation
iCPI	immune checkpoint inhibitor
IEC	Independent Ethics Committee
IFN	interferon
imAE	Immune mediated adverse event
INR	international normalized ratio
IRB	Institutional Review Board
ISH	In situ hybridization
IT	intratumoral(ly)
IV	intravenous
LTSFU	long-term survival follow-up
MCC	Merkel cell carcinoma
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NSCLC	Non-small cell lung cancer
ODN	oligodeoxynucleotide
OPSCC	Oropharyngeal squamous cell carcinoma
ORR	objective response rate
OS	overall survival
pCR	pathological complete response
PD	progressive disease
PD-1	programmed cell death protein 1
pDC	plasmacytoid dendritic cell
PD-L1	programmed cell death ligand 1
PET	positron emission tomography
PFS	progression-free survival
pMR	pathological major response
pPR	pathological partial response
PR	partial response
PTFU	posttreatment follow-up
PTT	partial thromboplastin time

Abbreviation or Specialist Term	Definition
Q3W	every 3 weeks
QTc	QT corrected
QTcF	QT corrected using Fridericia's formula
R/M	Recurrent / Metastatic
RECIST	Response Evaluation Criteria in Solid Tumors
RVT	residual viable tumor
SAD	short axis diameter
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous(ly)
SOC	system organ class
SOP	standard operating procedure
TEAE	treatment-emergent adverse event
TL	target lesion
TLR9	Toll-like receptor 9
TNBC	triple-negative breast cancer
TPS	Tumor proportion score
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information
VLP	virus-like particle
W1D1	Week 1 Day 1
WNL	within normal limits
WOCBP	women of childbearing potential

1. INTRODUCTION

1.1. Background

Tumor types being evaluated in this study include cutaneous squamous cell carcinoma (CSCC), Merkel cell carcinoma (MCC), basal cell carcinoma (BCC), triple negative breast cancer (TNBC), and PD-L1 CPS ≥1, HPV-positive oropharyngeal squamous cell carcinoma (OPSCC). These selected tumor types are typically accessible using intratumoral (IT) injections. The study also includes a non-small cell lung cancer (NSCLC) cohort, a common cancer type in which a subset of subjects will have lesions that are accessible for intratumoral (IT) injections. For each of the tumor types in this study, there are currently unmet medical needs for efficacious and safe combination treatments that include systemic programmed cell death protein 1 (PD-1)–blocking antibodies. Rationale for selected tumor types in this study is provided in Section 1.3.3.

1.2. Vidutolimod (CMP-001)

Vidutolimod (CMP-001) is a Toll-like receptor 9 (TLR9) agonist composed of G10, a CpG-A oligodeoxynucleotide (ODN) with a native DNA backbone that is encapsulated in a virus-like particle (VLP) formed by a capsid protein derived from bacteriophage Qbeta (Lemke-Miltner, 2020)(Miller, 2020). Once administered to a subject, an antidrug antibody response to the VLP develops (i.e. anti-Qbeta antibodies). Antibody-coated vidutolimod is then taken up by immune cells through Fc receptors. In plasmacytoid dendritic cells (pDCs), antibody-coated vidutolimod is taken up via FcγRIIA into endosomes where the G10 is released and activates TLR9 (Lemke-Miltner, 2020)(Miller, 2020).

TLR9 is highly expressed in human pDCs and B cells. G10 and other CpG-A ODN appear to have relatively little effect on B cells; their anti-tumor efficacy is believed to be due to pDC activation (Lemke-Miltner, 2020). The pDCs normally circulate in blood and can be recruited into tumors and tumor-draining lymph nodes. Inactivated tumor-associated pDCs contribute to tumor growth and are associated with an adverse prognosis in cancer subjects (Demoulin, 2013)(Lombardi, 2015). Activation and maturation of pDCs through TLR9 agonism induces Type I interferons (IFN) (), which in turn mediate the release of IFN-inducible chemokines such as C-X-C motif chemokine 9 (CXCL9) and C-X-C motif chemokine 10 (CXCL10)(Swiecki, 2015). Activated pDCs also take up tumor specific antigens for presentation to T cells and other immune cells, facilitating the development of an antigen-specific, antitumor T cell response (Fu, 2020). Together, the Type I IFNs, IFN inducible chemokines, and antigen presentation by activated pDC and other dendritic cell populations are believed to promote the activation and differentiation of anti-tumor $CD8^+$ cytotoxic T lymphocytes capable of circulating throughout the body and infiltrating and attacking distant tumor sites.

Administration of vidutolimod is hypothesized to change the pDC functional phenotype from tumor promoting to one that promotes an antigen-specific, antitumor $CD8^+$ T cell response.

1.2.1. Rationale for Intratumoral Administration of TLR9 Agonists

Administration of vidutolimod IT is intended to activate tumor-associated pDCs, and subsequently induce and activate anti-tumor $CD8^+$ T cells within the tumor and tumor-draining lymph nodes where tumor-specific antigen is most likely to exist. Systemic administration of TLR9 agonists is

expected to result in uptake by the liver, spleen, and reticuloendothelial system, which may lead to suboptimal activation of pDCs in tumor and tumor-draining lymph nodes.

IT administration of vidutolimod is expected to activate resting tumor-associated pDCs thereby overcoming their tumor-promoting phenotype and ultimately inducing an antitumor $CD8^+$ T cell response in the tumor microenvironment and/or in the tumor-draining lymph nodes. In preclinical models, IT dosing of TLR9 agonists was more effective than distant subcutaneous (SC) dosing, and induced regression not only in the directly injected tumor lesion, but also distant metastases (Shirota, 2012)(Lemke-Miltner, 2020).

1.3. Study Rationale

1.3.1. Rationale for Combining a TLR9 Agonist with a PD-1–Blocking Antibody

In prior clinical trials, TLR9 agonism resulted in strong induction of cytotoxic T cell responses; however, very few objective responses were observed, and the T cell responses were not sustained, especially within tumors (Appay, 2006).This may be because TLR9-mediated T cell activation induces PD-1 expression on activated T cells (Fourcade, 2014). TLR9 agonists are capable of inducing tumor-specific $CD8^+$ T cells in cancer subjects, but the expression of PD-1 on these T cells is believed to block their anti-tumor function. Therefore, PD-1 blockade may facilitate and sustain the TLR9 mediated activation of tumor-specific T cells.

Blockade of programmed cell death protein 1 (PD-1) is an effective and important therapy in the treatment of select cancer types; however, resistance to PD-1 limits efficacy of this treatment approach. PD-1 negatively regulates T cell function when it interacts with its ligand, PD-L1, which is commonly expressed on tumors (Chen, 2013). A major mechanism of resistance to PD-1 blockade is the absence of activated effector T cells in the tumor. Therefore, activation of T cells by TLR9 agonism, and subsequent trafficking to tumor sites, has the potential to improve the response to PD-1 blockade, particularly in non-inflamed tumors.

Several nonclinical and clinical reports support the hypothesis that TLR9 agonism may enhance the antitumor response to PD-1 blockade, as described further in the following sections.

1.3.1.1. Nonclinical Evaluations of TLR9 Agonism in Combination with PD-1 Blockade

The ex vivo addition of a PD-1–blocking antibody to $CD8^+$ T cells from melanoma subjects who had been treated with a TLR9 agonist significantly increased the T cell function for cytokine secretion (Fourcade, 2014), providing a strong rationale for the use of the combination of TLR9 agonists and PD-1–blocking antibodies in cancer therapy.

Several TLR9 agonists have shown antitumor efficacy in mouse tumor models in combination with PD-1 blockade. In mice with MB49 bladder cancer, a CpG-B ODN in combination with anti-cytotoxic T lymphocyte-associated protein 4 (anti–CTLA-4) or a PD-1–blocking antibody increased survival, and PD-1 blockade plus CpG treatment was superior to either agent alone. CpG plus anti–CTLA-4 or PD-1–blocking antibody increased the numbers of circulating tumor-specific CD107a expressing, $CD8^+$ T cells as well as activated ($CD25^+FoxP3^-$) $CD4^+$ splenocytes. Furthermore, regulatory T cells were decreased in the tumor area of treated animals after anti–CTLA-4 or a PD-1–blocking antibody plus CpG therapy (Mangsbo, 2010).

Additionally, mice treated with a CpG-B TLR9 agonist in combination with PD-1 blockade in an ovarian cancer model also had improved survival. Mechanistic studies in the PD-1–resistant mouse tumor models including CT26 and MCA38 colon carcinoma and TSA mammary adenocarcinoma demonstrated that IT injection of a CpG-C ODN reversed resistance to PD-1 blockade by inducing the infiltration of activated CD8+ T cells expressing IFN-g (Wang, 2016a). Finally, injection of vidutolimod IT in a mouse A20 lymphoma model reduced the growth of both injected and noninjected tumors and improved survival, and these antitumor effects were enhanced by combining with systemic PD-1–blocking therapy (Lemke-Miltner, 2020). The VLP appeared to contribute to the antitumor efficacy of CpG-A therapy since a reduced systemic antitumor effect was seen if the CpG-A TLR9 agonist was administered without the VLP.

1.3.1.2. Rationale for Biomarker Evaluation

Preclinical mechanism of action of vidutolimod is dependent on induction of anti-Qb opsonizing antibody response, TLR9 induced pDC activation resulting in increased T cell antigen presentation activity in tumor and draining lymph nodes, and corresponding increase in priming and activation of intra-tumoral effector T cell response. Vidutolimod showed anti-tumor efficacy in syngeneic mouse tumor models when used alone, and the activity of combination treatment with an anti PD 1 antibody was greater than either therapeutic agent alone. A variety of observations support the potential for CpG ODNs to enhance the anti-tumor effects of checkpoint inhibitors (Chen, 2013) (Wang, 2016b)(Diab, 2017).

Serum concentration of CXCL10 has been used as a PD marker for TLR-9 induced pDC activation in vivo (Blackwell, 2003). CXCL10 chemokine induced by type I or type II IFN, is strongly associated with Th1 immune responses. Exploratory translational studies with serum samples from the CMP-001 001 Part 1 Dose Escalation study were conducted to evaluate the pharmacodynamic effects of the combination of Vidutolimod and pembrolizumab. A multiplex Luminex assay was used to quantify a panel of 25 cytokines/chemokines in serum samples from various time points before and after administration of vidutolimod. At 24 hours after injection of vidutolimod, a strong induction of CXCL10 was seen in many of the subject's sera, although the magnitude of the response was highly variable. Serum induction of CXCL10 was associated with clinical activity of vidutolimod + pembrolizumab (Luke, 2021). In this study, analysis of serum CXCL10, other soluble biomarkers associated with type I interferon signaling and peripheral blood T cell activation will be examined for potential association with clinical outcomes.

Matched screening (pre-treatment) and post-treatment tumor biopsies were collected in CMP-001 studies. Biomarker data from CMP-001-001 study reported objective responses in subjects treated with vidutolimod + pembrolizumab irrespective of PD-L1 status and TMB score (Luke, 2021), consistent with therapeutic activity in subjects with lower baseline probability of anti-PD1 monotherapy response. Exploratory analysis of clinical data suggests potential association of immune markers (immune gene signature induction and CD8+ T cell infiltration) with clinical efficacy. Additional samples collected in this study will be utilized to evaluate these effects more rigorously across multiple tumor types. Baseline and post-treatment tumor characteristics will be evaluated for infiltration of immune cells and for changes in tumor microenvironment using multiplex immunohistochemical analysis. In addition, the tumor gene expression profiling/transcriptomic analysis will be carried out using whole exome and RNA sequencing to study gene signatures implicated in anti-tumor immune responses. The gene signatures evaluated will include but not limited to IFNgamma, TIS, vehicle trafficking, etc.

CMP-001 is postulated to exert its beneficial effect by converting programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1)-resistant tumors from an uninflamed to an inflamed state, and by inducing a predominant T helper (Th) 1 type response against tumor antigens. Proof-of-concept assessments for vidutolimod activity would include evidence of activated TLR9 signaling: density of pDC target cells, induction of type I IFNα gene signature, increase in CD8 TIL density following cemiplimab + vidutolimod treatment. Vidutolimod treatment may further enhance tumor T cell effector activity, including in subjects with immunologically "cold" tumors at baseline (low PD-L1, low TIL density, low IFNgamma inflammatory signaling), demonstrated to result in inferior clinical and tumor immune responses to anti-PD1 monotherapy, in studies of cemiplimab and other PD(L)1 agents.

1.3.1.3. Previous Clinical Studies with Vidutolimod

Several clinical studies evaluating the addition of a TLR9 agonist to immune checkpoint inhibition have been conducted, including vidutolimod in combination with pembrolizumab in subjects with PD-1 refractory melanoma (Study CMP-001-001) and in treatment-naïve Stage III melanoma (Study HCC 17-169), as described below.

The clinical benefit of vidutolimod IT in combination with intravenous (IV) pembrolizumab has been demonstrated in patients with melanoma refractory to PD-1 blockade in the ongoing Study CMP-001-001 (subjects treated with pembrolizumab according to the KEYTRUDA® (pembrolizumab) United States Prescribing Information (USPI) (KEYTRUDA, 2020) in combination with vidutolimod 10 mg IT every week for 7 weeks then every 3 weeks (Q3W) thereafter, the objective response rate (ORR) was 27.6% (27/98; 95% CI 19.0%, 37.6%), including subjects with responses after initial progressive disease (PD), and the best ORR by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) was 23.5% (23/98; 95% CI 15.5%, 33.1%), including 7 complete responses (CR) and 16 partial responses (PR). This ORR is substantially higher than the 7.7% response rate observed in the 6 of 78 subjects who received treatment beyond progression with pembrolizumab in the Keynote-002 study (Ahmed, 2020). The clinical benefit of this combination treatment includes durable CRs and PRs in injected and noninjected target lesions and non-target lesions of the skin, lymph nodes, and viscera. The Kaplan-Meier estimate for median duration of response (DOR) for both RECIST v1.1 responders and RECIST v1.1 responders plus post-PD responders was 19.9 months (95% CI 6, 19.9). Most treatment-related adverse events (AEs) were Grade 1 or 2 and included flu-like symptoms, including chills, fever, fatigue, nausea, vomiting, and headache, and injection site pain. The most common treatment-related Grade 3 or 4 AEs were hypotension (6.3%) and hypertension (5.0%). No Grade 5 treatment-related AEs were reported. Additional information is provided in the Vidutolimod Investigator's Brochure (IB).

Preliminary safety and efficacy data from an ongoing Phase 2 Investigator-sponsored study of vidutolimod IT in combination with nivolumab in subjects with high-risk resectable melanoma (Study HCC 17-169) demonstrated clinical activity and a tolerable safety profile (Davar, 2020). Pathological responses, defined as ≤ 50% residual viable tumor (RVT), was reported in 70% of subjects 21/30) and included pathological complete response (pCR), defined as 0% RVT, in 50% (15/30) of subjects, pathological major response (pMR), defined as 1% to 10% RVT, in 10% (3/30) of subjects, and pathological partial response (pPR), defined as 11% to 50% RVT, in 10% (3/30) of subjects. In the 31 subjects evaluable for safety, vidutolimod in combination with nivolumab was generally well tolerated with an acute toxicity profile consisting predominantly of Grade 1 or

2 treatment-related AEs. The only treatment-related Grade 3 AE in more than 1 subject was hypertension (3 subjects, 9.7%). No Grade 4/5 treatment-related AEs were reported. There were no dose-limiting toxicities or delays in surgery related to neoadjuvant treatment. One-year relapse-free survival was 89% in subjects with major pathological response (pCR and pMR) and 90% in subjects with any pathological response (pCR, pMR, and pPR).

1.3.2. Cemiplimab (REGN2810)

Cemiplimab (REGN2810; LIBTAYO®) is a high-affinity recombinant human immunoglobulin G ($IgG4^P$) monoclonal antibody that binds to PD-1 and blocks its interaction with programmed death ligand 1 (PD-L1) and programmed death-ligand 2 (PD-L2), countering PD-1-mediated inhibition of the anti-tumor immune response.

LIBTAYO (cemiplimab) 350 mg as an intravenous (IV) infusion over 30 minutes every 3 weeks (Q3W) was approved in the United States (US) on 28 Sep 2018 and in the European Union (EU) on 28 Jun 2019 and is also approved in several countries worldwide for the treatment of subjects with locally advanced cutaneous squamous cell carcinoma (CSCC; laCSCC) or metastatic cutaneous squamous cell carcinoma (mCSCC). LIBTAYO is also approved for the treatment of subjects with locally advanced basal cell carcinoma (BCC; laBCC) or metastatic BCC (mBCC) previously treated with a hedgehog pathway inhibitor (HHI); the term "advanced BCC" encompasses both mBCC and laBCC in subjects who are not candidates for curative intent surgery or curative intent radiation (Bichakjian, 2018)(Peris, 2019) and the treatment of adult subjects with recurrent or metastatic cervical cancer with disease progression on or after platinum-based chemotherapy. Cemiplimab is also approved in combination with platinum based chemotherapy for first line treatment of adult subjects with locally advanced and metastatic NSCLC. Additional indications for which LIBTAYO is approved include treatment first-line treatment of subjects with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose tumors have high (tumor proportion score [TPS] ≥50%) PD-L1 expression.

1.3.3. Rationale for the Indications Selected for this Study

1.3.3.1. Non-Melanoma Skin Cancer (NMSC)

There are limited treatment options for skin cancers that have metastasized to distant sites and/or locally progressed to the point that they cannot be effectively treated with surgery. Until recently, there was no approved systemic therapy for subjects with advanced CSCC or MCC, and there were no treatment options for BCC subjects other than hedgehog pathway inhibitors (ie, vismodegib, sonidegib).

Cutaneous Squamous Cell Carcinoma (CSCC)

Significant progress was achieved in the treatment of CSCC with the introduction of PD-1-blocking antibodies. Among subjects with advanced CSCC, cemiplimab achieves objective response rates (ORRs) of 45–50% with durable disease control (Migden, 2018) (Migden, 2020a)(Rischin, 2021). Other PD-1 inhibitors such as pembrolizumab also have activity in advanced CSCC (Grob, 2020)(Shalhout, 2021) The high efficacy of anti-PD1 therapy in advanced CSCC may be associated with its high tumor mutational burden (TMB) due to sun-related ultraviolet mutagenesis (Chalmers, 2017). However, there remains unmet need for new

treatment options, because approximately 50% of advanced CSCC subjects do not respond to anti-PD-1 therapy and there are no approved treatment options after progression on anti-PD-1 therapy.

Clinical study of vidutolimod in advanced CSCC is supported by historical data demonstrating that advanced CSCC is sensitive to recombinant interferon-α2a (Roferon-A) + 13-cis-retinoic acid, but subsequent development was limited by toxicities of systemic interferon (Lippman, 1992). Because the proposed mechanism of action of vidutolimod involves endogenous tumoral production of Type 1 interferons (Section 1.2), it may provide an efficacious treatment for advanced CSCC subjects with a safety profile that is differentiated from that of systemic interferon-α treatments.

