REGENERON
Biostatistics and Data Management

NCT04646005

STATISTICAL ANALYSIS PLAN
VERSION 2.0 FINAL

Clinical Study Protocol Title: A Phase 2 Study of Cemiplimab, an Anti-PD-1 Monoclonal Antibody, and ISA101b Vaccine in Patients with Recurrent/Metastatic HPV16 Cervical Cancer who Have Experienced Disease Progression after First Line Chemotherapy

Compound:	Cemiplimab (REGN2810 [anti-PD-1 mAb])
	ISA101b
Protocol Number:	R2810-ONC-ISA-1981
Clinical Phase:	Phase 2
Sponsor:	Regeneron Pharmaceuticals, Inc.
Study Biostatistician:	[redacted]
Clinical Study Lead:	[redacted]
Study Medical Director:	[redacted]
Version/Date:	Version 2.0 / October 12, 2022

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The approval signatures below indicate that these individuals have reviewed the Statistical Analysis Plan (SAP) and agreed on the planned analysis defined in this document for reporting.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CI	Confidence Interval
CR	Complete response
CRF	Case report form (electronic or paper)
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FAS	Full analysis set
FDA	Food and Drug Administration
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
ICF	Informed consent form
ICH	International Council for Harmonisation
INR	International Normalized Ratio
irAE	Immune-related adverse event
IRR	Infusion-related reaction
ISA	ISA Pharmaceuticals B.V.
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
ORR	Objective response rate
OS	Overall survival
PD-1	Programmed death-1 (receptor)

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PD-L1	Programmed death ligand 1
PD-L2	Programmed death ligand 2
PFS	Progression-free survival
PK	Pharmacokinetic
PR	Partial response
PT	Preferred term
Q3W	Every 3 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
Regeneron	Regeneron Pharmaceuticals, Inc.
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SC	Subcutaneous
SD	Stable disease
SOC	System organ class
TEAE	Treatment-emergent adverse event
TSH	Thyroid-stimulating hormone
WBC	White blood cell
WHO	World Health Organization

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1. OVERVIEW

The purpose of the statistical analysis plan (SAP) is to ensure the credibility of the study results by pre-specifying the statistical approaches for the analysis of study data prior to database lock. The SAP is intended to be a comprehensive and detailed description of the strategy and statistical methods to be used in the analysis of data for R2810-ONC-ISA-1981 study.

This plan may be revised during the study to accommodate protocol amendments and/or to make changes to adapt to unexpected issues in study execution and/or data that affect planned analyses. The final plan, if revised, will document all changes and be issued prior to database lock.

1.1. Background/Rationale

1.1.1. Background

The global annual incidence of cervical cancer is approximately 527,000 cases per year, and there are approximately 265,000 deaths (Torre, 2015). Most cases are due to infection with human papillomavirus (HPV). Although vaccination against high risk strains of HPV is projected to gradually decrease the global incidence of cervical cancer in the next 15 years, the burden of this disease remains profound (Bray, 2012). Internationally, the etiologic fraction of HPV-associated malignancy, based on HPV detection, varies by geography and anatomic site, but overall suggests that 70% of cervical cancers are caused by HPV16/18, and HPV16 is the primary oncogenic virus in other anogenital and oropharyngeal cancers.

Cemiplimab is a high-affinity, recombinant human immunoglobulin G (IgG4P) monoclonal antibody that binds to programmed cell death 1 (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. Cemiplimab is being evaluated in more than 20 phase 1 through phase 3 clinical studies in a variety of tumor types. The safety profile of cemiplimab demonstrated in these clinical trials is consistent with the expected safety profile of an anti-PD-1 antibody. LIBTAYO® (cemiplimab) is approved for the treatment of patients with metastatic cutaneous squamous cell carcinoma or patients with locally advanced cutaneous squamous cell carcinoma who are not candidates for curative surgery or curative radiation.

ISA101b is a therapeutic vaccine targeting the HPV type 16 E6/E7 proteins. The HPV16 synthetic long peptides in ISA101b act as a therapeutic vaccine that stimulates the actions of both CD4+ T-helper cells and CD8+ cytotoxic T-cells against the known oncogenic sequences of the HPV16 virus.

1.1.2. Rationale

Combination therapy may stimulate convergent aspects of host immunity by employing complementary immunomodulators and immune-stimulatory aspects of conventional modalities. Combination therapy may result in the development of more effective cancer therapies.

Treatment with the PD-1 inhibitor pembrolizumab has shown initial efficacy as monotherapy in recurrent or metastatic cervical cancer after disease progression on or after chemotherapy (FDA, 2018). While the response rates with monotherapy Pembrolizumab are similar to chemotherapy in the 2L or greater setting, responses with pembrolizumab have shown greater durability

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(Takeuchi , 1991; Look, 1998; Bookman, 2000; Muggia, 2004; Muggia, 2005; Schilder, 2005; Miller, 2008; Lorusso, 2010; Chung, 2019).

ISA101 has demonstrated a robust and clinically active immune responses against HPV16 E6/E7 in HPV16 positive patients with pre-malignant lesions, such as vulvar intraepithelial neoplasia (VIN) (Kenter, 2009; van Poelgeest , 2016). A single arm study in women with HPV16+ advanced cervical cancer receiving ISA101/101b after carboplatin and paclitaxel showed a potent and durable immune response to HPV16 epitopes. An increase in OS was associated with strength of induced vaccine responses (Melief, 2020). Data from a combination study with ISA101b and nivolumab in a variety of recurrent/metastatic incurable HPV16 positive malignancies showed an ORR of 33% with a safety profile consistent with PD-1 inhibitors (Gillison, 2016).

