	The study includes 3 periods: screening, treatment, and follow-up. The screening period begins with the signing of the informed consent form (ICF). The screening period ends when the patient has been confirmed as fully eligible for the study and is randomized, or with confirmation that the patient is ineligible and is a screen failure. The treatment period begins within 5 days of randomization to 1 of the treatment arms. Cycle length is 6 weeks, and tumor imaging is planned to be conducted on day 42 (±7 days) of cycles 1–4, 6, 8, 10, 12, 14, and 16. Planned treatment is for up to 96 weeks. The treatment phase ends when the patient discontinues study therapy. There is no cross-over during this study. After completion of the treatment period, patients enter the follow up period. After the follow-up period, patients will be followed for survival. The second interim analysis demonstrated survival advantage for patients treated with cemiplimab over IC chemotherapy. As such, Amendment 7 will allow for an cemiplimab Extension Phase. Patients randomized to IC chemotherapy will have the option to receive monotherapy with cemiplimab. All randomized patients are eligible for this option provide they meet criteria per Section 7.1.7.1 and have not received anticancer immunotherapy. Patients randomized to and continuing treatment with cemiplimab will also enter the cemiplimab Extension Phase. Retreatment is no longer an option as of Amendment 7. Study closeout procedures will be implemented following the last patient last visit of the cemiplimab Extension Phase
Study Duration	The duration of the study treatment period for a patient is up to 96 weeks (up to 16 cycles of 6 weeks each), excluding the screening period. The follow-up period continues until death or study completion, per the sponsor and the Gynecologic Oncology Group (GOG).
Population	
Sample Size:	Approximately 460 SCC patients will be randomized 1:1 (230 per treatment arm) at approximately 100 sites globally. Approximately 590 patients in the overall population are projected to have accrued when the enrollment of SCC patients is completed. However, the actual number of patients in the overall population depends on the proportion of adenocarcinoma patients in the patient population and the time when Amendment 5 is implemented at each of the study sites.
Target Population:	The study will enroll women ≥18 years old with recurrent, persistent, and/or metastatic cervical cancer that has progressed after platinum-containing chemotherapy given to treat recurrent or metastatic cervical cancer. Patients who only received prior platinum-based therapy concurrently with radiation

Abbreviation	Definition of Term
Gy	Gray
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HCG	β-human chorionic gonadotropin
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
HR	Hazard ratio
IC	Investigator's choice
ICF	Informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IHC	Immunohistochemistry
ILD	Interstitial lung disease
irAE	Immune-related adverse event
IRB	Institutional Review Board
IV	Intravenous(ly)
IVRS	Interactive voice response system
IWRS	Interactive web response system
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cells
PD	Progressive disease
PD-1	Programmed death-1
PD-L1	Programmed death ligand 1
PD-L2	Programmed death ligand 2
PFS	Progression-free survival
PI 3-K	Phosphatidylinositol 3-kinase
PK	Pharmacokinetic(s)
PR	Partial response

- To compare the safety profiles of cemiplimab versus IC chemotherapy by describing adverse events (AE)
- To compare quality of life (QOL) for patients treated with cemiplimab versus IC chemotherapy using European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30)

2.3. Exploratory Objectives

- To measure concentrations of cemiplimab in serum and characterize the pharmacokinetics (PK) of cemiplimab
- To assess the immunogenicity of cemiplimab
- To explore associations between the clinical efficacy of cemiplimab and molecular features in pretreatment tumor samples
- To explore the pharmacodynamic activity of cemiplimab on the immune system in peripheral blood samples

3. HYPOTHESIS AND RATIONALE

3.1. Hypothesis

Human papillomavirus viral proteins are recognized as foreign antigens by effector T cells in cervical cancer, and an anti-tumor immune response can be unleashed by blockade of the PD-1 immune checkpoint. Cemiplimab will improve OS compared to IC chemotherapy for cervical cancer patients who experienced progression of disease after treatment with platinum chemotherapy that was administered in the recurrent or metastatic disease setting, in SCC and in the overall population.

3.2. Rationale

3.2.1. Rationale for Patient Population and Study Design

This is an open-label, randomized, phase 3 trial of cemiplimab versus IC chemotherapy in patients with recurrent or metastatic cervical cancer that has progressed after platinum-containing chemotherapy. The GOG240 study established the efficacy of first line-therapy for recurrent or metastatic cervical cancer with the regimen of platinum + paclitaxel + bevacizumab (Tewari 2014). There is no standard-of-care regimen in the second line setting. Agents that may be considered in this setting are the IC options in this study: pemetrexed, topotecan, irinotecan, gemcitabine, and vinorelbine. Despite the availability of various chemotherapy options, patients treated with these agents for cervical cancer have a median survival time of approximately 7 months (Section 3.2.3).