Merkel Cell Carcinoma (MCC)

Similar progress was made in the treatment of metastatic MCC, where PD-1/PD-L1–blocking antibodies have demonstrated objective response rates 39-56% in treatment-naïve subjects (Nghiem, 2016)(Nghiem, 2018)(D'Angelo, 2018)). For recurrent MCC, a case report describes a partial response to recombinant interferon-α2a + topical imiquimod cream (Wahl, 2016). In the dose escalation portion of the phase 1 study of TLR9 agonist cavrotolimod in combination with pembrolizumab, 2 objective responses were observed in advanced MCC subjects with prior disease progression during or after prior anti-PD-1 therapy. Therefore, the combination of cemiplimab + vidutolimod is an appropriate study option for MCC subjects in both the PD-1 naïve and PD-1 resistant settings.

Basal Cell Carcinoma (BCC)

For subjects with locally advanced BCC, orally administered hedgehog pathway inhibitors (HHIs) such as vismodegib and sonidegib produce objective response rates of 48-56% in pivotal studies (Sekulic, 2015)(Dummer, 2016), and the reported response rate for vismodegib in the real-world setting is 68% (Basset-Seguin, 2017). However, these treatments are associated with adverse events such as muscle spasms, dysgeusia, alopecia, and weight decrease. Because approximately half of advanced BCC subjects do not respond to HHIs, and because the safety profile of these agents can be difficult for some subjects, new treatment options are needed.

BCC has similar clinical risk factors as CSCC and is also a hypermutated tumor (Chalmers, 2017)(Yarchoan, 2017)(Nehal, 2018). Cemiplimab produces an ORR of 31% in locally advanced BCC subjects in the second line after HHI inhibitors and is approved therapy in this setting (Stratigos, 2021).

Vidutolimod merits study in BCC for several reasons. As with CSCC, it is a tumor type that is responsive to interferon-α (Chimenti, 1995) . In a pilot study of the TLR9 agonist PF-3512676, local regressions were observed in all 5 BCC subjects, including four partial regressions and one complete regression (Hofmann, 2008). The topical TLR7 agonist imiquimod, which also induces production of Type 1 interferons, is approved therapy for superficial BCC but not for advanced BCC (Geisse, 2002). Therefore, the combination of vidutolimod + cemiplimab could enhance the activity of single agent cemiplimab in the first line setting and is of interest as an investigational option for advanced BCC subjects.

1.3.3.2. Triple-Negative Breast Cancer (TNBC)

The most common systemic therapies for the treatment of advanced/metastatic TNBC are platinum- and taxane-containing chemotherapy regimens. However, disease progression and/or recurrences develop quickly in vast majority of subjects with TNBC. Treatment with single agent pembrolizumab has demonstrated low to modest activity in subjects with TNBC positive for programmed cell death ligand 1 (PD-L1) who were previously treated (ORR 5.7%, disease control rate 9.5%) and previously untreated (ORR 21.4%) (Adams, 2019a)(Adams, 2019b).

In addition, atezolizumab had previously received accelerated FDA approval for treatment of subjects with unresectable locally advanced or metastatic TNBC with positive PD-L1 expression based on improved PFS with atezolizumab in combination with nab-paclitaxel compared with placebo plus nab-paclitaxel (Schmid, 2018). However, a confirmatory study (Impassion131) evaluating atezolizumab in combination with paclitaxel (i.e., non-protein bound) was negative (Miles, 2020).

1.3.3.3. Non-Small Cell Lung Cancer (NSCLC)

Immune checkpoint inhibitors have revolutionized the treatment of NSCLC. PD-L1 is an important biomarker for selection of subjects more likely to respond to immunotherapy. Among subjects with newly diagnosed advanced NSCLC with PD-L1 CPS of at least 50% and without EGFR, ALK, or ROS1 genomic alterations, cemiplimab has demonstrated durable objective response rate (ORRs) of approximately 40% and superiority over chemotherapy in improving progression-free survival and overall survival (Sezer, 2021). Other checkpoint inhibitors (pembrolizumab, atezolizumab) have also demonstrated improved efficacy compared to platinum-based chemotherapy, as first line monotherapy in advanced NSCLC patients with high PD-L1 expression (CPS ≥50%) (Reck, 2016)(Herbst, 2020). In terms of OS, Cemiplimab ranked highest compared to atezolizumab and pembrolizumab (Majem, 2021). However, there are limited non-chemotherapy treatment options for subjects PD-L1 high NSCLC subjects who do not respond or progress after the initial response to anti-PD-1 therapy.

A clinical trial (CMP-001-003) has evaluated vidutolimod in combination with atezolizumab with and without radiation therapy in subjects with PD-1/PD-L1 blockade–resistant NSCLC (Negrao, 2022). On this study, intratumoral injections of vidutolimod were administered safely and successfully, including injection of visceral lesions.

No objective responses were observed in this heavily pretreated NSCLC patient population, but two subjects had tumor shrinkage (<30% decrease in tumor size, nonirradiated) and this correlated with strong induction of CXCL10. Study CMP-001-003 demonstrated the feasibility of IT therapy in NSCLC, and the lack of efficacy in the PD-1 refractory setting does not preclude possible meaningful antitumor activity in immunotherapy naïve patients. Vidutolimod in combination with standard cemiplimab warrants further development and evaluation in NSCLC in the favorable population of newly diagnosed advanced NSCLC patients with high PD-L1 expression (≥50%), with disease that is amenable to IT injections.

1.3.3.4. Head and Neck (HPV-Positive)

HPV-positive OPSCC represents a distinct subset of HN cancer, at both the clinical and molecular levels (Ferris, 2023). In patients with oropharynx primary, HPV positivity can be established by a positive p16 immunohistochemistry (IHC) result. Alternatively, the presence of HPV E6/E7

mRNA transcripts in the tumor, as directly demonstrated by RNA ISH, can establish that an oropharynx SCC is HPV-positive (Ferris, 2023). A positive HPV DNA ISH result also establishes than an oropharynx primary tumor is HPV associated, although this test is less commonly used (Gillison, 2016). In HNSCC patients who present with cervical lymphadenopathy and occult primary, the diagnosis of HPV-associated disease with occult oropharynx primary is accepted when HPV positivity is documented by HPV RNA or DNA ISH (NCCN, 2023).

Patients with HPV-positive oropharynx squamous cell carcinoma (OPSCC) have lower risk of disease recurrence after curative intent therapy for locally advanced disease, compared to patients with HPV-negative oropharynx cancer (Ang, 2010). However, for patients who do experience recurrent or metastatic HPV-positive HNSCC and received pembrolizumab (either as monotherapy or in combination with chemotherapy), the median overall survival is less than 20 months (Black, 2023). Therefore, there is an urgent need for new treatment options for patients with R/M HPV-positive OPSCC.

In a phase 2 study, HNSCC patients received pembrolizumab + SD-101, a TLR9 agonist of CpG-C class, in the 1L R/M setting. Overall, the objective response rate (ORR) was 24% for all HNSCC patients. Among patients with HPV-positive disease, ORR was 44% (7/16). Among patients with HPV-negative disease, ORR was 12% (2/17) (Cohen, 2022). These findings are consistent with results in a phase 2 study of pembrolizumab + vidutolimod in 1L R/M HNSCC patients, which enrolled 6 patients with HPV-positive R/M OPSSCC. Among these 6 patients, there was one durable partial response, and one near-partial response (-29% reduction in target lesions by RECIST) (NCT04633278; Regeneron data on file). In these two studies, there was no signal for enhanced efficacy with the addition of TLR9 agonist to pembrolizumab in HPV-negative patients, compared with historical experience with pembrolizumab monotherapy in 1L R/M HNCC (Burtness, 2019). The mechanistic basis of potential enhanced efficacy of TLR9 agonist in HPV-positive OPSCC has not been established, but plasmacytoid dendritic cells (pDCs) from HPV-positive OPSCC tumors may secrete immune-supportive cytokines such as IFNalpha, whereas pDCs from HPV-negative tumors may secrete immune-suppressive cytokines such as IL-10 and TNFalpha(Koucký, 2021).

The current study will evaluate cemiplimab + vidutolimod in R/M, PD-L1 CPS score ≥1, HPV-positive OPSCC among patients who have not received prior systemic therapy for R/M disease.

1.3.4. Rationale for Doses and Schedules

1.3.4.1. Rationale for Vidutolimod Dose and Schedule

In the Phase 1b clinical study CMP-001-001, vidutolimod IT was evaluated at doses of 1 to 10 mg using 2 dosing schedules and with preparations containing 2 different concentrations of the excipient polysorbate 20 (0.01% and 0.00167%) in combination with pembrolizumab IV in subjects with PD-1 refractory melanoma. The safety profile was similar and manageable across the vidutolimod doses of 1 to 10 mg. Antitumor activity, as shown by durable CRs and PRs according to RECIST, was observed in 23% of subjects who initiated treatment with the proposed dose and schedule for this study: vidutolimod 10 mg (0.01% polysorbate 20) IT every week for 7 doses, followed by administration Q3W in combination with pembrolizumab 200 mg IV Q3W. This dose and schedule were selected for further development with PD-1-blocking antibodies. Further details can be found in vidutolimod IB.

1.3.4.2. Rationale for Cemiplimab Dose

Cemiplimab is currently approved as a monotherapy treatment at 350 mg IV Q3W for patients with metastatic or locally advanced CSCC who were not candidates for curative surgery or curative radiation, for the treatment of patients with metastatic BCC or locally advanced BCC who were previously treated with a HHI, and for the first-line treatment of patients with locally advanced or metastatic NSCLC whose tumors have high (tumor proportion score [TPS] ≥50%) PD-L1 expression. The approved dose will be utilized for this study.

1.4. Benefit-Risk

More detailed information about the known and expected benefits and risks, and reasonably expected adverse events may be found in the vidutolimod and cemiplimab IBs.

Included in this amendment are measures to account for the "Coronavirus Disease 2019" (COVID-19) pandemic and to minimize the risks to the patients in the study as well as healthcare providers by allowing flexibility in the visit schedule while social distancing suggestions are in place. Allowing for this flexibility does not increase the risk of participating in this study as there will be continued contact between the patients and study personnel despite postponement of in-person clinic visits.

The primary objective of this study is to evaluate the efficacy (ORR) of vidutolimod administered by IT injection in combination with cemiplimab IV in subjects with selected types of advanced or metastatic cancer.

A major mechanism of resistance to PD-1 blockade is the absence of activated effector T cells in the tumor. Therefore, activation of T cells by TLR9 agonism, and subsequent trafficking to tumor sites, has the potential to improve the response to PD-1 blockade, particularly in non-inflamed tumors. The efficacy of vidutolimod in combination with pembrolizumab has been demonstrated in patients with melanoma refractory to PD-1 blockade in the ongoing Study CMP-001-001. The objective response rate (ORR) was 27.6% (27/98; 95% CI 19.0%, 37.6%), including patients with responses after initial progressive disease (PD), and the best ORR by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) was 23.5% (23/98; 95% CI 15.5%, 33.1%), including 7 complete responses (CR) and 16 partial responses (PR). Additional details are provided in Section 1.3.1.3 and Section 5.4 of the vidutolimod IB. Rationale for combining vidutolimod with cemiplimab in various indications is described in Section 1.3.3.

Although vidutolimod has not been studied with cemiplimab except in this current study, the safety profile of vidutolimod in combination with other PD-1/PD-L1 agents is described below.

The analysis of available cumulative safety data from ongoing studies demonstrates a safety profile for vidutolimod in combination with pembrolizumab or nivolumab that predominantly consists of Grade 1 to Grade 2 AEs of flu-like symptoms (which can include, but may not be limited to, fever, nausea, vomiting, chills, and/or rigors; headache, tachycardia, rash, or hypoxia may also occur), cytokine release syndrome (CRS), hypotension, and injection site reactions. Treatment-related TEAEs involved events of chills, pyrexia, fatigue, nausea, vomiting, injection site pain, and headache. Commonly reported SAEs that have been observed across these clinical studies with vidutolimod were chills, pyrexia, fatigue, and hypotension.

The TEAEs of fever (pyrexia), chills, nausea, vomiting, diarrhea, headache, rash, and hypotension typically present after the second and subsequent vidutolimod doses and generally resolve within a few hours with supportive care. Stress dose corticosteroids may be required for hypotension unresponsive to IV fluids or in subjects that experience a prior Grade ≥3 vidutolimod-related event. Please refer to Vidutolimod IB Section 5.3 for a summary of all available cumulative safety data in the 6 studies.

In clinical studies, there is no evidence to suggest that vidutolimod in combination with a PD-1/PD-L1-blocking antibody or as monotherapy increases the frequency or severity of immune-related AEs.

No treatment-related Grade 5 TEAEs were reported across clinical studies.

Thus, taking into account the risk minimization measures outlined in this phase 2 protocol to minimize important risks to patients, the potential for therapeutic benefit and medical need for new combination therapy, the risk-benefit profile is anticipated to be positive for coadministration of vidutolimod, with cemiplimab, anti-PD-1, in the phase 2 study, in the population of subjects with selected types of advanced or metastatic cancer.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objective

The primary objective of this study is to determine the confirmed ORR with vidutolimod in combination with cemiplimab.

2.1.2. Secondary Objectives

The secondary objectives of the study are to:

- Evaluate the safety and tolerability of vidutolimod administered by IT injection in combination with cemiplimab
- Evaluate the efficacy of vidutolimod in combination with cemiplimab

2.1.3. Exploratory Objectives

The exploratory objectives of this study are to:

- Evaluate the effect of vidutolimod in combination with cemiplimab on injected and noninjected target lesions
- To demonstrate treatment induced immune effects consistent with vidutolimod mechanism of action, including TLR9 signaling, increase in pDC activation, corresponding increase in CD8 T cell tumor infiltration, and activation status

2.2. Endpoints

2.2.1. Primary Endpoint

The primary endpoint is ORR, defined as the proportion of subjects with a confirmed objective response of CR or PR based on Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1).

2.2.2. Secondary Endpoints

The secondary endpoints are as follows:

- AEs, SAEs, and AEs leading to discontinuation or death, and severity of AEs as assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE v5.0)
- DOR, defined as the time from date of first documented response (CR or PR) to date of documented PD, based on RECIST v1.1
- Response in injected and noninjected target lesions per RECIST v1.1
- PFS, defined as the time from date of first dose of study treatment to date of documented PD based on RECIST v1.1 or death, whichever occurs first

- Overall survival (OS), defined as the time from date of first dose of study treatment to date of death

2.2.3. Exploratory Endpoints

The exploratory endpoints of the study are as follows:

- Baseline and post-treatment changes in downstream targets of TLR9 signaling (serum CXCL10), other peripheral blood biomarkers related to pDC activation, type I interferon and effector T cell activation and explore association with clinical outcomes.
- Baseline and post-treatment changes in tumor CD8 T cell density, activation and/or proliferation status and tumor inflammatory gene expression (including IFN-gamma, Golgi gene expression signature).

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design

This is a multicenter, open-label, Phase 2 clinical study of vidutolimod administered by IT injection in combination with cemiplimab IV in subjects with selected types of advanced or metastatic cancer with or without prior PD-1–blocking antibody treatment, as follows:

- Cohorts A1 and A2: Subjects with metastatic or locally and/or regionally advanced unresectable CSCC:
  - **Cohort A1:** Subjects who had not received prior systemic therapy for CSCC and who are not eligible for curative radiation
  - **Cohort A2:** Subjects who have progressed while receiving a PD-1–blocking antibody or within 12 weeks of discontinuation
- Cohorts B1 and B2: Subjects with metastatic or locally and/or regionally advanced unresectable MCC:
  - **Cohort B1:** Subjects who had not received prior systemic therapy for MCC
  - **Cohort B2:** Subjects who have progressed while receiving a PD-1–blocking antibody or within 12 weeks of discontinuation
- Cohorts C1 and C2: Previously treated subjects with advanced or metastatic TNBC. Patients must have previously received treatment with sacituzumab govitecan (all TNBC patients), with trastuzumab deruxtecan (HER2-low patients) and with PARP inhibitor (for BRCA) patients:
  - **Cohort C1:** Subjects who had not received prior therapy with immune checkpoint inhibitors (iCPIs)
  - **Cohort C2:** Subjects who have progressed while receiving a PD-1–-blocking antibody or within 12 weeks of discontinuation
- **Cohort D:** Subjects with newly diagnosed metastatic or locally and/or regionally advanced unresectable basal cell carcinoma (BCC) who have not received prior hedgehog pathway inhibitor therapy or prior anti-PD-1/PD-L1 therapy and who do not wish to receive or who are not candidates for a hedgehog inhibitor.
- **Cohort E (not conducted in Europe):** Advanced non-small cell lung cancer (NSCLC) subjects (locally advanced who are not candidates for surgical resection or definitive chemoradiation or metastatic) whose tumors have high PD-L1 expression (tumor proportion score [TPS] ≥50%) based on a prior PD-L1 result as determined by CAP/CLIA (or equivalently licensed) lab, with no EGFR, ALK, or ROS1 aberrations, and who have not received prior anti-PD-1/PD-L1 therapy and are amenable to IT therapy and do not wish to receive chemotherapy.
- **Cohort F:** R/M OPSCC subjects with HPV-positive, PD-L1 CPS score ≥ 1 disease who have not received prior systemic therapy for R/M disease. HPV-positive status, based on a prior result, must be established in a surgical specimen or a core biopsy

specimen from any site of OPSCC (primary site, nodal site, and/or distant metastatic site, either at time of diagnosis or later) in a CAP/CLIA (or equivalently licensed) lab, as follows:

For subjects with documented history of oropharynx primary disease, either of the following will be accepted as evidence of HPV-positive OPSCC: positive p16 immunohistochemistry (IHC) or positive HPV DNA or RNA in situ hybridization (ISH).

For subjects with HNSCC of unknown primary, positive HPV DNA or RNA ISH is required as evidence of HPV-positive disease.

PD-L1 expression (CPS ≥1) is based on a prior PD-L1 result as determined by CAP/CLIA (or equivalently licensed) lab.

Vidutolimod 10 mg will be administered weekly for 7 doses, after which it will be administered Q3W until the subject meets a condition for discontinuation of study treatment. The first dose of vidutolimod may be administered SC or by IT injection, at the discretion of the Investigator; all subsequent doses are planned to be administered IT. The initial 7 vidutolimod doses, administered on a weekly schedule, must be completed before moving on to the Q3W vidutolimod dosing schedule.

The PD-1–blocking antibody administered in this study is cemiplimab. Treatment with cemiplimab will be administered IV infusion over 30 minutes (±10 minutes) at Week 1 Day 1 (W1D1) and Q3W thereafter. Cemiplimab administration will occur after vidutolimod administration.

All subjects will receive vidutolimod and cemiplimab according to the treatment schedule up to 2 years or until a reason for treatment discontinuation is reached.

Disease status will be assessed by computed tomography (CT) or magnetic resonance imaging (MRI) and other appropriate measures beginning predose at Week 10 Day 1 (W10D1) and will be repeated every 9 weeks (e.g. W19D1, W28D1, etc.) while the subject is on treatment. All scans should be performed at least 2 weeks after the previous vidutolimod IT injection to prevent detection of injection-related pseudoprogression. Imaging should not be delayed for delays in treatment.