These data together support a single arm phase 2 trial with combination therapy of ISA101b and cemiplimab in recurrent/metastatic cervical cancer.

1.2. Study Objectives

1.2.1. Primary Objectives

The primary objective of the study is to estimate the clinical benefit of cemiplimab + ISA101b after progression on first line chemotherapy, as assessed by objective response rate (ORR).

1.2.2. Secondary Objectives

The secondary objectives of the study are:

- To characterize the safety profile of cemiplimab + ISA101b
- To assess preliminary efficacy of cemiplimab + ISA101b as measured by duration of response (DOR), progression-free survival (PFS), and overall survival (OS)

1.2.3. Exploratory Objectives

The exploratory objectives of the study are:

- To correlate clinical efficacy with baseline tumor tissue immune biomarkers including PD-L1, immune cell subsets, MHC class I/II, gene expression profile and tumor mutational burden.
- To correlate clinical efficacy with on-treatment changes in HPV antigen specific T cell responses, immune cell subsets and serum cytokine biomarkers
- Explore novel molecular and cellular predictive and pharmacodynamic biomarkers associated with clinical efficacy, including cellular and molecular parameters in tumor tissue and peripheral blood.
- To assess the immunogenicity of cemiplimab when combined with ISA101b
- To explore other HPV serotypes present in HPV16+ tumors

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1.2.4. Modifications from the Statistical Section in the Final Protocol

TTR, DCR, and dDCR were added as secondary endpoints.

1.2.5. Revision History for SAP Amendments

This is the second version of the SAP, based on the study protocol of R2810-ONC-ISA-1981 Amendment 2 dated August 31, 2021.

The main changes from SAP 1.0 dated November 3, 2020 (based on the original protocol) include:

- Updated the sample size to 105 patients per protocol amendment 2
- Removed statistical hypothesis testing and added the option for an administrative efficacy review per protocol amendment 2
- Removed safety analysis set per protocol amendment 2. The full analysis set will be used to summarize efficacy, safety, and baseline variables.

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2. INVESTIGATION PLAN

2.1. Study Design

This is a single-arm, phase 2, global study of treatment with cemiplimab + ISA101b in HPV16 positive cervical cancer patients with disease progression on first line chemotherapy in the recurrent or metastatic setting.

2.2. Sample Size and Power Considerations

The planned total sample size for this study is 105 patients.

The primary objective of the study is to estimate the clinical benefit of cemiplimab + ISA101b after progression on first line chemotherapy, as assessed by objective response rate (ORR). With105 patients, Table 1 below presents various response rates and associated 2-sided 95% CIs using a normal approximation of the binomial distribution, and precision of estimation defined as distance from the boundary to the center (i.e., half-width of the 95% CI). If observed ORR ranges from 20.0% to 34.3%, the precision estimation using 105 patients ranges from 7.7% to 9.1%.

Table 1: The 2-sided 95% Confidence Intervals for Observed ORR Based on a Sample Size of 105 Patients

Number of Responders	Observed ORR	95% CI	Precision
21	20.0%	(12.4, 27.7)	7.7%
24	22.9%	(14.8, 30.9)	8.0%
27	25.7%	(17.4, 34.1)	8.4%
31	29.5%	(20.8, 38.3)	8.8%
36	34.3%	(25.2, 43.4)	9.1%

2.3. Study Plan

After a screening period of up to 28 days, all patients will receive the following regimen:

- ISA101b 100 µg/peptide by SC injection on Day 1, Day 29, and Day 50 (total of 3 doses).
- Cemiplimab 350 mg given by IV infusion over 30 minutes every 3 weeks (Q3W) on Days 8 and 29 in Cycle 1, on Days 1 and 22 in Cycles 2 through 4, and on Days 1, 22, and 43 in all subsequent cycles or until disease progression or discontinuation of study drug for any other reason.

Cycle 1 will be 7 weeks long, Cycles 2 through 4 will be 6 weeks long, and all subsequent cycles will be 9 weeks long.

Patients will be assessed for response at week 7, then every 6 weeks for 3 cycles, then every 9 weeks in all subsequent cycles or until disease progression or discontinuation of study drug for any other reason. Patients with confirmed CR after a minimum of 48 weeks of treatment may elect

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to discontinue treatment and continue with all relevant study assessments (eg, efficacy assessments).

There will be a 90-day safety follow-up after the last dose of cemiplimab. Patients who discontinue study drug for reasons other than progression will be followed approximately every 4 months by scans until disease progression or until the patient commences another anticancer systemic therapy, whichever comes first. After progression, survival follow-up should occur approximately every 4 months.

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3. ANALYSIS POPULATIONS

In accordance with guidance from the International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline ICH E9 Statistical Principles for Clinical Trials (ICH, 1998), the following population of analysis will be used for all statistical analysis:

3.1. Full Analysis Set (FAS)

The full analysis set (FAS) includes all enrolled patients who received any study drug. Efficacy, safety, and baseline variables will be analyzed or summarized using the FAS.

3.2. The Pharmacokinetic Analysis Set

The PK analysis population includes all patients who received any study drug and who had at least 1 non-missing result following the first dose of cemiplimab.

