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Regeneron Pharmaceuticals, Inc.

Clinical Study Protocol

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])
Clinical Phase:	2
Protocol Number:	R2810-ONC-ISA-1981
Protocol Version:	R2810-ONC-ISA-1981 Amendment 2
Amendment 2 Date of Issue:	*See appended electronic signature page*
Amendment 1 Date of Issue:	14 Sep 2020
Original Date of Issue:	07 Apr 2020
Medical/Study Director:	[redacted] Regeneron Pharmaceuticals, Inc. 777 Old Saw Mill River Road Tarrytown, NY 10591

AMENDMENT HISTORY

Amendment 2

The main reasons for this amendment are to allow:

1. The enrollment of patients with adenocarcinoma/adenosquamous as well as squamous cell histologies of cervical cancer. Patients with adenocarcinoma/adenosquamous histology will account for up to approximately 20% of the patient population, and this is not expected to impact the primary endpoint of ORR estimation.
2. A change in the primary endpoint of this single arm study from statistical hypothesis testing to estimation of the ORR with associated confidence intervals, and to permit an administrative assessment after the first 53 patients have had the opportunity for at least 4 tumor assessments.

The following table outlines the changes made to the protocol and the affected sections.

Description of Change	Brief Rationale	Section # and Name
Added patients with adenocarcinoma/adenosquamous histology and increased the sample size to 105 patients.	Based on clinical experience with cemiplimab, patients with adenocarcinoma/adenosquamous histologies may potentially benefit from treatment with cemiplimab and ISA101b.	List of Abbreviations and Definitions of Terms Clinical Study Protocol Synopsis (Study Design, Population, Statistical Plan) Section 1.1 Background of Cervical Cancer Section 3.1 Hypothesis Section 6.1 Study Description and Duration Section 7.1 Number of Patients Planned Section 7.2 Study Population Section 7.2.1 Inclusion Criteria, criterion #2 Section 11.2 Justification of Sample Size Section 11.3.1 Full Analysis Set Section 11.3.2 Safety Analysis Set (removed) Section 11.4.3.1 Primary Efficacy Analysis Section 11.4.4 Control of Multiplicity
Removed statistical hypothesis testing and added the option for an administrative efficacy review when at least 4 tumor assessments are collected for the first 53 patients.	To analyze data without a formal hypothesis.	Clinical Study Protocol Synopsis (Statistical Plan) Section 3.1 Hypothesis Section 6.2 Planned Interim Analysis Section 11.1 Statistical Hypothesis Section 11.4.3 Efficacy Analysis Section 11.5 Interim Analysis

Description of Change	Brief Rationale	Section # and Name
Added approved indications for cemiplimab and updated clinical trial data.	To reflect recent approvals in basal cell carcinoma (BCC) and non-small cell lung cancer (NSCLC)	Section 1.2 Background on Cemiplimab Section 3.3.2.1 Benefit for Cemiplimab Section 8.1 Investigational and Reference Treatments
The risk-benefit and permitted concomitant medication sections have been updated to provide guidance about when patients may receive a COVID-19 vaccine prior to and while enrolled in this study.	Guidance has been added about when patients may be vaccinated prior to and while enrolled in this study to support global vaccination activities during the COVID-19 pandemic.	Section 3.3.1.1 COVID-19 Vaccination During the Study Section 8.7.2 Permitted Medications Section 11 Statistical Plan
Added language regarding the formulation of ISA101b	To clarify that ISA101b constitutes 2 separate injections.	Section 8.1.2 ISA101b
Added language for study drug discontinuation due to myocarditis/pericarditis	To better monitor the safety of study patients.	Section 8.2.2.1 Reasons for Permanent Discontinuation of Study Drug
Clarified safety guidelines guidance for management of immune-mediated adverse events (imAEs).	To align with most current safety guidance.	Section 8.2.2.2 Reasons for Temporary Discontinuation of Study Drug (new) Section 8.2.3 Immune-Mediated Adverse Events Section 8.2.3.1 Identification of Immune-mediated Adverse Events Section 8.2.3.2 Management of Immune-Mediated Adverse Events Section 8.2.4 General Guidance for Management of Adverse Events (new) Table 1 General Guidelines for Management of Treatment-Related Adverse Events (new) Section 8.3 Management of Acute Reactions Section 8.3.1 Acute Intravenous Infusion Reactions Section 8.3.1.1 Interruption of Intravenous Infusion Section 10.1.1 Adverse Events Section 10.1.2 Serious Adverse Events Section 10.1.3 Other Events that Require Accelerated Reporting to Sponsor Section 10.1.3.1 Immune-Mediated Adverse Events Section 10.1.4 Reporting Adverse Events Leading to Withdrawal from the Study

Description of Change	Brief Rationale	Section # and Name
		Section 10.1.5 Abnormal Laboratory, Vital Signs, or Electrocardiogram Results Appendix 2 Guidelines for Management of Immune-Mediated Adverse Events
Schedule of events updates: - Changed imaging window from 3 days to 7 days - Added footnote 6 to tumor tissue sample	To provide clarity on timing of assessments	Section 9.1 Schedule of Events Table 2 Schedule of Events Section 9.1.1 Footnotes for the Schedule of Events Table, footnote #6, #10 Section 9.2.2.1 Computed Tomography and/or Magnetic Resonance Imaging
Information was added regarding immunogenicity characterization by status and level of observed response of antidrug antibody (ADA) analysis.	This update clarifies that ADA analysis also includes an ADA Negative category	Section 11.4.8 Analysis of Immunogenicity Data
Administrative updates	To correct administrative language	Title Page
Minor editorial changes	To correct typographical, grammatical, and formatting errors.	Throughout the document

Amendment 1

The main reasons for this amendment are as follows:

- To provide total study duration including time for enrollment, time to primary analysis, and time for survival follow up.
- To provide clarification that the order of ISA101b and cemiplimab administration is as follows: cemiplimab first, then ISA101b one hour later. Additionally, patients need to be observed for 4 hours after each administration of ISA101b.
- To allow archival tissue to be sent during the time between signing of the informed consent form and the start of the screening period.
- To provide language regarding study-conduct during the Coronavirus Disease 2019 (COVID-19) pandemic.

Description of Change	Brief Rationale	Section # and Name
The study duration was edited to include values for time for enrollment, time to primary analysis, and time for survival follow up.	Text updated based on health authority feedback.	Clinical Study Protocol Synopsis: Study Duration Section 6.1 Study Description and Duration
Edited inclusion criteria to specify that the legal age of consent depends on the country of enrollment.	Text updated to conform to country-specific legal age of consent globally.	Section 7.2.1Inclusion Criteria, #1
Clarification added that ISA101b needs to be given 1 hour after cemiplimab administration on days 29 and 50, and that patients need to be observed for 4 hours after each ISA101b administration.	Text updated for consistency with other ISA + cemiplimab programs and to help distinguish between immune-mediated adverse events and injection site reactions.	Clinical Study Protocol Synopsis: Study Design Section 6.1 Study Description Duration Section 9.1.1 Footnotes for the Schedule of Events Table, footnote #8 and #9
Edited text to allow archival tissue to be sent during the time between signing of the informed consent form and the start of the screening period.	To clarify that samples may be sent as soon as informed consent is obtained.	Section 9.2.1.1 HPV16 Diagnostic Test
Added language regarding site enrollment and initiation in light of COVID-19.	To describe the plan, during the public health emergency due to COVID-19, for trial sites that have not already begun patient screening or enrollment in the study.	Section 3.3.1 Patient Screening and Site Initiation in Response to COVID-19
Added language regarding the continuity of clinical study conduct and oversight related to COVID-19.	To describe the continuity plan for conducting clinical study activities and study oversight activities during the public health emergency due to COVID-19	Section 9.1 Schedule of Events
Removed concentration of cemiplimab in vials.	To not specify concentration of cemiplimab provided to study sites in the event that concentrations change during the study.	Section 8.1.1 Cemiplimab

Description of Change	Brief Rationale	Section # and Name
Added language to allow the continuation of treatment with cemiplimab after toxicity due to ISA101b.	Text added to mirror the present language regarding the continuation of treatment with ISA101b after toxicity due to cemiplimab.	Section 8.2.1 Dose Modification
Added ±3-day window to timing of dose administration if a dose of ISA101b is missed.	To provide flexibility in the administration of dosing due to ISA101b-specific adverse events.	Section 8.3.3.3.1 Management of ISA101b-Specific Adverse Events
The schedule of events footnote regarding pregnancy testing was edited to allow either serum or urine testing at all time points.	The text was changed for clarification purposes.	Section 7.2.2 Exclusion Criteria, #21 Section 9.1.1 Footnotes for the Schedule of Events Table, footnote #17 Section 9.2.1 Procedures Performed Only at the Screening Visit Section 9.2.3.6 Laboratory Testing
Updated schedule of events as follows: Added assessment of concomitant medications at the screening visit Added anti-drug antibody (ADA) assessments at C1D1, C3D1, and C5D1	To provide consistency across the study. To match the ADA footnote	Table 1 Schedule of Events
Added hourly vital sign measurements during the 4-hour observation period after administration of ISA101b.	To confirm patient safety immediately following administration of ISA101b.	Section 9.1.1 Footnotes for the Schedule of Events Table, footnote #14 Section 9.2.3.4 Vital Signs
Clarified that peripheral blood mononuclear cells (PBMC) collection is also performed on day 1 of cycles 2 through 4 and 5+.	To be consistent with the schedule of events table	Section 9.1.1 Footnotes for the Schedule of Events Table, footnote #20
Edited details regarding CT/MRI scans and confirmation of complete response or partial response.	To clarify which tests, modalities, and techniques are acceptable for efficacy measurements.	Section 5.2 Efficacy Variables Section 9.1.1 Footnotes for the Schedule of Events Table, #10 Section 9.2.2.1 Computed Tomography and/or Magnetic Resonance Imaging Appendix 3 Response Evaluation Criteria in Solid Tumors: RECIST Guideline (Version 1.1) Response According to Revised Response Evaluation Criteria in Solid Tumors (Version 1.1) in Patients with Target (and Non-Target Lesions When Confirmation is Required (table revised) Best Overall Response When Confirmation of CR and PR are Required (new table)

Description of Change	Brief Rationale	Section # and Name
Added language to allow total T3 and total T4 samples to be measured at the site's local laboratory if free T3 and free T4 cannot be collected.	Text updated to provide leniency in the event that free T3 and free T4 cannot be measured at the site's local laboratory.	Section 9.2.3.6 Laboratory Testing
Edited text regarding tumor assessments to clarify that assessments are performed after every 2 doses of cemiplimab for the first 4 cycles, and subsequent cycles will have assessments after every 3 doses of cemiplimab.	For clarification.	Section 3.3.2.2 Risk for Cemiplimab
Replaced immune-related adverse events (irAEs) with immune-mediated adverse events (imAEs).	To be consistent with company-wide language.	Throughout the protocol
Minor typographical edits.	For correction and clarity	Throughout the protocol

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AC	Adenocarcinoma/adenosquamous
ADA	Anti-drug antibody
ADL	Activities of daily living
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APC	Antigen presenting cell
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CI	Confidence Interval
CNS	Central nervous system
COVID-19	Coronavirus Disease 2019
CR	Complete response
CRF	Case report form (electronic or paper)
CRO	Contract research organization
CRP	C-reactive protein
CRS	Cytokine release syndrome
CSR	Clinical Study Report
CSCC	Cutaneous squamous cell carcinoma
CT	Computed tomography
CTC	Circulating tumor cell
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor deoxyribonucleic acid
DOR	Duration of response
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
FAS	Full analysis set
FDA	Food and Drug Administration
FIH	First-in-human
GCP	Good Clinical Practice
HBsAg +	Hepatitis B virus surface antigen positive
HBV	Hepatitis B virus

HCV	Hepatitis C virus
HCV Ab +	Hepatitis C virus antibody positive
HDR	Homologous DNA repair gene
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HPV	Human papillomavirus
ICF	Informed consent form
ICH	International Council for Harmonisation
$IgG4^{P}$	Immunoglobulin G subclass 4
IHC	Immunohistochemistry
imAE	Immune-mediated adverse event
INR	International Normalized Ratio
IRB	Institutional Review Board
IRR	Infusion-related reaction
ISA	ISA Pharmaceuticals B.V.
ISR	Injection site reaction
IV	Intravenous
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NOAEL	No-observed-adverse-effect-level
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cells
PCSV	Potentially clinically significant value
PD-1	Programmed death-1 (receptor)
PD-L1	Programmed death ligand 1
PD-L2	Programmed death ligand 2
PET	Positron emission tomography
PFS	Progression-free survival
PI3K	Phosphatidylinositol 3-kinase
PK	Pharmacokinetic
PR	Partial response
PT	Preferred term
Q3W	Every 3 weeks

RBC	Red blood cell
rDOR	Duration of Response based upon radiographic response
RECIST	Response Evaluation Criteria in Solid Tumors
Regeneron	Regeneron Pharmaceuticals, Inc.
RP2D	Recommended phase 2 dose
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
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TIL	Tumor-infiltrating lymphocytes
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WHO	World Health Organization

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CLINICAL STUDY PROTOCOL SYNOPSIS

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
Site Location(s)	Multiple sites globally.
Objective(s)	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). 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)
Study Design	This will be 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. Study treatment and duration include cemiplimab every 3 weeks (Q3W) (with 3 doses of ISA101b on days 1, 29, and 50) until progression or any reason for early discontinuation. The primary endpoint is ORR. Patients will undergo screening evaluations to determine eligibility within 28 days prior to first treatment. All patients will receive the following regimen: • ISA101b 100 µg/peptide by subcutaneous (SC) injection on day 1, day 29, and day 50 (total of 3 doses). • Cemiplimab 350 mg given by intravenous (IV) infusion over 30 minutes Q3W on days 8 and 29 in cycle 1, on days 1 and 22 in cycle 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. **Note:** On days 29 and 50, cemiplimab will be administered first, and ISA101b will be administered approximately 1 hour after the end of the cemiplimab infusion. Patients must be observed for 4 hours after each ISA101b administration. 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 (eg, CT scan and/or MRI) 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.
Study Duration	Study duration includes a 28-day screening period. During the treatment period, 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. Additionally, there will be a 90-day safety follow-up after the last dose. Patients will be assessed for response at cycle 1 day 50 (week 7), then once per cycle (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 complete response (CR) after a minimum of 48 weeks of treatment may elect to discontinue treatment and continue with all relevant study assessments (eg, efficacy assessments). The total duration of study from start of screening to final analysis of OS is expected to be approximately 36 months (approximately 12 months of accrual, approximately 12 months of treatment, and approximately 12 months of follow up).
End of Study Definition	The end of the study is defined as the date of the last contact of the last patient in the study.
Population	
Sample Size:	Approximately 105 patients are planned to be enrolled in the study.
Target Population:	The study population is patients with HPV16 positive cervical cancer with squamous histology or adenocarcinoma/adenosquamous histology who have progressed on first line chemotherapy in the recurrent or metastatic setting.
Treatment(s)	
Study Drug	Cemiplimab
Dose/Route/Schedule:	Cemiplimab will be administered IV at a dose of 350 mg over 30 minutes (±10 minutes) Q3W.
Study Drug	ISA101b
Dose/Route/Schedule:	ISA101b 100 μg/peptide will be administered by 2 separate SC injections per dose on day 1, day 29, and day 50 (total of 3 doses).
Endpoint(s)	
Primary:	The primary endpoint is ORR based on radiographic response, measured by RECIST version 1.1.

Secondary:	The secondary endpoints are: • Incidence and severity of treatment-emergent adverse events (TEAEs)/adverse events of special interest (AESIs)/serious adverse events (SAEs) and ≥ grade 3 laboratory abnormalities during the treatment period and up to 90 days after the last dose of study treatment • DOR • PFS • OS
Procedures and Assessments	Tumor imaging (computed tomography [CT] or magnetic resonance imaging [MRI]) will be performed to measure tumor burden and to characterize the efficacy profile of study treatments using response criteria. Every effort will be made to collect survival data on all patients, including patients who withdraw from the study for any reason but have not withdrawn consent to collect survival information. Physical examination, laboratory tests, vital signs, electrocardiogram (ECG), pregnancy test for women of childbearing potential, and recording of adverse events (AEs) and concomitant medications will be performed to ensure patient safety and to characterize the safety profiles of study treatments. Other assessments will include: • Blood samples for pharmacokinetics (PK) • Blood samples to assess anti-cemiplimab antibodies • Baseline tumor tissue analysis of PD-L1 expression, tumor DNA and RNA sequence profiling and in situ tumor infiltrating immune cell subsets and density by IHC/RNAscope • Peripheral blood mononuclear cell sample analysis of HPV16 antigen specific T-cell responses
Statistical Plan	Primary efficacy analysis will be performed when the last patient enrolled has had the opportunity for at least 4 tumor assessments. 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). With 105 patients, the table 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. If observed

ORR ranges from 20.0% to 34.3%, the precision estimation using 105 patients ranges from 7.7% to 9.1%.

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%

The primary endpoint for efficacy analyses is the investigator-assessed ORR as determined by RECIST version 1.1. The ORR along with the 2-sided 95% confidence interval using a normal approximation of the binomial distribution will be summarized.

The secondary efficacy endpoints as measured by DOR, PFS, and OS will be summarized by median and its 95% confidence interval using the Kaplan-Meier method.

Treatment-emergent AEs/AESIs/SAEs and grade 3 or greater laboratory abnormalities will be summarized using descriptive statistics.

1. INTRODUCTION

1.1. Background on Cervical Cancer

The global annual incidence of cervical cancer is approximately 527,000 cases per year, and there are approximately 265,000 deaths (Torre, 2015). The highest incidence rates are in the Caribbean, Africa, Eastern Europe, and South America (Forman, 2012). In the United States (US), there are approximately 13,170 new cases and 4,250 deaths annually (Siegel, 2019). In most cases, causation is 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. In a study of 777 cervical cancer tissue samples, the HPV16 genotype was detected in 50.1% while the HPV18 genotype was detected in 16.1%, comprising 66.2% of HPV-associated cervical cancers. Widespread uptake of HPV16/18 vaccines has already been shown to decrease high-grade cervical lesions and is anticipated to substantially reduce the burden of HPV-associated cancers (Saraiya, 2015).

For patients with locally advanced disease, the curative intent therapy is definitive radiation with concurrent cisplatin. However, recurrent or metastatic disease occurs in approximately one third of cervical cancer patients in the US. For women with recurrent or metastatic disease, the GOG240 study established that standard first line therapy is platinum plus taxane doublet with the addition of bevacizumab, if clinically appropriate. Median survival with the triplet regimen is 17 months (Tewari, 2014).

After progression on first line platinum-taxane based chemotherapy for recurrent or metastatic disease, conventional cytotoxic chemotherapy has limited efficacy. Non-randomized phase 2 trials have demonstrated survival times of 7.4 to 8.1 months (N = 29 and N = 43 patients, respectively) with single agent pemetrexed, gemcitabine, topotecan, vinorelbine, or irinotecan monotherapy (Lorusso, 2010), (Miller, 2008), (Schilder, 2005), (Bookman, 2000), (Muggia, 2004), (Muggia, 2005), (Look, 1998), (Takeuchi, 1991).