Objective responses will be assessed by the Investigator according to RECIST v1.1.

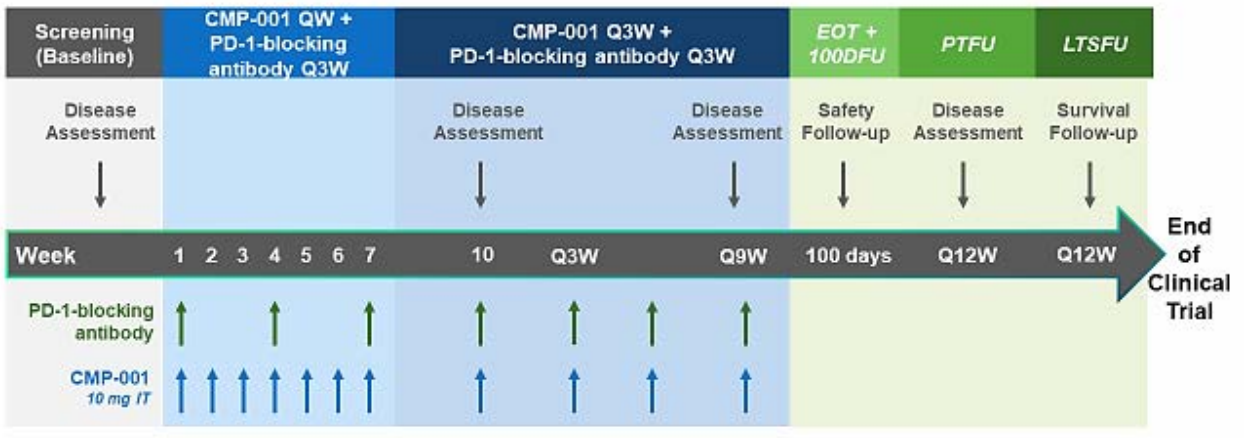
Subjects who discontinue study treatment should complete the end of treatment (EOT) visit. AEs and concomitant medications data will be collected until 100 days after the last dose of study drug (vidutolimod or cemiplimab) or until an alternative anticancer treatment is initiated, whichever occurs first, including at a 100-day safety follow-up visit.

Subjects who are posttreatment but have not met criteria for study discontinuation should remain on study for posttreatment follow-up (PTFU), which includes disease assessments every 3 months until discontinuation. Long-term survival follow-up (LTSFU) will be conducted every 3 months after the EOT visit or the last disease assessment date in PTFU.

At the end of the treatment period (2 years), the Sponsor will not continue to provide supplied study treatment to subjects/investigators unless the Sponsor chooses to extend the study. The

investigator should ensure that the subjects receive appropriate standard of care to treat the condition under study.

Figure 1: Vidutolimod Study Schema



Abbreviations: 100DFU = 100-Day Follow-up; EOT = end of treatment; LTSFU = long-term survival follow-up; IT = intratumoral; PD-1 = programmed cell death protein 1; PTFU = posttreatment follow-up; Q3W = every 3 weeks; Q9W = every 9 weeks; Q12W = every 12 weeks; QW = every week; SC = subcutaneous.
Note: The first dose of vidutolimod may be administered by SC or IT injection, per Investigator discretion. All subsequent doses of vidutolimod are planned to be administered IT.

3.2. Treatment Discontinuation

Study treatment should continue until 1 of the following occurs:

- Unacceptable AE that precludes further study treatment (see Section 4.1.1.5.4 and Section 4.1.2.2)
- 2 years of study treatment
- PD per RECIST v1.1; continuation of treatment through suspected pseudoprogression is permitted as described in Section 3.2.1
- Upon request of the Sponsor or regulatory agency
- Clinical disease progression
- If medically necessary in the opinion of the Investigator
- Subject withdraws consent for treatment (Note: A subject who withdraws consent for additional study treatment and procedures but not for antitumor response will continue to be followed.)
- Subject becomes pregnant or begins breastfeeding
- Subject is lost to follow-up (at least 3 documented attempts to contact the subject)
- Death
- End of clinical trial

Subjects who permanently discontinue treatment with cemiplimab because of immune-mediated AEs (imAEs) must also permanently discontinue treatment with vidutolimod.

If a subject achieves and maintains a confirmed CR by Investigator review, treatment with vidutolimod or the combination of vidutolimod and cemiplimab may be discontinued at the Investigator's discretion once they meet both of the following criteria:

- Subject has been treated with both study drugs for at least 24 weeks
- Subject has received at least 3 doses of both study drugs beyond the date of the initial CR

Subjects who discontinue study treatment should undergo the EOT assessments. Subjects who discontinue study treatment for reasons other than disease progression (per RECIST v1.1 by Investigator, or clinical PD per Investigator) should remain on study for PTFU and receive disease assessments according to the Schedule of Assessments (Table 1). Long-term survival follow-up will be conducted every 3 months after the EOT visit or the last disease assessment date in PTFU.

3.2.1. Treatment Beyond Progression

Subjects with a single tumor assessment of PD (per RECIST v1.1) may continue treatment until the next tumor assessment, at the discretion of the investigator based on the clinical state of the patient after communication with the Sponsor, if the following conditions are met:

- The subject has no decline in performance status (as defined by ECOG)
- The subject has absence of clinical symptoms or signs indicating clinically significant disease progression; absence of rapid disease progression or threat to vital organs or critical anatomical sites (eg, central nervous system metastasis, respiratory failure due to tumor compression, spinal cord compression) requiring urgent alternative medical intervention
- The subject has no significant, unacceptable or irreversible toxicities related to study treatments, including any AE(s) that would require permanent discontinuation of either vidutolimod or cemiplimab
- The subject provides consent prior to resuming treatment; this will be done by repeating the informed consent process that was conducted prior to initial study enrollment, with the subject signing (or having their legally authorized representative sign, as appropriate) the current version of the informed consent form (ICF)

Subjects will continue on the same schedule of assessments, with treatment continuing according to the next scheduled clinic visit (ie, treatments missed outside of the visit window will not be made up). As a general rule, if further progression occurs after study treatment is resumed (≥20% increase in tumor measurements by RECIST 1.1 criteria, using the initial progression scan as the comparator, and/or development of new lesions) that study drugs will be discontinued.

Treatment beyond the second progression may be allowed in selected cases after communication with the Sponsor (e.g., progression of lesion(s) that has(have) not been injected at the time of documented progression if the plan to inject the progressing lesion(s) after documented progression).

3.3. Study Withdrawal

Subjects may withdraw from the study at any time and without penalty or loss of future medical care, or any other benefits to which they are otherwise entitled. Subjects will be withdrawn from the study for any of the following reasons:

- Subject withdraws consent for the study
- Subject lost to follow-up
- Death
- End of clinical trial

For subjects who withdraw consent from overall study participation (not only study treatment) will not have the EOT visit, safety follow-up visits, or further evaluations performed.

3.4. End of Clinical Trial

The definition for End of Study (Trial) is the date of global last subject's last visit (100 days ±7 days after the last dose of study drug: vidutolimod or cemiplimab), or the date of withdrawal from the study, or lost to follow-up (i.e., the study subject can no longer be contacted by the investigator) whichever comes first. The sponsor has the right to terminate the study at any time. All data collection will cease in all subjects when the end of the clinical trial is reached.

3.5. Subject Inclusion Criteria

Subjects enrolled into this study must meet the following inclusion criteria to be eligible.

1. Histopathologically-confirmed diagnosis of cancer that is metastatic or unresectable at Screening.
    - Subjects with metastatic or locally and/or regionally advanced unresectable CSCC. Note 1: CSCC subjects without radiographically measurable disease are not excluded if there is at least 1 lesion ≥ 10 mm in at least 1 dimension documented by color photography.

      Note 2: Subjects with tumors that arise in the setting of chronic inflammation (Marjolin's ulcer) such as chronic wounds and/or scars are excluded.
    - **Cohort A1**: Subjects who have not received prior systemic therapy for CSCC and who are not eligible for curative radiation.
    - **Cohort A2:** Subjects who have progressed while receiving a PD-1–blocking antibody or within 12 weeks of discontinuation. PD-1–blocking antibody treatment may have been administered in the adjuvant and/or neoadjuvant and/or locally advanced or metastatic setting.
    - Subjects with metastatic or locally and/or regionally advanced unresectable MCC.

      Note: MCC subjects without radiographically measurable disease are not excluded if there is at least 1 lesion ≥ 10 mm in at least 1 dimension documented by color photography./

- **Cohort B1**: Subjects who have not received prior systemic therapy for MCC.
- **Cohort B2:** Subjects who have progressed while receiving a PD-1–blocking antibody or within 12 weeks of discontinuation. PD-1–blocking antibody treatment may have been administered in the adjuvant and/or neoadjuvant and/or locally advanced or metastatic setting.
- **Cohorts C1 and C2**: Previously treated subjects with advanced or metastatic TNBC must have disease that is HER2-negative, estrogen and progesterone receptor-negative, or < 5% expression based on American Society of Clinical Oncology/College of American Pathologists guidelines (Hammond, 2010a)(Hammond, 2010b)(Wolff, 2013). Subjects with disease recurrence or progression following neoadjuvant or adjuvant therapy are eligible. Subjects with advanced or metastatic disease may have up to 5 lines of systemic therapy. Patients must have previously received treatment with sacituzumab govitecan (all TNBC patients), with trastuzumab deruxtecan (HER2-low patients) and with PARP inhibitor (for BRCA) patients.
  - **Cohort C1**: Subjects who have not received prior therapy with iCPIs.
  - **Cohort C2**: Subjects who have progressed while receiving a PD-1–blocking antibody or within 12 weeks of discontinuation.
- **Cohort D:** Advanced BCC subjects (metastatic or locally advanced) who are not candidates for curative surgery and have not received prior therapy with a hedgehog pathway inhibitor (vismodegib or sonidegib) or prior anti-PD-1/PD-L1 therapy and who do not wish to receive or who are not candidates for a hedgehog inhibitor.

  Note: BCC subjects without radiographically measurable disease are not excluded if there is at least 1 lesion ≥10 mm in at least 1 dimension documented by color photography.
- **Cohort E (not conducted in Europe)**: Advanced non-small cell lung cancer (NSCLC) subjects (locally advanced who are not candidates for surgical resection or definitive chemoradiation or metastatic) whose tumors have high PD-L1 expression (TPS ≥50%) based on a prior PD-L1 result as determined by a CAP/CLIA (or equivalently licensed) lab, with no EGFR, ALK or ROS1 aberrations, and who have not received prior anti-PD-1/PD-L1 therapy and are amenable to IT therapy and do not wish to receive chemotherapy.
- **Cohort F**: R/M Oropharyngeal squamous cell carcinoma (OPSCC) subjects with PD-L1 CPS score ≥1, HPV-positive disease who have not received prior systemic therapy for R/M disease. HPV-positive status, based on a prior result, must be established in a surgical specimen or a core biopsy specimen from any site of OPSCC (primary site, nodal site, and/or distant metastatic site, either at time of diagnosis or later) in a CAP/CLIA (or equivalently licensed) lab, as follows:
  - For subjects with documented history of oropharynx primary disease, either of the following will be accepted as evidence of HPV-positive OPSCC: positive p16 immunohistochemistry (IHC) or positive HPV DNA or RNA in situ hybridization (ISH).

  - For subjects with HNSCC of unknown primary, positive HPV DNA or RNA ISH is required as evidence of HPV-positive disease.
  - PD-L1 expression (CPS ≥1) is based on a prior PD-L1 result as determined by CAP/CLIA (or equivalently licensed) lab.

2. Measurable disease, as defined by RECIST v1.1 and all of the following:
   - At least 1 accessible lesion amenable to repeated IT injection.
   - A previously irradiated lesion may be used as a target lesion if subsequent disease progression in that lesion (at least 20% increase in dimensions with a 5 mm absolute increase) was documented.
3. Able to provide tissue from a core or excisional/incisional biopsy (fine needle aspirate is not sufficient). A newly obtained biopsy (within 90 days before the start of study treatment) is preferred but an archival sample is acceptable if no intervening therapy was received.

   Note: Refer to the laboratory manual for tissue sampling details.
4. Adequate organ function based on most recent laboratory values within 3 weeks before first dose of study treatment on W1D1:
   - Bone marrow function:
     - neutrophil count ≥ 1500/mm^3
     - platelet count ≥ 100,000/mm^3
     - hemoglobin concentration ≥ 9 g/dL
   - Liver function:
     - total bilirubin ≤ 1.5 times the upper limit of normal (ULN) with the following exception: subjects with Gilbert Disease total serum bilirubin ≤ 3 times ULN
     - aspartate aminotransferase and alanine aminotransferase ≤ 3 times the ULN
   - Renal function: estimated (Cockcroft-Gault) or measured creatinine clearance ≥ 30 mL/min
   - Coagulation:
     - International normalized ratio (INR) or prothrombin time (PT) ≤ 1.5 times ULN unless subject is receiving anticoagulant therapy, as long as PT or partial thromboplastin time (PTT) is within therapeutic range of intended use of anticoagulants.
     - Activated partial thromboplastin time or PTT ≤ 1.5 times ULN unless subject is receiving anticoagulant therapy, as long as PT or PTT is within therapeutic range of intended use of anticoagulants.
5. Age ≥ 18 years at time of consent.
6. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 1 at Screening.
7. Capable of understanding and complying with protocol requirements.

8. Criterion removed in Amendment 3.
9. Able and willing to provide written informed consent and to follow study instructions. Subjects unable to provide written informed consent on their own behalf will not be eligible for the study.

3.6. Subject Exclusion Criteria

Subjects presenting with any of the following will not qualify for entry into the study:

1. Received radiation therapy (or other non-systemic therapy) within 2 weeks before first dose of study treatment on W1D1. Subjects should have recovered (i.e. Grade ≤ 1 or at baseline) from radiation-related toxicities.
2. Treatment with complementary medications (e.g. herbal supplements or traditional Chinese medicines) to treat the disease under study within 2 weeks prior to start of study treatment or at any time during the treatment phase of the study. Refer to Section 3.8 for prohibited treatments.
3. Received systemic pharmacologic doses of corticosteroids > 10 mg/day prednisone within 15 days before first dose of study treatment on W1D1.
   a. Subjects who are currently receiving steroids at a prednisone-equivalent dose of ≤ 10 mg/day do not need to discontinue steroids prior to enrollment.
   b. Replacement doses, topical, ophthalmologic, and inhalational steroids are permitted.
   c. Stress-dose corticosteroids will be required in subjects with adrenal insufficiency (see Section 4.1.1.1.1).
4. History of immune-mediated AE leading to permanent discontinuation due to prior PD1–blocking antibody.
5. Not fully recovered from AEs due to prior treatment (to Grade 1 or less, per CTCAE), with the exception of persistent vitiligo, alopecia, hypothyroidism, diabetes mellitus, and adrenal and/or pituitary insufficiency.

   NOTE: Subjects previously treated with a CTLA-4–blocking antibody, subjects receiving corticosteroids with daily doses > 5 mg and ≤ 10 mg of prednisone equivalent for > 2 weeks, and subjects with clinical symptoms and/or laboratory findings suggesting risk for adrenal insufficiency should undergo diagnostic tests for adrenal insufficiency via local laboratory.
6. Active pneumonitis or history of noninfectious pneumonitis that required steroids.
7. Severe uncontrolled medical disease within 12 months of Screening, including but not limited to poorly controlled hypertension, unstable angina, myocardial infarction, congestive heart failure (New York Heart Association Class II or greater), pericarditis, cerebrovascular accident, or implanted or continuous use of a pacemaker or defibrillator, or emphysema with FEV1 ≤ 50% predicted.
8. Known history of immunodeficiency.
9. Known additional malignancy that is progressing or required active treatment within the past 3 years. Exceptions include cancers that have undergone potentially curative therapy,

e.g. basal cell carcinoma of the skin, squamous cell carcinoma of the skin, localized prostate cancer with prostate-specific antigen level below 4.0 ng/mL, in situ cervical cancer on biopsy or a squamous intraepithelial lesion on Papanicolaou smear, and thyroid cancer (except anaplastic), in situ breast cancer, and adjuvant hormonal therapy for breast cancer > 3 years from curative-intent surgical resection.

10. Active autoimmune disease that required systemic treatment in past 2 years; replacement therapy is not considered a form of systemic treatment.
11. Untreated, symptomatic, or enlarging central nervous system (CNS) metastases or carcinomatous meningitis (including leptomeningeal metastases from solid tumors).
12. Prior allogenic tissue/solid organ transplant.
13. Active infection requiring systemic therapy.
14. Known or suspected active infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).
15. Known or suspected active infection with human immunodeficiency virus, hepatitis B virus, or hepatitis C virus (testing is not required unless suspected).
16. Received a live virus/attenuated vaccination within 30 days before first dose of study treatment on W1D1.
17. Received blood products (including platelets or red blood cells) or colony stimulating factors (including granulocyte colony stimulating factor, granulocyte/macrophage colony stimulating factor, or recombinant erythropoietin) within 3 weeks before the W1D1 visit.
18. History of permanent discontinuation of cemiplimab due to infusion reactions or hypersensitivity to the investigational agents or their excipients.
19. Any concurrent uncontrolled illness, including mental illness or substance abuse, which in the opinion of the Investigator would make the subject unable to cooperate or participate in the study.
20. Participation in another clinical study of an investigational anticancer therapy or device within 30 days before first dose of study treatment on W1D1. Note: Participation in the follow-up phase (receiving no study treatment) of a prior study is allowed.
21. Requires prohibited treatment (i.e. non-protocol specified anticancer pharmacotherapy, surgery, or conventional radiotherapy) for treatment of malignant tumor.
22. Has a life expectancy of less than 3 months and/or has rapidly progressing disease (e.g. tumor bleeding, uncontrolled tumor pain) in the opinion of the treating Investigator.
23. Received previous vidutolimod treatment.
24. Pregnant or breastfeeding or expecting to conceive children within the projected duration of the study, from the time of consent until at least 150 days after last dose of study treatment.
25. Sexually active men and women of childbearing potential* who are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the

study, and for at least 6 months after the last dose. Highly effective contraceptive measures include:

- Stable use of combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening
- Intrauterine device (IUD); intrauterine hormone-releasing system (IUS)
- Bilateral tubal ligation/occlusion
- Vasectomized man or partner, and/or
- Sexual abstinence†, ‡.

*Postmenopausal women must be amenorrheic for at least 12 months in order not to be considered of childbearing potential. Pregnancy testing and contraception are not required for women with documented hysterectomy.

†Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments.

‡Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.

26. Had major surgeries (including complete oncologic resection) within last 4 weeks prior to enrollment, and/or have not recovered adequately from the toxicities and/or complications from the intervention. Minor surgeries (including routine resections of early stage CSCCs and BCCs that may be due to field cancerization) require a 7-day washout.

3.7. Replacement of Subjects

Subjects enrolled and withdrawn from study any time prior to first dose of study drugs will not be considered evaluable for assessment and will be replaced with another subject. All subjects who have received a dose of study drugs will be included in an as treated analysis.