3.3. Immunogenicity Analysis Set

The ADA analysis set includes all patients who received cemiplimab and had at least 1 non-missing ADA result following the first cemiplimab dose.

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4. ANALYSIS VARIABLES

4.1. Demographic and Baseline Characteristics

The following demographic and baseline characteristics variables will be summarized:

- Age at screening in years (quantitative and qualitative variable: <65, ≥65 - < 75, ≥75)
- Race (American Indian/Alaskan Native, Asian, Black/African American, Native Hawaiian/Other Pacific Islander, White, and Other)
- Ethnicity (Hispanic/Latino or not)
- Weight (kg)
- Height (cm)
- Body mass index (BMI) calculated from weight and height: weight (kg) / [height (m)]^2
- ECOG performance status (0, 1)

Baseline tumor characteristics variables include:

- Primary diagnosis
- Time from initial diagnosis to first study dose
- Histologic grade
- Cancer stages at initial diagnosis

4.2. Medical History

Medical history will be coded to a Preferred Term (PT) and associated primary System Organ Class (SOC) according to the latest available version of Medical Dictionary for Regulatory Activities (MedDRA®).

4.3. Pre-Treatment / Concomitant Medication

Medications/Procedures will be recorded from the day of informed consent until 90 days after the last study treatment or 1 day prior to starting a new treatment for cervical cancer, whichever is first. Medications will be coded to the ATC level 2 (therapeutic main group) and ATC level 4 (chemical/therapeutic subgroup), according to the latest available version of WHO Drug Dictionary (WHODD). Patients will be counted once in all ATC categories linked to the medication.

Prior cancer related medications/procedures: medications taken, or procedures performed prior to administration of the study drug, particularly, prior cancer related surgery, prior cancer related radiotherapy, and prior cancer related systemic therapy will be summarized.

Pre-treatment medications/procedures: non-study medications for which administration started and discontinued before a patient received the first dose of study drug.

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Concomitant medications/procedures: any treatment administered from the time of informed consent until 90 days after the last study treatment or start of another systemic anticancer therapy, whichever comes first, will be considered concomitant treatment. This includes medications and other therapies for which administration started 30 days before the first dose of the study and will continue during the study, as well as any therapies started in the follow-up period to treat a study-drug-related AE.

Post treatment anti-cancer medications/procedures: anti-cancer medications and other anti-cancer therapies that started after discontinuation of the study drug.

4.4. Efficacy Variable

4.4.1. Primary Efficacy Variable

Overall response is determined by RECIST version 1.1 (Eisenhauer, 2009).

Best overall response (BOR) is determined once all the overall response data for the patient are known. The best overall response is the best response recorded during the study:

- Best overall response of CR or PR must be confirmed by consecutive evaluations of overall response of CR or PR at time points at least 4 weeks apart.
- Best overall response of SD must have met the response SD criteria at least once ≥ 42 days (7 weeks - 7 days) after start of study treatment. Best overall response of (early) PD does not require confirmation using the RECIST.
- The best overall response for patients who do not have any post-baseline tumor assessment will be not evaluable (NE). Patients with best overall response of NE will be considered as not reaching an objective response of CR or PR.

Objective response rate (ORR) is determined by the proportion of patients with best overall response of CR or PR in the FAS.

4.4.2. Secondary Efficacy Variables

Duration of response (DOR) is determined for patients with BOR of CR or PR. DOR is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date of recurrent or progressive disease (radiographic), or death due to any cause.

- Patients who do not have a documented tumor progression or death will be censored at the last evaluable tumor assessment.
- Patients who do not have a documented tumor progression or death before initiation of new anti-cancer therapy will be censored at the last evaluable tumor assessment prior to or on the date of new anti-cancer therapy.

Progression-free survival (PFS) is measured from the start of treatment until the first date of recurrent or progressive disease (radiographic), or death due to any cause.

- Patients who do not have a documented tumor progression or death will be censored at the last evaluable tumor assessment.

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- Patients who do not have a documented tumor progression or death before initiation of new anti-cancer therapy will be censored at the last evaluable tumor assessment prior to or on the date of new anti-cancer therapy.
- Patients who do not have any evaluable post-baseline tumor assessment and do not die will be censored on the date of first study treatment.

Overall survival (OS) is measured from the start of treatment until death due to any cause. Patients who do not die will be censored at the last date that patient is documented to be alive. As many patients may receive new anti-cancer therapy after disease progression, a sensitivity analysis of OS will be conducted by censoring patients at the first date of a new anti-cancer therapy is taken.

Time to tumor response (TTR) is determined for patients with BOR of CR or PR. TTR is measured from the start of treatment until the time measurement criteria are first met for CR/PR (whichever is first recorded).

For all the above time-to-event variables, the time to event (day) is the date of event/censor - the date of first study treatment + 1.

Disease control rate (DCR) is determined by the portion of patients with BOR of CR, PR, or SD.

Durable disease control rate (dDCR) is defined as the proportion of patients best overall response of CR, PR, or SD without progression for at least 12 weeks.

4.4.3. Exploratory Efficacy Variables

The following exploratory efficacy variables will be analyzed.