Immunotherapy for advanced cervical cancer is a burgeoning field. Almost all cervical cancer is associated with high risk strains of HPV (Cancer Genome Atlas Research, 2017), and the presence of viral antigen may support anti-tumor immune responses. An example of a virally-associated tumor for which immunotherapy has demonstrated efficacy is Merkel Cell carcinoma (Gillison, 2016), (Nghiem, 2016). Cervical squamous cell carcinoma (SCC) may evade immune response by expression of PD-L1 (programmed-death ligand 1), the ligand for the immune-checkpoint receptor PD-1 (programmed death-1) on T cells (Heeren, 2016).

A non-randomized phase 2 trial of the anti-PD1 antibody pembrolizumab showed a durable response rate for patients with PD-L1 positive metastatic or recurrent cervical cancer treated with pembrolizumab monotherapy. Response rate for these patients was 14.6% (12/82 patients) with a median follow up time of 10.2 months (0.6 to 22.7 months) (Chung, 2019). These data led to an accelerated approval by the US FDA for patients with PD-L1 positive tumors in the United States. A non-randomized phase 1/2 trial showed a durable response rate for patients with metastatic or

recurrent cervical cancer treated with nivolumab monotherapy. Response rate for these patients was 26.3% (5/19 patients) with a median follow up of 19.2 months (1.4 to 31.4 months) (Naumann, 2019). An ongoing multicohort phase 1/2 trial showed early signals of durable responses in both first and second line metastatic cervical cancer with combination therapy with nivolumab and ipilimumab, an antibody directed against the CTLA-4 immune checkpoint. Responses ranged from 23.1% (6/26 patients) to 45.8% (11/24 patients) in varying dose levels. Median follow-up time ranged from 10.7 to 13.9 months (Naumann, 2019). The anti-PD1 monoclonal antibody cemiplimab (also known as REGN2810) has also demonstrated preliminary efficacy against cervical cancer, as described in Section 1.2.

These data are reassuring that immunotherapy has a role in recurrent/metastatic cervical cancer. While PD-1/PD-L1 blockade alone has a modest response rate, the consistent durability of these responses make it into a reasonable backbone for future combination therapies.

Taken together, these data support a single arm study of the anti-PD1 antibody cemiplimab in combination with other agents such that may enhance anti-tumor immune responses, such as ISA101b in patients with recurrent or metastatic HPV16+ cervical cancer with SCC and AC histology who have experienced disease progression after first line chemotherapy (Section 1.3).

1.2. Background on Cemiplimab

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. It is also approved for the treatment of patients with locally advanced basal cell carcinoma, and as a first-line treatment option in advanced non-small cell lung cancer. In the United States, it is approved with a suffix as cemiplimab-rwlc.

Cemiplimab is a high-affinity, recombinant human immunoglobulin G (IgG4P) 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. 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.

In the cemiplimab phase 1 study (R2810-ONC-1423), patients with cervical cancer were enrolled in the dose escalation phase and in 2 expansion cohorts. Cumulatively, there were 4/23 (17%) responses. All responses were in SCC patients. Duration of response ranged from 6.4 to 14.7 months (NCT03257267).

Cemiplimab is currently under investigation in R2810-ONC-1676, an open-label, randomized, multi-center, phase 3 trial comparing cemiplimab versus investigator's choice (IC) chemotherapy in patients with recurrent or metastatic cervical cancer after platinum-based therapy. The primary objective is to compare overall survival (OS) between the arms. The trial showed a clinically and statistically significant survival benefit in patients with squamous cell carcinoma (SCC) and adenosquamous/adenocarcinoma (AC) histology. A total of 608 patients, including 477 patients with SCC histology and 131 patients with AC histology, were randomized in a 1:1 ratio to receive either monotherapy with cemiplimab or IC chemotherapy. Patients on the cemiplimab arm had a median survival of 12.0 months (95% CI 10.3 months to 13.5 months). Patients on the

chemotherapy arm had a median survival of 8.5 months (95% CI 7.5 months to 9.6 months). In addition to a survival benefit, patients had a clinically and statistically significant improvement in progression free survival (PFS) and overall response rate (ORR) (Tewari, 2021). Patients on the cemiplimab arm had an ORR of 16.4% (95% CI 12.5% to 21.1%). Patients on the chemotherapy arm had an ORR of 6.3% (95% CI 3.8 to 9.6%) (Press Release: Phase 3 Trial of Libtayo® (cemiplimab) Monotherapy in Advanced Cervical Cancer Stopped Early for Positive Result on Overall Survival, 2021).

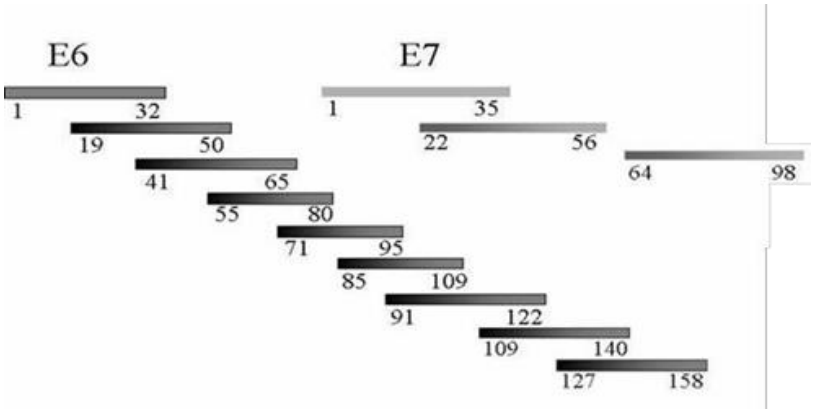
Additional information, including preclinical and clinical safety data, is available in the Investigator's Brochure.

1.3. Background on ISA101b

ISA101/ISA101b[1] is a therapeutic vaccine targeting the HPV type 16 E6/E7 proteins. The HPV16 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. These long peptides, containing multiple cytotoxic T-lymphocyte (CTL) and T-helper epitopes, are predominantly processed by professional antigen presenting cells (APCs), the dendritic cells (Bijker, 2007), (Bijker, 2008), (Rosalia, 2013). This leads to presentation of the exact amino acid sequences (epitopes) by human leukocyte antigen (HLA) class I and II molecules on dendritic cells.

ISA101b consists of 9 overlapping long E6 peptides (five 32-mer and four 25-mer E6 peptides) and three 35-mer E7 peptides as shown in Figure 1. These peptides overlap by 10 to 18 residues and cover the complete sequence of HPV16 E6. The E7 oncoprotein sequence is almost completely represented by the peptide sequences (only amino acids 57 to 63 are not covered), due to the omission of 1 poorly manufacturable peptide (G-3980-R).

Figure 1: Composition of ISA101b (HPV-DP-5P and HPV-DP-7P) Vaccine Containing Peptides Covering HPV16 E6 and E7 Oncoprotein Sequences



The peptide sequences are synthetically produced and individually released and stored as bulk drug substances according to current good manufacturing processes.

[1] The formerly developed product is called ISA101. ISA101b is a refined and reformulated version of ISA101 designed to improve the ability to manufacture the vaccine at large scale and to increase the stability of the product.

A dose of 100 μg/peptide has been selected for further study based on both the strength of the induced HPV16 immune response and safety data in clinical trials. Additional details are provided in the ISA101b Investigator's Brochure.

1.3.1. Nonclinical Data

ISA101b is designed as a therapeutic vaccine, which targets distinct human pathogenic viral antigens and triggers a highly human-specific immune response. The involved immunostimulatory/ immunomodulatory effects (eg, cascades of involved chemokines/cytokines and cells of the immune system but also organ and target antigen structures), as well as the HPV induced effects/target structures are highly human specific. Consequently, there are no known suitable animal species for the non-clinical safety testing of peptide vaccines. The HLA structure differs significantly between animal species; therefore, no other animal species shares an identical HLA structure with humans.

The synthetic long peptides (SLP) used in ISA101b are not able to directly bind to the major histocompatibility complex (MHC), but act by being processed by Dendritic cells (DC) of experimental animals or human beings, followed by loading into the available MHC class I or II molecules of the individual animal or person. A selected long peptide of HPV16 E7, when formulated with one of several adjuvants, including Montanide ISA 51 VG (Montanide), has shown substantial beneficial activity by inducing murine-specific T-cell responses against established tumors in mice induced by HPV16 E6/E7, particularly when combined with chemotherapeutics such as cisplatin or a combination of carboplatin and paclitaxel. In rabbits a set of overlapping SLP of the 2 tumorigenic proteins E6 and E7 of cottontail rabbit papilloma virus (CRPV) formulated in Montanide induced rabbit-specific immune responses and cured rabbits of CRPV-induced papillomas. In summary, efficacy/induction of the targeted immune response was demonstrated in mouse and rabbit disease models. Toxicology studies in rats (HPV-16-SLP) and rabbits (ISA101) showed high vaccine-induced antibody levels against the immunogen. The therapeutic vaccine was well tolerated systemically after SC administration at high doses. In these studies, the vaccine was given together with the adjuvant Montanide to mimic clinical studies. Doses in the rat were up to 120 μg/peptide per injection, while in the rabbit study the animal dose (300 μg/peptide per injection) was the same absolute dose as used in earlier clinical trials, not adjusted for body weight or surface area. The only findings consisted of injection site findings related to the local, immunostimulatory effects of the vaccination.

Nonclinical data including immunogenicity and toxicology are described in the ISA101b Investigator's Brochure.

1.3.2. Clinical Experience

Previous Experience with HPV-16-SLP

HPV-16-SLP (a prototype vaccine predecessor of ISA101b produced at the Leiden University Medical Center) was tested in several investigator-sponsored studies in patients with HPV16 positive gynaecological premalignant and malignant diseases. The combined studies of the Leiden University Medical Center research group have shown that in the majority of patients with premalignant cervical intraepithelial neoplasia or vulvar intraepithelial neoplasia lesions, and in slightly more than half of the patients with recurrent or metastatic cervical cancer, a positive T-cell

response can be induced by vaccination with HPV-16-SLP in Montanide adjuvant compared with a weak or nondemonstrable T-cell response in patients who were not vaccinated. These results were recently confirmed in an independent study with vulvar intraepithelial neoplasia patients (van Poelgeest, 2016).

In a pilot study in patients with late stage cervical cancer, the T-cell immune responses induced by a single dose of HPV-16-SLP were considerably augmented by timing the vaccination 15 days after the second cycle of carboplatin/paclitaxel chemotherapy, due to the much lower levels of myeloid-derived suppressor cells, but intact T cell numbers and function at this time point (Welters, 2018).

CervISA Study of ISA101/101b in Patients with Advanced, Metastatic, or Recurrent HPV16 Positive Cervical Cancer

Encouraging results using ISA101/ISA101b have been observed in a single arm study (CervISA) in women with advanced HPV16 positive cervical cancer. This study evaluated the safety, tolerability, immune responses, and clinical outcomes of ISA101/101b given in sequence with carboplatin and paclitaxel in women with HPV16 positive advanced cervical cancer. The maximum treatment duration was six 21-day cycles of carboplatin and paclitaxel (total 18 weeks) if there were no dose interruptions or delays. On day 15 (± 3 days) of cycles 2, 3, and 4, patients were vaccinated with ISA101 without or with pegylated IFNα (depending on cohort assignment). The patients were vaccinated with a fixed dose of ISA101/101b every 3 weeks (Q3W) for a total of 3 vaccinations. The enrollment in the CervISA study has been completed, including 72 patients that received ISA101 vaccination at a dose level of up to 300 µg/peptide. In addition, in a bridging cohort, 12 patients received ISA101b vaccination at the recommended phase 2 dose (RP2D) of 100 µg/peptide without or with bevacizumab.

Administration of ISA101/101b induced potent, specific, and durable immune responses to HPV16 epitopes. The HPV16 immune response was minimal at baseline and after the first cycle of chemotherapy, before the first dose of ISA101. After 2 or 3 doses of vaccination with ISA101, the HPV16-specific immune response was substantially increased, particularly at the 40 and 100 µg/peptide dose levels. A further increase in the HPV16-specific T-cell immune response was not observed at the 300 µg/peptide dose level. Though only measured in 9 patients in each of the expansion cohorts vaccinated with the 40 and 100 µg/ peptide doses, the HPV-specific response appeared to be durable and was sustained for several months after the first vaccination.

The T-cell response against common microbial recall antigens (memory mix, MRM) not present in the vaccine showed that these immune responses increased following the first 2 cycles of chemotherapy but was unaffected by administration of ISA101.

An increase in OS was associated with the strength of the vaccine-induced HPV16 T-cell response to ISA101. ISA101/101b was generally well tolerated. The most common associated adverse events (AEs) were grade 1 or 2 local injection site reactions (ISRs). The ISRs were dose related and observed in approximately 85 to 90% of the patients who received the RP2D of 100 µg/peptide. In addition, systemic allergic reactions were observed, particularly in patients receiving ISA101 at the 300 µg/peptide dose level. No clinically important overlapping toxicities of ISA101/ISA101b were identified with chemotherapy (paclitaxel and carboplatin).

Additional information on this study is provided in the ISA101b Investigator's Brochure.

Study ISA101-MDACC in Patients with HPV16 Positive Tumors

Study ISA101-MDACC was an investigator-sponsored study at the MD Anderson Cancer Center (MDACC), designed to evaluate the overall response rate of patients with recurrent/metastatic incurable HPV16 positive malignancies after ISA101 vaccination in combination with the PD-1 inhibitor nivolumab. Patients in this study had tumors with a confirmed HPV16 genotype as judged by Cervista HPV16/18. Patients had an Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1 and could have had up to 1 prior regimen for recurrence. ISA101 100 µg/peptide was given SC on days 1, 22, and 50. Nivolumab 3 mg/kg was given intravenously (IV) every 2 weeks beginning on day 8 for up to 1 year.

The trial was completed in January 2017 after accruing 24 patients in 1 year; 22 with oropharyngeal carcinoma (OPC) and 1 patient each with anal and cervical cancer. Eighteen patients (75%) had progression within 6 months of prior platinum therapy and 1 was platinum-naïve. Twelve patients (50%) had prior cetuximab treatment. Study treatment was frontline for recurrence in 10/24 and second-line in 14/24. The patients with anal or cervical cancer did not show objective tumor regression, but 1 had stable disease (SD).

The overall response rate in the 24 patients overall was 8/24 (33%), and in the subset with OPC 8/22 (36%). There were 2 (9%) complete responders (CR), 6 (27%) partial responders (PR), 2 (9%) patients with SD, and 12 (55%) patients with progressive disease (PD). As of 01 Sep 2017, 5 of 8 patients with response remained without progression with median duration of response (DOR) 10.3 months (95% CI: 10.3 – inestimable). Of these 8 patients, all had OPC, 6 had progressed within 6 months of prior platinum therapy, 1 was platinum-naïve, 6 had prior cetuximab, 5 had progressed within 6 months of cetuximab, and 4 were treated in second-line. Toxicity included grade 3 transaminase and grade 4 lipase elevation in 1 patient each. Grade 1 to 2 toxicity included fever (5 patients); injection site reaction (6 patients); and transaminase elevation, fatigue, nausea (3 patients each) (Massarelli, 2019).

ISA101 was generally well tolerated in patients with HPV16 positive cancers, including OPC, and there did not appear to be overlapping toxicities with nivolumab. Based on its composition and clinical data, the safety, tolerability, and immune responses of ISA101b are comparable to ISA101. Additional details are provided in the ISA101b Investigator's Brochure.

1.3.3. Safety Profile

Clinical experience in approximately 100 patients who have received ISA101 indicates that the most common AEs associated with ISA101 are local ISRs. The ISRs were dose related and observed in approximately 90% of the patients who received the RP2D of 100 µg/peptide. In addition, systemic allergic reactions have been observed, particularly in patients receiving higher doses of 300 µg/peptide (33%) compared to <5% at the 100 µg/peptide dose.

Based on its composition and initial clinical data, ISA101b appears to have a comparable safety profile to ISA101. The available safety data with ISA101b indicate that it has an acceptable safety profile for use at 100 µg/peptide. The most frequent toxicities are local ISRs (predominantly grade 1 to 2). Systemic allergic reactions are potentially the most serious adverse reactions to ISA101/ISA101b.

No overlapping toxicities of ISA101/ISA101b with either chemotherapy (paclitaxel and carboplatin) or anti-PD-1 therapy (nivolumab) have been detected. No autoimmune AEs have been reported in relationship to HPV-16-SLP, ISA101 or ISA101b. Immune-mediated treatment-emergent adverse events (TEAEs) have been reported with anti-PD-1 antibodies. For further information on ISA101b regarding appropriate recommendations and precautions, refer to the ISA101b Investigator's Brochure.

1.3.4. Pharmacokinetics

The pharmacokinetic (PK) characteristics of ISA101/ISA101b have not been studied since the PK of a vaccine is not considered clinically relevant and does not correlate with its pharmacodynamic or immunologic actions. Pharmacodynamic effects are best assessed by the immunogenicity studies that have been incorporated in the clinical studies.

Furthermore, ISA101/ISA101b is not metabolized in the conventional sense: the long peptides are taken up by antigen presenting cells (APCs), which process them to smaller peptides, called T-cell epitopes, which are then presented in HLA molecules on the surface of the APC. In the meantime, the APC traffics to a draining lymph node, where naive T cells recognize the presented T-cell epitopes and are activated by these epitopes. The peptides are processed within APCs through the standard HLA class I and II processing pathways.

2. STUDY OBJECTIVES

2.1. Primary Objective

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).

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 DOR, progression-free survival (PFS), and OS

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

3. HYPOTHESIS AND RATIONALE

3.1. Hypothesis

In recurrent/metastatic HPV16 cervical cancer patients who have progressed on or after first line chemotherapy in the recurrent or metastatic setting, cemiplimab + ISA101b will lead to durable objective responses in a clinically meaningful proportion of patients, and these will be associated with the production of increased anti-HPV16 E6/E7 effector T-cell responses.

3.2. Rationale

3.2.1. Rationale for Study Design

Unmet medical need in cervical cancer after progression on first line chemotherapy

For women with recurrent or metastatic cervical cancer, the GOG240 study established that standard first line therapy is platinum plus taxane doublet with the addition of bevacizumab if clinically appropriate. Median survival with the triplet regimen is 17 months (Tewari, 2017). After progression on first line platinum-taxane based chemotherapy for recurrent or metastatic disease, the efficacy of cytotoxic chemotherapy is low with an approximate median survival of 7 months.

Study of immunotherapeutic approaches in cervical cancer is of interest due to the presence of HPV viral antigen in virtually all tumors. Blockade of the PD-1 immune checkpoint with pembrolizumab achieved objective responses in 12% (12/98) of patients with recurrent/metastatic cervical cancer (Chung, 2019). In the subset of patients with PD-L1 positive tumors (CPS ≥1%), ORR was 14.6% (12/82). These observations led the US Food and Drug Administration (FDA) to grant accelerated approval for pembrolizumab for the treatment of this subgroup of patients. A randomized phase 3 trial of cemiplimab versus chemotherapy will determine if PD-1 blockade improves overall survival in second line (or greater) cervical cancer patients (NCT03257267). Cemiplimab is also being explored in monotherapy and combination therapy in a variety of solid and liquid tumor types. Cemiplimab received regulatory approval for advanced cutaneous squamous cell carcinoma with an overall ORR of 47.2% (Cemiplimab Investigator's Brochure).