3.8. Prohibited Treatments

Medications intended solely for supportive care are allowed (i.e. antiemetics, analgesics, megestrol acetate for anorexia).

The following concomitant medications are prohibited:

- Concurrent systemic anticancer therapy with agents other than the combination study drug therapy (vidutolimod + cemiplimab) is not allowed at any time during the study. Topical anticancer therapy agents are allowed provided they are not used for the target or non-target lesions
- Agents known to have TLR9 antagonist activity are prohibited throughout the study. The current known antagonists are chloroquine, hydroxychloroquine, and quinacrine.
- Systemic pharmacologic doses of corticosteroids > 10 mg/day of prednisone equivalent are not permitted within 15 days of study enrollment. However, corticosteroid administration is allowed in the following circumstances:
  - In the treatment of subjects with known adrenal insufficiency (see Section 4.1.1.1.1). Consultation with the Medical Monitor is required prior to enrollment of subjects with adrenal insufficiency.
  - Replacement doses, topical, ophthalmologic, and inhalational steroids are permitted.
  - For the management of immune-mediated toxicities and for palliation of pain or cancer related complications during study conduct. Note: Treatment on study cannot be resumed while on systemic pharmacologic doses of corticosteroids > 10 mg/day of prednisone equivalent
- Complementary medications to treat the disease under study (e.g. herbal supplements or traditional Chinese medicines).

3.8.1. Vaccinations

Subjects should not have received a live virus/attenuated vaccination within 30 days before first dose of study treatment on W1D1.

Given the potential for injection site reactions and flu-like symptoms, vaccination with a viral vector or mRNA vaccine should not be performed within 72 hours of vidutolimod injection.

COVID-19 vaccination, either as an initial series or as a booster dose, received during the study, will be treated as a concomitant medication. As noted, administration of a COVID-19 vaccination should be separated from the time of administration of the investigational product (at least 72 hours, ideally by at least 1 week) in order to avoid confounding the effects (eg, adverse effects) of the vaccine/booster with the effects of study drug.

3.8.2. Concomitant Procedures

Palliative radiotherapy or palliative surgery may be allowed after Medical Monitor consultation to ascertain whether clinical progression has occurred. If the lesion(s) targeted for palliation are target lesions, then the anatomic site requiring palliation must be assessed for disease status.

3.9. Concomitant Medications

IMPORTANT: Prophylactic medications are required prior to vidutolimod administration, as described in Section 4.1.1.1. Prophylactic medications administered before and after vidutolimod dosing will be collected in the electronic data capture (EDC) for each visit.

Allowed concomitant medications include those intended solely for supportive care (i.e. antiemetics, analgesics, megestrol acetate for anorexia).

Prohibited treatments are described in Section 3.8.

4. TREATMENT OF SUBJECTS

4.1. Administration of Study Drugs

All subjects will receive vidutolimod injection followed by cemiplimab administered IV according to the dosing schedules shown in the Schedule of Assessments (Table 1).

Table 3: Study Interventions Administered

Intervention Name	Vidutolimod	Cemiplimab
Dose Formulation	Sterile solution	Sterile solution
Unit Dose Strength(s)	5 mg/mL	50 mg/mL
Dosage Level(s)	See Section 4.1.1	See Section 4.1.2
Route of Administration	SC or IT	IV
Use	experimental	experimental
IMP and axMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor

4.1.1. Vidutolimod

Subjects will receive vidutolimod 10 mg weekly for 7 doses (W1D1 to W7D1), after which vidutolimod will be administered by IT injection Q3W (W10D1, W13D1, etc.). The first dose of vidutolimod may be administered SC or by IT injection, at the discretion of the Investigator; all subsequent doses are planned to be administered IT. On visits where both study drugs are administered, vidutolimod should be administered before cemiplimab. There is no specified waiting period between the end of vidutolimod administration and the initiation of cemiplimab infusion. Vidutolimod should be administered up to 2 years or until a reason for treatment discontinuation is reached (Section 3.2).

4.1.1.1. Required Prophylaxis Before and After Vidutolimod Injection

To reduce the incidence and severity of symptoms associated with vidutolimod injection, prophylaxis is required. All recommended prophylaxis should be administered before initiation of the vidutolimod injection. The medications are recommended for oral administration, but IV is acceptable at the discretion of the Investigator. There is no mandatory waiting period between the end of prophylaxis and the start of the vidutolimod injection.

The optimal recommended regimen that has been effective for the treatment of vidutolimod associated AEs should include all of the following components:

- Intravenous fluids (e.g. approximately 1000 cc IV normal saline). The rate, volume, and substitution fluids are at the Investigator's discretion.
- Antipyretics (e.g. acetaminophen 1000 mg and a non-steroidal anti-inflammatory agent such as indomethacin 50 mg or ibuprofen 600 to 800 mg)
- Antiemetics (e.g. ondansetron 8 mg)
- Antihistamine (e.g. diphenhydramine 50 mg, with or without an H2-antagonist)

- Recommended hydrocortisone 25 mg at the Investigator's discretion. Subjects with adrenal insufficiency should be treated with stress dose steroids as described in Section 4.1.1.1.1.

It is also highly recommended to continue to administer IV fluids during the observation period immediately following the vidutolimod injection, rather than waiting to initiate fluids if hypotension is detected. Antipyretics, antiemetics, and antihistamines may be repeated at the Investigator's discretion.

Each medication given prophylactically before and after vidutolimod dosing must be recorded separately and for each visit.

4.1.1.1.1. Prophylaxis for Subjects with Adrenal Insufficiency

Subjects with adrenal insufficiency are at increased risk for moderate to severe AEs such as hypotension, which may occur within 1 to 4 hours after vidutolimod injection but may also occur outside this window. Subjects with known adrenal insufficiency may be allowed in the study.

At Screening, subjects previously treated with a CTLA-4 blocking antibody, subjects with clinical symptoms and/or laboratory findings suggesting risk for adrenal insufficiency, or subjects receiving corticosteroids with daily doses > 5 mg and ≤ 10 mg of prednisone equivalent for > 2 weeks should undergo diagnostic tests for adrenocorticotropic hormone (ACTH) and morning cortisol, and/or high-dose ACTH stimulation test (preferred testing method), if clinically indicated, via local laboratory, unless the diagnosis of adrenal insufficiency had been previously established.

All subjects with adrenal insufficiency must receive prophylactic stress-dose steroids (e.g. 50 to 100 mg hydrocortisone or equivalent orally every 8 hours) before and for 24 to 48 hours after each vidutolimod injection.

4.1.1.2. Observation Following Vidutolimod Dosing

Subjects must be observed for at least 4 hours following each of the first 6 injections (W1D1 to W6D1). Beginning with the seventh injection (W7D1), the observation period may be reduced to a minimum of 1 hour following injection at the Investigator's discretion based on the AE profile of the individual subject.

4.1.1.3. Vidutolimod Injections

Refer to Appendix A and the Intratumoral injection manual.

4.1.1.3.1. Tumor Selection

Cutaneous, SC, and/or nodal tumors that are visible, palpable, or detectable by ultrasound or CT guidance are acceptable for IT injection. Systematic support from interventional radiology is required in case of IT injections to visceral lesions. For subjects who have lesions that are not externally visible, guidance on tumor selection and IT injections is included in a separate procedure manual.

Vigilance should be used when selecting lesions for injection that are in close proximity to critical structures (e.g. major airways).

- Special attention and judgment should be exercised before injection of a lesion in the following areas: the "mask areas" of the face (central face, eyelids, eyebrows, periorbital nose, lips [cutaneous and vermilion], chin, mandible, preauricular and postauricular skin/sulci, temple, ear, genitalia, hands, and feet).
- Unsuitable sites for intratumoral or subcutaneous injection would include, for example, the palm of the hand or the sole of the foot.
- Tumors should be at least 0.5 cm in longest diameter and need not be the largest lesion. A visceral tumor may be injected with the use of interventional radiology if, in the opinion of the Investigator and after discussion with the Medical Monitor, it is considered to be the most appropriate site for IT injection. A preferred tumor for IT injection is an accessible lesion that is most rapidly progressing in the judgment of the Investigator. Injected lesions may or may not be target lesions.
- It is allowed to inject all palpable lesions, even if they are all target lesions.
- It is allowed to biopsy injected lesions.

When more than 1 tumor is amenable to IT injection, the Investigator may inject up to 3 tumors per vidutolimod treatment visit. The total dose of vidutolimod may be divided across the tumors at the Investigator's discretion, and the volume injected into each tumor must be recorded.

- The same tumor(s) should be injected with each individual vidutolimod administration, if possible.

If an injected tumor is clearly decreasing in size and another accessible noninjected tumor is not, then the Investigator may divide the vidutolimod dose between the 2 tumors or switch from injecting the regressing tumor to injecting the nonresponding (or growing) tumor Subjects with metastatic disease who have regression of all injectable lesions, or who have an injection site reaction that precludes injection of the tumor, should receive vidutolimod SC near an original tumor (peritumoral) or in the area of the draining lymph nodes (see Appendix A).

4.1.1.3.2. Method of Vidutolimod Administration

Topical or local anesthesia may be used at the Investigator's discretion.

For guidance on selection of syringe and needles for vidutolimod IT and vidutolimod SC injection, see the Pharmacy Manual.

For vidutolimod injection guidelines, see Appendix A.

4.1.1.4. Dose Modifications for Vidutolimod

Vidutolimod dose should remain unchanged during the study.

If a planned dose cannot be given on schedule due to a vidutolimod-related toxicity, the injection should be delayed until the toxicity has improved or resolved. If a subject has vidutolimod dosing withheld for more than 3 consecutive doses for any reason, resumption of treatment must be discussed with the Medical Monitor; otherwise, the subject will be discontinued from study treatment and will have all EOT assessments performed.

If a planned cemiplimab dose is delayed, vidutolimod dosing may be delayed.

4.1.1.5. Management of Adverse Events Associated with Vidutolimod

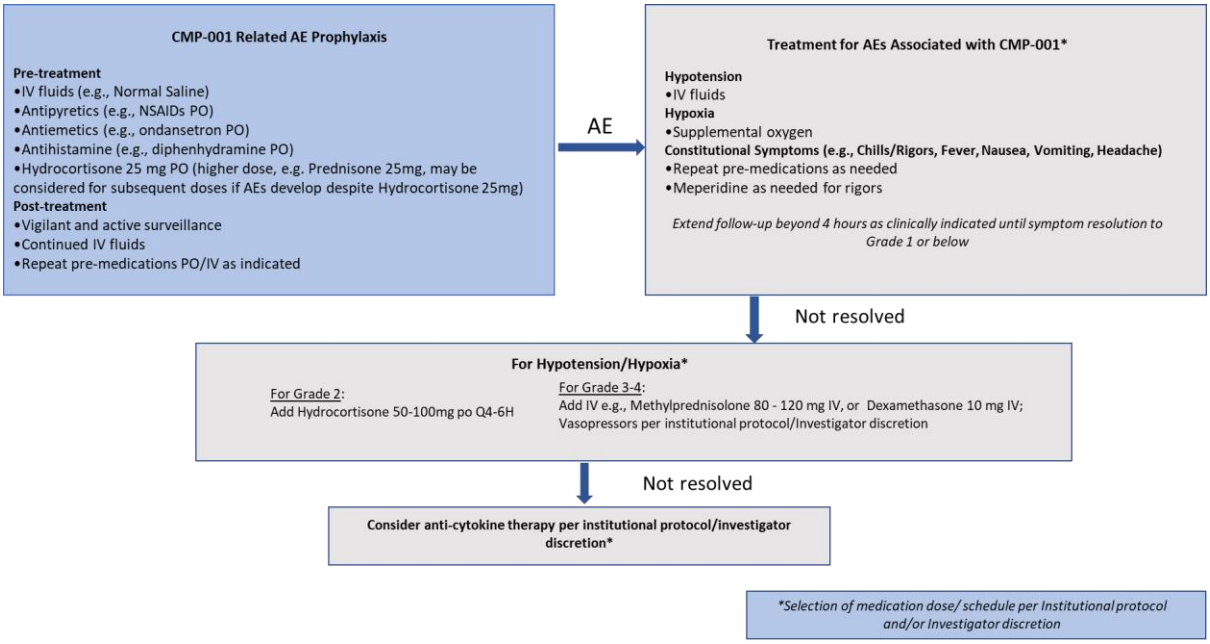
Based on observations in earlier studies, vidutolimod has been associated with AEs such as injection site reactions (see Section 4.1.1.5.1), hypotension, CRS, and flu-like symptoms. Flu-like symptoms could include fever, nausea, vomiting, chills, rigors, and/or hypotension. Additional symptoms may occur, such as headache, tachycardia, rash, and hypoxia. Symptoms should be expected within 1 to 4 hours following the injection but may also occur outside this window.

Sites are to capture oxygen saturation every time an AE of hypoxia or cytokine release syndrome (CRS) is reported for a subject.

Required prophylaxis is designed to prevent or minimize the severity of these symptoms (see Section 4.1.1.1).

The following algorithm (Figure 2) is provided as guidance for prophylaxis and treatment of AEs associated with vidutolimod.

Figure 2: Prophylaxis and Treatment for Adverse Events Associated with Vidutolimod



Abbreviations: AE = adverse event; IV = intravenous(ly); NSAID = non-steroidal anti-inflammatory drug; PO = orally.

4.1.1.5.1. Allergic Reactions

Allergic reactions of an immediate type, including anaphylaxis, have been observed after vidutolimod administration. Please refer to the Vidutolimod IB for details.

Investigators must be vigilant in identifying and managing these disorders according to institutional guidelines. Precautionary measures consisting of pre-treatment prophylaxis and post-injection observation are in place to mitigate the risk of known adverse events associated with vidutolimod, and these measures may prevent or lessen the potential for allergic reactions. Each site should have appropriate emergency equipment, medication, and skills necessary to diagnose and treat anaphylaxis and allergic reactions. Vidutolimod should not be readministered to a subject

who developed a suspected clinically significant allergic reaction without discussion with the Medical Monitor. The diagnosis and management of anaphylaxis should follow institutional guidelines.

4.1.1.5.2. Injection Site Reactions (ISRs)

Injection site inflammation is expected following the second and subsequent injections. If a subject develop inflammation at the injection site, this may be managed using cold compresses and medications for pain and inflammation, such as acetaminophen or non-steroidal anti-inflammatory agents. If, in the Investigator's opinion, a tumor cannot be injected due to injection site reaction or pain, refer to Section 4.1.1.3.1 on changing the site of injection.

For this study, NCI-CTCAE v5 toxicity criteria lack sufficient specificity for safety evaluation of ISRs. Injection site reactions will be graded according to the following scale (Table 4).

Table 4: Severity Criteria for Injection Site Reactions

Grade	Severity	Description
1	Mild	Mildly increased erythema, pruritis, erosion, excoriation, flaking, and/or tenderness
2	Moderate	Moderately increased erythema, pruritis, ulceration, excoriation, necrosis, and/or pain
3	Severe	Severe pain, ulceration, and/or necrosis

4.1.1.5.3. Hypotension

If hypotension is unresponsive to IV fluids, stress dose steroids should be administered (Figure 2).

4.1.1.5.4. Grade 3 or Higher Adverse Events Related to Vidutolimod

For subjects who experienced a Grade 3 or higher AE deemed related to vidutolimod, prophylaxis with prednisone 25 mg or equivalent (at the Investigator's discretion) is required for subsequent vidutolimod doses. If treatment-related Grade 3 or higher hypotension, hypoxia or cytokine release syndrome, or any related Grade 4 AE occurs despite premedication with 25 mg prednisone or equivalent, vidutolimod should be discontinued.

4.1.2. Cemiplimab

Cemiplimab 350 mg IV infusion over 30 minutes (±10 minutes) Q3W, according to the IB will be used in this study.

On visits where both study drugs are administered (W1D1 and Q3W thereafter), vidutolimod should be administered before cemiplimab. There is no specified waiting period between the end of vidutolimod administration and the initiation of cemiplimab infusion.

Cemiplimab should be administered for up to 2 years or until the subject satisfies a condition for study treatment discontinuation (Section 3.2).

4.1.2.1. Treatment Modifications

There will be no dose escalations or reductions allowed for cemiplimab. Doses may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment, as described further in the next section.

Dosing visits are not skipped, only delayed. However, tumor assessments should continue per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.

Prior to re-initiating treatment in a participant with a dosing delay lasting > 9 weeks, the Medical Monitor (or designee) must be consulted.

4.1.2.2. Management of Adverse Events Associated with Cemiplimab

Cemiplimab has been associated with a variety of AEs, especially imAEs. No dose reductions are recommended, and specific treatment guidance on withholding or discontinuing treatment is provided in Table 5. The current IB and local prescribing information should be consulted for guidance on treatment modifications to manage AEs.