- Association of clinical efficacy endpoints with baseline tumor biomarker parameters (PD-L1, immune cell subsets, MHC class I/II, gene expression profile and tumor mutational burden)
- In a subset of study sites: Association of clinical efficacy endpoints with post-treatment changes in frequency and clonal repertoire of HPV antigen specific T cells, peripheral blood immune cell subsets (Teff, Treg, myeloid, dendritic and NK cells) and serum cytokine levels when available
- Cemiplimab immunogenicity as measured by anti-drug antibodies (ADA) to cemiplimab
- HPV serotyping of archival tumor

4.5. Safety Variables

Patient safety will be assessed through the collection of reported adverse events (AEs), clinical laboratory data, vital signs, ECG, and physical exam.

Period of observation: The observation period will be divided into three segments: pretreatment, on-treatment, and posttreatment.

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- The pretreatment period is defined as the time from signing the ICF to before the first dose of study drug.
- The on-treatment period is defined as the day from first dose of study drug to the last dose of study drug plus 90 days, or 1 day prior to starting a new treatment for cervical cancer, whichever is first.
  - The period from the first dose of ISA 101b to the first dose of cemiplimab reflects the on-treatment period associated with ISA 101b alone.
- The posttreatment period is defined as the day after the on-treatment period until 1 year after the end of the on-treatment period or the start of a new treatment for cervical cancer, whichever is first.

4.5.1. Adverse Events and Serious Adverse Events

An AE is any untoward medical occurrence in a patient administered a study drug which may or may not have a causal relationship with the study drug. Therefore, an AE is any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease which is temporally associated with the use of a study drug, whether or not considered related to the study drug.

The investigator (or designee) will seek information on AEs at each patient contact and record all AEs that occur from the time the informed consent is signed until 90 days after the last dose of study drug. Prior to initiation of study drug, only the following categories of AEs should be reported on the AE CRF:

- Serious Adverse Events (SAEs)
- Events associated with a protocol-mandated intervention and which are not drug related (eg, AEs related to an invasive procedure such as a biopsy)

Other AEs that occur prior to first treatment should be reported on the medical history CRF.

All AEs after initiation of study treatment and until 90 days after the last dose of study treatment or 1 day prior to starting a new treatment for cervical cancer, whichever is first, regardless of relationship to study treatment, will be reported on the AE CRF. Additionally, any SAE or AE that the investigator believes may be related to study drug(s) and that occurs later than 90 days after last dose of study drug should be reported.

Pre-treatment AEs are defined as AEs that developed during the pretreatment period and are not treatment-emergent as defined below.

Treatment-emergent AEs (TEAEs) are defined as AEs that developed or worsened during the on-treatment period and treatment-related AEs that occur during post-treatment period.

Post-treatment AEs are defined as AEs that developed or worsened during the post-treatment period and are not considered drug related by the investigator.

All AEs are to be coded to a Preferred Term (PT) and associated primary System Organ Class (SOC) according to the latest version of Medical Dictionary for Regulatory Activities (MedDRA).

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A SAE is an AE that is classified as serious according to the criteria specified in the protocol.

The severity of AEs (including test findings classified as AEs) will be graded using the current National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) grading system (v5.0). Adverse events not listed in the NCI-CTCAE v5.0 will be graded according to the following scale:

- 1 (Mild): Mild AE (minor; no specific medical intervention; asymptomatic laboratory findings only, radiographic findings only; marginal clinical relevance)
- 2 (Moderate): Moderate AE (minimal intervention; local intervention; noninvasive intervention [packing, cautery])
- 3 (Severe): Severe and undesirable AE (significant symptoms requiring hospitalization or invasive intervention; transfusion; elective interventional radiological procedure; therapeutic endoscopy or operation)
- 4 (Life-threatening): Life-threatening or disabling AE (complicated by acute, life threatening metabolic or cardiovascular complications such as circulatory failure, hemorrhage, sepsis. Life-threatening physiologic consequences; need for intensive care or emergent invasive procedure; emergent interventional radiological procedure, therapeutic endoscopy or operation)
- 5 (Death): Death associated with an AE.

The relationship of AEs to study drugs will be assessed by the investigator and be determined based on protocol specified criteria.

Laboratory results, vital signs, or ECG abnormalities are to be recorded as AEs if they are medically relevant: for example, symptomatic, requiring corrective therapy, leading to treatment discontinuation and/or fulfilling a seriousness criterion.

4.5.2. Adverse Events of Special Interest (applicable to cemiplimab only)

All AEs of special interest (AESI), serious and nonserious, must be reported to the Sponsor within 24 hours of identification. AEs of special interest for this study include:

- Grade ≥2 infusion-related reaction (IRR)
- Grade ≥2 allergic/hypersensitivity reactions
- Grade ≥3 immune-medicated adverse event (imAE)
- An imAE of any grade in a patient previously treated with a PI3-Kinase inhibitor

  Note: An imAE can occur shortly after the first dose, several months after the last dose of treatment, or any time in-between. All AEs of unknown etiology associated with drug exposure should be evaluated to determine possible immune etiology. If an imAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an AE as an imAE.

4.5.3. Laboratory Safety Variables

The clinical laboratory data consists of serum chemistry, hematology, urinalysis and other.