Generating HPV-specific T cells with ISA101b synthetic long peptide vaccine is a research strategy to achieve anti-tumor immune responses. However, vaccination alone of advanced stage cervical cancer patients did not achieve clinical benefit (Welters, 2018), possibly due to intratumoral expression of inhibitory immune molecules such as PD-L1. This possibility is supported by the results of a phase 2 study of nivolumab + ISA101 in 22 patients with OPC (and 2 others, of which, 1 had cervical cancer), in which the observed ORR of 33% is greater than that which would be expected with PD-1 blockade alone (Massarelli, 2019).

Combinatorial approaches to stimulate convergent aspects of host immunity by employing complementary immunomodulators, as well as, immune-stimulatory aspects of conventional modalities, 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). In order to achieve higher and longer duration of responses and survival, however, combining anti-PD-1 mAb treatment with novel immunotherapy approaches will be required. In addition, while initial data obtained with ISA101 indicated that a robust and clinically active immune responses against

HPV16 E6/E7 could be obtained in HPV16 positive patients with pre-malignant lesions, such as vulvar intraepithelial neoplasia (VIN) (Kenter, 2009), patients with advanced malignancies are known to have a variety of mechanisms that limit the immune response, including changes in the local tumor microenvironment. In order to observe robust and clinically active immune responses in patients with advanced cervical cancer, the HPV16 vaccine will need to be combined with one or more immune-modulatory strategies to overcome the tumor-induced local and generalized immunosuppression. Encouraging results using ISA101/ISA101b have been observed in a single arm study (CervISA) in women with advanced HPV16 positive cervical cancer.

Study ISA101-MDACC was an investigator-initiated study at the MD Anderson Cancer Center (MDACC), which was designed to evaluate the ORR of ISA101 vaccination in combination with the PD-1 inhibitor, nivolumab, in patients with recurrent/ metastatic incurable HPV16 positive malignancies. The primary objective was assessment of overall clinical response rate targeting 30% using a Simon 2-stage MiniMax design. This was based on an estimated overall clinical response rate of approximately 20% with nivolumab alone in patients with recurrent p16+ oropharynx cancer. Secondary objectives included tolerability, PFS, OS, and HPV-specific immune response.

This study showed that ISA101 increases the overall clinical response rate in metastatic HPV16 positive OPC patients when administered in combination with nivolumab (33%) (Massarelli, 2019) compared to historical controls (Ferris, 2016), which was coupled to an approximate doubling of the expected median OS of these patients. This suggests that the efficacy of anti-PD-1 therapy may be enhanced by the addition of an HPV16 specific therapeutic cancer vaccine such as ISA101(b). The combination of stimulating the HPV16 specific immune response, while mitigating the impact of the immunosuppressive microenvironment, appears to be a promising strategy that warrants further evaluation.

To confirm and extend these results, a randomized phase 2 study is ongoing to compare cemiplimab + ISA101b versus cemiplimab in patients with recurrent/metastatic HPV16 Oropharyngeal Cancer (OPC) (ISA101b-HN-01-17). Approximately 194 patients will be enrolled, and the primary endpoint is ORR.

The current study seeks to address the unmet need in recurrent or metastatic cervical cancer patients who have progressed on first line chemotherapy.

3.2.2. Rationale for Dose Selection

The dose and schedule for both ISA101b and cemiplimab are the same as in the phase 2 study ISA101b-HN-01-17. The dose of cemiplimab 350 mg Q3W is consistent with cemiplimab dosing in solid tumor development.

3.3. Risk-Benefit

3.3.1. Patient Screening and Site Initiation in Response to COVID-19

Recognizing that the “Coronavirus Disease 2019” (COVID-19) pandemic will have an impact on the conduct of clinical trials, the Sponsor does not intend to screen any patients in this study until the impact of the COVID-19 pandemic is deemed manageable and no longer interfering with the conduct of trials at individual sites, and patients can safely participate in this study. Until then, the

Sponsor plans to obtain approvals from Health Authorities/Ethics Committees to enable initiation of study sites for this study, as allowed by local laws and regulations.

3.3.1.1. COVID-19 Vaccination During the Study

It is recommended for patients to complete COVID-19 vaccination at least 14 days prior to receiving the first dose of ISA101b or to delay COVID-19 vaccination until at least 14 days after the final dose of ISA101b.

For more information regarding the permitted timing of COVID-19 vaccinations, see Section 8.7.2.

3.3.2. Risk-Benefit for Cemiplimab

3.3.2.1. Benefit for Cemiplimab

Cemiplimab is a fully human monoclonal antibody against PD-1 and is currently being evaluated in patients with advanced solid malignancies and B-cell lymphomas whose cancers are incurable and/or have failed to respond to or showed tumor progression despite standard therapy, or patients who are not candidates for standard therapy, or for whom no available therapy is expected to convey clinical benefit. Cemiplimab has demonstrated efficacy (based on ORR and DOR) and is approved in the US for patients with advanced cutaneous squamous cell carcinoma (CSCC), locally advanced basal cell carcinoma, and as a first-line treatment option in advanced non-small cell lung cancer.

As described in earlier sections, antibodies to PD-1/PDL-1 have been shown to be effective therapeutic options for metastatic cervical cancer. Cemiplimab is currently being evaluated in a phase 3 randomized study for survival benefit over chemotherapy. The potential benefit for patients includes increased response rate, longer duration of response, avoidance of risks associated with chemotherapy and increased survival.

3.3.2.2. Risk for Cemiplimab

To mitigate this risk, tumor assessments are performed after every 2 doses of cemiplimab for the first 4 cycles. Subsequent cycles will have tumor assessments after every 3 doses of cemiplimab. Tumor assessments are designed to allow patients to pursue other treatment plans if clinically indicated.

The safety profile of cemiplimab is similar to the safety profile of other anti-PD-1/PD-L1. The important identified risks are immune-mediated adverse events (imAEs) and infusion-related reactions (IRRs). The mitigation strategies for these risks are described in Section 8.2.3.1 through Section 8.3.1.

More detailed information about the known and expected risks and reasonably expected AEs of cemiplimab may be found in the most recent approved version of the Investigator's Brochures.

3.3.2.3. Benefit:Risk for Cemiplimab

Based on the currently available safety information for cemiplimab, safety information from other anti-PD-1 antibodies, the adequate risk identification and minimization described in the Investigator's Brochure/protocols/informed consent forms (ICFs), the emerging preliminary

activity of cemiplimab on solid malignancies (including CSCC, non-small cell lung cancer [NSCLC] and cervical), the benefit-risk is considered favorable for continued clinical studies in these and other indications.

3.3.3. Risk-Benefit for ISA101b

3.3.3.1. Benefit of ISA101b

ISA101b is designed as a therapeutic vaccine, which targets distinct human pathogenic viral antigens and triggers a highly human-specific immune response. The involved immunostimulatory/ immunomodulatory effects (eg, cascades of involved chemokines/cytokines and cells of the immune system but also organ and target antigen structures), but also the HPV induced effects/target structures are highly human specific.

As described in earlier sections, ISA101b and its precursor have been shown to initiate and/or stimulate an HPV16 specific immune response in patients with HPV16 induced lesions. This was specifically evident in patients with HPV16 metastatic cervical cancer. A pilot study with combination of ISA101b showed an increased response rate and overall survival. Therefore, the potential benefits for patients receiving ISA101b include increased response rate, longer duration of response, avoidance of risks associated with chemotherapy and increased survival.

3.3.3.2. Risk of ISA101b

The fundamental risk is a lack of response. To mitigate this risk, patients will undergo frequent tumor assessments. This will allow patients to pursue other treatment plans.

As with all immunomodulation agents, the TEAEs of interest are local and systemic immune-mediated AEs. Local ISRs are detailed in Section 8.3.1.3. ImAEs and IRRs are detailed in Section 8.2.3 and Section 8.3.1.

More detailed information about the known and expected risks and reasonably expected AEs of ISA101b may be found in the most recent approved version of the Investigator's Brochures.

3.3.3.3. Benefit:Risk for Cemiplimab/ISA101b Combination

The combination of ISA101b and cemiplimab in this study is expected to have a positive benefit-risk profile for the treatment of patients with HPV16 positive cervical cancer. Anti-PD1 inhibitors given as monotherapy have shown activity and a well-established acceptable toxicity profile in recurrent/metastatic cervical cancer patients. ISA101b has been demonstrated to induce a robust and persistent T-cell response in patients with HPV16 driven malignancies, including cervical cancer and OPC. The combination of ISA101b with the anti-PD1 nivolumab achieved higher response rates compared to a historical control of nivolumab alone in the treatment of HPV16 positive OPC, albeit in a small number of patients with heterogeneous prior therapy. Finally, the combination of ISA101 with nivolumab has shown no unexpected toxicities in patients with OPC (Massarelli, 2019).

Since HPV-positive OPC patients with recurrent cancer routinely receive checkpoint inhibitors in first or second-line treatment, the use of cemiplimab as the treatment backbone is acceptable in order to objectively test the hypothesis of improved efficacy with the addition of ISA101b to an anti-PD-1 inhibitor in HPV-driven malignancies.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of cemiplimab and ISA101b may be found in the most recent approved versions of the respective Investigator's Brochures.

4. ENDPOINTS

4.1. Primary Endpoint

The primary endpoint is ORR based on radiographic response, measured by RECIST version 1.1.

4.2. Secondary Endpoints

The secondary endpoints are:

- Incidence and severity of TEAEs/adverse events of special interest (AESIs)/serious adverse events (SAEs) and ≥ grade 3 laboratory abnormalities during the treatment period and up to 90 days after the last dose of study treatment
- DOR
- PFS
- OS

4.3. Exploratory Endpoints

The exploratory endpoints are:

- 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
- Cemiplimab immunogenicity as measured by anti-drug antibodies (ADA) to cemiplimab
- HPV serotyping of archival tumor

5. STUDY VARIABLES

5.1. Demographic and Baseline Characteristics

Baseline characteristics will include standard demography (eg, age, race, weight, height, etc), disease characteristics, medical history, and medication history for each patient.

5.2. Efficacy Variables

Efficacy variables include, but are not limited to, the following:

- Tumor Assessments for Response: CT and/or MRI scan
- ORR with confirmed CR or PR per RECIST 1.1 when evaluating best overall response (BOR)
- DOR
- PFS
- OS

Variables are further defined in Section 11.4.

5.3. Safety Variables

Safety variables include, but are not limited to, the incidence and severity of the following:

- TEAEs (Section 10.2.1)
- SAEs (see Section 10.2.2)
- AESIs (see Section 10.2.3)
- ≥3 grade laboratory abnormalities (see Section 10.1.3)

Variables are further defined in Section 11.4.

5.4. Immunogenicity Variables

The immunogenicity variables for cemiplimab are ADA status, titer, and time-point/visit. Samples in this study will be collected at the clinic visits specified in Table 2.

5.5. Pharmacodynamic and Other Biomarker Variables

Pharmacodynamic and biomarker variables are:

- Baseline tumor tissue PD-L1 expression by immunohistochemistry (IHC)
- Baseline tumor tissue density of immune cell subsets (Teff, Treg, myeloid cell, others)
- Changes in peripheral HPV16 E6/E7 specific T cell frequency, clonal repertoire and functional phenotype (cytokine secretion profile, surface marker expression)

- Changes in peripheral blood immune cell subsets (Teff, Treg, myeloid, dendritic and NK cells)
- Changes in systemic inflammatory markers (IFNγ, TNF-alpha, others)
- HPV serotyping of archival tumor

6. STUDY DESIGN

6.1. Study Description and Duration

This will be 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. Study treatment and duration include cemiplimab every 3 weeks (with 3 doses of ISA101b on days 1, 29, and 50) until progression or any reason for early discontinuation as outlined in Section 7.3 and Section 8.2.2.

Patients will undergo screening evaluations to determine eligibility within 28 days prior to first treatment. 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 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.

  Note: On days 29 and 50, cemiplimab will be administered first, and ISA101b will be administered approximately 1 hour after the end of the cemiplimab infusion. Patients must be observed for 4 hours after each ISA101b administration.

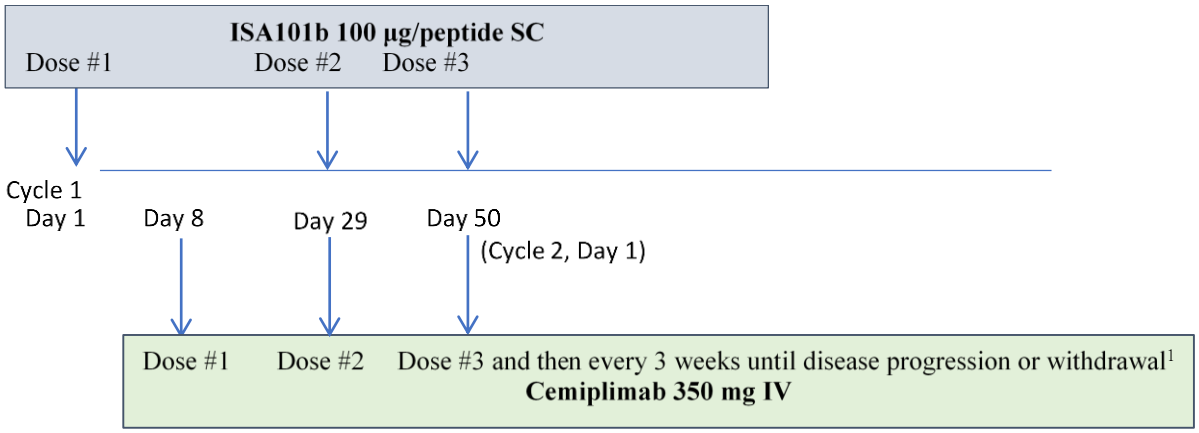
The timing of doses is summarized in Figure 2. Cycle 1 will be 7 weeks long, cycles 2 through 4 will be 6 weeks long, and all subsequent cycles will be 9 weeks long.

Patients will be assessed for response at cycle 1 day 50 (week 7), then once per cycle (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; Section 8.8, Section 8.2.2, and Section 7.3, respectively). Patients with confirmed CR after a minimum of 48 weeks of treatment may elect 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.

The total duration of study from start of screening to final analysis of OS is expected to be approximately 36 months (approximately 12 months of accrual, approximately 12 months of treatment, and approximately 12 months of follow up).

Figure 2: Study Flow Diagram



[1] Withdrawal due to reasons as listed in Section 7.3 and Section 8.2.2.

End of treatment is defined as the end of study drug. Patients may discontinue study drug for progression of disease or for any reason listed in Section 7.3 and Section 8.2.2. Thirty days after the last dose of study drug, patients will have EOT visit. Ninety days after the last dose of study drug, patients will have the safety follow-up visit (Table 2).

A patient who progresses on treatment will have EOT visit and safety follow-up visit. End of study (EOS) disposition will be on or after the safety follow-up visit. They will then enter survival follow-up.

A patient who discontinues treatment for reasons other than progression, as listed in Section 7.3 and Section 8.2.2, will have EOT and safety follow-up visit. They will then have tumor assessments until progression or the start of another anticancer therapy. At progression or start of another anticancer therapy, patients will have EOS disposition and then enter survival follow-up.

6.1.1. End of Study Definition

The end of the study is defined as the date of the last contact of the last patient of the last investigational site in the study.

6.2. Planned Interim Analysis

There will be no formal interim analysis in this study. Administrative efficacy review may be performed when at least 4 tumor assessments are collected for the first 53 patients.

7. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

7.1. Number of Patients Planned

Approximately 105 patients are planned to be enrolled in the study.

7.2. Study Population

The study population is patients with HPV16 positive cervical cancer with squamous histology (SCC) or adenocarcinoma/adenosquamous (AC) histology who have progressed on first line chemotherapy in the recurrent or metastatic setting. Patients with AC histology will be capped at approximately 20% of total enrollment.

7.2.1. Inclusion Criteria

A patient must meet the following criteria to be eligible for inclusion in the study:

1. Adult patients ≥18 years of age (or the legal age of adults to consent to participate in a clinical study per country specific regulations).
2. Has histologically confirmed recurrent or metastatic HPV16 positive cervical cancer as determined by an investigational HPV16 PCR assay by Qiagen, who have experienced disease progression after treatment with platinum containing therapy (must have been used to treat metastatic, persistent, or recurrent cervical cancer). NOTE: Platinum-therapy given in other settings (eg, concurrent with radiation therapy as part of curative-intent therapy, after radiation [or chemoradiation] as adjuvant treatment in a patient with no evidence of disease) does not satisfy the eligibility requirement regarding prior platinum therapy.

   Acceptable histology is squamous carcinoma and adenocarcinoma/adenosquamous carcinomas. Sarcomas and neuro-endocrine carcinomas are not eligible histologies.
3. Patient must be determined to be positive for HPV16 genotype, as determined by a specified central reference laboratory.
4. Patient must have measurable disease as defined by RECIST 1.1. Measurable disease is defined as at least 1 lesion that can be accurately measured in at least 1 dimension (longest dimension to be recorded). Each lesion must be ≥10 mm when measured by computed tomography (CT), magnetic resonance imaging (MRI), or caliper measurement by clinical exam or must be ≥20 mm when measured by chest x-ray. Lymph nodes must be ≥15 mm in short axis when measured by CT or MRI. Tumors within a previously irradiated field will be designated as non-measurable lesions unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy.
5. Patients must meet at least 1 of the following criteria regarding prior bevacizumab therapy:
   a. Received prior bevacizumab-containing therapy and experienced subsequent progression of disease
   b. Received prior bevacizumab-containing therapy which was discontinued due to toxicity

c. Was unsuitable for bevacizumab due to i) unacceptable risk of fistula formation, ii) poorly controlled hypertension, iii) low risk disease according to Moore criteria
d. Refused prior bevacizumab
e. Did not have access to bevacizumab

6. Patients must meet at least 1 of the following criteria regarding prior taxol therapy
   a. Received prior taxol-containing therapy and experienced subsequent progression of disease
   b. Received prior taxol-containing therapy which was discontinued due to toxicity
   c. Was unsuitable for taxol therapy due to i) neuropathy, ii) allergy or intolerance to taxol or one of its components
   d. Refused prior taxol
7. ECOG performance status of 0 or 1.
8. Has adequate organ and bone marrow function documented by:
   a. Hemoglobin ≥8 g/dL
   b. Absolute neutrophil count ≥1.0 x 10^9/L
   c. Platelet count ≥75 x 10^9/L
   d. Serum creatinine ≤1.5 x upper limit of normal (ULN) or estimated glomerular filtration rate >30 mL/min/1.73m^2. A 24-hour urine creatinine collection may substitute for the calculated creatinine clearance to meet eligibility criteria.
   e. Adequate hepatic function:
   (i) Total bilirubin ≤1.5 x ULN (≤3 x ULN if tumor liver involvement)
   (ii) Aspartate Aminotransferase (AST) ≤2.5 x ULN (≤3 x ULN if tumor liver involvement)
   (iii) Alanine Aminotransferase (ALT) ≤2.5 x ULN (≤3 x ULN if tumor liver involvement)
   (iv) Alkaline Phosphatase (ALP) ≤2.5 x ULN (≤3 x ULN if tumor liver or bone involvement)

   NOTES:

   – In patients with tumor liver involvement if levels of AST ≥3 x ULN or ALT ≥3 x ULN, and bilirubin levels ≥2 x ULN will be excluded regardless of the above criteria

   – Patients with Gilbert's syndrome do not need to meet total bilirubin requirements provided their total bilirubin is not greater from their historical level. Gilbert's syndrome must be documented appropriately as past medical history
9. Anticipated life expectancy ≥20 weeks.
10. Is willing and able to comply with clinic visits and study-related procedures and requirements
11. Able to understand and complete study-related questionnaires
12. Provide informed consent signed by study patient or legally acceptable representative

7.2.2. Exclusion Criteria

A patient who meets any of the following criteria will be excluded from the study:

1. Prior treatment with an agent that blocks the PD-1/PD-L1 pathway.
2. Prior treatment with other systemic immune-modulating agents that was
   a. less than 4 weeks (28 days) of the enrollment date, or
   b. associated with imAEs of any grade within 90 days prior to enrollment, or
   c. associated with toxicity that resulted in discontinuation of the immune-modulating agent.