Table 5: Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity[a]	Dosage Modifications	Additional Intervention
Immune-Mediated Adverse Reactions			
Pneumonitis	Grade 2	Withhold	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
		Resume if pneumonitis improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent	
	Grade 3 or 4 or recurrent Grade 2	Permanently discontinue	Initial dose of 2 to 4 mg/kg/day prednisone or equivalent followed by a taper
Colitis	Grade 2 or 3	Withhold	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
		Resume if colitis or diarrhea improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent	
	Grade 4 or recurrent Grade 3	Permanently discontinue	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper

Adverse Reaction	**Severity**[a]	**Dosage Modifications**	**Additional Intervention**
Hepatitis	Grade 2 with AST or ALT >3 and ≤5×ULN or total bilirubin >1.5 and ≤3×ULN	Withhold	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
		Resume if hepatitis improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent or returns to baseline AST or ALT after completion of corticosteroid taper	
	Grade ≥3 with AST or ALT >5×ULN or total bilirubin >3×ULN	Permanently discontinue	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
Hypothyroidism	Grade 3 or 4	Withhold	Initiate thyroid hormone replacement as clinically indicated
		Resume when hypothyroidism returns to Grade 0 to 1 or is otherwise clinically stable	
Hyperthyroidism	Grade 3 or 4	Withhold	Initiate symptomatic management
		Resume when hyperthyroidism returns to Grade 0 to 1 or is otherwise clinically stable	
Thyroiditis	Grade 3 or 4	Withhold	Initiate symptomatic management
		Resume when thyroiditis returns to Grade 0 to 1 or is otherwise clinically stable	
Hypophysitis	Grade 2 to 4	Withhold	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper and hormone replacement as clinically indicated
		Resume if hypophysitis improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent or is otherwise clinically stable	
Adrenal insufficiency[b]	Grade 2 to 4	Withhold	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper and hormone replacement as clinically indicated

Adverse Reaction	Severity[a]	Dosage Modifications	Additional Intervention
		Resume if adrenal insufficiency improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent or is otherwise clinically stable	
Type 1 diabetes mellitus	Grade 3 or 4 (hyperglycaemia)	Withhold	Initiate treatment with anti-hyperglycaemics as clinically indicated
		Resume when diabetes mellitus returns to Grade 0 to 1 or is otherwise clinically stable	
Skin adverse reactions	Grade 2 lasting longer than 1 week, Grade 3 or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
		Resume if skin reaction improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent	
	Grade 4 or confirmed SJS or TEN	Permanently discontinue	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
Immune-mediated skin reaction or other immune-mediated adverse reactions in patients with prior treatment with idelalisib	Grade 2	Withhold	Initiate management immediately, including initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
		Resume if skin reaction or other immune-mediated adverse reaction improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent	
	Grade 3 or 4 (excluding endocrinopathies) or recurrent Grade 2	Permanently discontinue	Initiate management immediately, including initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
Nephritis with renal dysfunction	Grade 2 creatinine increased	Withhold	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
		Resume if nephritis improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent	

Adverse Reaction	Severity[a]	Dosage Modifications	Additional Intervention
	Grade 3 or 4 creatinine increased	Permanently discontinue	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
Other immune-mediated adverse reactions (including but not limited to paraneoplastic encephalomyelitis, meningitis, myositis, solid organ transplant rejection, graft-vs-host disease, Guillain-Barre syndrome, central nervous system inflammation, chronic inflammatory demyelinating polyradiculoneuropathy, encephalitis, myasthenia gravis, neuropathy peripheral, myocarditis, pericarditis, immune thrombocytopenia, vasculitis, arthralgia, arthritis, muscular weakness, myalgia, polymyalgia rheumatica, Sjogren's syndrome, pruritis, keratitis, immune-mediated gastritis, stomatitis, and haemophagocytic lymphohistiocytosis)	Grade 2 or 3 based on type of reaction	Withhold	Initiate symptomatic management including initial dose of 1 to 2 mg/kg/day prednisone or equivalent as clinically indicated followed by a taper
		Resume if other immune-mediated adverse reaction improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent	
	– Grade 3 based on type of reaction or Grade 4 (excluding endocrinopathies) – Grade 3 or 4 neurologic toxicity – Grade 3 or 4 myocarditis or pericarditis – Confirmed haemophagocytic lymphohistiocytosis – Recurrent Grade 3 immune-mediated adverse reaction – Persistent Grade 2 or 3 immune-mediated adverse reactions lasting 12 weeks or longer (excluding endocrinopathies) – Inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks	Permanently discontinue	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent as clinically indicated followed by a taper
Infusion-related Reactions			
Infusion-related reactions	Grade 1 or 2	Interrupt or slow the rate of infusion	Initiate symptomatic management
	Grade 3 or 4	Permanently discontinue	

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; DRESS = Drug Rash with Eosinophilia and Systemic Symptoms; ULN = upper limit of normal; SJS = Stevens-Johnson Syndrome; TEN = toxic epidermal necrolysis.
[a.] Based on National Cancer Institute Common Terminology Criteria for Adverse Events,

When cemiplimab is permanently discontinued for an imAE, vidutolimod must also be permanently discontinued.

4.2. Management of Acute Reactions for Cemiplimab

4.2.1. Acute Intravenous Infusion Reactions

Emergency equipment and medication for the treatment of infusion reactions must be available for immediate use. All infusion reactions must be reported as AEs (as defined in Section 6.4.1) and graded using the grading scales as instructed in Section 7.2.1

4.2.1.1. Interruption of the Intravenous Infusion

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

- Sustained/severe cough
- Rigors/chills
- Rash, pruritus (itching)
- Urticaria (hives, welts, wheals)
- Diaphoresis (sweating)
- Hypotension
- Dyspnea (shortness of breath)
- Vomiting
- Flushing

The reaction(s) should be treated symptomatically, and the infusion may be restarted at 50% of the original rate.

If investigators feel there is a medical need for treatment or discontinuation of the infusion other than described above, they should use clinical judgment to provide the appropriate response according to typical clinical practice.

4.2.1.2. Termination of the Intravenous Infusion

The infusion should be terminated and NOT restarted if any of the following AEs occur:

- Anaphylaxis*
- Laryngeal/pharyngeal edema
- Severe bronchospasm
- Chest pain
- Seizure

- Severe hypotension
- Other neurological symptoms (confusion, loss of consciousness, paresthesia, paralysis, etc)
- Any other symptom or sign that, in the opinion of the investigator, warrants termination of the IV infusion

*Consider anaphylaxis if the following is observed (Sampson, 2006): acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING

- Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
- Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

4.3. Treatment Compliance

Vidutolimod injections must be performed by qualified, trained, site personnel. Any deviations in planned dosing, including fully missed study visits, will be documented in the source documents, verified by the Clinical Research Associate (CRA), and recorded as a protocol deviation as appropriate.

Cemiplimab will be administered by trained site personnel at the clinic site according to the dosing instructions provided in the IB.

4.4. Randomization and Blinding

This is an open-label study.

4.5. Method of Assigning Subject Identifiers

Each enrolled subject will be assigned a unique Subject identification number using an Interactive Web Response System. This number will be recorded on the subject's eCRF pages and used to identify the subject throughout the study. Once a subject number is assigned, it cannot be reassigned to any other subject. Subjects who discontinue the study before receiving the first dose of vidutolimod may be replaced to ensure statistical validity of the study.

5. STUDY TREATMENT MATERIALS AND MANAGEMENT

5.1. Study Treatment

Vidutolimod is an investigational study drug and will be provided by the Sponsor as a 5 mg/mL solution in single-use vial(s). Please review the Pharmacy Manual for the physical characteristics and other details about vidutolimod, including guidance on extracting a full 2 mL from vials based on their labeled fill volumes.

The physical characteristics and other details about cemiplimab can be found in the cemiplimab IB.

At the end of the treatment period (2 years), study treatment will no longer be provided to subjects/investigators unless the Sponsor chooses to extend the study. The Investigator should ensure that the subject receives appropriate standard of care to treat the condition under study.

5.2. Study Treatment Packaging and Labeling

Study drug will display the product lot number on the label. Details of the study drug labeling and packaging are provided in the Pharmacy Manual. Study drug will be stored at the site at a temperature of 2ºC to 8ºC; storage instructions will be provided in the pharmacy manual.

5.3. Study Treatment Handling, Storage, and Accountability

Study drug will be shipped at a temperature of 2ºC to 8ºC to the investigator or designee at regular intervals or as needed during the study. At specified time points during the study (eg, interim site monitoring visits), at the site close-out visit, and following drug reconciliation and documentation by the site monitor, all opened and unopened study drug will be destroyed or returned to the sponsor or designee, according to site procedures.

All drug accountability records must be kept current.

The investigator must be able to account for all opened and unopened study drug. These records should contain the dates, quantity, and study medication:

- Dispensed to each subject,
- Returned from each subject (if applicable), and
- Disposed of at the site or returned to the sponsor or designee

All accountability records must be made available for inspection by the sponsor and regulatory agency inspectors; photocopies must be provided to the sponsor at the conclusion of the study.

5.4. Study Drug Dispensing

Vidutolimod and cemiplimab will be dispensed, prepared, and administered according to the Pharmacy Manual and site SOPs. Details regarding the preparation, dilution, and administration of the vidutolimod and cemiplimab is outlined in the Pharmacy Manual. Only eligible subjects participating in the study may receive vidutolimod and cemiplimab. Vidutolimod and cemiplimab study drug is dedicated to each study and is labeled specifically for each study. Only authorized and qualified site staff may dispense, prepare, or administer vidutolimod and cemiplimab.

6. STUDY ASSESSMENTS AND PROCEDURES

6.1. Procedures and Assessments

All procedures and assessments will be completed according to the Schedule of Assessments (Table 1).

6.1.1. Informed Consent

Subjects must sign a written informed consent form (ICF) prior to the initiation of any study procedures and thereafter if there are any ICF changes. Subjects will be given a signed copy of the ICF to take home. Subjects unable to provide written informed consent on their own behalf will not be eligible for the study.

6.1.2. Eligibility Criteria

Subjects must meet all inclusion and exclusion criteria to be eligible for the study (see Section 3.5 and Section 3.6).

6.1.3. Demographics

Demographic data will be collected during Screening. Demographic data will include date of birth, sex, ethnicity, and race (i.e. white, black or African American, Asian, American Indian/Alaskan Native, Native Hawaiian/other Pacific Islander, or other).

6.1.4. Medical History

At Screening, a general medical history will be obtained, including chronic conditions and comorbidities, relevant acute conditions or infections, surgical procedures unrelated to cancer, and any reported conditions affecting major body systems during the 10 years prior to Screening.

6.1.5. Cancer History

Eligible subjects must have been diagnosed with a histopathologically-confirmed diagnosis of advanced cancer, as described in the inclusion criteria (Section 3.5).

Sites should refer to the Eighth Edition American Joint Committee on Cancer Staging Manual for cancer staging (Amin, 2017).

For enrollment in cohorts open to subjects with progression while receiving a PD-1–blocking antibody (see Section 3.5), the documentation required at Screening to meet eligibility includes radiographic and/or photographic images from 2 timepoints separated by at least 4 weeks that demonstrate confirmed disease progression during or within 12 weeks of prior treatment that included an approved PD-1–blocking antibody. If necessary, additional prior images may be requested for central review.

PD-L1 status from prior biopsies, if available, will be recorded in the EDC.

6.1.6. Prior and Concomitant Medications

All medications administered to the subject from 30 days before the first dose of study drug (W1D1) until 100 days after the last dose of study drug (vidutolimod and cemiplimab) or until an

alternative anticancer treatment is initiated, whichever occurs first, will be recorded in the EDC. Documentation for each medication will include the generic name of the medication, total daily dose, route of administration, dates of administration, and indication for use. Combination drugs must be listed separately by each component product and dose. Prior cancer treatment will be recorded separately (see Section 6.1.7).

Treatment medications for AEs related to study treatment that occur more than 100 days after the last dose of study treatment will be collected. Subjects who discontinue vidutolimod but remain on treatment with cemiplimab will continue to have concomitant medications/treatment medications collected according to the Schedule of Assessments (Table 1).

In addition, at each LTSFU contact, an inquiry will be made regarding the start of any new cancer treatments since the date of the last contact.

6.1.7. Prior Cancer Treatments

Details regarding all prior cancer treatments, including drug generic name, dose (if available), route of administration, start date, end date, best response, and last response to prior therapy, will be documented on a separate page in the EDC. Combination treatments should be considered as a single regimen and recorded as such in the EDC. Data on prior surgical procedures and prior radiation therapy to treat cancer will also be captured on the same eCRF.

6.1.8. Physical Examination

A full physical examination will be conducted at Screening and EOT. If the Screening full physical examination is performed > 72 hours before the W1D1 visit, then a brief (symptom directed) physical examination must be performed within 72 hours before the first injection of vidutolimod. Brief physical examinations focused on areas of disease or AEs may be performed at any clinically indicated time but must be obtained before the first, third, and seventh weekly vidutolimod injections (W1D1, W3D1, W7D1), and at each vidutolimod injection visit thereafter. Height will be obtained at Screening only and weight at all physical examination assessments. Body mass index (BMI) will be calculated by the EDC system each time weight is entered.

6.1.9. Vital Signs

Vital signs include measurement of blood pressure (systolic and diastolic blood pressure), respiratory rate, heart rate, and body temperature. Blood pressure and heart rate should be taken in the seated position following ≥ 3 minutes of rest. When vital signs are scheduled at the same time as collection of a blood sample, the vital sign measurements should be obtained before the scheduled phlebotomy. If a study visit occurs where only cemiplimab is administered, vital signs must be collected before the start of cemiplimab infusion. If an indwelling cannula is being used to obtain blood, blood pressure should be measured in the arm opposite to the cannula placement.

Oxygen saturation is not a required parameter to be collected. Sites are to capture oxygen saturation every time an AE of hypoxia or CRS is reported for a subject.

6.1.10. Eastern Cooperative Oncology Group Performance Status

At Screening, the ECOG Performance Status must be either 0 or 1 for the subject to be eligible (Table 6).

Table 6: ECOG Performance Status Grades

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

Reference: (Oken, 1982)
Abbreviations: ECOG = Eastern Cooperative Oncology Group.

6.1.11. Electrocardiogram

A single standard, 12-lead electrocardiogram (ECG) will be obtained as specified in the Schedule of Assessments (Table 1). Assessed ECG parameters will include heart rate and PR, QRS, QT, and QT corrected for heart rate (QTc) intervals. QT will be corrected using Fridericia's (QTcF) formula. ECGs will be performed after the subject has been resting in supine or semi-supine position for at least 5 minutes. When an ECG is scheduled at the same time as a blood sampling, the ECG reading should be obtained before the scheduled blood sampling. The ECG results will be interpreted at the site by a medically qualified person. If indicated, the ECG must be evaluated by a cardiologist or qualified internist.

6.1.12. Clinical Laboratory Assessments

Clinical laboratory tests will be performed as specified in the Schedule of Assessments (Table 1). Additional tests may be performed as clinically indicated.

Clinical laboratory parameters to be obtained include the following (see also Table 7):

- Hematology, chemistry, and urinalysis assessments
- Coagulation (partial thromboplastin time, prothrombin time, and INR) assessments
- Thyroid function tests (thyroid stimulating hormone, free triiodothyronine, and free thyroxine) for clinical signs and symptoms of thyroid disorder
- Adrenal function tests, if indicated

Note: At Screening, patients assessed as at risk for adrenal insufficiency should undergo diagnostic tests for ACTH and morning cortisol, and/or high-dose ACTH stimulation test (preferred testing method), if clinically indicated, via local laboratory.

- HIV, Hepatitis C/B, if indicated

A central laboratory will be used for clinical laboratory safety assessments; local laboratories may be used for eligibility and treatment decisions. The central laboratory will provide collection supplies and perform analysis of clinical laboratory evaluations. Specimens will be appropriately processed, and laboratory reports will be provided to the Investigator.

The Investigator is responsible for reviewing central laboratory results and assessing all out-of-range findings as either clinically significant or non-clinically significant. Clinically significant laboratory results should be recorded as medical history if prior to vidutolimod dosing at W1D1, or AEs following vidutolimod dosing at W1D1 in the eCRF.

Table 7: Clinical Laboratory Assessments

Hematology	Serum Chemistry	Urinalysis	Other Laboratory Tests
RBCs WBCs Differential WBC count Hemoglobin Hematocrit Platelets	Alanine aminotransferase Albumin Alkaline phosphatase Amylase Aspartate aminotransferase Bilirubin Blood urea nitrogen Calcium Chloride Creatinine Glucose Lactate dehydrogenase Lipase Phosphorous Potassium Sodium Total protein	Blood Glucose Nitrites pH Protein Specific gravity WBCs **Microscopic Battery:** RBCs, WBCs, epithelial cells, casts (only if significant positive findings on urinalysis)	**Coagulation:** Partial thromboplastin time Prothrombin time International normalized ratio **Thyroid Function Studies:** Thyroid stimulating hormone, Free T3, Free T4 **Tests to be performed as clinically indicated:** Human immunodeficiency virus Hepatitis B and C

Abbreviations: Anti-dsDNA = anti-double stranded DNA; RBC = red blood cell; T3 = triiodothyronine; T4 = thyroxine; WBC = white blood cell.
Note: Refer to the Study Laboratory Manual for additional information.

Retesting of laboratory parameters and/or other assessments within any single Screening or Lead-in period will be permitted (in addition to any parameters that require a confirmatory value). Laboratory parameters and/or assessments that are included in the Schedule of Assessments (Table 1) may be repeated in an effort to find all possible well-qualified participants. Consultation with the Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

6.1.13. Pregnancy Testing

Pregnancy testing will be performed on WOCBP at the time points specified in the Schedule of Assessments (Table 1). A serum pregnancy test is required during Screening. A serum or urine pregnancy test will be completed for time points after Screening.

A WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin) within 24 hours prior to the start of study treatment. An extension up to 72 hours prior to the start of study treatment is permissible in situations where results cannot be obtained within the standard 24-hour window. A final pregnancy test must be conducted at the end of relevant systemic exposure ie, 16 to 18 weeks after last study dose treatment. A urine test conducted at home and communicated to the investigator by phone would be acceptable. Pregnancy testing should be performed in women having bilateral tubal ligation.

If a urine pregnancy test is positive at any time point, the test must be confirmed with a serum sample. If a serum pregnancy test is required based on a positive urine pregnancy test, serum test results must be confirmed as negative prior to enrollment or subsequent treatment of the subject. If the serum test confirms the subject is pregnant, they must have the EOT visit and the pregnancy must be reported to the Medical Monitor.

6.2. Disease Assessments

Disease assessments (radiographic and/or photographic imaging) will be collected according to the Schedule of Assessments (Table 1). Acceptable assessment methods, definition of measurable disease, and selection of target and non-target lesions will be defined by RECIST v1.1.

The same disease assessment method(s) used to confirm eligibility during Screening (CT, MRI) should be used throughout the study for all disease assessments. Changes in imaging modalities may be acceptable with Medical Monitor approval if required for the subject's safety. All scans should be performed at least 2 weeks after the previous vidutolimod IT injection to prevent detection of injection-related pseudoprogression.

Photographic and/or radiographic images demonstrating disease progression on prior PD-1–blocking antibody treatment will be collected whenever available.

All disease assessments will be evaluated by the Investigator according to RECIST v1.1. Although efficacy assessments are per investigator assessment, the sponsor may subsequently obtain independent central review of efficacy results using imaging studies (CT, MRI, photography) on file with imaging vendor(s).

6.2.1. Radiographic Imaging

Contrast-enhanced CT and MRI are the only acceptable radiographic imaging modalities for disease assessment. Contrast-enhanced CT imaging is required when contraindications are not present. Contrast-enhanced CT assessments may be combined with positron emission tomography (PET) as long as disease status can be thoroughly assessed. Radiographic images will be collected by the imaging vendor.

6.2.2. Photographic Imaging

Digital photographs of visible vidutolimod–injected and noninjected skin lesions should be taken at baseline and if a clinically relevant change occurs. Photographic imaging will be collected by the site staff. These photographs will be utilized to demonstrate response in visible tumors. Photos should be taken with a digital camera of adequate resolution. To clearly capture the morphology of the tumor, both the skin lesion and the surrounding tissue should be included in the field of view. Care should be taken to ensure subject privacy. Each lesion should be clearly labeled with a unique identifier which must be used throughout the trial. A metric ruler must also be included in the photograph field of view as a size reference.

Photographic imaging will be collected by the site staff and delivered to the imaging vendor.

If a CR is observed, sites should continue to obtain confirmation photographs according to the Schedule of Assessments (Table 1).

6.2.3. Central Nervous System Imaging

Baseline brain imaging by contrast-enhanced CT or MRI (per site local standards) should be provided at Screening for subjects with known or suspected brain metastases. On-study brain imaging is only required for subjects with current or prior history of brain metastases or clinical signs or symptoms of CNS disease.

The same modality of brain imaging should be utilized throughout the study for an individual subject.

6.2.4. On-Treatment Disease Assessment

On-treatment disease assessments will be collected per the time points specified in the Schedule of Assessments (Table 1).