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Clinical laboratory values will be converted to standard international (SI) units and grouped by function in summary tables. Conventional units may be provided. Functions are defined as follows:

Blood Chemistry: Sodium, Potassium; Chloride; Calcium; Glucose; Albumin; Total protein, serum; Creatinine; Aspartate aminotransferase (AST); Alanine aminotransferase (ALT); Alkaline phosphatase; Carbon dioxide (bicarbonate); Blood urea nitrogen (BUN); Bilirubin (total/direct); Uric acid

Hematology: Hemoglobin; White blood cells (WBCs); Platelet count; Differential (Neutrophils, Lymphocytes, Monocytes)

Urinalysis: pH; Ketones; Glucose; Specific gravity; Protein; Blood

Other Laboratory Tests: Thyroid Function Tests; Coagulation Tests; Viral Serology Tests; Pregnancy Tests

4.5.4. Vital Signs

Vital signs will be collected according to the protocol: Body temperature (°C); Resting systolic blood pressure and diastolic blood pressure (mmHg); Pulse (beats/minute); Respiratory rate (breaths/minute)

4.5.5. 12-Lead Electrocardiography (ECG)

A standard 12-lead ECG will be performed at time points according to the protocol. 12-Lead ECG parameters include PR, QRS, RR, and QT (identify QTcB or QTcF) intervals; Heart Rate (recorded from the ventricular rate)

Any ECG finding that is judged by the investigator as a clinically significant change (worsening) compared to the baseline value will be considered an AE, recorded, and monitored. If a clinically significant finding is identified and assessed as not related to study drugs by the investigator, an alternative aetiology for the abnormality should be provided in the AE page.

4.5.6. Physical Examination Variables

A complete or limited physical examination will be performed at visits specified in the protocol. Care should be taken to examine and assess any abnormalities that may be present, as indicated by the patient's medical history.

Complete physical examination will include examination of head and neck, lungs, heart, abdomen (including liver and spleen), lymph nodes, extremities, and skin, as well as a brief neurologic examination.

Limited physical examination will include examination of lungs, heart, abdomen, skin, and other organ systems.

Any finding that is judged by the investigator as a clinically significant change (worsening) compared to the baseline value will be considered an AE, recorded, and monitored. If a clinically significant finding is identified and assessed as not related to study drugs by the investigator, an alternative aetiology for the abnormality should be provided in the AE page.

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4.6. Pharmacokinetic Variables and Anti-Drug Antibody Variables (ADA)

4.6.1. Pharmacokinetic Variables

Serum samples for cemiplimab will be collected from all patients as follows:

- Pre-dose (C_{trough}) on cycle 1 day 1 and every other cycle for the first 2 years of treatment
- Pre-dose (C_{trough}) every 6 months (24 weeks) thereafter during therapy and at EOT.

4.6.2. Immunogenicity Variables

The immunogenicity variables are ADA status, titer, and time-point/visit. Serum samples for ADA will be collected at the clinic visits specified in the table 1of the protocol.

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5. STATISTICAL METHODS

For continuous variables, descriptive statistics will include the following: the number of patients reflected in the calculation (n), mean, median, standard deviation, minimum, and maximum. In addition, 25th percentile and 75th percentile will be provided.

For categorical or ordinal data, frequencies and percentages will be displayed for each category. The denominator will be determined by the analysis population used for the summary.

For time-to-event variables, median time-to-event (and the survival rate at a fixed time point) and its two-sided 95% confidence intervals will be summarized by the Kaplan-Meier method, unless otherwise specified.

5.1. Demographics and Baseline Characteristics

Patient demographics and baseline characteristics variables listed in Section 4.1 will be summarized descriptively.

5.2. Medical History

Medical history will be summarized by SOC and PT. Tables will be sorted by decreasing frequency of SOC followed by PT.

5.3. Prior/concomitant Medications and Procedures

Prior medications and procedures will be summarized.

The number and percentage of patients who received any prior cancer related medications, prior cancer related radiotherapy, or prior cancer related surgery will be summarized.

Concomitant medications will be summarized by ATC level 2 and ATC level 4. Concomitant procedures will be summarized by SOC and PT.

5.4. Subject Disposition

For subject disposition, the following summaries will be provided:

- The total number of screened patients
- The total number of patients in each analysis set
- The total number of patients who discontinued the study treatment and the reasons for the treatment discontinuation
- The total number of patients who discontinued the study, and the reasons for the study discontinuation

5.5. Protocol Deviation

Protocol deviations will be defined in separate protocol deviation plan (PDP). Listing of all patients with protocol deviations and the reason of deviation will be provided. The important protocol deviation, such as violation of inclusion/exclusion criteria; post-enrollment deviations

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which will impact assessment of efficacy or safety endpoints, will be determined before database lock and be summarized.

5.6. Extent of Study Treatment Exposure and Compliance

5.6.1. Measurement of Compliance

Drug compliance records, including actual drug administration will be provided.

5.6.2. Exposure to Investigational Product

Exposure to ISA 101b and cemiplimab will be examined for each subject and the following variables will be calculated:

- The total number of study doses administered
- The total dosage of study drug administered
- Duration of treatment exposure (in weeks) calculated as the minimum of
  - [date of last dose – date of first dose + 21 days] /7

    or
  - [date of clinical data cut-off or date of death - date of first dose + 1] /7

  The number and percentage of subjects exposed to cemiplimab will be presented by specific time point of interest.
- The actual dose intensity (µg /week) = total dose received (µg) / duration of treatment exposure (week) for ISA 101b

  The actual dose intensity (mg /week) = total dose received (mg) / duration of treatment exposure (week) for cemiplimab
- The relative dose intensity = actual dose intensity / planned dose intensity
  - Planned dose intensity (µg /week) = planned dose (µg) /3 for ISA 101b
  - Planned dose intensity (mg /week) = planned dose (mg) /3 for cemiplimab

5.7. Analyses of Efficacy Variables

The analysis of efficacy data will be performed based on the FAS, as defined in Section 3.1.