   Examples of immune-modulating include therapeutic vaccines, cytokine treatments (other than granulocyte colony stimulating factor, thrombopoietin analogues, or erythropoietin), or agents that target cytotoxic T lymphocyte antigen 4 (CTLA-4), 4-1BB (CD137), PI 3-K-delta, LAG3, or OX-40.
3. Major surgery or radiation therapy within 14 days of first administration of study drug
4. Has received treatment with an approved systemic therapy within 4 weeks of first dose of study drug, or has not yet recovered (ie, grade ≤1 or baseline) from any acute toxicities except for laboratory changes as described in inclusion criteria and as below:
   a. Neuropathy of grade ≤2
   b. Alopecia of any grade
5. Has another malignancy that is progressing or requires active treatment and/or history of malignancy other than cervical cancer within 3 years of date of first planned dose of study drug, except:
   a. Non-melanoma skin cancer that has undergone potentially curative therapy
   b. Ductal carcinoma in situ of the breast
   c. Any tumor that has been deemed to be effectively treated with definitive local control (with or without continued adjuvant hormonal therapy), and the patient is deemed to be in complete remission for at least 2 years prior to first dose of study drug, and no additional therapy is required during the study period.

   Note: Patients with hematologic malignancies (eg, chronic lymphocytic leukemia) are excluded.
6. Has any condition that requires ongoing/continuous corticosteroid therapy (>10 mg prednisone/day or anti-inflammatory equivalent) within 4 weeks prior to the first dose of study drug. Patients who require a brief course of steroids (up to 2 days in the week before enrollment) or physiologic replacement are not excluded.
7. Has ongoing or recent (within 5 years) evidence of significant autoimmune disease that required treatment with systemic immunosuppressive treatments. The following are not exclusionary: vitiligo, childhood asthma that has resolved, endocrinopathies (such as hypothyroidism or type 1 diabetes) that require only hormone replacement, or psoriasis that does not require systemic treatment.
8. Has untreated or active primary brain tumor, CNS metastases, leptomeningeal disease or spinal cord compression.

   Exception: Patients with previously treated brain metastases may participate provided that the lesions are stable (without evidence of progression between 2 consecutive scans

(eg, CT scan and/or MRI) at least 6 weeks prior to imaging obtained during the screening period), there is no evidence of new or enlarging brain metastases, and the patient does not require any immunosuppressive doses of systemic corticosteroids for management of brain metastases within 4 weeks of the first dose of study drug.

9. Has encephalitis, meningitis, organic brain disease (eg, Parkinson's disease) or uncontrolled seizures in the year prior to first dose of study drug.
10. Has a known history of, or any evidence of interstitial lung disease, or active, non-infectious pneumonitis within 5 years prior to the first dose of study drug. A history of radiation pneumonitis in the radiation field is permitted.
11. Has participated in a study of an investigational agent or an investigational device within 4 weeks of first dose of study drug.
12. Has uncontrolled infection with human immunodeficiency virus (HIV), hepatitis B or hepatitis C infection; or diagnosis of immunodeficiency.

    NOTES:

    - Patients will be tested for hepatitis C virus (HCV) and hepatitis B virus (HBV) at screening.
    - Patients with known HIV infection who have controlled infection (undetectable viral load (HIV RNA PCR) and CD4 count above 350 either spontaneously or on a stable antiviral regimen) are permitted. For patients with controlled HIV infection, monitoring will be performed per local standards.
    - Patients with hepatitis B (HepBsAg+) who have controlled infection (serum hepatitis B virus DNA PCR that is below the limit of detection AND receiving anti-viral therapy for hepatitis B) are permitted. Patients with controlled infections must undergo periodic monitoring of HBV DNA. Patients must remain on anti-viral therapy for at least 6 months beyond the last dose of investigational study drug.
    - Patients who are hepatitis C antibody positive (HCV Ab+) who have controlled infection (undetectable HCV RNA by PCR either spontaneously or in response to a successful prior course of anti-HCV therapy) are permitted.
13. Has any infection requiring hospitalization or treatment with IV anti-infectives within 2 weeks of first dose of study drug.
14. Has received a live vaccine within 4 weeks of planned start of study medication.
15. Has had prior allogeneic stem cell transplantation, or autologous stem cell transplantation within 12 weeks of the start of study drug, unless discussed with and approved by the sponsor.
16. Recipients of organ transplants at any time unless discussed with and approved by the medical monitor.
17. Has known allergy or hypersensitivity to components of study drug
18. Has known psychiatric or substance abuse disorders that would interfere with participation with the requirements of the study.

19. Has any medical condition, co-morbidity, physical examination finding, or metabolic dysfunction, or clinical laboratory abnormality that, in the opinion of the investigator, renders the patient unsuitable for participation in a clinical trial due to high safety risks and/or potential to affect interpretation of results of the study
20. Member of the clinical site study team or his/her immediate family, unless prior approval granted by the sponsor.
21. Patients with a positive serum/urine hCG pregnancy test must have pregnancy medically ruled out to be eligible for study. Breastfeeding women are also excluded.
22. Continued sexual activity in women of childbearing potential (WOCBP)*, or sexually active men, 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:
    a. 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
    b. intrauterine device (IUD); intrauterine hormone releasing system (IUS);
    c. bilateral tubal ligation
    d. vasectomized partner (provided that the male vasectomized partner is the sole sexual partner of the WOCBP study participant and that the vasectomized partner has obtained medical assessment of surgical success for the procedure)
    e. and/or sexual abstinence[†,‡].

    * WOCBP are defined as women who are fertile following menarche until becoming postmenopausal, unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

    A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient to determine the occurrence of a postmenopausal state. The above definitions are according to Clinical Trial Facilitation Group (CTFG) guidance. Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation.

    † 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 drugs. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

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

7.3. Premature Withdrawal from the Study

A patient has the right to withdraw from the study at any time, for any reason, and without repercussion.

The investigator and sponsor have the right to discontinue a patient from study treatment or withdraw a patient from the study at any time.

Reasons for discontinuation of study treatment or withdrawal from the study may include, but are not limited to:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or sponsor determines may jeopardize the patient's safety if he or she continues in the study or continues treatment with study drug
- The investigator or sponsor determines it is in the best interest of the patient
- Patient noncompliance (eg, not complying with protocol required visits, assessments, and dosing instructions)
- Pregnancy.

Every effort should be made to obtain information on patients who discontinue study treatment but who do not withdraw consent to continue participation in the study by completing study assessments, as described in Section 9.1.4.

Rules for discontinuation of study treatment (permanent or temporary) are discussed in Section 8.2.2.

7.4. Replacement of Patients

Patients prematurely discontinued from the study who had received at least 1 treatment with cemiplimab and/or ISA101b will not be replaced (Section 7.3).

8. STUDY TREATMENTS

8.1. Investigational and Reference Treatments

ISA101b is an investigational treatment. Cemiplimab is being used as an investigational treatment for cervical cancer and is approved for the treatment for advanced cutaneous squamous cell cancer (CSCC), locally advanced basal cell carcinoma, and as a first-line treatment option in advanced non-small cell lung cancer.

Additional information regarding cemiplimab and ISA101b is provided in the respective Investigator's Brochures.

8.1.1. Cemiplimab

Cemiplimab (REGN2810) is supplied as a liquid in sterile, single use vials. Cemiplimab will be administered IV at a dose of 350 mg over 30 minutes (±10 minutes) Q3W.

8.1.2. ISA101b

The study drug product ISA101b is provided in 2 vials, HPV-DP-5P containing 5 peptides and HPV-DP-7P containing 7 peptides. Bulk preparation, sterile filtration, filling, and lyophilization have been developed for each drug product. ISA101b 100 µg/peptide will be administered by SC injections. ISA101b is not provided or prepared as an individual product. Two discrete injections, one of HPV-DP-5P and one of HPV-DP-7P, together *in vivo* constitute ISA101b.

Instructions on dose preparation are provided in the pharmacy manual.

8.2. Dose Modification and Study Treatment Discontinuation Rules

8.2.1. Dose Modification

Dose modification of cemiplimab for an individual patient is not allowed.

If cemiplimab is delayed, interrupted, or discontinued due to toxicity clearly related to cemiplimab as described in the cemiplimab Investigator's Brochure, and this toxicity is not considered related to ISA101b, the remaining doses of ISA101b may be administered. It is recommended to discuss such cases with the Medical Monitor.

If ISA101b is delayed, interrupted, or discontinued due to toxicity clearly related to ISA101b as described in the ISA101b Investigator's Brochure, and this toxicity is not considered related to cemiplimab, the remaining doses of cemiplimab may be administered. It is recommended to discuss such cases with the Medical Monitor.

There will be no dose reduction for ISA101b in this study.

8.2.2. Study Drug Discontinuation

Patients who permanently discontinue from study drug due to disease progression, toxicity, or another reason who do not withdraw consent from study participation will be asked to return to the clinic for all remaining study visits per the visit schedule (Table 2) and will be expected to continue with safety follow-up assessments.

8.2.2.1. Reasons for Permanent Discontinuation of Study Drug

Study drug (cemiplimab and/or ISA101b) will be permanently stopped in the event of:

- Serious or severe allergic reactions considered related to study drug
- Grade 3 infusion related reaction
- Grade 3 uveitis
- Grade 3 or 4 neurologic toxicity
- Grade 3 or 4 myocarditis/pericarditis
- Any grade 4 non-hematologic toxicity except for clinically insignificant laboratory abnormalities
- Any non-hematologic toxicity that led to temporary withholding of study treatment which does not resolve to grade 1 or baseline within 12 weeks of last study drug infusion except for immune-mediated endocrinopathies controlled with hormonal therapy
- Grade 4 hematologic toxicity that does not resolve to less than grade 4 within 2 weeks of last infusion or to grade 2 (neutropenia) or grade 1 or baseline (others) within 12 weeks of last study drug infusion.
- Physician/patient decision
- Treatment delay of ≥84 consecutive days from last dose of study drug

8.2.2.2. Reasons for Temporary Discontinuation of Study Drug

Study treatment may be temporarily stopped due to events that meet the criteria for treatment interruption described in Section 8.2.3 (and Appendix 2) or Section 8.3.

8.2.3. Immune-Mediated Adverse Events

8.2.3.1. Identification of Immune-mediated Adverse Events

Investigators must be extremely vigilant and be ready to intervene early in the management of imAEs, as the onset of symptoms of imAEs (eg, pneumonitis) may be subtle. An imAE can occur at any time during treatment or several months after the last dose of treatment. All AEs of unknown etiology associated with study 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.

Based on the emerging safety profile of cemiplimab and other antibodies targeting the PD-1/PD-L1 axis, working case definitions are provided in the Investigator's Brochure to help investigators distinguish imAEs from non-immune AEs commonly associated with PD-1 inhibition (Naidoo, 2015), (Weber, 2015). This is not exhaustive of all possible imAEs. Clinical presentations of less common imAEs, including neurologic, musculoskeletal, cardiac, renal, and ocular events (Hofmann, 2016), (Zimmer, 2016), should be reviewed in patients with concerning presentations.

The case definitions in the Investigator's Brochure have not been validated and are intended only as guidance for investigators to help distinguish imAEs from non-immune AEs. These definitions may evolve as clinical experience increases with cemiplimab and other antibodies targeting the PD-1/PD-L1 axis. Investigators' clinical judgment may include other factors when determining if an AE is immune-mediated.

8.2.3.2. Management of Immune-Mediated Adverse Events

Adverse events that meet the criteria for imAEs, as noted above in the Investigator's Brochure, should be reported as imAEs in the eCRF. If AEs corresponding to the common terms for imAEs are attributed as NOT related to cemiplimab by the investigator, additional information should be provided to substantiate an alternative attribution (eg, infectious diarrhea).

If not provided at the outset, this information may be requested by immediate edit checks or in subsequent queries. The sponsor may request additional information for any AE that is of a type known to be potentially immune-mediated (eg, rash, colitis, elevated transaminases, endocrine events), but is deemed not an imAE by the investigator.

Any grade 3 or greater imAE should be reported as an AESI (Section 10.2.3).

The following general principles apply to management of imAEs, unless otherwise specified in Appendix 2:

Grade 1: Continue study treatment with close monitoring and provide symptomatic management

Grade 2: Consider withholding study treatment

Grade 3: Withhold study treatment

Grade 4: Discontinue study treatment

If cemiplimab is held for ≤ grade 3 imAE, consider resuming when symptoms and/or laboratory values revert to baseline or ≤ grade 1 after corticosteroid taper (typically, to ≤10 mg/day prednisone or equivalent).

Permanently discontinue study treatment for:

- Recurrent grade 3 imAEs
- Grade ≥3 or recurrent grade 2 Pneumonitis
- Grade ≥3 Hepatitis with AST/ALT >5×ULN or total bilirubin >3×ULN
- Grade ≥3 Nephritis with renal dysfunction
- Grade ≥3 Uveitis
- Grade ≥3 Neurologic toxicity
- Grade ≥3 Myocarditis or pericarditis
- Grade ≥3 Infusion related reaction
- Confirmed Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), or drug reaction with eosinophilia and systemic symptoms (DRESS)

- Grade ≥3 or recurrent grade 2 imAEs in patients previously treated with idelalisib
- Grade ≥3 infusion-related reaction
- Grade 2 or 3 imAEs persistent for ≥12 weeks after the last study treatment (excluding endocrinopathies
- Requirement for ≥10 mg per day prednisone or equivalent lasting ≥12 weeks after the last study treatment

Further guidance regarding management of selected imAEs is provided in Appendix 2. Additional information about the safety profile of cemiplimab is in the Investigators Brochure. Expert consensus guidelines that provide guidance managing less common imAEs are available and may be updated periodically (Brahmer, 2018) (Haanen, 2017) (Puzanov, 2017) (Thompson, 2018).

The management considerations provided here should not supersede clinical judgment in the setting of an individual patient. The investigator may choose to hold study treatment at his/her clinical judgment regarding the safety of an individual patient, even if hold criteria are not formally met per protocol.

Any patient currently receiving cemiplimab who was previously treated with a phosphatidylinositol 3-kinase (PI3K) inhibitor and who develops stomatitis or mucositis should temporarily suspend study treatment. If this or any other imAE occurs among these patients, the sponsor should be informed as soon as possible to discuss further management of the patient. An imAE of any grade in a patient previously treated with a PI3K inhibitor should be reported as an AESI.

8.2.4. General Guidance for Management of Adverse Events

This subsection provides general guidance of treatment-related AEs (Table 1) that are not specifically addressed in guidelines for management of imAEs (Section 8.2.3.2 or Appendix 2) or in management of acute infusion reactions (Section 8.3). In the event of discrepancy between this section and a section that provides for detailed guidance (ie, Section 8.2.3.2, Appendix 2 or Section 8.3), the section that provides the more detailed guidance will supersede the general guidance in this section.

Table 1: General Guidelines for Management of Treatment-Related Adverse Events

Toxicity	Grade	Hold Treatment	Restarting Criteria
Hematological Toxicity (other than grade 3 thrombocytopenia greater than 7 days or associated with bleeding, or Grade 4 thrombocytopenia.)	1, 2, 3	No	N/A
	4	Yes	Toxicity resolves to grade ≤1 or baseline
Grade 3 thrombocytopenia greater than 7 days or associated with bleeding	3	Yes	Toxicity resolves to grade ≤1 or baseline

Toxicity	Grade	Hold Treatment	Restarting Criteria
Grade 4 thrombocytopenia	4	Yes	Discontinue permanently
Nonhematological Toxicity Note: Exceptions to be treated as for Grade 1 toxicity: • Grade 2 alopecia • Grade 2 fatigue • Clinically insignificant lab abnormality not meeting AE criteria	1	No	N/A
	2	Consider withholding for persistent symptoms	Toxicity resolves to grade ≤1
	3	Yes	Toxicity resolves to grade ≤1
	4	Discontinue permanently	Discontinue permanently

N/A = not applicable

Treatment after an AE may resume at the discretion of the investigator if it is in accordance with the toxicity management guidelines in this protocol, if resumption of treatment is thought to be in the best interest of the patient and if either of the following conditions are met:

- After resolution of an AE to ≤ grade 1 (or baseline)
- The AE is considered to be manageable through supportive/medical therapy (eg, grade 3 hypertension that can be controlled with the addition of a second anti-hypertensive agent).

8.3. Management of Acute Reactions

8.3.1. Acute Intravenous Infusion Reactions

Infusion-related reactions (IRRs) are known to occur with infusions of therapeutic proteins and have been observed in cemiplimab studies. To assist investigators in identifying IRRs, the following case definition is provided:

- Typical symptoms may include fever, chills, rigors, skin flushing, dyspnea, back pain, abdominal pain, and nausea
- Infusion reactions usually occur either during the infusion or within 24 hours after the infusion is completed
- Vital signs may be notable for hypotension and/or tachycardia
- Signs and symptoms generally resolve completely within 24 hours of onset

The investigator's clinical judgment may include other factors when evaluating a possible IRR.

See the Investigator's Brochure for further information about IRRs with cemiplimab. Such reactions may also be referred to as systemic hypersensitivity 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 10.2.4) and graded using the grading scales as instructed in Section 10.2.5.

In the event of an infusion reaction of ≥ grade 3 severity during or directly following infusion of cemiplimab, dosing should be stopped, and the patient must be permanently discontinued from study treatment.

Case report forms must capture start and stop time of the event, signs and symptoms, and management interventions (medications, interruption of infusion, rate reduction).

8.3.1.1. 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 once symptoms resolve.

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.