Because the volume from the IT injection of vidutolimod and related inflammation may cause a tumor to transiently enlarge leading to an inaccurate assessment, disease imaging that includes a lesion injected with vidutolimod should not be performed within 2 weeks after the injection unless medically necessary.

6.2.5. Treatment and Disease Assessment Beyond Progressive Disease

Clinically stable subjects may continue to be treated beyond RECIST v1.1 progression at the Investigator's discretion as described in Section 3.2.1.

6.3. Translational Assessments

6.3.1. Collection of Blood for Translational Biomarker Analyses

Blood samples, including serum and/or plasma, will be collected for exploratory biomarker assessments as specified in the Schedule of Assessments (Table 1).

The procedures for sample collection, processing, storage, and shipment are provided in the Laboratory Manual. Blood samples will be tested using Luminex and/or MSD based testing for multiplex soluble protein profiling to quantify the levels of cytokines (including CXCL10), chemokines, anti-Qb Ab and growth factors associated with immune response. Samples may be

used for additional exploratory analysis of biomarkers thought to play a role in cancer immunotherapy, or TLR9 signaling, including but not limited to concentration of serum/plasma analytes, additional peripheral blood-based biomarkers related to activation of pDCs, type 1 IFN and effector T Cells and gene expression analyses (at baseline and on-treatment). These findings may be further analyzed for association with observed clinical responses to the combination of vidutolimod and cemiplimab, and subsequent exploration of factors associated with resistance to vidutolimod in combination with cemiplimab. These samples may be also used for research to develop methods, assays, prognostics and/or companion diagnostics related to TLR9 agonism and cancer immunotherapy.

Plasma ctDNA will be analyzed to measure presence of tumor mutations in blood (oncogenic drivers, as well as indicators of overall mutational load) as identified in each tumor sample tested by whole exome sequencing. These circulating tumor mutations will be measured as proxies of tumor aggressiveness, growth potential, residual disease, and altered tumor evolution under selective drug-mediated pressure. This exploratory method will aid to evaluate treatment response, risk of relapse, as well as potential for longer-term efficacy. Mutations will be measured in DNA and RNA isolated from plasma samples collected at selected time points indicated in the schedule of assessments. Modulation of mutations pertaining to tumor cell function, genomic landscape, and immunogenicity, among other parameters, may be assessed.

6.3.2. Collection of Tumor Biopsies for Translational Assessments Analyses

Fresh tumor biopsy samples (screening and on-treatment) are mandatory, if safe and medically feasible, as specified in the Schedule of Assessments (Table 1). If the Investigator believes it is unsafe to perform a biopsy, the subject may be considered eligible for study enrollment after discussion with the Medical Monitor. The decision and rationale to forego biopsy samples should be clearly documented. Archival tumor biopsy samples should also be collected during Screening, if available.

Tumor biopsies will be used to assess PD-L1 expression (immunohistochemistry) and evaluate tumor immune cell infiltrates, such as T cells ($CD3^+$ and $CD8^+$ T cells), B cells, monocytes, macrophages etc and changes to the TME using multiplex IHC methodologies and gene expression analyses (at baseline and on-treatment). Biopsies may be used for additional exploratory analysis of biomarkers thought to play a role in cancer immunotherapy or TLR9 signaling, pDC activation (including but not limited to CD303) including RNA analyses to monitor gene expression and DNA analyses to determine tumor mutational burden (TMB) and identify gene mutations associated with cancer. These findings may be analyzed for association with observed clinical response, resistance and/or AEs to the combination of vidutolimod and cemiplimab.

Determination of PD-L1 status is planned. If tumor PD-L1 status has been obtained prior to study entry, this value and method (detection antibody) will be recorded in the eCRF. If tumor PD-L1 status has not been obtained prior to study entry and archival tissue is available, it should be obtained from the archival biopsy sample at Screening. The PD-L1 value will be recorded in the EDC.

Additional tumor biopsies may also be collected at unscheduled time points at the discretion of the Investigator.

6.3.3. Pharmacogenomic Analysis (Optional)

Subjects who agree to participate in the genomics sub-study will be required to indicate their consent to participate in the sub-study on the ICF form before collection of the samples. Subjects are not required to participate in the genomics sub-study to enroll in the primary study. A blood sample for optional genomic DNA extraction will be collected prior to the first dose of Vidutolimod. If a sample is not obtained at screening, a sample may be collected at any other study visit.

DNA samples for the genomics sub-study will be single-coded as defined by the International Council for Harmonisation (ICH) guideline E15. Sub-study samples will be stored for up to 15 years after the final date of the database lock and may be used for research purposes. The purpose of the genomic analyses is to identify genomic associations with clinical or biomarker response, other clinical outcome measures, and possible AEs. In addition, associations between genomic variants and prognosis or progression of tumor types being studied, as well as other related diseases may also be studied. These data may be used or combined with data collected from other studies to identify and validate genomic markers related to the study drug or to other diseases. Analyses may include sequence determination or single nucleotide polymorphism studies of candidate genes and surrounding genomic regions. Other methods, including whole-exome sequencing, whole-genome sequencing, and DNA and copy number variation may also be performed. The list of methods may be expanded to include novel methodology that may be developed during the course of this study or during the sample storage period.

Results from the genomics sub-study will not be included in the CSR.

6.4. Safety Assessments

Safety will be assessed on an ongoing basis throughout this study. All safety assessments and AEs will be recorded on the appropriate eCRF and reported to the Sponsor or its representatives (as applicable). All other medical occurrences (non-adverse events) that begin before the start of study treatment administration should be recorded on the Medical History/Current Medical Conditions section of the eCRF, not the AE section. Refer to Section 6.4.1 for additional guidance on AE reporting.

Abnormal vital sign measurements, clinical laboratory test results, and/or physical examination findings deemed clinically significant by the Investigator may be repeated, until the value returns to baseline, within normal limits (WNL), or reaches a clinically stable endpoint, as determined by the Investigator. Any post-baseline abnormal findings that are considered clinically significant by the Investigator will be recorded on the AE page of the eCRF. The Investigator is responsible for reviewing all clinical laboratory results.

Some of the assessments referred to in this section may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

A safety analysis will be conducted with quarterly reviews of cumulative adverse events starting after the first approximately 12 subjects are treated. If an observed rate of Grade ≥ 3 imAE > 30%, an enrollment hold will be considered until a safety review is completed. Further, the development of Grade 5 imAEs or other TEAEs assessed by the Investigator as at least possibly related to

vidutolimod at any time during the study will result in enrollment being suspended until the event has been assessed and the attribution has been ascertained.

If such events occur, study site Principal Investigators will be notified in an expedited manner.

6.4.1. Adverse Events

AEs should be monitored and captured in the eCRF from the time that the ICF is signed through 100 days after the last dose of study drug (both vidutolimod and cemiplimab) or until an alternative anticancer treatment is initiated, whichever occurs first. Subjects who discontinue vidutolimod but remain on treatment with cemiplimab will continue to have AEs collected according to this schedule until 100 days after the last dose of study treatment. After 100 days post-treatment, only treatment-related SAEs will be recorded on the eCRF.

All AEs that started or worsened in severity on or after the date that study drug was first administered (W1D1) will be considered treatment-emergent adverse events (TEAEs). AEs that worsened (i.e. increase to higher severity/grade) should be recorded as new AEs. Ongoing AEs with a decrease in severity/grade do not need to be captured as new AEs. TEAEs will be graded according to CTCAE v5.0 and coded using the Medical Dictionary for Regulatory Activities (MedDRA). ISRs will be graded according to Table 4.

AEs that are consistent with the mechanism of PD-1/PD-L1 blockade, or immune-mediated AEs for which other etiologies have been ruled out (e.g. infection or tumor progression), should be diagnosed and treated according to available guidelines (i.e. Brahmer, 2018). Immune-mediated AEs may include events with an alternate etiology that were exacerbated by the induction of autoimmunity. Information supporting the assessment will be collected on the eCRF.

A full description of AE collection and reporting procedures during this study is in Section 7.3.

6.4.2. Appropriateness of Safety Measures

The safety assessments in this protocol (i.e. AEs, concomitant medications, physical examination, vital signs, laboratory parameters [hematology, serum chemistry, urinalysis, coagulation, thyroid function] and ECGs) are widely used and generally recognized as reliable, accurate, and relevant for an early phase oncology study. The safety assessments are adequate to protect the subjects' safety.

6.5. 100-Day Follow-Up Contact

Adverse events and concomitant medications data will be collected until 100 days (±7) after the last dose of study drug or until an alternative anticancer treatment is initiated, whichever occurs first.

The 100-Day Follow-up contact is a safety follow-up visit that should be conducted in the study clinic or via phone. The subject should be questioned for any new AEs, resolution of prior AEs, and use of concomitant medications, including other cancer treatments. No other safety assessments are required unless the Investigator identifies a new safety concern that requires further follow-up.

6.6. Posttreatment Follow-Up

Subjects who discontinue study treatment and transition into PTFU will continue to have assessments collected per the time points specified in the Schedule of Assessments (Table 1). Posttreatment follow-up disease assessments will continue until disease progression, initiation of another cancer treatment, death, lost to follow-up (at least 3 documented attempts to contact the subject), withdrawal of consent, End of Clinical Trial, or maximum of 18 months- in PTFU for an individual subject.

6.7. Long-Term Survival Follow-Up

Subjects who discontinue study treatment and PTFU will be contacted by the site for LTSFU, according to the Schedule of Assessments (Table 1), which will continue until death, withdrawal of consent, lost to follow-up (at least 3 documented attempts to contact the subject), or End of Clinical Trial.

7. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

7.1. Adverse Events

7.1.1. Definition of an Adverse Event

An AE is an untoward or medical occurrence associated with the use of study drug (active or placebo drug, biologic, or device) in clinical investigation subjects, which does not necessarily have a causal relationship with the study drug. An AE can therefore be any unfavorable and unintended symptom, sign, disease condition, or test abnormality whether or not considered related to study drug. AEs that do not meet the definition for an SAE are considered non-SAEs.

Adverse events should be recorded upon first occurrence and followed until resolution. A persistent AE is continuous and does not resolve between Q3W dosing visits. The AE is documented only once unless the grade becomes more severe. If the grade becomes more severe the AE must be reported again with the new grade. Any recurrent AE should be reported as new AE.

Adverse events include:

- Changes in health status described by the subject or signs observed by the Investigator or medical staff.
- Test abnormalities (e.g. laboratory tests) that result in an alteration in medical care (diagnostic or therapeutic) and/or are considered clinically significant by the Investigator.

Adverse events that are considered to be immune-mediated should be reported as such (see also Section 6.4.1).

Disease progression, and associated hospitalizations, are not considered an AE or SAE in this study.

Abnormalities present at baseline will be recorded as medical history and will only be considered AEs if they reoccur after resolution or worsen during the study.

7.1.2. Definition of a Serious Adverse Event

An SAE is any AE that fulfills 1 of the criteria outlined in Table 8.

Table 8: Criteria for Determination of Serious Adverse Events

Death	An AE that results in death. **Note:** In this study, deaths due to disease progression are not to be reported as SAEs.
Life-threatening AE	An AE that places the subject, in the view of the Investigator, at immediate risk of death from the AE as it occurred (i.e. does not include an AE that had it occurred in a more severe form, might have caused death).
Required or prolonged in-patient hospitalization [a]	An AE that results in an initial in-patient hospitalization or prolongs an existing hospitalization of the subject. If a subject is hospitalized as part of the clinical use of the study drug, a period of normal hospitalization will be outlined in the protocol or by the judgment of the Investigator. Hospitalizations longer than this period will be prolonged hospitalizations.
Persistent or significant disability/incapacity	An AE that results in a substantial disruption of a subject's ability to conduct normal life functions.
Congenital anomaly/birth defect	A congenital anomaly/birth defect that occurs in the offspring of a subject exposed to the study drug.
Important medical event	An AE that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed above, in the opinion of the Investigator.

Abbreviations: AE = adverse event; D = day; SAE = serious adverse event; W = week.

[a] Planned hospital admissions or surgical procedures for elective procedures or for an illness or disease that existed before the W1D1 visit will not be captured as SAEs.

Examples of "important medical events" include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as with important medical events described above.

Events that meet SAE criteria must be recorded and reported regardless of expectedness or assessed association with study drug.

Hospitalization due solely to the progression of underlying cancer should not be reported as an SAE.

7.1.3. Adverse Events of Special Interest

An adverse event of special interest (AESI; serious or non-serious) is one of scientific and medical interest specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor be appropriate. Such an event might warrant further investigation in order to characterize and understand it.

AESIs are defined in Section 7.3.4.

7.2. Evaluation of Adverse Events and Serious Adverse Events

The Investigator or designee is responsible for making an assessment as to the severity (CTCAE v5.0 Grade), causality/relationship to vidutolimod and cemiplimab separately, and outcome of AEs and SAEs (as defined in Section 7.2.3). Every attempt should be made to provide the causality/relationship at the time at the time of reporting the SAE. In addition, the Investigator or designee must report any actions taken as a result of an AE or SAE separately for vidutolimod and cemiplimab.

7.2.1. Adverse Event Severity

For each recorded AE or SAE, the Investigator or designee must provide an assessment of Severity/Grade using the CTCAE v5.0 (U.S. Department of Health and Human Services, 2017). AE terms not found in the CTCAE v5.0 will be graded according to Table 9.

Note that severity is not the same as "seriousness" (defined in Section 7.1.2). Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

ISRs will be graded as defined in Table 4.

Worsening of an ongoing TEAE (i.e. an increase to higher grade) should be recorded as a new AE. Ongoing AEs that decrease in severity/grade should not be captured as new AEs.

Table 9: CTCAE Adverse Event Grades

Classification	Definition
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local, or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limited self-care activities of daily living
Grade 4	Life-threatening consequences: urgent intervention indicated
Grade 5	Death related to adverse event

Reference: (U.S. Department of Health and Human Services, 2017).
Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events.

7.2.2. Relationship to Study Drug

For each AE or SAE, the Investigator will determine whether there is a reasonable possibility demonstrated by evidence that suggests a causal relationship between the study treatment and each AE according to the categories provided below. Attribution of AEs will be determined for each of the individual components (vidutolimod and cemiplimab) of the study treatment. The Investigator may change their opinion of causality in light of follow-up information; if this occurs, the Investigator must amend the AE or SAE information in the EDC and on the paper SAE form accordingly.

Every AE must be assessed by the Investigator with regard to whether it is considered immune-mediated. For events that are potentially immune-mediated, additional information will be collected on the eCRF.

The following factors should be considered when assessing causality:

- Temporal relationship: time to onset vs time drug was administered
- Nature of the reactions: immediate vs. long term
- Clinical and pathological features of the events
- Existing information about the drug & same class of drugs
- Concomitant medications
- Underlying and concurrent illnesses
- Response to dechallenge (drug discontinuation) or dose interruption
- Response to rechallenge (re-introduction of the drug) or dose increase, when applicable
- Patient's medical and social history

Causality to the study drug (including study drug administration):

- Related:
  - The AE follows a reasonable temporal sequence from study drug administration and cannot be reasonably explained by the nature of the reaction, patient's clinical (eg, disease under study, concurrent diseases, concomitant medications), or other external factors.

  Or

  - The AE follows a reasonable temporal sequence from study drug administration, and is a known reaction to the drug under study or its class of drugs or is predicted by known pharmacology.
- Not Related:
  - The AE does not follow a reasonable sequence from study drug administration or can be reasonably explained by the nature of the reaction, patient's clinical state (eg, disease under study, concurrent diseases, and concomitant medications) or other external factors.

Causality to the study conduct (protocol specified procedure):

- Related:
  - The AE follows a reasonable temporal sequence from a protocol specified procedure and cannot be reasonably explained by the nature of the reaction, patient's clinical (eg, disease under study, concurrent diseases, concomitant medications), or other external factors.
- Not Related:
  - The AE does not follow a reasonable sequence from a protocol specified procedure or can be reasonably explained by the nature of the reaction, patient's clinical state (eg, disease under study, concurrent diseases, and concomitant medications) or other external factors.

7.2.3. Classification of Adverse Event Outcome

AE outcome describes the status of the AE at the last observation. The Investigator will document the outcomes of each AE using the categories provided in below Table 10.

Table 10: Classifications for Adverse Event Outcomes

Classification	Definition
Fatal	Termination of life as a result of an AE
Not recovered/not resolved	Subject has not recuperated, or the AE has not improved
Recovered/resolved	Subject has recuperated, the AE resolved, or returned to baseline status / stabilized
Recovered/resolved with sequelae	AE has resolved, but the subject has been left with symptoms or pathology
Unknown	Not known, not observed, not recorded, or refused

7.2.4. Action Taken Related to Study Drug Administration Regarding the Adverse Event

The Investigator will provide the action taken regarding study treatment separately for vidutolimod and cemiplimab in response to the AE. Refer to Section 4.1.1.4 and Section 4.1.2.2 for vidutolimod and cemiplimab allowed dose modifications. Classification for each of the potential actions taken are provided in Table 11.

Table 11: Classifications for Actions Taken Related to Study Drug Administration Regarding an Adverse Event

Classification	Definition
No change	No change in administration of study drug
Study drug delayed	Temporary delay in administration of the study drug
Study drug withheld	One or more planned doses of study drug completely withheld (skipped)
Study drug permanently withdrawn	Administration of the study drug terminated (no further dosing)
Not applicable	Determination of a value is not relevant in the current context

7.3. Procedures for Recording and Reporting Adverse Events

7.3.1. Individual Case Safety Reporting (ICSR)

All events (serious and non-serious) must be reported with investigator's assessment of the event's seriousness, severity, and causality to the (when applicable, blinded) study drug. For SAEs and AESIs, a detailed narrative summarizing the course of the event, including its evaluation, treatment, and outcome should be provided on the AE CRF. Specific or estimated dates of event onset, treatment, and resolution should be included, when available. Medical history, concomitant medications, and laboratory data that are relevant to the event should also be summarized in the narrative. For fatal events, the narrative should state whether an autopsy was or will be performed

and include the results if available. Information not available at the time of the initial report must be documented in a follow-up report. Source documents (including hospital or medical records, diagnostic reports, etc.) will be summarized in the narrative on the AE CRF and retained at the study center and available upon request.

Urgent safety queries must be followed up and addressed promptly. Follow-up information and response to non-urgent safety queries should be combined for reporting to provide the most complete data possible within each follow-up.

Adverse events will be recorded from the time of informed consent until 100 days after the last dose of study drug (both vidutolimod and cemiplimab) or until an alternative anticancer treatment is initiated, whichever occurs first. AEs starting more than 100 days after the last dose of study drug should not be recorded on the AE eCRF unless they are considered to be related to study treatment. The date, time of onset, resolution, determination of seriousness, severity, action taken, outcome and relationship to vidutolimod and cemiplimab will be recorded for all AEs.

All AEs and SAEs experienced by a subject will be recorded on the appropriate eCRF. In addition, for all SAEs a paper SAE Report Form will be completed and submitted within 24 hours of awareness.