5.7.1. Analysis of Primary Efficacy Variable

Primary efficacy analysis will be performed when the last patient enrolled has had the opportunity for at least 4 tumor assessments.

The ORR according to investigator review will be summarized and the corresponding 2-sided 95% confidence interval will be derived using a normal approximation of the binomial distribution.

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5.7.2. Analysis of Secondary Efficacy Variables

DOR: The distribution of DOR will be estimated using the Kaplan-Meier method. The median DOR along with its 95% CI will be presented and Kaplan-Meier estimates with 2-sided 95% CIs at specific time points will be summarized. DOR will also be summarized descriptively by range. Number and percentage of patients with DOR at specific time periods of interest will be summarized.

PFS: The distribution of PFS will be estimated using the Kaplan-Meier method. The median PFS along with its 95% CI will be presented and Kaplan-Meier estimates with 2-sided 95% CIs at specific time points will be summarized.

OS: The distribution of OS will be estimated using the Kaplan-Meier method. The median OS along with its 95% CI will be presented and Kaplan-Meier estimates with 2-sided 95% CIs at specific time points will be summarized. A variant of OS defined by censoring patients at the start date of subsequent therapy will be summarized and displayed by Kaplan-Meier approach as a sensitivity analysis.

TTR will be summarized descriptively and at specific time periods of interest.

DCR and dDCR will be summarized and the corresponding 2-sided 95% confidence intervals will be derived using a normal approximation of the binomial distribution.

The duration of response and the best percentage change from baseline in target lesions will be presented by swimmer plot and waterfall plot, respectively.

5.7.3. Subgroup Efficacy Analysis

Subgroup efficacy analyses will be performed based on the following factors, respectively:

- Age group (<65, ≥65 - < 75, ≥75)
- Race
- Geographical region
- Number of prior systemic therapies
- ECOG (0, 1)
- Prior radiotherapy (Yes, No)

5.8. Analysis of Safety Data

The analysis of safety and tolerance will be performed on the FAS, as defined in Section 3.1 .

5.8.1. Adverse Events

Summaries that include frequencies and proportions of patients reporting AEs will include the PTs and the SOCs.

Summaries of TEAEs will include: TEAEs, Treatment related TEAEs, Serious TEAEs, Treatment-related Serious TEAEs, treatment-emergent AESI, and imAEs. For TEAEs, the following will be summarized:

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- The number and proportions of patients reporting at least 1 TEAE, presented by SOC and PT
- TEAEs by severity (NCI-CTCAE, version 5.0), presented by SOC and PT
- TEAEs related to treatment, presented by SOC and PT
- SAEs, presented by SOC, PT and NCI-CTCAE grade
- TEAEs leading to permanent treatment discontinuation, presented by SOC, PT and NCI-CTCAE grade
- TEAEs leading to death, presented by SOC and PT
- IRRs by SOC, PT and NCI-CTCAE grade
- Injection site reaction by SOC, PT, and NCI-CTCAE grade
- AESIs by SOC, PT and NCI-CTCAE grade
- Treatment-emergent imAEs by SOC, PT and NCI-CTCAE grade

For each TEAE summary presented by SOC and PT, the summary table will be sorted by decreasing frequency of SOC and PT. For TEAE summary presented by PT, the summary table will be sorted by decreasing frequency of PT.

5.8.2. Clinical Laboratory Measurements

Laboratory test results will be summarized by baseline and change from baseline to each visit with descriptive statistics.

Summary tables for worst laboratory values during on-treatment period with NCI CTCAE all grade and grade ≥ 3 will be generated. Shift tables from baseline to worst post-treatment NCI CTCAE grade during on-treatment period will be generated.

5.8.3. Analysis of Vital Signs

Vital signs (pulse, sitting blood pressures, and temperature) will be summarized by Baseline and change from Baseline to each scheduled assessment time with descriptive statistics.

5.8.4. Analysis of 12-Lead ECG

ECG parameters will be summarized by Baseline and change from Baseline to each scheduled assessment time with descriptive statistics.

ECG status (ie, normal, abnormal, not clinically significant, and abnormal clinically significant) will be reported. Shift tables from baseline to worst post-baseline findings (normal, abnormal not clinically significant, and abnormal clinically significant) during on-treatment period will be generated.

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5.9. Analysis of Pharmacokinetic and Antibody Data

5.9.1. Analysis of Pharmacokinetic Data

The concentrations of total cemiplimab will be assessed at multiple time points throughout the study treatment and summarized by descriptive statistics and listed by patient, timepoint, and dose.