For patients who experience infusion-related hypersensitivity reactions that are ≤grade 2 during infusion, infusion should be interrupted or infusion rate reduced. For those who plan to continue treatment, premedication listed below are recommended for re-treatment.

For grade 1 symptoms (mild reaction; infusion interruption not indicated; intervention not indicated), the following prophylactic medications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 mg to 1000 mg at least 30 minutes prior to subsequent study treatment infusions.

For grade 2 symptoms (moderate reaction that requires therapy or infusion interruption, but for which symptoms resolve promptly with appropriate treatment such as antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, corticosteroids, and/or IV fluids; prophylactic medications

indicated at ≤24 hours), the following prophylactic medications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 mg to 1000 mg at least 30 minutes prior to subsequent study treatment infusions. If necessary, corticosteroids (up to 25 mg of hydrocortisone or equivalent) may be used.

8.3.1.2. 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 (eg, 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)

8.3.1.3. Local Injection Site Reactions

Local ISRs must be reported as AEs and graded according to Section 10.2.5.

8.3.1.3.1. Management of ISA101b-Specific Adverse Events

ISA101b will be discontinued for any severe (≥ grade 3) ISR. Severity will be graded according to Section 10.2.5.

ISA101b administration should be delayed for the following:

- Any ≥ grade 3 ISA101b-related AE.
- Temperature >38°C over the last 24 hours prior to administration.
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of ISA101b.

The occurrence of an ISA101b -associated systemic allergic reaction will be managed according to standard practice, including close observation, antihistamines, and fluids, as well as steroids or epinephrine if clinically indicated. ISA101b should not be administered again following resolution of a grade 4 systemic allergic reaction. Refer to the ISA101b Investigator's Brochure for details.

Local ISR at site(s) of previous administration of ISA101b of > grade 3 should be treated symptomatically and followed until resolution to grade 1 is observed.

Patients may resume treatment with the next dose of ISA101b when study drug-related AEs resolve to grade ≤1 or baseline value, with the following exception: patients may resume treatment in the presence of grade 2 fatigue.

If day 29 of ISA101b is missed, the second dose of ISA101b will be given on day 45 (±3 days) and the third dose will be given on day 66 (±3 days). If day 29 was missed due to an AE or lab abnormality, this must have resolved prior to resumption of dosing.

If day 50 of ISA101b is missed, the third dose of ISA101b will be given on day 66 (±3 days). If day 50 was missed due to an AE or lab abnormality, this must have resolved prior to resumption of dosing.

8.4. Method of Treatment Assignment

Each patient who signs the ICF will be assigned a patient number and tracked centrally.

Eligible patients will be enrolled sequentially as confirmed and tracked by the sponsor.

Details on treatment assignment can be found in the Interactive Web Response System (IWRS) manual.

8.5. Blinding

This is a single arm study. Blinding is not applicable.

8.6. Treatment Logistics and Accountability

8.6.1. Packaging, Labeling, and Storage

8.6.1.1. Cemiplimab

Study drug will display the product lot number on the label.

Study drug will be stored at the site at a temperature of 2ºC to 8ºC; storage instructions will be provided in the pharmacy manual.

8.6.1.2. ISA101b

ISA101b is provided in 2 vials, HPV-DP-5P containing 5 peptides and HPV-DP-7P containing 7 peptides. Bulk preparation, sterile filtration, filling, and lyophilization have been developed for each product.

Lyophilized powder of the 2 drug products is stored in glass vials in the dark at -20°C.

Before SC injection, the peptide compositions of each of the 2 drug products will be reconstituted in Reconstitution Solution (containing Water For Injection, Ethanol, Propylene Glycol, Citric acid and Macrogolglycerol Ricinoleate) and mixed with Montanide.

8.6.2. Supply and Disposition of Treatments

8.6.2.1. Cemiplimab

Cemiplimab 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 at the site or returned to the sponsor or designee.

8.6.2.2. ISA101b

The Sponsor will provide ISA101b to the study sites.

The maximum recommended hold time between ISA101b vaccine preparation and administration is 2 hours. Instructions for vaccine preparation and administration are given in the Pharmacy Manual. The ISA101b vaccine consists of 2 separate injections and is administered in 2 different limbs. It is recommended to administer the vaccine in 2 different limbs and rotate injection sites between administrations, eg, first ISA101b vaccination in the upper-legs, second ISA101b vaccination in the upper-arms and third ISA101b vaccination in the upper-legs.

Additional information regarding ISA101b is provided in the ISA101b Investigator's Brochure.

8.6.3. Treatment Accountability

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 patient
- Returned from each patient (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.

8.6.4. Treatment Compliance

All drug compliance records must be kept current and made available for inspection by the sponsor and regulatory agency inspectors.

8.7. Concomitant Medications

Any procedure performed or treatment administered (prescription medications and over-the-counter preparations) 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 drug and will continue during the study, as well as any therapies started in the follow-up period to treat a study-drug-related AE. All concomitant treatments must be recorded in the study eCRF with the generic name, dose, dose unit, frequency, indication, and start/stop date, as appropriate.

8.7.1. Prohibited Medications

While participating in this study, a patient may not receive any standard or investigational agent for treatment of a tumor other than cemiplimab as monotherapy or in combination with ISA101b, per the study's specified dosing regimens.

- After communication with the sponsor, focal palliative treatment (eg, radiation) is allowed under the following circumstances:
  - For local control of a tumor once a patient has completed 24 weeks of study treatment.
  - For pain management at sites of bone disease or lesions in the brain (as long as the lesions are not followed for treatment response evaluation).
- Patients using immunosuppressive doses (>10 mg per day of prednisone or equivalent) of systemic corticosteroids other than for corticosteroid replacement will not be eligible for the study. It is recommended that patients do not receive systemic corticosteroids such as hydrocortisone, prednisone, prednisolone (Solu-Medrol®), or dexamethasone (Decadron®) at any time throughout the study except in the case of a life-threatening illness and/or to treat an imAE.
- It is recommended that patients do not receive other immunosuppressive medications at any time throughout the study except in the case of a life-threatening emergency and/or to treat and imAE or IRR. Examples of immunosuppressives that may be used for treatment of imAEs are mentioned in Appendix 2. Investigators are allowed to treat adverse events requiring immunosuppressive medication using their institutional standard, which may involve medications not specifically mentioned in the protocol.
- Prophylactic or therapeutic anticoagulation therapy is allowed after discussion with study sponsor as gastrointestinal adverse events are common with immune checkpoint inhibitors. Patients on anticoagulants have to be monitored closely.
- Patients are not allowed to undergo surgical resection of the primary tumor site.

8.7.2. Permitted Medications

While participating in this study, a patient may receive medications or therapies other than study drug under the following conditions:

- Physiologic replacement doses of systemic corticosteroids are permitted, even if >10 mg/day prednisone equivalents.

- A brief course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by contact allergen) is permitted.
- Gonadotropin-releasing hormone agonist therapy (eg, for prostate cancer) may be continued and is not prohibited.
- Hormone-replacement therapy is allowed.
- Inhaled, topical, ophthalmologic, or intranasal steroids are allowed.
- Treatments for bone metastases (bisphosphonates, denosumab) are allowed.
- Any other medication which is considered necessary for the patient's welfare, and which is not expected to interfere with the evaluation of the study drug, may be given at the discretion of the investigator.

COVID-19 Vaccination During the Study

COVID-19 vaccination may be administered to patients enrolled in R2810-ONC-ISA-1981 in accordance with local regulatory guidance. Currently, there is limited data on safety and efficacy interactions between approved COVID-19 vaccines and cemiplimab and/or ISA101b.

It is recommended for patients to complete COVID-19 vaccination at least 14 days prior to receiving the first dose of ISA101b or to delay COVID-19 vaccination until at least 14 days after the final dose of ISA101b.

It is recommended to use different limbs for the administration of a COVID-19 vaccine and contiguous ISA101b vaccine. It is recommended not to receive a COVID-19 vaccine if the patient has a known allergy to the COVID-19 vaccine or one of its components.

There should be an individual risk/benefit analysis for each patient when receiving COVID-19 vaccination while enrolled in R2810-ONC-ISA-1981.

8.8. Treatment with Cemiplimab Beyond Disease Progression

It is recognized that a minority of patients treated with immunotherapy may derive clinical benefit despite initial evidence of progressive disease.

Patients who experience RECIST 1.1-defined progressive disease will be permitted to continue treatment until further progression is observed, provided the following criteria are met:

- Investigator assesses continued use of a PD-1 therapy is appropriate
- Patient continues to meet all other study eligibility criteria, as defined in the inclusion/exclusion criteria (Section 7.2)
- Patient is tolerant of cemiplimab and has a stable performance status.
- Patient provides written informed consent prior to resuming treatment by signing the current version of the ICF (eg, the patient repeats the written informed consent that was done prior to initial study enrollment).
- Patients do not have evidence of rapidly progressing disease

It is understood that, if there is further progression after resumption of treatment (≥30% increase in tumor burden from the time of initial progressive disease by RECIST criteria; this includes an increase in the sum of all target lesions and/or the development of new lesions), that cemiplimab will be discontinued.

Patients should continue with assessments according to Table 2.

9. STUDY SCHEDULE OF EVENTS AND PROCEDURES

9.1. Schedule of Events

Study assessments and procedures are presented by study period and visit in Table 2.

The allowable window for all visit days and assessments is ±3 business days (excluding weekends and holidays), unless otherwise stated. All other "days" in the protocol refer to calendar days. For tumor assessments (CT or MRI), the window is ±7 days from planned scan dates, unless otherwise stated.

Missed doses of cemiplimab or visits will not be made up. In the case of missed doses of cemiplimab, tumor assessments should still follow original schedule. If a patient is unable to undergo scans within the window due to logistical or medical reasons, tumor assessment will be obtained at the next available date.

Missed doses of ISA101b are detailed in Section 8.3.1.3.1.

In light of the public health emergency related to COVID-19, the continuity of clinical study conduct and oversight may require implementation of temporary or alternative mechanisms. Examples of such mechanisms may include, but are not limited to, any of the following: phone contact, virtual visits, telemedicine visits, online meetings, non-invasive remote monitoring devices, use of local clinic or laboratory locations, and home visits by skilled staff. Additionally, no waivers to deviate from protocol enrollment criteria due to COVID-19 will be granted. All temporary mechanisms utilized, and deviations from planned study procedures are to be documented as being related to COVID-19 and will remain in effect only for the duration of the public health emergency.

Table 2: Schedule of Events

Study Procedure	Screening Visit[1]	Cycle 1[2, 3]				Cycle 2 to 4[2, 3]			Cycles 5+[2, 3]				EOT Visit[4,5]	Safety Follow-up[4,5]	Tumor Assessment[5]	Survival Follow-up[4,5]
	Day -28 to Day -1	Day 1	Day 8 ±3	Day 29 ±3	Day 50 ±3	Day 1 ±3	Day 22 ±3	Day 43 ±3	Day 1 ±3	Day 22 ±3	Day 43 ±3	Day 64 ±3	30 days after last dose ±7 days	90 days after last dose ±10 days	Every 4 months (±10 days)	Every 4 months (±10 days)
Inclusion/exclusion	X															
Informed consent[6]	X															
Genomics substudy informed consent (optional)	X															
PBMC consent (optional)	X															
Future biomedical research consent (optional)	X															
Medical history and demographics	X															
Electrocardiogram[7]	X												X	X		
Performance status	X												X	X		
Tumor tissue sample	X[6]															
Treatment:																
Cemiplimab (experimental)[8]			X	X		X	X		X	X	X					
ISA101b (experimental)[8, 9]		X		X	X											
Efficacy (Radiologic):																
CT scan and/or MRI[10]	X				X			X				X	X[11]	X	X	
Safety:																
Weight and height (height at screening only)	X	X[12]				X			X							
Complete physical examination[13]	X												X			

Study Procedure	Screening Visit[1]	Cycle 1[2, 3]				Cycle 2 to 4[2, 3]			Cycles 5+[2, 3]				EOT Visit[4,5]	Safety Follow-up[4,5]	Tumor Assessment[5]	Survival Follow-up[4,5]
	Day -28 to Day -1	Day 1	Day 8 ±3	Day 29 ±3	Day 50 ±3	Day 1 ±3	Day 22 ±3	Day 43 ±3	Day 1 ±3	Day 22 ±3	Day 43 ±3	Day 64 ±3	30 days after last dose ±7 days	90 days after last dose ±10 days	Every 4 months (±10 days)	Every 4 months (±10 days)
Limited physical examination[14]		X[12]	X	X	X	X	X	X	X	X	X	X		X		
Vital signs[15]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Adverse events		Continuous Monitoring for Adverse Events												X		
Phone contact																X
Laboratory Testing:																
Hematology[16]	X	X[12]	X	X	X	X	X	X	X	X	X	X	X	X		
Blood chemistry[16]	X	X[12]		X	X	X	X	X	X	X	X	X	X	X		
Prothrombin time Activated partial thromboplastin time	X					X			X				X			
TSH (with reflex T3, free T4)	X					X			X				X			
HBV, HCV, HIV	X															
Pregnancy test for WOCBP[17]	X	X[12]				X			X				X			
Urinalysis	X					X			X				X	X		
PK, ADA, Biomarkers:																
PK sample (cemiplimab)[18]		X				X			X				X			
ADA sample (cemiplimab)[19]		X				X			X				X			
Soluble biomarkers (serum)		X	X	X									X			
ctDNA plasma sample		X		X		X										
T cell immune monitoring PBMC sample[20]		X	X	X		X			X				X			

Study Procedure	Screening Visit[1]	Cycle 1[2, 3]				Cycle 2 to 4[2, 3]			Cycles 5+[2, 3]				EOT Visit[4,5]	Safety Follow-up[4,5]	Tumor Assessment[5]	Survival Follow-up[4,5]
	Day -28 to Day -1	Day 1	Day 8 ±3	Day 29 ±3	Day 50 ±3	Day 1 ±3	Day 22 ±3	Day 43 ±3	Day 1 ±3	Day 22 ±3	Day 43 ±3	Day 64 ±3	30 days after last dose ±7 days	90 days after last dose ±10 days	Every 4 months (±10 days)	Every 4 months (±10 days)
Pharmacogenomics (optional sub-study)[21]	X															

9.1.1. Footnotes for the Schedule of Events Table

1. Patients who fail screening may be screened 1 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 28 days prior to cycle 1 day 1.
2. Cycle 1 is 7 weeks long, cycles 2 through 4 are 6 weeks long, and all subsequent cycles are 9 weeks long.
3. Due to ±3-day windows of visits, the last day of a cycle may coincide with the first day of the next cycle (eg, C1D50 may be the same visit as C2D1, etc).
4. Patients who discontinue study drug due to progression of disease should proceed to the EOT visit, safety follow-up, and survival follow-up.
5. Patients who discontinue study drug for reasons other than progression of disease (as detailed in Section 7.3 and Section 8.2.2) should proceed to the EOT visit, safety follow-up, and tumor assessments. If these patients experience progression during tumor assessments, they should proceed to survival follow-up.
6. Informed consent must be provided before the initiation of screening procedures and must be obtained within 45 days prior to cycle1 day 1. All screening assessments must be performed within 28 days prior to cycle 1 day 1 (for tumor tissue sample, see Section 9.2.1.1). 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.
7. Local electrocardiograms (ECG) should be performed before blood is drawn during visits requiring blood draws.
8. On days when cemiplimab and ISA101b are administered together, cemiplimab will be administered first, and ISA101b will be administered approximately 1 hour after the end of the cemiplimab infusion.
9. Patients must be observed for 4 hours after each ISA101b administration.
10. During the treatment period, imaging should be acquired in the window of the scheduled imaging day (scheduled imaging day ±7 days). Brain imaging is optional as clinically indicated.
11. If the EOT visit falls within 30 days of the last cycle tumor assessment, the CT scan and/or MRI does not need to be repeated.
12. If cycle 1 day 1 is within 72 hours of screening, this assessment does not need to be repeated at cycle 1 day 1.
13. Complete physical examination includes head and neck, lungs, heart, abdomen, lymph nodes, extremities, and skin. A brief neurologic examination should also be performed.
14. Limited physical exam includes lungs, heart, abdomen, and skin.
15. Vital signs are collected within 10 minutes prior to infusion, and approximately 15 minutes (±10 minutes) after the completion of the infusion. Vital signs will also be taken every hour

during the 4-hour observation after administration of ISA101b. Note: Blood pressure should be measured after the patient has been resting quietly for at least 5 minutes. Blood pressure may be obtained from a seated or recumbent position and should be done consistently throughout the study. When scheduled at the same time as other procedures, vital signs should be measured prior to clinical laboratory assessments, PK, or exploratory sample collection.

16. Hematology and chemistry samples may be obtained ≤72 hours prior to cemiplimab treatment.
17. Pre-dose serum or urine β-human chorionic gonadotropin (HCG) up to 72 hours prior to study drug administration. Serum/urine pregnancy tests are requirements for women of child bearing potential only.
18. Serum samples for cemiplimab concentration will be collected from all patients pre-dose (C_{trough}) on cycle 1 day 1 and every other cycle for the first 2 years of treatment. After 2 years, samples for cemiplimab concentration will be collected pre-dose every 6 months (24 weeks) during therapy and at EOT.
19. ADA serum samples for cemiplimab will be collected pre-dose of cemiplimab administration on day 1 of cycle 1, and pre-dose of cemiplimab on day 1 of cycles 3 and 5 for the first year of treatment, then pre-dose every 4 cycles for the subsequent years of treatment (eg, C9, C13 and so on) and at EOT. In the event of AESI, additional samples may be collected for ADA analysis at or near the event when possible.
20. Peripheral blood mononuclear cell (PBMC) collection is optional. PBMC samples will be collected pre-dose on day 1, 8, and 29 of cycle 1, pre-dose on day 1 of cycles 2 through 4, day 1 of cycles 5+, and at end of treatment.
21. Pharmacogenomics (optional sub-study): See Section 9.2.10.

9.1.2. End of Treatment Visit

All patients will attend an end of treatment visit 30 days after their last dose of study drug.

Patients who are withdrawn from the study before the primary endpoint visit (cycle 4 day 43) will be asked to return to the clinic once for an end of treatment visit consisting of the assessments described in Table 2.

9.1.3. Unscheduled Visits

All attempts should be made to keep patients on the study schedule. Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, or for any other reason, as warranted.

9.1.4. Follow-Up

After progression, patients will complete end of treatment visit, safety follow-up visit, and have survival follow-up approximately every 4 months (Table 2).

Patients who discontinue study drug for reasons other than progression will be followed approximately every 4 months by scans until disease progression or until patient commences another anticancer systemic therapy, whichever comes first.

After progression, survival follow-up should occur approximately every 4 months. This may be done by phone contact.

9.2. Study Procedures

9.2.1. Procedures Performed Only at the Screening Visit

The following procedures will be performed for the sole purpose of determining study eligibility or characterizing the baseline population:

- Inclusion/exclusion criteria
- Informed consent
- Medical history and demographics
- Tumor tissue sample for documentation of pathologic confirmation of cervical cancer and HPV16 diagnostic testing
- HBV, HCV, and HIV testing

Patients who fail screening may be screened 1 additional time. Some procedures may not need to be repeated if they were previously completed within 28 days prior to cycle 1 day 1, and an ICF will need to be re-signed if prior ICF signing is beyond 45 days of cycle 1 day 1.