7.3.2. Reporting Serious Adverse Events

All SAEs and associated source documents must be reported in written or typed English via completion of the eCRF AE page and accompanying paper SAE Report Form (following the same reporting process outlined in Section 7.3) within 24 hours of first knowledge of the event regardless of relationship to the study procedures or individual study drugs. The paper SAE Report form should be used to record pertinent information, regarding the SAE. The Investigator is requested to supply as much detailed information as possible regarding the event at the time of the initial report.

SAEs will be collected from completion of the ICF until 100 days after the last dose of any study allowed drug treatment. SAEs starting more than 100 days after the last dose of study drug should not be recorded on the eCRF unless they are considered to be related to study treatment.

If at any time after the subject has completed participation in the study, the Investigator or study staff becomes aware of an SAE during the study reporting period that they believe is possibly, probably, or definitely related to either study drug (see Section 7.2.2), then the event and any known details must be reported promptly to the Sponsor or its representatives. The following reporting instructions must be followed.

At minimum, the Investigator will be asked to provide the following information:

- For the initial SAE notification, the Investigator must provide, at a minimum, basic information such as the protocol number, subject's year of birth or age at onset, subject identification number, period of study drug intake, event term, nature of the event, detailed description of the clinical course of the event, seriousness criteria, causality of the event to vidutolimod and cemiplimab separately, and severity.

- In addition, the initial SAE information entered on the eCRF and paper SAE Report Form should include all pertinent known information about the SAE and the affected subject, such as the following: subject sex; description of the AE including reason for assessment as serious, and individual study drug information including doses, dates of dosing, and action taken with individual study drugs.

Follow-up information must be entered or uploaded into the eCRF system and paper SAE Report Form (following the same reporting process outlined in Section 7.3.2) within 24 hours of the Investigator's first knowledge of the new information. Follow-up SAE reports may describe the evolution of the reported events and any new assessment of their outcome and/or relationship to individual study drugs. Supporting documentation may be solicited from the site even if the SAE occurred at another institution. Such documentation may include copies of relevant subject/hospital records, and pathology or autopsy reports. For subject deaths, the cause of death is to be recorded as the SAE term. A death certificate and an autopsy report, if performed, should be submitted.

The Sponsor designee contact information is available for SAE reporting on a 24-hour basis and is reviewed during normal business hours. A paper SAE Report Form should be completed and submitted within 24 hours of awareness.

7.3.3. Reporting Pregnancies

Female subjects or the partners of male subjects who become pregnant within 150 days of their last vidutolimod dose will be instructed to notify the Investigator immediately.

If the Investigator learns of a report of pregnancy at any time after the W1D1 visit up to 150 days after the last dose of the study drug, the Investigator must complete and submit a paper Pregnancy Report Form and report the pregnancy to Regeneron within 24 hours of awareness (following the same reporting process outlined in Section 7.3.2).

The Investigator will inform the subject that the Sponsor or its representatives is required to gather information regarding the course and outcome of a pregnancy that has occurred after exposure to a study drug. The progress of the pregnancy must be followed until the outcome of the pregnancy is known (i.e. delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, additional follow-up information may be requested.

The Investigator will be asked to obtain follow-up information no later than 2 months after the gestational period to obtain maternal/fetal/neonatal outcome and any other relevant information.

Follow-up information may be requested at additional time points. All study-related contacts involving a known pregnancy should include pregnancy status assessment until pregnancy outcome is known.

Please note that pregnancy in and of itself is not an AE or an SAE. Pregnancy should not be entered into the eCRF as an AE unless the Investigator suspects an interaction between the study drug and the contraceptive method. Additionally, all information received will be assessed for any AEs and SAEs and processed per study guidelines. If the subject is discontinued because of pregnancy, pregnancy will be documented as the reason for study discontinuation. Spontaneous abortions and stillbirths will be reported as SAEs.

7.3.4. Events that Require Expedited Reporting to Sponsor

The following events also require reporting to the sponsor (or designee) within 24 hours of learning of the event:

- **SAEs**
- **Selected Adverse Events of Special Interest** (AESIs; serious and nonserious)**.** Adverse events of special interest for this study include the following:
  - Grade ≥2 Allergic /hypersensitivity reactions (cemiplimab and/or vidutolimod)
  - Grade ≥2 Injection site reactions (vidutolimod)
  - Grade ≥2 Infusion-related reactions (cemiplimab)
  - Grade ≥3 Hypotension (vidutolimod). Medical intervention beyond IV fluids indicated such as stress steroids (eg, 50 to 100 mg hydrocortisone orally or IV every 8 hours or equivalent, unless given prophylactically for adrenal insufficiency) or inpatient hospitalization
  - Grade ≥2 cytokine release syndrome (CRS, vidutolimod): Hypotension responding to fluids, and/or hypoxia responding to <40% O2. NOTE: Administration of prophylactic fluids per Section 4.1.1.1 will not be considered Grade 2 CRS. Report Grade ≥2 CRS if subject requires intensification of IV fluid administration over baseline prophylaxis for management of hypotension.
  - Grade 3 or greater imAE or Grade 2 or greater uveitis
- **Pregnancy:** See Section 7.3.3

7.3.5. Notifying Health Authorities, IRBs/Ethics Committees, and Investigators

During the study, the sponsor and/or the contract research organization (CRO) will inform health authorities, IECs/IRBs, and the participating investigators of any SUSARs (suspected unexpected serious adverse reactions) occurring in other study centers or other studies of the active study drug (vidutolimod and cemiplimab) as appropriate per local reporting requirements. In addition, the sponsor and/or CRO will comply with any additional local safety reporting requirements. All notifications to investigators will contain only blinded information.

Upon receipt of the sponsor's notification of a SUSAR that occurred with the study drug, the investigator will inform the Institutional Review Board (IRB)/Ethics Committee (EC) unless delegated to the sponsor.

Expectedness of SAE for study drug (vidutolimod in combination with cemiplimab) is assessed against the Reference Safety Information (RSI) section of the current version of the Investigator's Brochure for vidutolimod that is effective for expedited safety reporting. Expectedness of SAE for cemiplimab is assessed against the current version of the cemiplimab Investigator's Brochure. Any SAE not listed as an expected event in the RSI section of the Investigator's Brochures or in the reference safety document (eg, USPI or SmPC) will be considered as unexpected. In addition, the sponsor will report all other SAEs to the health authorities, according to local regulations.

At the completion of the study, the sponsor will report all safety observations made during the conduct of the trial in the Clinical Study Report to health authorities and IECs/IRB as appropriate.

7.3.6. Follow-Up of Adverse Events/Serious Adverse Events

All AEs and SAEs documented at a previous visit that are designated as not recovered/resolved, will be reviewed by the Investigator at subsequent visits.

All AEs will be followed until resolution of AE, completion of the subject's study participation, or study termination, whichever occurs first.

SAEs and AEs resulting in discontinuation will be followed until 1 of the following occurs:

- The event resolves.
- The event stabilizes.
- The event returns to a baseline value if a baseline value is available.
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct.
- The Investigator and Medical Monitor agree that follow-up is no longer necessary.

Follow-up reports from the Investigator must be provided via completion of the eCRF AE page and accompanying paper SAE page within 24 hours of the Investigator's first knowledge of the new information. Additional information (i.e. hospital records, laboratory, or other diagnostic test results) should be provided if requested and/or indicated. In addition, for SAEs, the follow-up information should be added using the same form the initial SAE was reported on.

Rules for AE/SAE follow-up apply to all subjects, including those who withdraw consent prior to study completion (to the extent allowed). The Investigator will ensure that follow up includes further investigations to elucidate the nature and/or causality of the AE/SAE. These investigations must be consistent with appropriate medical management and subject consent.

Investigators are not obligated to actively seek AEs or SAEs in former study subjects that occur pursuant to the follow-up period. However, if the Investigator or designee learns of any AE or SAE at any time after a subject has been discharged from the study and the event is considered as reasonably related to the study drug, the Investigator will notify the Sponsor.

8. STATISTICAL METHODS

This section provides the basis for the statistical analysis plan (SAP) for the study. The SAP will be revised prior to the end of the study, to accommodate amendments to the clinical study protocol and to make changes to adapt to unexpected issues in study execution and data that may affect the planned analyses. The final SAP will be issued before the first database lock. Statistical analyses will be performed using SAS® software version 9.4 or higher.

8.1. Sample Size Justification

The study is conducted as an exploratory trial. Each cohort of A1, A2, B1, B2, C1, C2, D, E, and F, will enroll approximately 25 subjects. The total number of subjects to be enrolled into this study is approximately 225. Based on historical data, the ORR of available treatment for each disease in Cohort is listed in Table 12. If the observed ORRs in these Cohorts A1, A2, B1, B2, C1, C2, D, E, and F are as listed in Table 12, then the lower bound of 90% confidence interval of ORR is listed in the table below.

Table 12: ORR of Available Treatment by Cohort

Cohort	ORR of Available Treatment	Observed ORR ≥	Lower Bound of 90% Confidence Interval
A1	50%	72%	>50%
A2	<10%	24%	>10%
B1	50%	72%	>50%
B2	<10%	24%	>10%
C1	21%	40%	>21%
C2	<10%	24%	>10%
D	50%	72%	>50%
E	39%	60%	>39%
F	19%	40%	>21%

8.2. Analysis Sets

The main analysis sets are defined in this section. Additional analysis sets may be defined in the SAP.

The **Safety Analysis Set** is defined as all subjects who receive at least 1 dose of study drug. This analysis set will be the primary analysis set for all efficacy and safety endpoints.

The **Pharmacodynamic Analysis Set** is defined as all subjects who receive vidutolimod and have evaluable samples at Baseline and after vidutolimod injection.

8.3. General Considerations

Data from all investigational sites will be pooled in the analyses.

Categorical variables will be summarized as the number and percentage of subjects within each category (with a category for missing data, if applicable). Continuous variables will be presented as number (n), mean, median, standard deviation, quartiles (Q1 and Q3), and range (minimum and maximum).

8.4. Background Characteristics

8.4.1. Disposition

The number and percentage of subjects who screen fail, enroll in the study (receive their first dose of study drug), discontinue study treatment, and who discontinue the study will be summarized by cohort. The primary reason for treatment and study discontinuation will also be summarized by cohort.

Subject disposition will be presented in a by-subject data listing.

8.4.2. Demographics and Other Baseline Characteristics

Demographics and other baseline characteristics (age, sex, race, ethnicity, body weight, height, and BMI) will be summarized by cohort using descriptive statistics for the Safety Analysis Set and listed by subject.

8.4.3. Eastern Cooperative Oncology Group Performance Status

ECOG data will be presented in a by-subject data listing. Change from baseline in ECOG Performance Status will be summarized by cohort for the Safety Analysis Set.

8.4.4. Cancer History

Cancer history (time since diagnosis, tumor stage, nodal status and metastatic disease status at time of diagnosis) will be summarized by cohort using descriptive statistics for the Safety Analysis Set and listed by subject. Cancer history will be captured on a separate eCRF in the EDC system. All prior cancer treatments will be captured on a Prior Cancer Treatment eCRF. Prior cancer treatments will be presented in the data listings.

8.4.5. Prior Cancer Treatments

All prior cancer treatments will be captured in the EDC separately from other prior medications. A summary of the number of prior lines of cancer therapy, best response on prior PD-1–blocking antibody treatment, and last response on prior PD-1–blocking antibody treatment will be generated by cohort for the Safety Analysis Set. Prior cancer treatment details will be presented in the data listings.

8.4.6. Medical and Surgical History

Medical and surgical history will be listed by subject. Medical history will be coded using MedDRA.

8.4.7. Protocol Deviations

All protocol deviations will be captured electronically and presented in a by-subject data listing. All deviations will be reviewed on an ongoing basis and classified as major or minor.

8.4.8. Prior and Concomitant Medications

Prior medications are those taken within 30 days of the first dose of study drug and discontinued before the first dose of study drug.

Concomitant medications will be assessed continually from 30 days before the first dose of study drug (W1D1) through 100 days after the last dose of study drug (both vidutolimod and cemiplimab) or until an alternative anticancer treatment is started, whichever comes first. Treatment medications for study-related AEs that occur more than 100 days after the last dose of study drug will be collected.

Medications will be coded using the most recent version of the World Health Organization drug dictionary and summarized according to the Anatomical Therapeutic Chemical (ATC) classes, and preferred term for each cohort for the Safety Analysis Set. Subjects will be counted only once for a given concomitant medication for each ATC class and preferred term in the summary tables.

Concomitant medications will be presented in a by-subject data listing.

8.5. Study Drug Exposure and Compliance

The number of vidutolimod and cemiplimab doses received by each subject will be summarized descriptively by cohort for the Safety Analysis Set. The duration of each treatment, dose intensity and relative dose intensity will also be summarized by cohort for the Safety Analysis Set.

Vidutolimod dosing, including date and time of each dose, route of administration, dose administered, location of each injection, and the volume injected into each tumor at each dosing visit will be presented in a by-subject data listing.

Cemiplimab dosing will be presented in a by subject data listing, including date, time, and dose administered.

8.6. Efficacy Analyses

All efficacy endpoints will be summarized by cohort.

8.6.1. Confirmed Objective Response Rate

The primary efficacy endpoint for the study is the confirmed ORR based on RECIST v1.1 as determined by the Investigator.

The confirmed ORR is defined as the proportion of the subjects in the Safety Analysis Set who have confirmed best response as CR or PR. The confirmed ORR will be calculated as the number of subjects with a confirmed CR or PR divided by the number of subjects in the analysis population [ORR = (CR + PR)/number of subjects] for the Safety Analysis Set per cohort. For the ORR, 95% Clopper-Pearson confidence intervals will be calculated.

Subjects who discontinue due to death as a result of disease progression, or disease progression prior to having a post-baseline tumor assessment will be classified as having a best response of

PD. Subjects who discontinue prior to having a post-baseline scan for other reasons will be counted as non-responders.

The primary efficacy analysis of confirmed ORR will be assessed according to RECIST v 1.1 by the Investigator for the Safety Analysis Set.

The primary analysis will be performed for each cohort and no multiplicity adjustment will be made since separate inferences will be drawn for each cohort.

8.6.2. Duration of Response

DOR will be based on RECIST v1.1 responses as determined by the Investigator and calculated for responders in the Safety Analysis Set. The DOR will be measured from the time at which criteria are first met for CR or PR (whichever is first recorded) until the first date that recurrence or PD is objectively documented (taking as reference for PD the smallest measurements recorded on study), or death, whichever occurs first. The duration of CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented, or death, whichever occurs first. Censoring details will be described in the SAP, including handling of subjects who continue to be followed for PTFU disease assessments. DOR will be analyzed using the Kaplan-Meier method by cohort for responders.

8.6.3. Progression-Free Survival

PFS is defined as the time from first vidutolimod injection to disease progression or death from any cause. PFS will be calculated based on RECIST v1.1 as determined by the Investigator. Subjects who are alive and progression-free at the time of analyses will be censored at the last disease assessment. Additional censoring rules may be defined in the SAP. PFS will be analyzed using the Kaplan-Meier method, by cohort, using the Safety Analysis Set. A Kaplan-Meier plot of PFS will be generated for each cohort.

8.6.4. Overall Survival

OS will be calculated as the time from first vidutolimod injection to death due to any cause. Subjects who are alive at the time of analyses will be censored in the analyses at the time of the last known alive date. OS will be analyzed using the Kaplan-Meier method, by cohort, using the Safety Analysis Set. A Kaplan-Meier plot of OS will be generated for each cohort.

8.7. Safety Analyses

The assessment of safety will be based on the following assessments, summarized by cohort and overall: TEAEs, clinical laboratory tests, vital sign measurements, ECGs, and physical examinations.

8.7.1. Adverse Events

AEs will be coded using MedDRA and data will be summarized by cohort and overall, for the Safety Analysis Set. The number and percent of subjects reporting each TEAE will be summarized, as well as the number of TEAEs. A subject with 2 or more TEAEs within the same level of summarization (i.e. system organ class [SOC] or preferred term) will be counted only once in that level using the most severe event or most related (for the relationship to study treatment tables).

Additional summary tables will be generated by cohort and overall, for Grade 3 or higher TEAEs, TEAEs considered related to treatment (possibly + probably + definitely), TEAEs by maximum grade and relationship, TEAEs resulting in death, SAEs, and TEAEs leading to treatment discontinuation.

A by-subject AE data listing will be generated, including verbatim term, SOC, preferred term, treatment, grade outcome, and relationship to treatment (vidutolimod and cemiplimab).

Separate listings will also be generated for TEAEs ≥ Grade 3, TEAEs considered related to study treatment (possibly, probably, or definitely), TEAEs resulting in death, SAEs, and TEAEs leading to treatment discontinuation.

8.7.2. Clinical Laboratory Assessments

Safety central laboratory data will be summarized by cohort and overall using descriptive statistics (mean, standard deviation, median, minimum, and maximum), and presented for each time point, including change from baseline, for the Safety Analysis Set. Shift from Baseline tables will also be created. The categories in the shift tables will be WNL, low, and high. WNL and normal will be used when appropriate for urinalysis parameters. Clinically significant post-baseline laboratory values will be reported as AEs. By-subject data listings of all central laboratory data will be generated, and all values outside the normal range will be flagged as High or Low. Listings of all clinically significant post-baseline laboratory values from central laboratory assessments will be presented in the data listings.

8.7.3. Vital Signs

Vital signs will be summarized by cohort and overall using descriptive statistics (mean, standard deviation, median, minimum, and maximum) and presented for each time point, including change from baseline, for the Safety Analysis Set. Clinically significant post-baseline vital sign findings will be reported as AEs. A by-subject data listing of all vital sign data will be generated.

8.7.4. Physical Examinations

Detailed information on the physical examinations will be listed by subject. Clinically significant post-baseline physical examination findings will be reported as AEs.

8.7.5. Electrocardiograms

Heart rate, PR interval, QRS interval, QT interval, and QTcF interval will be summarized by cohort and overall using descriptive statistics (mean, standard deviation, median, minimum, and maximum) and presented for each time point, including change from baseline, for the Safety Analysis Set. Clinically significant post-baseline ECG findings will be reported as AEs. A by-subject data listing of all ECG data will be generated.

8.8. Pharmacodynamic Analyses

Concentrations of peripheral biomarkers including CXCL10 and other chemokine or cytokine biomarkers will be summarized using descriptive statistics for all time points for the Pharmacodynamic Analysis Set.

8.9. Exploratory Tumor Biopsy Analyses

Tumor biopsy obtained at baseline and specified time points during the study may be analyzed for protein, RNA, DNA, or other biomarkers related to TLR9, immune checkpoints, and potential markers of resistance or response to immunotherapy. Results will be summarized using descriptive statistics for all time points for the Pharmacodynamic Analysis Set in comparison to findings from previous studies in advanced melanoma. For example, baseline biopsies will be examined for PD-L1 expression and tumor inflammation signatures (low baseline PD-L1 expression and tumor inflammation appeared to be associated with response to vidutolimod in advanced melanoma) and on-treatment biopsies will be compared with baseline biopsies for the expected induction of TLR9 activation signatures.

9. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

9.1. Study Monitoring

Before an investigational site can enter a subject into the study, a representative of the Sponsor will determine the adequacy of the facilities and discuss with the Investigator(s) and other site personnel their responsibilities with regard to protocol adherence, and the responsibilities of the Sponsor or its representatives. This will be documented in a Clinical Study Agreement between the Sponsor and the Investigator.

During the study, a monitor from the Sponsor or its representatives will have regular contacts with the investigational site, for the following:

- Provide information and support the Investigator(s)
- Confirm that the facilities remain acceptable
- Confirm that the study team is adhering to the protocol, data are being accurately recorded in the eCRFs, and the investigational product is being properly maintained and accountability records are current
- Perform source data verification with access to all original clinical records for each subject

Additional details regarding monitoring procedures and responsibilities are provided in the Clinical Monitoring Plan.

9.2. Case Report Forms

Electronic case report form (eCRF) will be used in this study. An eCRF is required and should be completed for each screened and enrolled subject. The completed eCRFs are the sole property of Regeneron Pharmaceuticals, Inc. and should not be made available in any form to third parties without written permission from Regeneron Pharmaceuticals, Inc. Limited data will be collected for Screen Failures.

The Investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the eCRFs 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 eCRFs must be electronically signed by the Investigator to attest that the data contained on the eCRF is true. Any corrections to entries made in the 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's or physician's subject chart. In these cases, data collected on the eCRFs must match the data in those charts.

10. QUALITY CONTROL AND QUALITY ASSURANCE

10.1. Data Quality Assurance

Steps will be taken to ensure the accuracy and reliability of data. Such steps will include the selection of qualified Investigators and appropriate sites, review of protocol procedures with Investigators and associated personnel before study start, and periodic site monitoring visits by the Sponsor or its representatives. Before study initiation, Investigators and site personnel will receive specific training with regards to study procedures and systems as required. Training will include use of clinical laboratory kits and central laboratory operations.

Data management representatives will be available to provide assistance to study center personnel regarding entering subject data. The Sponsor or its representatives will review data contained within eCRFs for accuracy and completeness during remote and/or on-site monitoring visits and after entry into the database. Identified discrepancies will be queried and resolved with the Investigator (or designee) as indicated.

10.2. Quality Assurance Audits

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor and/or designee may also conduct a quality assurance audit. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements.

10.3. Audits and Inspections by Regulatory Authorities

A regulatory authority or an IRB may visit the site to perform audits or inspections. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

10.4. Retention of Records

The Investigator must maintain all documentation relating to the study for a period of 2 years after a marketing application is approved for the test article, or if not approved, or if no application is to be filed, 2 years following the discontinuance of the test article for investigation [21 CFR 312.6I)]. If it becomes necessary for the Sponsor or a Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

Note: under EU CTR, the sponsor should archive the content of the Clinical Trial Master File for at least 25 years after the end of the clinical trial, unless other Union law requires archiving for longer.

10.4.1. Recruitment Strategy

Potential study subjects may be identified by the investigator through a variety of means, such as publicizing the trial or using existing patient lists. Recruitment resources may include, but are not limited to, recruitment flyers, brochures, social media ads, newspaper ads, radio ads, etc. A third-party vendor may assist in recruitment efforts, such as the development of recruitment materials.

All subject-facing recruitment material, including media advertising and receptionist scripts, will be reviewed and approved by the appropriate IRB/EC/authority prior to use. Resources may be in paper or electronic form. Regeneron will not access any patient identifiable information as part of recruitment efforts.

10.4.2. Data Protection

- Subjects will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.
- The subject must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject who will be required to give consent for their data to be used as described in the informed consent
- The subject must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The contract between sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

11. ETHICS

11.1. Ethics Review

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB or Independent Ethics Committee (IEC) as appropriate. The Investigator must submit written approval to Sponsor or its representatives before he or she can enroll any subject/subject into the study. Initial IRB approval and all materials approved by the IRB for this study, including the ICF and recruitment materials, must be maintained by the Investigator and made available for inspection.

The Principal Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. No changes will be made in the study without IRB approval, except when required to eliminate apparent immediate hazards to human subjects. In addition, the IRB or IEC must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. Sponsor or its representatives will provide this information to the Principal Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

Notification of the End of Clinical Trial will be sent to the IRB within 90 days after completion of follow-up for the last subject or per local regulations and guidelines.

In case the study is ended prematurely, the IRB will be notified within 15 days or per local regulations and guidelines, including the reasons for the premature termination.

The Clinical Study Report will be sent to the sites, and IRB where appropriate per local regulations and guidance, within one year after the End of Clinical Trial.

11.2. Ethical Conduct of the Study

It is the responsibility of both the Sponsor and the investigator(s) to ensure that this clinical study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the ICH guidelines for GCP and applicable regulatory requirements.

11.3. Written Informed Consent

The ICF should be written in accordance with the current revision of the Declaration of Helsinki and current ICH and GCP guidelines. The Sponsor or its representatives will provide template ICF to the Investigator. The final ICF must be approved by the Sponsor or representatives prior to being reviewed and approved by the IRB. The final IRB approved ICFs must be provided to the Sponsor or its representatives for regulatory purposes.

The Investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. Subjects must also be notified

that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

Each subject must provide voluntary written informed consent (and sign other locally required documents) according to local requirements after the nature of the study has been fully explained. Each subject must sign an ICF before any study-related activities are performed and before participation in the study. A copy of the signed ICF must be provided to the subject, and the original signed ICF must remain in each subject's study file and must be available for verification by the study monitor at any time. The Investigator will also ensure each subject follows the proper re-consenting procedures for all applicable or additional versions of the ICF that become effective while they are enrolled in the study.

11.4. Subjects Confidentiality and Data Protection

The investigator must take all appropriate measures to ensure that the anonymity of each study subject will be maintained. Subjects should be identified by a subject identification number only, on CRFs or other documents submitted to the sponsor. Documents that will not be submitted to the sponsor (eg, signed ICF) must be kept in strict confidence.

The subject 's and investigator's personal data, which may be included in the sponsor database, will be treated in compliance with all applicable laws and regulations. The sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

11.5. Clinical Study Data Transparency

Final study results will be published on a public clinical trial registries according to applicable local guidelines and regulations. For data integrity, scientific, and statistical reasons, published results from all participants will be disclosed following End of Study (see Section 3.4).

Treatment codes will be disseminated to each investigation site thereafter.

12. PUBLICATION POLICY

All information concerning vidutolimod and cemiplimab, Sponsor operations, patent application, formulas, manufacturing processes, basic scientific data, and formulation information, supplied by the Sponsor or its representatives to the Investigator and not previously published, is confidential and remains the sole property of the Sponsor. The Investigator agrees to use this information only to complete this study and not for other purposes without the Sponsor written consent.

The institution and Investigator understand that the information developed in this study will be used by the Sponsor in connection with the continued development of vidutolimod and cemiplimab, and thus may be disclosed as required to other Investigators, government regulatory agencies, or other scientific groups. To permit the information derived from this study to be used, the Investigator is obligated to provide the Sponsor with all data obtained in the study.

13. APPENDICES

APPENDIX A. VIDUTOLIMOD INJECTION GUIDELINES

Refer to Section 4.1.1.3. Vidutolimod Injections and the current Intratumoral and Pharmacy Manual for tumor selection and additional information.

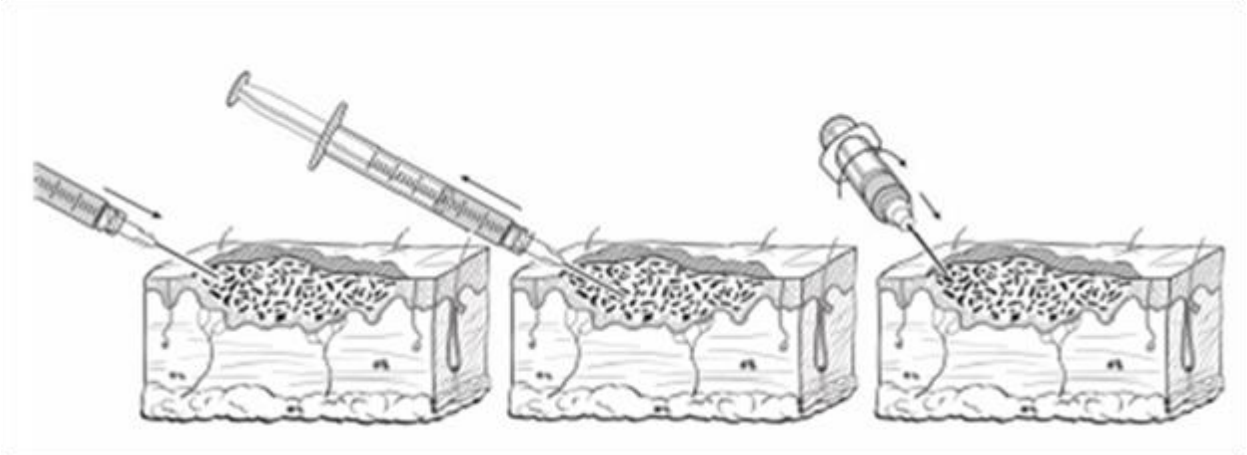
Method of Vidutolimod Administration

Intratumoral Injection

Using standard aseptic technique, the needle should be inserted near the tumor periphery (Appendix Figure 1 left panel) and advanced into the tumor to the desired depth while maintaining gentle backward pressure on the syringe plunger to confirm an extravascular location of the needle tip. The syringe and needle should be slowly withdrawn to within a few millimeters of the skin or tumor surface while maintaining gentle downward pressure on the plunger to inject the desired volume of vidutolimod along the needle track (Appendix Figure 1 middle panel).

With the tip of the needle still under the skin, the syringe should be rotated by ~20º to 40º and the process of insertion and injection during needle withdrawal repeated (Appendix Figure 1 right panel). Using this process, vidutolimod is injected IT along multiple tracks through a single insertion point as far as the radial reach of the needle allows within the tumor; 2 insertion points may be used if the tumor is larger than the radial reach of the needle or the intended volume cannot be delivered through a single insertion point. If gentle injection pressure along 5 needle tracks within the tumor has not succeeded in delivering the desired volume, then the remainder of the vidutolimod may be injected peritumorally around the same lesion.

Appendix Figure 1: Method for Vidutolimod Intratumoral Injection



Recommended Intratumoral Injection Volume Based on Lesion Size

Lesion Size (longest dimension)	Vidutolimod Injection Volume
< 0.5 cm	Up to 0.25 mL
0.5 to 1.5 cm	Up to 0.5mL
1.5 to 2.5 cm	Up to 1 mL
> 2.5 cm	2 mL

Note: 2 mL is the maximum vidutolimod injection volume allowed in up to 3 accessible lesion(s) regardless of the lesion size. If the accessible lesion(s) cannot accommodate the full 2 mL volume, then the remaining volume may be injected peritumorally.
If the full volume cannot be injected within the tumor, the remaining drug volume should be injected into a second accessible tumor, if present; otherwise, the remaining volume should be injected SC near an original tumor (peritumoral). Vidutolimod dose should remain unchanged during the study.

Additional Guidance on Imaging Guided Injection of Vidutolimod

See Intratumoral Injection Manual

Subcutaneous Injection

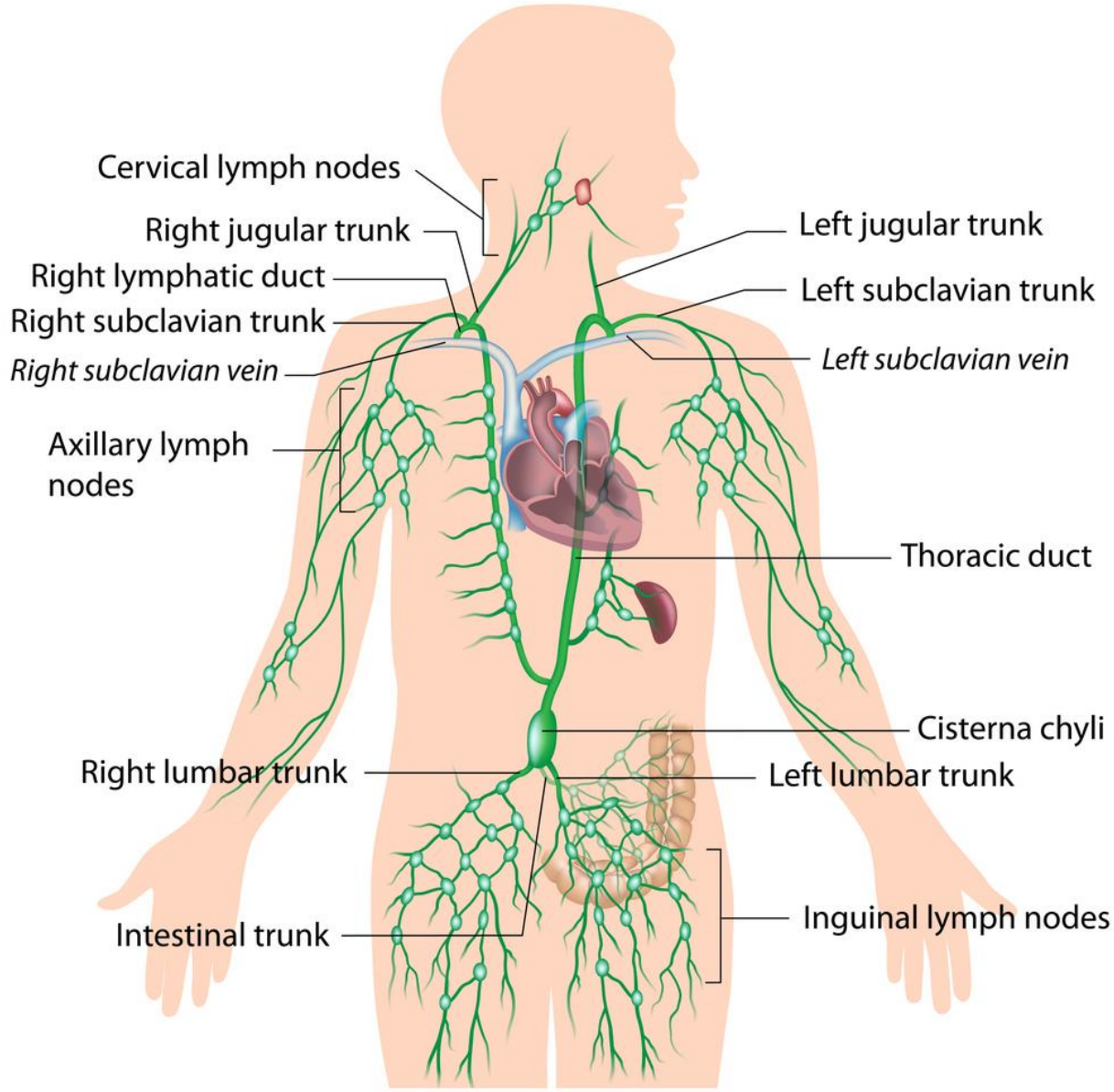
SC administration of Vidutolimod should only occur when all accessible lesions have regressed. vidutolimod SC can be administered within the area of lymphatic drainage corresponding to the site of metastatic disease and follow local standards for SC injection.

In order to maximize the distribution and exposure to vidutolimod, the full volume from a single dose should be distributed to as many SC sites as is practical. It is recommended that equal amounts of drug be injected at each SC site.

Preferred sites of injection include the following (see also Appendix Figure 2):

- Location of the primary tumor.
- Within the area of lymphatic drainage corresponding to the site of metastatic disease. For example, in a subject with a muscle or bone metastasis in the lower leg, preferred SC injection sites would be in the same leg, with the expectation that at least some of the vidutolimod will drain to lymph nodes that also contain tumor antigens. Likewise, in a subject with metastases in an upper lobe of the lung, a preferred SC injection site would be in the ipsilateral supraclavicular fossa, where the injection may activate pDC in the supraclavicular lymph nodes that also can drain the upper lung.
- Unsuitable sites for injection would include, for example, the palm of the hand or the sole of the foot.

Appendix Figure 2: Preferred Sites of Subcutaneous Injection



APPENDIX B. RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST)

Response Evaluation Criteria in Solid Tumors: RECIST (Version 1.1)

For the purposes of this study, patients should be re-evaluated for response every 9 weeks.

Response and progression will be evaluated in this study using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1; (Eisenhauer, 2009). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the short axis in the case of malignant lymph nodes are used in the RECIST criteria.

Selection of Lesions

- **Measurable disease:** Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with axial CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).
- **Malignant lymph nodes:** To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). At baseline and in follow-up, only the short axis will be measured and followed.
- **Non-measurable disease:** All other lesions (or sites of disease), including small lesions (longest diameter <10 mm [<1 cm] or pathological lymph nodes with ≥10 to <15 mm [≥1 to <1.5 cm] short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

  Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. ‘Cystic lesions’ thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.
- **Target lesions:** All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be

used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

- **Non-target lesions:** All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

- **Color Photography**. Clinical lesions will only be considered measurable when they are superficial (eg, skin nodules and palpable lymph nodes) and ≥10 mm (≥1 cm) diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler visible in each image to estimate the size of the lesion, is required. (NOTE: Radiologic imaging should be use for lymph nodes)
- **Chest x-ray**. Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- **Conventional CT and MRI**. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situation.
- **PET-CT**. At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.
- **Ultrasound**. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in

the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

- **Endoscopy, Laparoscopy**. The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.
- **Tumor markers**. Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
- **Cytology, Histology**. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (eg, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).
- The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.
- **FDG-PET**. While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A ‘positive’ FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

Response Criteria

Evaluation of Target Lesions

- **Complete Response (CR):** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (<1 cm).
- **Partial Response (PR):** At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive Disease (PD):** At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (0.5 cm). (Note: the appearance of one or more new lesions is also considered progressions).
- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Evaluation of Non-Target Lesions

- **Complete Response (CR):** Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis).
- Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
- **Non-CR/Non-PD:** Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- **Progressive Disease (PD):** Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

EVALUATION OF OVERALL RESPONSE CRITERIA

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. Revised Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (Eisenhauer, 2009) are summarized in tables within this section.

Response According to Revised Response Evaluation Criteria in Solid Tumors (Version 1.1): Patients with Target (± Non-Target) Disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required[a]
CR	CR	No	CR	≥4 weeks confirmation
CR	Non-CR/Non-PD	No	PR	≥4 weeks confirmation
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not all evaluated	No	PR	
SD	Non-CR/Non-PD/not all evaluated	No	SD	Documented at least once ≥4 weeks from baseline
PD	Any	Yes or No	PD	no prior SD, PR, or CR
Any	PD[a]	Yes or No	PD	
Any	Any	Yes	PD	

CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease.

[a] In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as PD.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

Response According to Revised Response Evaluation Criteria in Solid Tumors (Version 1.1): Patients with Non-Target Disease Only

Overall Lesion Response at Each Assessment		
Non-Target Lesions	**New Lesions**	**Timepoint Response**
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD*
Not evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD
None	No	ND

* 'Non-CR/Non-PD' is preferred over 'stable disease' for non-target disease, since stable disease is increasingly used as an endpoint for assessment of efficacy in some trials. Therefore, to assign this category when no lesions can be measured is not advised.

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