5.9.2. Analysis of Anti-Drug Antibody Data

The immunogenicity variables described in Section 4.6.2 will be summarized using descriptive statistics. Immunogenicity for cemiplimab will be characterized by the ADA response observed:

- ADA Negative, defined as ADA negative response in the REGN2810 ADA assay at all time points, regardless of any missing samples.
- Pre-existing immunoreactivity, defined as a positive response in the cemiplimab ADA assay at baseline, with all post-dose ADA results negative, or a positive assay response at baseline, with all post-dose ADA assay responses less than 9-fold over baseline titer levels
- Treatment-emergent ADA response, defined as any post-dose positive response in the cemiplimab ADA assay when the baseline results are negative
  - Treatment-emergent ADA response may be further characterized as persistent, transient, or indeterminate.
  - Persistent Response – Treatment-emergent ADA positive response with two or more consecutive ADA positive sampling time points, separated by at least 16-week period (based on nominal sampling time), with no ADA negative samples in between, regardless of any missing samples.
  - Indeterminate Response –Treatment-emergent ADA positive response with only the last collected sample positive in the ADA assay, regardless of any missing samples.
  - Transient Response –Treatment-emergent ADA positive response that is not considered persistent or indeterminate, regardless of any missing samples.
- Treatment boosted ADA response, defined as any post-dose positive response in cemiplimab ADA assay that is 9-fold over baseline titer levels when baseline is positive in the ADA assay
- Maximum ADA Titer values
  - Low (titer <1,000)
  - Moderate (1,000? titer ≤10,000)
  - High (titer >10,000)

Listings of pre-existing, treatment-boosted, and treatment-emergent ADA responses, ADA titers positivity presented by patient and time point will be provided. Incidence of treatment-emergent

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ADA will be assessed as absolute occurrence (N) and percent of patients (%), grouped by study cohorts and ADA titer level.

5.10. Association of Immunogenicity with Exposure, Safety and Efficacy

5.10.1. Immunogenicity and Exposure

Potential association between immunogenicity and systemic exposure to cemiplimab will be explored. Plots of individual cemiplimab concentration time profiles may be provided to examine the potential impact of ADA category and maximum titer category on these profiles.

5.10.2. Immunogenicity and Safety and Efficacy

Potential association between immunogenicity variables and safety may be explored with a primary focus on the following safety events during the TEAE period:

- Infusion reactions
- Hypersensitivity (SMQ: Hypersensitivity [Narrow])
- Anaphylaxis (SMQ: Anaphylactic Reaction [Narrow])

Potential association between immunogenicity variables and efficacy endpoints may be explored (e.g., scatter plot or spaghetti plot).

The safety and efficacy analyses mentioned above will be conducted using the following categories:

- ADA Positive
  - Treatment-emergent
  - Treatment-boosted
- Maximum post-baseline titer category in ADA positive patients

5.11. Analysis of Exploratory Biomarker Data

The association of PD-L1 expression in tumor and infiltrating immune cells with clinical efficacy and available data on changes is HPV antigen specific T cell responses in a subset of patients will be included in the CSR. Analysis of all other exploratory pharmacodynamic and baseline predictive biomarker data will be included in a separate biomarker analysis report.

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6. DATA CONVENTIONS

The following analysis conventions will be used in the statistical analysis.

6.1. Definition of Baseline for Efficacy/Safety Variables

Unless otherwise specified, the Baseline assessment for all measurements will be the latest available valid measurement taken prior to the administration of investigational product.

6.2. Data Handling Convention for Efficacy Variables

Patients who are deemed NE according to RECIST version 1.1. will be considered as not reaching PR/CR in calculating ORR, i.e. they are not considered as responders in the numerator of ORR, but they are counted in the denominator of ORR.

6.3. Definition of Study Day

Study day 1 is the day of patient receiving first dose of study drug. Study day –1 is the day before patient receiving first dose of study drug. There is no Day 0.

For events prior to the first day a patient receiving study drug, the study day is defined as date of the date of event - first dose of study drug; for events on or after the first dose of study drug, the study day is defined as date of event - date of the first dose of study drug +1.

6.4. Data Handling Convention for Missing Data

No missing data imputation is planned in this study unless specified otherwise.

For categorical variables, patients with missing data are not included in calculations of percentages unless otherwise specified. When relevant, the number of patients with missing data is presented.

Medication missing/partial dates

To determine whether a medication is prior, concomitant or post-treatment medication, the missing medication start date is estimated as early as possible up to date of the first study treatment, and the missing medication end date is estimated as late as possible. If the medication start date is missing, the onset day will not be imputed in medication listings.

Date of first / last study treatment

Date of first injection or infusion is the first non-missing start date of dosing filled in the CRF "Investigational Product" module.

If a patient's date of the last dose is totally missing or unknown, his/her last visit date will be substituted.

6.5. Unscheduled Assessments

Unscheduled visit measurements may be used to provide a measurement for a baseline or endpoint value if appropriate according to their definition. The measurements may also be used to determine abnormal laboratory or ECG values.

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The determination of baselines and worst post-baseline values for both efficacy and safety variables will be based on scheduled available assessments and unscheduled available assessments.

Extra assessments (laboratory data or vital signs associated with non-protocol clinical visits or obtained in the course of investigating or managing adverse events) will be included in listings, but not summaries except for the endpoint determination. If more than one laboratory value is available for a given visit, the first observation will be used in summaries and all observations will be presented in listings.

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7. MULTIPLICITY CONSIDERATIONS

Adjustments to the significance level for the purposes of multiple testing are not applicable for this study.

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8. INTERIM ANALYSIS

No formal interim analysis is planned for the primary endpoint. Administrative efficacy review may be performed when at least 4 tumor assessments are collected for the first 53 patients.

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9. SOFTWARE

All statistical analyses will be done using SAS Version 9.4 or above.