9.2.1.1. HPV16 Diagnostic Test

For HPV16 determination, a formalin-fixed, paraffin-embedded tissue block or unstained slides of tumor samples must be provided after the ICF is signed. Tumor biopsies should be of sufficient size or quantity to ensure an adequate amount of tissue for analysis. Complete instructions on the collection, processing, handling and shipment of all samples will be provided in the laboratory manual. A validated assay at a central laboratory will be used for determination of HPV16 genotyping in patient samples and to determine eligibility based on HPV16 positivity. Samples should be sent to the central laboratory at any point during the period between ICF signing and cycle 1 day 1 (including prior to the screening period; effort should be made to ship the sample just after the ICF is signed to ensure the result is received on time to confirm eligibility). The use of HPV16 for decisions regarding treatment with ISA101/ISA101b is considered investigational.

9.2.2. Efficacy Procedures

9.2.2.1. Computed Tomography and/or Magnetic Resonance Imaging

Diagnostic quality contrast-enhanced CT and contrast-enhanced MRI are the preferred imaging modalities for assessing radiographic tumor response. In patients whom contrast is strictly contraindicated, non-contrast MRI scans and CT chest scans are acceptable. The chest, abdomen, and pelvis must be imaged along with any other known or suspected sites of disease. If more than one imaging modality is used at screening for the same anatomies, the most accurate imaging

modality according to RECIST 1.1 should be used when recording data. The same imaging modality and techniques used at screening should be used for all subsequent assessments. At screening, MRI of the brain with contrast or without contrast if contrast is contraindicated, or CT with contrast when MRI is contraindicated, should be performed in patients with a known history of treated brain metastasis. Additional sites of known disease (including CNS) should be imaged at screening. Refer to the Site Imaging Manual for details of imaging requirements.

After the baseline tumor assessment, radiographic tumor assessments will be obtained in all patients at the time points indicated in Table 2 (with a window of ±7 days). During safety follow-up, radiographic evaluation will be performed every 4 months until RECIST 1.1-defined progressive disease, withdrawal of consent, death, or initiation of another anticancer treatment.

Tumor assessments should be performed even if dosing is interrupted. Weeks and months are in reference to the calendar week and month and should not be adjusted due to dosing delays/interruptions. Cycle 1 day 1 date is the reference for all visits including tumor assessments visits.

De-identified scans will be collected and, at the Sponsor's discretion, reviewed by independent radiologists using RECIST criteria at a later date, or at any time during the study.

9.2.2.1.1. Tumor Burden Assessments

Tumor measurements will be performed in accordance with RECIST 1.1. Criteria (Eisenhauer, 2009) (Appendix 3) and should be done by the same investigator or radiologist for each assessment of a patient, to the extent feasible.

Investigators will assess response to therapy using RECIST 1.1 criteria. RECIST 1.1-defined progressive disease determined by the investigator will be used for clinical management of the patient. RECIST 1.1-based tumor burden assessments will be used for evaluation of efficacy endpoints.

9.2.3. Safety Procedures

9.2.3.1. Electrocardiogram

Local ECGs should be performed before blood is drawn during visits requiring blood draws. A standard 12-lead ECG will be performed at time points according to Table 2. Heart rate will be recorded from the ventricular rate, and the PR, QRS, RR and QT (identify QTcB or QTcF) intervals will be recorded. The ECG strips or reports will be retained with the source.

9.2.3.2. Performance Status

Eastern Cooperative Oncology Group performance status will be performed at the time points according to Table 2. Performance status will be assessed according to ECOG criteria in Appendix 1.

9.2.3.3. Body Weight and Height

Body weight will be assessed using calibrated scales. Patients should void (empty bladder) prior to weight assessment. Patients should be wearing undergarments only and no shoes during weight assessments. Body weight will be recorded to the nearest 0.1 kg.

Height will be assessed at screening only.

9.2.3.4. Vital Signs

Vital signs, including temperature, sitting blood pressure, pulse, and respiration will be collected pre-dose and post-dose at time points according to Table 2. Vital signs will also be taken every hour during the 4-hour observation period following ISA101b administration.

Note: Blood pressure should be measured after the patient has been resting quietly for at least 5 minutes. Blood pressure may be obtained from a seated or recumbent position and should be done consistently throughout the study. When scheduled at the same time as other procedures, vital signs should be measured prior to clinical laboratory assessments, PK, or exploratory sample collection.

9.2.3.5. Physical Examination

A thorough and complete physical examination will be performed at visits specified in Table 2. 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 at visits specified in Table 2.

9.2.3.6. Laboratory Testing

Hematology, blood chemistry, coagulation, TSH (with reflex T3, free T4), urinalysis, and pregnancy testing samples will be analyzed by the site's local laboratory.

Samples for laboratory testing will be collected at visits according to Table 2. Tests will include:

Blood Chemistry

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

*At sites at which the bicarbonate assay is not performed as part of the routine chemistry panel, it may be omitted

**At sites at which a urea assay is performed instead of BUN, the urea assay will be acceptable.

***Total or direct bilirubin may be measured, whichever is standard per site.

Hematology

Hemoglobin	Differential:
White blood cells (WBCs)	Neutrophils
Platelet count	Lymphocytes

Monocytes

Urinalysis

pH	Ketones	Glucose
Specific gravity	Protein	Blood

Other Laboratory Tests

Thyroid Function Tests: Thyroid-stimulating hormone (with reflex T3, free T4) will be tested at visits specified in Table 2 while the patient is on treatment. If TSH is abnormal, T3 and free T4 should be measured at the investigative site's local laboratory. If an investigative site routinely performs total T3 and/or total T4 tests, these measurements will be acceptable in lieu of free T3 or free T4.

Coagulation Tests: Prothrombin time and activated partial thromboplastin time testing will be performed at visits specified in Table 2 while the patient is on treatment. Sites may report INR and activated PTT if it is the standard of care at that site.

Viral Serology Tests: HBV, HCV, and HIV serum antibodies will be tested at visits specified in Table 2.

Pregnancy Tests: Serum β-HCG or urine β-HCG will be measured ≤72 hours prior to study drug administration) and serum/urine β-HCG will be measure at all other time points as specified in Table 2.

Abnormal Laboratory Values and Laboratory Adverse Events

All laboratory values must be reviewed by the investigator or authorized designee.

Significantly abnormal test results that occur after start of treatment must be repeated to confirm the nature and degree of the abnormality. When necessary, appropriate ancillary investigations should be initiated. If the abnormality fails to resolve or cannot be explained by events or conditions unrelated to the study medication or its administration, the Medical/Study Director must be consulted.

The clinical significance of an abnormal test value, within the context of the disease under study, must be determined by the investigator.

Criteria for reporting laboratory values as an AE are provided in Section 10.1.1.

9.2.3.7. Additional Samples

Any additional samples (eg, pulmonary effusion fluid, ascites fluid, etc) collected as a part of standard-of-care or symptomatic management while on study may be sent for analysis. These collections are optional but encouraged for further understanding of interactions between patients, disease, and study drugs.

9.2.4. Drug Concentration and Pharmacokinetic Measurements

Samples for cemiplimab concentration will be collected at visits listed in Table 2.

Any unused samples may be used for exploratory biomarker research or to investigate AEs as appropriate.

9.2.5. Immunogenicity Measurements and Samples

Samples for ADA assessment of cemiplimab will be collected at time points listed in Table 2. In response to AESI like anaphylaxis or hypersensitivity, additional ADA samples closer to the event may be collected and analyzed when possible, based on the judgement of the medical investigator and/or medical monitor (in treatment, follow-up, or resumption of treatment). The exact date and time of sample collection must be recorded and entered into the electronic data capture (EDC).

Any unused samples may be used for exploratory biomarker research or to investigate AEs as appropriate.

9.2.6. Pharmacodynamic and Exploratory Biomarker Procedures

In this study, research assessments will be performed to better understand the baseline predictive biomarkers of cemiplimab + ISA101b response that may include but are not limited to tumor tissue analysis of PD-L1 expression and immune cell subsets by IHC or RNAScope, tumor DNA and RNA sequencing. Pharmacodynamic and tumor biomarker samples will be collected at time points according to Table 2, and measurements will be performed to determine treatment effect on the disease and relevant physiological processes. The biomarkers studied are believed to be relevant to the pathophysiology of indication target engagement, mechanism of action of cemiplimab and possible toxicities.

Biomarker assays may include, but will not be limited to, the following:

- Tumor specific and HPV gene panel (circulating tumor DNA sequence profile)
- T cell effector and innate immune cytokine panel (serum cytokines)
- T cell, myeloid cell subset analysis, functional HPV E6/E7 specific T cell assays

9.2.7. Peripheral Blood Biomarkers

Samples for peripheral blood (plasma, serum, and PBMC samples) biomarker assessments will be collected at time points listed in Table 2.

PBMC collection is optional. PBMCs from patients receiving cemiplimab may be used for characterization of immune cell subsets including T cells, B cells, natural killer cells, monocytes, dendritic cells, and subsets of these cell types. Peripheral blood mononuclear cell samples may also be used to assess immune cell function, including T cell activation and proliferation.

9.2.8. Survival Data Collection

Every effort will be made to collect survival data on all patients, including patients who discontinued the study for any reason but have not withdrawn consent to collect survival information. If the death of a patient is not reported, the date of the last patient contact in this study will be used in the determination of the patient's last known date of alive. Use of publicly available information should only be in accordance with local law.

9.2.9. Future Biomedical Research (Optional)

Patients who agree to participate in the future biomedical research sub-study will be required to consent to this optional sub-study before samples are banked in long-term storage. The unused

biomarker samples for study-related research, as well as unused PK and ADA samples, will be stored for up to 15 years after the final date of the database lock. The unused samples may be utilized for future biomedical research. Future biomedical research may include assay development and/or validation, and the samples may be used as references or controls in unrelated experiments After 15 years, any residual samples will be destroyed. The results of these future biomedical research analyses will not be presented in the CSR.

9.2.10. Pharmacogenomic Analysis (Optional)

Patients who agree to participate in the genomics sub-study will be required to consent to this optional sub-study before collection of a pharmacogenomics-specific whole blood sample. This sample may be collected during screening or any other time point for study-related research (Table 2), and genomic DNA will be extracted for analysis as described below.

The DNA samples for pharmacogenomics analyses will be single-coded as defined by the International Council for Harmonisation (ICH) guideline E15 samples. Samples will be stored for up to 15 years after the final date of the database lock. If there are specific site or country requirements involving the pharmacogenomic analyses with which the sponsor is unable to comply, samples will not be collected at those sites.

The purpose of the pharmacogenomic analyses is to identify genomic associations with clinical (safety or efficacy) or biomarker response to cemiplimab, clinical outcome measures, and possible AEs. In addition, associations between genomic variants and prognosis or progression of cervical cancer or 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, target pathway, or cervical cancer and related 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, DNA copy number variation, methods for quantifying epigenetic modifications, and sequencing of the somatically recombined adaptive immune receptor loci may also be performed, including comparison to DNA extracted from tumor tissue biopsies. The list of methods may be expanded to include novel methodology that may be developed during the course of this study or sample storage period.

10. SAFETY EVALUATION AND REPORTING

10.1. Recording and Reporting Adverse Events

10.1.1. Adverse Events

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 study treatment, or until the patient commences another anticancer systemic therapy, whichever comes first. After informed consent has been obtained but prior to initiation of study drug, only the following AEs should be reported:

- SAEs
- Non-SAEs caused by a protocol-mandated intervention (eg, non-SAEs related to invasive procedures such as biopsies)

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

All AEs after initiation of study treatment and until 90 days after the last study treatment, regardless of relationship to study treatment, will be reported on the AE CRF. Additionally, any SAE or other AE of concern that the investigator believes may be related to study treatment and that occurs later than 90 days after last study treatment, or after the patient has commenced another anticancer systemic therapy (whichever comes first) should be reported.

Study treatment includes cemiplimab and ISA101b.

Information on follow-up for AEs is provided in Section 10.1.2. Laboratory, vital signs, or ECG abnormalities are to be recorded as AEs as outlined in Section 10.1.5.

10.1.2. Serious Adverse Events

All SAEs, regardless of assessment of causal relationship to study treatment must be reported to the sponsor (or designee) within 24 hours. Refer to the study reference manuals for the procedure to be followed.

Information not available at the time of the initial report must be documented in a follow-up report. Substantiating data such as relevant hospital or medical records and diagnostic test reports may also be requested.

In the event the investigator is informed of an SAE that occurs after 90 days after the last dose of study treatment, or after the patient commences another anticancer systemic therapy (whichever comes first), only those SAEs or other AEs of concern deemed by the investigator to be related to study treatment will be reported to the sponsor. The investigator should make every effort to obtain follow-up information on the outcome of a treatment-related SAE until the event is considered chronic and/or stable.

10.1.3. Other Events that Require Accelerated Reporting to Sponsor

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

Symptomatic Overdose of Study Drug: Accidental or intentional overdose of at least 2 times the intended dose of study drug within the intended therapeutic window, if associated with an AE.

Pregnancy: Although pregnancy is not considered an AE, it is the responsibility of the investigator to report to the sponsor (or designee), within 24 hours of identification, any pregnancy occurring in a female during the study or within 6 months of the last dose of study drug. Any complication of pregnancy affecting a female study patient and/or fetus and/or newborn that meets the SAE criteria must be reported as an SAE. Outcome for all pregnancies should be reported to the sponsor.

Adverse Events of Special Interest (applicable to cemiplimab only): All AESI, serious and nonserious, must be reported within 24 hours of identification using the same reporting process as for SAE reporting, per Section 10.1.2. Adverse events of special interest for this study include the following:

The following will be considered AESI for this study:

- Grade ≥2 infusion related reactions
- Grade ≥2 allergic/hypersensitivity reactions
- Grade ≥3 imAEs (see Section 10.1.3.1)
- An imAE of any grade in a patient previously treated with a PI 3-K inhibitor

NOTE (Applicable to cemiplimab only): An imAE can occur shortly after the first dose or several months after the last dose of treatment. 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.

10.1.3.1. Immune-Mediated Adverse Events

Detailed guidance of management of imAEs is provided in Section 8.2.3 and Appendix 2.

NOTE: Regarding imAEs, for any AE that is of a type known to be potentially immune-related (eg rash, colitis, elevated transaminases, or endocrine) but is deemed not to be an imAE by the investigator, the sponsor may request additional information.

10.1.4. Reporting Adverse Events Leading to Withdrawal from the Study

All AEs that lead to a patient's withdrawal from the study must be reported to the sponsor's medical monitor within 30 days.

10.1.5. Abnormal Laboratory, Vital Signs, or Electrocardiogram Results

The criteria for determining whether an abnormal objective test finding should be reported as an AE include:

- The test result is associated with accompanying symptoms, and/or

- The test result requires additional diagnostic testing or medical/surgical intervention, and/or
- The test result leads to a change in dosing (outside of protocol-stipulated dose adjustments), discontinuation from the study, significant additional concomitant drug treatment, or other therapy

Contact the medical monitor in the event the investigator feels that an abnormal test finding should be reported as an AE, although it does not meet any of the above criteria.

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

Evaluation of severity of laboratory abnormalities will be assessed according to the scale outlined in Section 10.2.5.

10.2. Definitions

10.2.1. Adverse Event

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 (ICH, Oct 1994).

10.2.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in **death** – includes all deaths, even those that appear to be completely unrelated to study drug (eg, a car accident in which a patient is a passenger).
- Is **life-threatening** – in the view of the investigator, the patient is at immediate risk of death at the time of the event. This does not include an AE that had it occurred in a more severe form, might have caused death.
- Requires in-patient **hospitalization** or **prolongation of existing hospitalization**. In-patient hospitalization is defined as a hospital admission (any duration) or an emergency room visit for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than was originally anticipated for the event or is prolonged due to the development of a new AE as determined by the investigator or treating physician.
- Results in persistent or significant **disability/incapacity** (substantial disruption of one's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**
- Is an **important medical event** - Important medical events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or

may require intervention to prevent one of the other serious outcomes listed above (eg, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse).

Hospitalization or death due solely to manifestations consistent with typical progression of underlying malignancy will not be considered an SAE.

Criteria for reporting SAEs must be followed for these events.

10.2.3. Adverse Events of Special Interest

An 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 can be appropriate. Such an event might warrant further investigation in order to characterize and understand it.

10.2.4. Infusion Reactions

Infusion reactions are defined as any relevant AE that occurs during the infusion or within 24 hours after the infusion is completed.

All infusion reactions must be reported as AEs (defined in Section 10.2.1) and graded using the grading scales as instructed in Section 10.2.5.

10.2.5. Severity

The severity of AEs, infusion reactions, and injection site reactions will be graded using the NCI-CTCAE v5.0 grading system. 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.

10.2.6. Causality

The investigator must provide causality assessment as whether or not there is a reasonable possibility that the drug caused the adverse event, based on evidence or facts, his/her clinical

judgment, and the following definitions. The causality assessment must be made based on the available information and can be updated as new information becomes available.

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 reduction
- 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.

10.3. Safety Monitoring

The investigator will monitor the safety of study patient at his/her site(s) as per the requirements of this protocol and consistent with current Good Clinical Practice (GCP). Any questions or concerns should be discussed with the sponsor in a timely fashion. The sponsor will monitor the safety data from across all study sites. The Medical/Study Director will have primary responsibility for the emerging safety profile of the compound, but will be supported by other departments (eg, Pharmacovigilance; Risk Management; Biostatistics and Data Management). Safety monitoring will be performed on an ongoing basis (eg, individual review of SAEs) and on a periodic cumulative aggregate basis.

10.4. Notifying Health Authorities, Institutional Review Board/Ethics Committee, and Investigators

During the study, the sponsor and/or the 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 (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 masked 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.

Event expectedness for study drug (cemiplimab) is assessed against the Reference Safety Information section of the most recently approved version of the Investigator's Brochure that is effective for expedited safety reporting.

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.

11. STATISTICAL PLAN

This section provides the basis for the statistical analysis plan (SAP) for the study. The SAP will be revised prior to the database lock 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.

Endpoints are listed in Section 4. Analysis variables are listed in Section 5.

Data collected regarding the impact of the COVID-19 pandemic on the patients will be summarized (eg, discontinuation due to COVID-19). Any additional analyses and methods required to investigate the impact of COVID-19 on the efficacy (eg, missing data due to COVID-19) and safety evaluation will be specified in the SAP.

11.1. Statistical Hypothesis

This is a single arm, open label study and there is no formal statistical hypothesis in this study.

11.2. Justification of Sample Size

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). With 105 patients, Table 3 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. If observed ORR ranges from 20.0% to 34.3%, the precision estimation using 105 patients ranges from 7.7% to 9.1%.

Table 3: 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%

11.3. Analysis Sets

11.3.1. Full Analysis Set

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.

11.3.2. Pharmacokinetic Analysis Sets

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

11.3.3. Immunogenicity Analysis Sets

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

11.4. Statistical Methods

In general, the descriptive summary for continuous variables will include the number of observation(n), mean, standard deviation (SD), Q1, median, Q3, minimum, and maximum.

For categorical or ordinal data, frequencies and percentages will be displayed for each category.

For time to event data, the descriptive summary will include the median time-to event and its 95% confidence interval using the Kaplan-Meier method.

11.4.1. Patient Disposition

The following will be provided:

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

11.4.2. Demography and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively.

11.4.3. Efficacy Analyses

In order to describe ORR, the interim data cutoff for efficacy analysis will be after the 53rd patient enrolled has had an opportunity for 4 tumor assessments.

The final data cutoff for efficacy analysis will be when the last patient enrolled has had the opportunity for 4 tumor assessments.

11.4.3.1. Primary Efficacy Analysis

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

The primary endpoint for efficacy analyses is the investigator-assessed ORR as determined by RECIST version 1.1 (Eisenhauer, 2009). The ORR is defined as the proportion of patients who achieve a best overall response (BOR) of CR or PR. Patients who are not evaluable for BOR will

be considered as non-responders. The ORR along with the 2-sided 95% confidence interval using a normal approximation of the binomial distribution will be summarized.

11.4.3.2. Secondary Efficacy Analysis

The secondary efficacy endpoints as measured by DOR, PFS, and OS will be summarized by median and its 95% confidence interval using the Kaplan-Meier method.

11.4.4. Control of Multiplicity

This a single arm, open label, and observational study. Multiplicity control is not applicable.

11.4.5. Safety Analysis

Treatment-emergent AEs/AESIs/SAEs and grade 3 or greater laboratory abnormalities will be summarized using descriptive statistics.

11.4.5.1. Adverse Events

Definitions

For safety variables, 3 observation periods are defined:

- 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 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.

Treatment-emergent adverse events are defined as those that are not present at baseline or represent the exacerbation of a pre-existing condition during the on-treatment period.

Analysis

All AEs reported in this study will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®).

Summaries of all TEAEs by treatment group will include:

- The number (n) and percentage (%) of patients with at least 1 TEAE by SOC and PT
- TEAEs by severity (NCI-CTCAE, version 5.0 grade), presented by SOC and PT
- Treatment-related TEAEs, presented by SOC and PT
- Treatment-emergent AESIs (defined with a PT or a prespecified grouping)

11.4.5.2. Deaths, other SAEs, and TEAEs leading to permanent treatment discontinuation will be summarized.Other Safety

Vital Signs

Vital signs (temperature, pulse, blood pressure, and respiration rate) will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

Laboratory Tests

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

Number and percentage of patients with a potentially clinically significant value (PCSV) will be summarized for each clinical laboratory test.

Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for laboratory tests of interest.

11.4.5.3. Treatment Exposure

Duration of exposure, number of doses administered, and dose intensity will be summarized.

11.4.5.4. Treatment Compliance

Patients will be administered study drug, and treatment compliance will be defined in detail in the SAP.

11.4.6. Pharmacokinetics

11.4.6.1. Analysis of Drug Concentration Data

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.

The concentrations of total cemiplimab over time will be summarized by descriptive statistics.

No formal statistical hypothesis testing will be performed.

11.4.7. Analysis of Pharmacodynamic and 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.

11.4.8. Analysis of Immunogenicity Data

Immunogenicity for cemiplimab will be characterized by the ADA response observed:

- ADA negative, defined as ADA negative response in the ADA assay for all time points regardless of any missing samples
- Pre-existing immunoreactivity, defined as a positive ADA assay response 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 ADA assay response when the baseline results are negative
  - Treatment-emergent ADA response may be further characterized as persistent, transient, or indeterminate.
- Treatment-boosted ADA response, defined as any post-dose positive ADA assay response 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 ADA will be assessed as absolute occurrence (N) and percent of patients (%), grouped by study cohorts and ADA titer level.

Plots of drug concentrations will be examined and the influence of ADAs on individual PK profiles evaluated. Assessment of impact of ADA on safety and efficacy may be provided.

11.5. Interim Analysis

There will be no formal interim analysis in this study.

11.6. Statistical Considerations Surrounding the Premature Termination of a Study

If the study is terminated prematurely, only those parameters required for the development program and/or reporting to regulatory authorities will be summarized. Investigator and sponsor responsibilities surrounding the premature termination of a study are presented in Section 15.1.

12. QUALITY CONTROL AND QUALITY ASSURANCE

In accordance with ICH E6, the sponsor is responsible for quality assurance to ensure that the study is conducted and the data generated, recorded, and reported in compliance with the protocol, GCP, and any applicable regulatory requirement(s). The planned quality assurance and quality control procedures for the study are described in this section.

12.1. Data Management and Electronic Systems

12.1.1. Data Management

A data management plan specifying all relevant aspects of data processing for the study (including data validation [quality-checking], cleaning, correcting, releasing) will be maintained and stored at the sponsor.

A medical coding plan will specify the processes and the dictionary used for coding. All data coding (eg, AEs, baseline findings, medication, medical history) will be done using internationally recognized and accepted dictionaries.

The CRF data for this study will be collected with an EDC.

12.1.2. Electronic Systems

Electronic systems that may be used to process and/or collect data in this study will include the following:

- Interactive Response Technology (IRT)/IVRS/IWRS system –study drug supply
- EDC system – data capture – Medidata Rave
- Statistical Analysis System (SAS) – statistical review and analysis
- Pharmacovigilance safety database

12.2. Study Monitoring

12.2.1. Monitoring of Study Sites

The study monitor and/or designee (eg, contract research organization [CRO] monitor) will visit each site prior to enrollment of the first patient, and periodically during the study. This study will use the principles of risk-based monitoring (ICH). This means that the number of visits for any given site may vary based on site risk indicators. The investigator must allow study-related monitoring.

The study monitors will perform ongoing source data review to verify that data recorded in the CRF by authorized site personnel are accurate, complete, and verifiable from source documents, that the safety and rights of patients are being protected, and that the study is being conducted in accordance with the current approved protocol version and any other study agreements, ICH GCP, and all applicable regulatory requirements.

12.2.2. Source Document Requirements

Investigators are required to prepare and maintain adequate and accurate patient records (source documents). The site is responsible to ensure quality within their records and systems and are accountable for ensuring that all source data and CRF data are timely, accurate and complete.

The investigator must keep all source documents on file with the CRF (throughout this protocol, CRF refers to either a paper CRF or an electronic CRF). Case report forms and source documents must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

12.2.3. Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded on electronic Case Report Forms (CRFs) within the EDC system by trained site personnel. All required CRFs must be completed for each and every patient enrolled in the study. The investigator must ensure the accuracy, completeness, and timeliness of the data reported to the sponsor in the CRFs. After review of the clinical data for each patient, the investigator must provide an electronic signature. A copy of each patient CRF casebook is to be retained by the investigator as part of the study record and must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

Corrections to the CRF will be entered in the CRF by the investigator or an authorized designee. All changes, including date and person performing corrections, will be available via the audit trail, which is part of the EDC system. For corrections made via data queries, a reason for any alteration must be provided.

12.3. Audits and Inspections

This study may be subject to a quality assurance audit or inspection by the sponsor or regulatory authorities. Should this occur, the investigator is responsible for:

- Informing the sponsor of a planned inspection by the authorities as soon as notification is received, and authorizing the sponsor's participation in the inspection
- Providing access to all necessary facilities, study data, and documents for the inspection or audit
- Communicating any information arising from inspection by the regulatory authorities to the sponsor immediately
- Taking all appropriate measures requested by the sponsor to resolve the problems found during the audit or inspection

Documents subject to audit or inspection include but are not limited to all source documents, CRFs, medical records, correspondence, ICFs, IRB/EC files, documentation of certification and quality control of supporting laboratories, and records relevant to the study maintained in any supporting pharmacy facilities. Conditions of study material storage are also subject to inspection. In addition, representatives of the sponsor may observe the conduct of any aspect of the clinical study or its supporting activities both within and outside of the investigator's institution.

In all instances, the confidentiality of the data must be respected.

12.4. Study Documentation

12.4.1. Certification of Accuracy of Data

A declaration assuring the accuracy and content of the data recorded on the eCRF must be signed electronically by the investigator. This signed declaration accompanies each set of patient final eCRFs that will be provided to the sponsor.

12.4.2. Retention of Records

The investigator must retain all essential study documents, including ICFs, source documents, investigator copies of CRFs, and drug accountability records for at least 15 years following the completion or discontinuation of the study, or longer, if a longer period is required by relevant regulatory authorities. The investigator must obtain written approval from the sponsor before discarding or destroying any essential study documents during the retention period following study completion or discontinuation. Records must be destroyed in a manner that ensures confidentiality.

If the investigator's personal situation is such that archiving can no longer be ensured, the investigator must inform the sponsor (written notification) and the relevant records will be transferred to a mutually agreed-upon destination.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice Statement

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.

13.2. Informed Consent

The principles of informed consent are described in ICH guidelines for GCP.

The ICF used by the investigator must be reviewed and approved by the sponsor prior to submission to the appropriate IRB/EC. A copy of the IRB/EC-approved ICF and documentation of approval must be provided to the sponsor before study drug will be shipped to the study site.

It is the responsibility of the investigator or designee (if acceptable by local regulations) to obtain written informed consent from each patient prior to his/her participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the patient in language that he/she can understand. The ICF should be signed and dated by the patient and by the investigator or authorized designee who reviewed the ICF with the patient.

- Patients who can write but cannot read will have the ICF read to them before signing and dating the ICF.
- Patients who can understand but who can neither write nor read will have the ICF read to them in presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given.

The original ICF must be retained by the investigator as part of the patient's study record, and a copy of the signed ICF must be given to the patient.

If new safety information results in significant changes in the risk/benefit assessment, or if there are significant changes to the study procedures, the ICF must be reviewed and updated appropriately. All study patients must be informed of the new information and provide their written consent if they wish to continue in the study. The original signed revised ICF must be maintained in the patient's study record and a copy must be given to the patient.

13.3. Patients Confidentiality and Data Protection

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

The patient'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.

13.4. Institutional Review Board/Ethics Committee

An appropriately constituted IRB/EC, as described in ICH guidelines for GCP, must review and approve:

- The protocol, ICF, and any other materials to be provided to the patients (eg, advertising) before any patient may be enrolled in the study
- Any amendment or modification to the study protocol or ICF before implementation, unless the change is necessary to eliminate an immediate hazard to the patient, in which case the IRB/EC should be informed as soon as possible
- Ongoing studies on an annual basis or at intervals appropriate to the degree of risk

In addition, the IRB/EC should be informed of any event likely to affect the safety of patients or the continued conduct of the clinical study.

A copy of the IRB/EC approval letter with a current list of the IRB/EC members and their functions must be received by the sponsor prior to shipment of drug supplies to the investigator. The approval letter should include the study number and title, the documents reviewed, and the date of the review.

Records of the IRB/EC review and approval of all study documents (including approval of ongoing studies) must be kept on file by the investigator.

13.5. Clinical Study Data Transparency

Final study results will be published on a public clinical trial website according to applicable local guidelines and regulations. Treatment codes will be disseminated to each investigation site thereafter.

14. PROTOCOL AMENDMENTS

The sponsor may not implement a change in the design of the protocol or ICF without an IRB/EC-approved amendment. Where required per local legislation, regulatory authority approval will also be sought.

15. PREMATURE TERMINATION OF THE STUDY OR CLOSE-OUT OF A SITE

15.1. Premature Termination of the Study

The sponsor has the right to terminate the study prematurely. Reasons may include efficacy, safety, or futility, among others. Should the sponsor decide to terminate the study, the investigator(s) will be notified in writing.

15.2. Close-out of a Site

The sponsor and the investigator have the right to close-out a site prematurely.

Investigator's Decision

The investigator must notify the sponsor of a desire to close-out a site in writing, providing at least 30 days' notice. The final decision should be made through mutual agreement with the sponsor. Both parties will arrange the close-out procedures after review and consultation.

Sponsor's Decision

The sponsor will notify the investigator(s) of a decision to close-out a study site in writing. Reasons may include the following, among others:

- The investigator has received all items and information necessary to perform the study, but has not enrolled any patient within a reasonable period of time
- The investigator has violated any fundamental obligation in the study agreement, including but not limited to, breach of this protocol (and any applicable amendments), breach of the applicable laws and regulations, or breach of any applicable ICH guidelines
- The total number of patients required for the study are enrolled earlier than expected

In all cases, the appropriate IRB/EC and Health Authorities must be informed according to applicable regulatory requirements, and adequate consideration must be given to the protection of the patients' interests.

16. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

17. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

18. PUBLICATION POLICY

Publication rights and procedures will be outlined in a separate clinical study agreement.

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20. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: 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 and agree to abide by all provisions set forth therein.

I agree to comply with the current International Council for Harmonisation Guideline for Good Clinical Practice and the laws, rules, regulations, and guidelines of the community, country, state, or locality relating to the conduct of the clinical study.

I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the sponsor or a partnership in which the sponsor is involved. I will immediately disclose it in writing to the sponsor if any person who is involved in the study is debarred, or if any proceeding for debarment is pending, or, to the best of my knowledge, threatened.

This document contains confidential information of the sponsor, which must not be disclosed to anyone other than the recipient study staff and members of the IRB/EC. I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the sponsor.

_____ _____

(Signature of Investigator) (Date)

_____

(Printed Name)

APPENDIX 1. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

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, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: (Oken, 1982)

APPENDIX 2. GUIDELINES FOR MANAGEMENT OF IMMUNE-MEDIATED ADVERSE EVENTS

Select immune-mediated adverse events (imAEs) and their management are described in this appendix. Additionally, the following general principles apply to management of imAEs, if not described in detail in this appendix:

Grade 1: Continue study treatment with close monitoring and provide symptomatic management.

Grade 2: Consider withholding study treatment

Grade 3: Withhold study treatment

Grade 4: Discontinue study treatment.

Temporary hold and resumption. Except as described for select imAEs, if cemiplimab is withheld for grade ≤3 imAE, consider resuming when the imAE improves to grade 0 or 1 after corticosteroid taper to ≤ prednisone 10 mg/day or equivalent.

Permanent discontinuation. Except as described for select imAEs, give an initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper and permanently discontinue study treatment for:

- Grade 4 adverse reactions (excluding endocrinopathies)
- Recurrent Grade 3 imAEs
- Grade 2 or 3 imAEs persistent for ≥12 weeks after the last study treatment
- Requirement for ≥10 mg per day prednisone or equivalent lasting ≥12 weeks after the last study treatment.

For guidance in addition to that provided here, please refer to regional imAE management guidelines, such as those provided by NCCN or ESMO. In countries where cemiplimab has a marketing authorization the local product information may be consulted. Note that local and regional treatment guidelines and cemiplimab product information may be updated periodically and the latest version should always be reviewed.

Recommended Adverse Event Management for Colitis/Diarrhea

CTCAE v5.0 Grade	Study Treatment Management	Action & Supportive Care Guidelines	Diagnostic Considerations
Grade 1 • **Colitis**: Asymptomatic; clinical or diagnostic observations only; intervention not indicated • **Diarrhea**: Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	• No change	• Treat symptomatically (loperamide, oral hydration, electrolyte substitution and American Dietic Association colitis diet) • Consider consultation with gastroenterologist for prolonged symptoms • If symptoms are persistent, consider endoscopic evaluation • If persists for >2 weeks, treat as grade 2	• All attempts should be made to rule out other causes such as metastatic disease, bacterial or parasitic infection, or

CTCAE v5.0 Grade	Study Treatment Management	Action & Supportive Care Guidelines	Diagnostic Considerations
Grade 2 • **Colitis**: Abdominal pain; mucus or blood in stool • **Diarrhea**: Increase of 4 to 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL	• Withhold study treatment until colitis or diarrhea improves and remains at grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent	• Treat symptomatically (loperamide, oral hydration, electrolyte substitution and American Dietetic Association colitis diet) • Consultation with gastroenterologist • Consider colonoscopy ± esophagogastroduodenoscopy (EGD), or endoscopy • Consider stool evaluation to rule out infectious etiology • Consider stool inflammatory marker evaluation (ie, lactoferrin and calprotectin) to differentiate functional vs. inflammatory diarrhea • Consider abdominal and pelvic CT with contrast • Treatment with systemic corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) until resolution to grade ≤1 and taper over at least a month • If no improvement within 2 to 3 days, treat as grade 3	viral gastroenteritis

CTCAE v5.0 Grade	Study Treatment Management	Action & Supportive Care Guidelines	Diagnostic Considerations
Grade 3 • **Colitis:** Severe abdominal pain; peritoneal signs • **Diarrhea**: Increase of ≥7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting selfcare ADL	• Withhold study treatment until colitis or diarrhea improves and remains at grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent • Permanently discontinue study treatment if patient develops a second episode of grade 3 colitis or diarrhea upon re-challenge	• Treat symptomatically (loperamide, oral hydration, electrolyte substitution and American Dietetic Association colitis diet) • Consultation with gastroenterologist • Consider colonoscopy ± esophagogastroduodenoscopy (EGD), or endoscopy • Consider stool evaluation to rule out infectious etiology • Consider stool inflammatory marker evaluation (ie, lactoferrin and calprotectin) to differentiate functional vs. inflammatory diarrhea • Consider abdominal and pelvic CT with contrast • Inpatient care for close monitoring and supportive care • Treatment with systemic corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) until resolution to grade ≤1 and taper over at least 1 month • If no improvement with corticosteroid within 2 to 3 days, consider additional immunosuppressive therapy ie, mycophenolate 0.5 to 1g BID, infliximab 5 mg/kg IV	
Grade 4 or Recurrent Grade 3 • **Colitis**: Life-threatening consequences: urgent intervention indicated • **Diarrhea**: Life-threatening consequences; urgent intervention indicated	• Permanently discontinue study treatment	• Same as above • Consider lower GI endoscopy if symptoms are refractory despite treatment or there is concern of new infections	

Recommended Adverse Events Management for Dermatologic Toxicities

Immune-related skin toxicities include maculopapular rash, dermatitis, rash generalized, dermatitis bullous, drug eruption, erythema, rash erythematous, rash macular, rash pruritic, and skin reaction. **Guidance here is provided for maculopapular rash**. For other immune-related skin toxicities, see expert consensus guidelines cited in Section 8.3.