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10. REFERENCES

1. Bookman MA, Blessing JA, Hanjani P, Herzog TJ, & Andersen WA. (2000) 'Topotecan in squamous cell carcinoma of the cervix: A Phase II study of the Gynecologic Oncology Group.', Gynecol Oncol. 77(3):446-9.
2. Bray F, Jemal A, Grey N, Ferlay J & Forman D. (2012) 'Global cancer transitions according to the Human Development Index (2008-2030): a population-based study. Lancet Oncology' 13(8):790-801.
3. Chung HC, Ros W, Delord JP, Perets R, Italiano A, Shapira-Frommer R, Manzuk L, Piha-Paul SA, Xu L, Zeigenfuss S, Pruitt Sk & Leary A (2019) 'Efficacy and Safety of Pembrolizumab in Previously Treated Advanced Cervical Cancer: Results from the Phase II KEYNOTE-158 Study.', Journal of Clinical Oncology 37:17, 1470-1478.
4. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D & Verweij J (2009), 'New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1).', Eur J Cancer 45(2), 228--247.
5. Forman D, de Martel C, Lacey CJ, Soerjomataram I, Lortet-Tieulent J, Bruni L, et al. (2012) 'Global burden of human papillomavirus and related diseases.' Vaccine 30 Suppl 5(F12-23).
6. Gillison ML. (2016) 'Human Papillomavirus and Oropharyngeal Cancer Stage.', J Clin Oncol. 34(16):1833-5.
7. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pembrolizumab-advanced-cervical-cancer-disease-progression-during-or-after-chemotherapy
8. ICH. (1998). ICH Harmonized tripartite guideline: Statistical principles for clinical trials (E9). International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.
9. Kenter GG1, Welters MJ, Valentijn AR, Lowik MJ, Berends-van der Meer DM, Vloon AP, Essahsah F, Fathers LM, Offringa R, Drijfhout JW, Wafelman AR, Oostendorp J, Fleuren GJ, van der Burg SH & Melief CJ (2009) 'Vaccination against HPV-16 oncoproteins for vulvar intraepithelial neoplasia.', Engl J Med. 5;361(19):1838-47. doi: 10.1056/NEJMoa0810097.
10. Look KY, Blessing JA, Levenback C, Kohler M, Chafe W, & Roman LD. (1998) 'A phase II trial of CPT-11 in recurrent squamous carcinoma of the cervix: a gynecologic oncology group study.', Gynecol Oncol. 70(3):334-8.
11. Lorusso D, Ferrandina G, Pignata S, Ludovisi M, Vigano R, Scalone S, et al. (2010) 'Evaluation of pemetrexed (Alimta, LY231514) as second-line chemotherapy in persistent or recurrent carcinoma of the cervix: the CERVIX 1 study of the MITO (Multicentre Italian Trials in Ovarian Cancer and Gynecologic Malignancies) Group.', Ann Oncol 21(1):61-6.

VV-RIM-00284310-1.0 Approved - 12 Dec 2022 GMT-5:00

12. Melief CJM, Welters MJP, Vergote I, Kroep JR, Kenter GG, Ottevanger PB, Denys H, van Poelgeest MIE, Nijman HW, Reyners AKL, Velu T, Goffin F, Lalisang, RI, Loof NM, Boekestijn S, Krebber WJ, Hooftman L, Visscher S, Blumenstein BA, Stead RB, Gerritsen W, & van der Burg SH (2020) 'Strong vaccine responses during chemotherapy are associated with prolonged cancer survival.', Science Translational Medicine. Vol. 12, Issue 535, eaaz8235

13. Miller DS, Blessing JA, Bodurka DC, Bonebrake AJ, & Schorge JO. (2008) 'Evaluation of pemetrexed (Alimta, LY231514) as second line chemotherapy in persistent or recurrent carcinoma of the cervix: a phase II study of the Gynecologic Oncology Group.', Gynecol Oncol. 110(1):65-70.

14. Muggia FM, Blessing JA, Method M, Miller DS, Johnson GA, Lee RB, et al. (2004) 'Evaluation of vinorelbine in persistent or recurrent squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study.', Gynecol Oncol. 92(2):639-43.

15. Muggia FM, Blessing JA, Waggoner S, Berek JS, Monk BJ, Sorosky J, et al. (2005) 'Evaluation of vinorelbine in persistent or recurrent nonsquamous carcinoma of the cervix: a Gynecologic Oncology Group Study.', Gynecol Oncol. 96(1):108-11.

16. Schilder RJ, Blessing J, & Cohn DE. (2005) 'Valuation of gemcitabine in previously treated patients with non-squamous cell carcinoma of the cervix: a phase II study of the Gynecologic Oncology Group.', Gynecol Oncol. 96(1):103-7.

17. Takeuchi S, Takamizawa H, Takeda Y, Ohkawa T, Tamaya T, Noda K, et al. (1991) 'An early phase II study of CPT-11 in gynecologic cancers. Research Group of CPT-11 in Gynecologic Cancers.', Gan To Kagaku Ryoho. 18(4):579-84.

18. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, & Jemal A. (2015) 'Global cancer statistics, 2012' CA: A Cancer Journal for Clinicians 65(2):87-108.

19. van Poelgeest MI, Welters MJ, Vermeij R, Stynenbosch LF, Loof NM, Berends-van der Meer DM, et al. (2016) 'Vaccination against Oncoproteins of HPV16 for Noninvasive Vulvar/Vaginal Lesions: Lesion Clearance Is Related to the Strength of the T-Cell Response.', Clin Cancer Res. 22(10):2342-50.

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