CTCAE v5.0 Grade	Study Treatment Management	Action & Supportive Care Guidelines	Diagnostic Considerations
Grade 1 or **Grade 2** lasting 1 week or less	• No change	• Treatment with mild to moderate potency topical steroids • Treatment with oral antihistamine	• All attempts should be made to rule out other causes such as metastatic disease, infection, contact dermatitis, effect of another drug, or a skin condition linked to another systemic disease
Grade 2 lasting longer than 1 week or **Grade 3** or **Suspected Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or Drug rash with eosinophilia and systemic symptoms (DRESS)**	• Withhold study treatment until skin reaction improves and remains at grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent	• Consider consultation with dermatologist and skin biopsy for diagnosis of bullous dermatitis • Treatment with systemic corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) until resolution to ≤ grade 1 and taper over at least one month • Consider treatment with medium to high potency topical steroids • Treatment with oral antihistamine	
Grade 4 or **Confirmed SJS, TEN, or DRESS**	• Permanently discontinue study treatment	• Consultation with dermatologist and skin biopsy • Treatment with high potency topical steroids and with systemic corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) until resolution to ≤ grade 1 and taper over at least one month	

Immune-Mediated Skin Adverse Reactions or other Immune-Related Adverse Reactions in Patients with Prior Treatment with Idelalisib CTCAE v5.0 Grade	**Study Treatment Management**	**Action & Supportive Care Guidelines**	**Diagnostic Considerations**
Grade 1	• No change	• Treatment as clinically indicated	• All attempts should be made to rule out other causes such as metastatic disease, infection, contact dermatitis, effect of another drug, or a skin condition linked to another systemic disease
Grade 2	• Withhold study treatment until skin reaction or other immune-related adverse reaction improves and remains at grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent	• Consider consultation with dermatologist and skin biopsy for diagnosis of bullous dermatitis • Immediate symptom management, including systemic corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) until resolution to ≤ grade 1 and taper over at least one month • Consider treatment with medium to high potency topical steroids and/or oral antihistamine for skin reactions	
Grade 3 or 4 (excluding endocrinopathies) or **Recurrent Grade 2**	• Permanently discontinue study treatment	• Consultation with dermatologist and skin biopsy for skin reactions • Treatment with high potency topical steroids if skin reaction • Treatment with systemic corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) until resolution to ≤ grade 1 and taper over at least one month	

Recommended Adverse Events Management for Endocrine Events: Hypothyroidism

CTCAE v5.0 Grade	Study Treatment Management	Action & Supportive Care Guidelines	Diagnostic Considerations
Grade 1	• No change	• Monitor thyroid function more frequently (every 3 to 6 weeks) until resolution to baseline • There should be low index of suspicion for immune-related endocrinopathy including checking TSH, T4, cortisol and adrenocorticotropic hormone levels if clinically appropriate	• Immune-related endocrinopathies can have subtle and wide-ranging presentations. Please refer to expert panel consensus guidance documents for further guidance • All attempts should be made to rule out other causes such as brain metastases, sepsis, and/or infection
Grade 2	• Withhold study treatment if clinically necessary	• Consult with endocrinologist and provide supportive care per institutional guidelines • Replacement of thyroid hormone as indicated	
Grade 3 or 4	• Withhold study treatment until hypothyroidism improves and remains at grade 0 to 1 or is otherwise clinically stable	• Consult with endocrinologist and provide supportive care per institutional guidelines • Replacement of thyroid hormone as indicated	

Recommended Adverse Events Management for Endocrine Events: Hyperthyroidism

CTCAE v5.0 Grade	Study Treatment Management	Action & Supportive Care Guidelines	Diagnostic Considerations
Grade 1	• No change	• Monitor thyroid function more frequently (every 2 to 3 weeks) until resolution to baseline • There should be low index of suspicion for immune-related endocrinopathy including checking TSH, T4, cortisol and adrenocorticotropic hormone levels if clinically appropriate	• Immune-related endocrinopathies can have subtle and wide-ranging presentations. Please refer to expert panel consensus guidance documents for further guidance • All attempts should be made to rule out other causes such as brain metastases, sepsis, and/or infection
Grade 2	• Withhold study treatment if clinically necessary	• Same as above • Consult with endocrinologist and provide supportive care per institutional guidelines • Consider β-blocker for symptomatic relief • For persistent hyperthyroidism (> 6weeks), consider work up for Graves disease and refer to endocrinology for Graves disease	
Grade 3 or 4	• Withhold study treatment until hyperthyroidism improves and remains at grade 0 to 1 or is otherwise clinically stable	• Same as above • For severe symptoms, inpatient care and consider systemic corticosteroids treatment (1 to 2 mg/kg/day prednisone or equivalent) until resolution to ≤ grade 1 and taper over 1 to 2 weeks in consultation with endocrinology • Consider use of saturated solution of potassium iodide (SSKI) or thionamide	

Recommended Adverse Events Management for Endocrine Events: Hypophysitis or Adrenal Insufficiency

CTCAE v5 Grade	Study Treatment Management	Action & Supportive Care Guidelines	Diagnostic Considerations
Grade 1	• No change	• There should be low index of suspicion for immune-related endocrinopathy including checking TSH, T4, cortisol and adrenocorticotropic hormone levels if clinically appropriate	• Immune related endocrinopathies can have subtle and wide-ranging presentations. Please refer to expert panel consensus guidance documents for further guidance • All attempts should be made to rule out other causes such as brain metastases, sepsis, and/or infection
Grades 2 to 4	• Withhold study treatment until hypophysitis or 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	• Consult with endocrinologist and provide supportive care per institutional guidelines • Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper • Replacement of relevant hormone(s) as indicated	

Recommended Adverse Events Management for Endocrine Events: Type I Diabetes Mellitus

CTCAE v5.0 Grade	Study Treatment Management	Action & Supportive Care Guidelines	Diagnostic Considerations
Grade 1	• No change	• Monitor glucose level more frequently until resolution to baseline • There should be low index of suspicion for immune-related endocrinopathy including checking TSH, T4, cortisol and adrenocorticotropic hormone levels if clinically appropriate	• Immune related endocrinopathies can have subtle and wide-ranging presentations. Please refer to expert panel consensus guidance documents for further guidance • All attempts should be made to rule out other causes such as brain metastases, sepsis, and/or infection
Grade 2	• Withhold study treatment if clinically necessary until glucose control is obtained	• Same as above • Consult with endocrinologist and provide supportive care per institutional guidelines	
Grade 3 or 4 (hyperglycemia)	• Withhold study treatment until diabetes mellitus returns to grade 0 to 1 or is otherwise clinically stable	• Consult with endocrinologist and provide supportive care per institutional guidelines • Initiate treatment with anti-hyperglycemics as clinically indicated	

Recommended Adverse Events Management for Hepatitis

CTCAE v5.0 Grade	Study Treatment Management	Action & Supportive Care Guidelines	Diagnostic Considerations
Grade 1	• No change	• Monitor liver function tests (LFT) more frequently until resolution to baseline values	• All attempts should be made to rule out other causes such as metastatic disease, progressive liver disease, viral hepatitis, alternative drug toxicity, infectious causes and/or myositis
Grade 2 with: Elevated ALT & AST >3 and ≤5x ULN Or total bilirubin >1.5x and ≤3x ULN	• Withhold study treatment until 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	• Monitor LFT more frequently until resolution to baseline values • Consider appropriate consultation with hepatologist and liver biopsy to establish etiology of hepatic injury, if necessary • Consider inpatient monitoring for patients with ALT/AST >8x ULN and or elevated total bilirubin >3x ULN • Treatment with systemic corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) until resolution to ≤ grade 1 and taper over at least 1 month • If no improvement within 3 days after initiation of systemic steroids, consider additional immunosuppressive therapy ie, mycophenolate mofetil 0.5 to 1 g BID • Several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased	
Grade 3 or 4 with: Elevated ALT & AST >5x ULN or total bilirubin >3x ULN	• Permanently discontinue study treatment	• Same as above	

Recommended Adverse Events Management for Neurotoxicity

CTCAE v5.0 Grade	Study Treatment Management	Action & Supportive Care Guidelines	Diagnostic Considerations
Grade 1	• No change	• Closely monitor the patient • If worsening, treat as grade 2 or 3 to 4, as clinically appropriate	• If immune-mediated encephalitis is suspected, consider radiologic assessment and, if possible, cerebrospinal fluid (CSF) assessment for auto-immune antibodies
Grade 2	• Withhold study treatment until improves and remains at grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent	• Treat symptoms per local guidelines, eg 0.5 to 1 mg/kg/day methylprednisolone IV or oral (PO) equivalent • If worsening, treat as grades 3 to 4 • Consider neurology consult	
Grade 3 or 4	• Permanently discontinue study treatment	• Neurology consult required • Treat symptoms per local guidelines AND give 1 to 2 mg/kg/day methylprednisolone IV • If improves to grade 2: taper with corticosteroids over at least 4 weeks • Consider adding prophylactic antibiotics for opportunistic infections • If worsening or atypical presentation, consider intravenous immunoglobulin (IVIG) or other immunosuppressive therapies per local guidelines	

Recommended Adverse Events Management for Pneumonitis

CTCAE v5.0 Grade	Study Treatment Management	Action & Supportive Care Guidelines	Diagnostic Considerations
Grade 1 Asymptomatic; clinical or diagnostic observations only; intervention not indicated	• Consider withholding study treatment	• Monitor symptoms every 2 to 3 days • Consider consultation with pulmonologist • Consider chest imaging (chest CT or chest x-ray) followed by serial imaging at least every 3 weeks to monitor resolution or progression • May resume study treatment upon improvement or resolution. If no improvement, treat as grade 2	• All attempts should be made to rule out other causes such as metastatic disease, bacterial or viral infection
Grade 2 Symptomatic; medical intervention indicated; limiting instrumental ADL	• Withhold study treatment until pneumonitis improves and remains at grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent • Permanently discontinue study treatment if patient develops a second episode of ≥ grade 2 pneumonitis upon re-challenge	• Monitor symptoms daily; consider hospitalization • Consider consultation with pulmonologist • Consider chest imaging (chest CT or chest x-ray) followed by serial imaging at least every 3 weeks to monitor resolution or progression • Consider bronchoscopy with bronchoalveolar lavage (BAL) to rule out infection and malignant lung infiltration • Consider pulmonary function tests and laboratory work up for infections • Treatment with systemic corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) until resolution to ≤ grade 1 and taper over at least a month • If symptoms do not improve within 48 to 72 hours of corticosteroid treatment, treat as grade 3 • Consider empiric antibiotics if infection has not yet been fully excluded	

CTCAE v5.0 Grade	Study Treatment Management	Action & Supportive Care Guidelines	Diagnostic Considerations
Grade 3 or 4 or Recurrent Grade 2 **Grade 3:** Severe symptoms; limiting selfcare ADL; oxygen indicated **Grade 4:** Life-threatening respiratory compromise; urgent intervention indicated (eg, tracheotomy or intubation)	• Permanently discontinue study treatment	• Inpatient care • Consultation with pulmonologist and infectious disease specialties • Treatment with systemic corticosteroids (2 to 4 mg/kg/day prednisone or equivalent) until resolution to ≤ grade 1 and taper over at least 6 weeks • If symptoms do not improve within 48 to 72 hours of corticosteroid treatment, consider additional immunosuppressive treatment ie, mycophenolate mofetil 1 to 1.5 g BID, infliximab 5 mg/kg IV • If symptoms worsen during steroid reduction, initiate a re-tapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper • Consider bronchoscopy with bronchoalveolar lavage (BAL) to rule out infection and malignant lung infiltration • Empiric antibiotics if infection has not yet been fully excluded • Consider adding prophylactic antibiotics for opportunistic infections	

Recommended Adverse Events Management for Renal Events

Immune-Mediated Nephritis with renal dysfunction CTCAE v5 Grade	Study Treatment Management	Action & Supportive Care Guidelines	Diagnostic Considerations
Grade 1	• No change	• Provide symptomatic treatment. • Monitor creatinine weekly; when it returns to baseline, resume routine creatinine monitoring per protocol	• All attempts should be made to rule out other causes such as obstructive uropathy, progression of disease, or injury to other chemotherapy agents
Grade 2 **Blood creatine increased > 1.5 to 3.0 X baseline or ULN**	• Withhold study treatment until nephritis improves and remains at grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent	• Consultation with nephrologist • Treatment with systemic corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) until resolution to ≤ grade 1 and taper over at least a month • Consider prophylactic antibiotics for opportunistic infections • Consider renal biopsy • If elevations persist >7 days or worsen, treat as severe AE	
Grade 3 **Blood creatinine increased > 3.0 X baseline or > 3.0 to 6.0 x ULN** **Grade 4** **Blood creatine increased > 6.0 X ULN**	• Permanently discontinue study treatment	• Consultation with nephrologist in consideration of ultrasound and/or biopsy as appropriate • Consider inpatient care and monitor creatinine daily • Treatment with systemic corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) until resolution to ≤ grade 1 and taper over at least a month • If no improvement within 7 days after initiation of systemic steroids, consider additional immunosuppressive therapy ie, mycophenolate mofetil 0.5 to 1 g BID	

Recommended Adverse Events Management for Uveitis

CTCAE v5.0 Grade	Study Treatment Management	Action & Supportive Care Guidelines	Diagnostic Considerations
Grade 1	• No change	• Consultation with ophthalmologist within 1 week • Treatment with artificial tears	• All attempts should be made to rule out other causes such as metastatic disease, infection, or other ocular disease (eg, glaucoma or cataracts)
Grade 2	• Withhold study treatment	• Urgent consultation with ophthalmologist • Treatment with topical/periocular/intravitreal corticosteroids and/or systemic corticosteroids guided by ophthalmologist • May resume study treatment if resolved to ≤ grade 1 and systemic steroid is reduced to ≤10 mg. Topical/ocular steroids are permitted during study treatment	
Grade 3 or 4	• Permanently discontinue study treatment	• Same as above • If severe or refractory to steroid treatment, consider infliximab	

Recommended Adverse Events Management for Myocarditis or Pericarditis

CTCAE v5.0 Grade	Study Treatment Management	Action & Supportive Care Guidelines	Diagnostic Considerations
Grade 1 or 2	• Consider withholding study treatment	• Immediate consultation with cardiologist • Inpatient care • Consider ECG, telemetry monitoring, cardiac MRI • Consider cardiac biomarker assessment (creatine kinase and troponin) or inflammatory biomarkers (ESR, CRP, WBC count, etc) • May offer immediate transfer to a coronary care unit for patient with elevated troponin or conduction abnormalities • Treatment with systemic corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) initiated rapidly (oral or IV depending on symptoms) until resolution to baseline and taper over 4 to 6 weeks • Manage cardiac symptoms according to American College of Cardiology (ACC)/AHA guidelines and with guidance from cardiology	• All attempts should be made to rule out other causes such as metastatic disease and viral infection
Grade 3 or 4	• Permanently discontinue study treatment	• Same as above • Consider 1 g methylprednisolone pulse dose • If severe or refractory to steroid treatment, consider additional immunosuppressive agents	

APPENDIX 3. RESPONSE EVALUATION CRITERIA IN SOLID TUMORS: RECIST GUIDELINE (VERSION 1.1)

This appendix has been excerpted from the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1); (Eisenhauer, 2009). For full details pertaining to the RECIST 1.1 criteria, please refer to the publication.

1. Assessment of Tumor Burden Measurable Disease at Baseline

Overall tumor burden must be assessed at baseline and will be used as comparator for subsequent measurements. Tumor lesions will be characterized as measurable or non-measurable as follows:

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 shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

1.1. Measurable disease

- Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of
  - 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (slice thickness recommended to be no greater than 5 mm)
  - 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- **Malignant lymph nodes:** To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT or MRI scan (slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

1.2. Nonmeasurable Disease

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered nonmeasurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT, MRI, or PET) are considered nonmeasurable.

1.2.1. Special Considerations

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT

or MRI can be considered measurable lesions if the soft tissue component meets the definition of measurability described above.

- Blastic bone lesions are non-measurable.

Cystic lesions:

Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor nonmeasurable) since they are, by definition, simple cysts. "Cystic lesions" thought to represent cystic metastases can be considered 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.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other locoregional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

1.3. Methods of Assessment

All measurements must be recorded in metric notation, using calipers if clinically assessed. 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.

- **CT and MRI**. CT is the best currently available and reproducible method to measure lesions selected for tumor assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable for body scans except chest. MRI is preferred for brain scans.

1.4. Baseline Documentation of Target and Non-Target Lesions

Target lesions: When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with larger size are generally preferred), be representative of all involved organs, have better defined boundaries, and should lend themselves to reproducible repeated measurements.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT or MRI scan. Only the short axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be

considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

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. The baseline sum of 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 pathological lymph nodes 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. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g., 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

1.5. Response Criteria

This section provides the definitions of the criteria used to determine objective tumor response for target and non-target lesions.

1.5.1. 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:** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters while on study.

Special notes on the assessment of target lesions:

- Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded and should be measured in the same anatomical plane as the baseline examination, even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm.
- Target lesions that become 'too small to measure': All lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). If the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm. However,

when such a lesion becomes difficult to assign an exact measure to then: (i) if it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. (ii) if the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (note: in case of a lymph node believed to be present and faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness).

- Lesions that split or coalesce on treatment: When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

1.5.2. Evaluation of Non-Target Lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

- **Complete Response:** Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be nonpathological in size (<10 mm short axis).
- **Non-CR/Non-PD:** Persistence of one or more nontarget lesion(s) and/or maintenance of tumor marker level above the normal limits.
- **Progressive Disease:** Appearance of one or more new lesions and/or unequivocal progression of existing nontarget 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 "nontarget" 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 investigator).

1.6. New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient

who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of progressive disease even if he/she did not have brain imaging at baseline. If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

1.7. Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until the end of treatment taking into account any requirement for confirmation. The patient's best response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

Revised Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (Eisenhauer, 2009) is summarized in the table below.

Response According to Revised Response Evaluation Criteria in Solid Tumors (Version 1.1) in Patients with Target (and Non-Target) Lesions When Confirmation is Required

Target Lesions	Non-target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required
CR	CR	No	CR	≥4 weeks confirmation
CR	Non-CR/non-PD*	No	PR	
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
Not all evaluated	Non-PD	No	NE	
PD	Any	Yes or no	PD	No prior SD, PR, or CR
Any	PD**	Yes or no	PD**	
Any	Any	Yes	PD	

Abbreviations: CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease; NE=not evaluable.

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

**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.

Best Overall Response When Confirmation of CR and PR are Required

Overall Response, First Time Point	Overall Response, Subsequent Time Point	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR*
CR	SD	SD if minimum criteria for SD duration met, otherwise PD
CR	PD	SD if minimum criteria for SD duration met, otherwise PD
CR	NE	SD if minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD if minimum criteria for SD duration met, otherwise PD
PR	NE	SD if minimum criteria for SD duration met, otherwise NE
NE	NE	NE

Adapted from (Eisenhauer, 2009)
Abbreviations: CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease; NE=not evaluable.
*If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS

(Medical/Study Director, Regulatory Representative, Clinical Study Lead, and Biostatistician)

To the best of my knowledge, this report accurately describes the planned conduct of the study.

Study 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

Protocol Number: R2810-ONC-ISA-1981

Protocol Version: R2810-ONC-ISA-1981 Amendment 2

See appended electronic signature page

Sponsor's Responsible Medical/Study Director

See appended electronic signature page

Sponsor's Responsible Regulatory Liaison

See appended electronic signature page

Sponsor's Responsible Clinical Study Lead

See appended electronic signature page

Sponsor's Responsible Biostatistician

Signature Page for VV-RIM-00164906 v1.0

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