A concept of "platinum-refractory" disease has been described in the cervical cancer literature, and is related to time since prior platinum therapy (Nishino 2016) (McLachlan 2016) (Tanioka 2011). However, it is not typical clinical practice to re-treat cervical cancer patients with platinum-based chemotherapy if they have already received it in the setting of recurrent or metastatic disease. The chemotherapy regimens in the control arm of this study represent the current treatment options for cervical cancer patients who have received prior platinum in the

setting of recurrent or metastatic disease. Regardless of the time interval between prior platinum therapy (for recurrent or metastatic cervical cancer) and subsequent progression, such patients have unmet medical need and are appropriate for consideration of the clinical study. 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 in this study.

> **NOTE**: The term persistent disease is sometimes used to refer to disease for which there was never documentation of complete resolution after chemoradiation. For such patients, first line therapy is the same as that for patients with recurrent or metastatic disease (ie, platinum + paclitaxel ± bevacizumab). As a convention in this study, patients with persistent disease are considered included in the category of "recurrent or metastatic" disease any time that term is used in the protocol.

The study population will have received prior paclitaxel and prior bevacizumab, refused such treatment, or been unsuitable for such treatment (or, in the case of bevacizumab, not had access). For patients who received prior paclitaxel and/or prior bevacizumab, disease progression at any time after prior paclitaxel and/or bevacizumab is an acceptable reason for discontinuation of paclitaxel and/or bevacizumab.

The study design is a randomized comparison of cemiplimab versus IC chemotherapy, with an OS endpoint. For patient populations in which there is no widely accepted standard of care, and in which randomization to a placebo or best-supportive care arm is considered unethical or unfeasible, health authorities have accepted IC as a comparator in studies that have led to regulatory approvals based on OS endpoints (Donoghue 2012) (Ferris 2016). Blinding is not practical in the current study due to differences in schedule and differences in AE profiles between cemiplimab and the IC options (ie, immune-related adverse events [irAEs] with cemiplimab and white blood cell count suppression with chemotherapy).

Overall survival directly measures clinical benefit, is not biased, and is not a surrogate endpoint. As such, OS has been selected as the primary endpoint, and this open-label study will compare cemiplimab versus IC chemotherapy in patients with cervical cancer who have progressed after prior treatment with a platinum containing regimen that was given in the recurrent or metastatic disease setting.

Rationale for Further Enrollment of only Patients with Squamous Histology

The International Collaboration of Epidemiological Studies of Cervical Cancer analyzed data from 23 published studies that included 9052 cervical cancer patients; histologic data was available for 8575 patients (Appleby 2006). In the overall analysis of studies globally, approximately 85% of cases had squamous histology, although this did appear to vary by geographic region.

Emerging data from anti-PD-1 studies in cervical cancer suggests that efficacy of these agents in cervical cancer may be associated with squamous histology. The phase 1 study of cemiplimab (R2810-ONC-1423) contained expansion cohorts for cervical cancer patients (Rischin 2018). Data from these expansion cohorts, combined with the results of 3 cervical cancer patients in the dose escalation portion of the study (Papadopoulos 2016), suggest an efficacy difference associated with histology: ORR among squamous cell cancer patients was 31% (4/13), and ORR among patients with adenocarcinoma/other histology was 0% (0/10) (Regeneron, data on file). Results with pembrolizumab also support the efficacy of PD-1 blockade in cervical cancer patients with

4.3. Exploratory Endpoints

4.3.1. Pharmacokinetic Variables

Cemiplimab concentrations in the serum will be assessed at multiple time points throughout the treatment and follow-up periods.

Pharmacokinetic variables may include, but are not limited to, the following:

- C_{eoi} – concentration at end of infusion
- C_{trough}

4.3.2. Anti-Drug Antibody Variables

Anti-drug antibody (ADA) variables include status of ADA response and titer as follows:

- Treatment-emergent ADA response - defined as any positive response post-treatment when baseline results are negative or missing

  Treatment-boosted ADA response - defined as any post treatment ADA response that is at least 9-fold over baseline titer levels when baseline results are positive
- Titer values (titer value category)
  - Low (titer <1,000)
  - Moderate (1,000≤ titer ≤10,000)
  - High (titer >10,000)
- Samples that are positive in the ADA assay may be analyzed for the neutralizing activities

4.3.3. Other Exploratory Variables

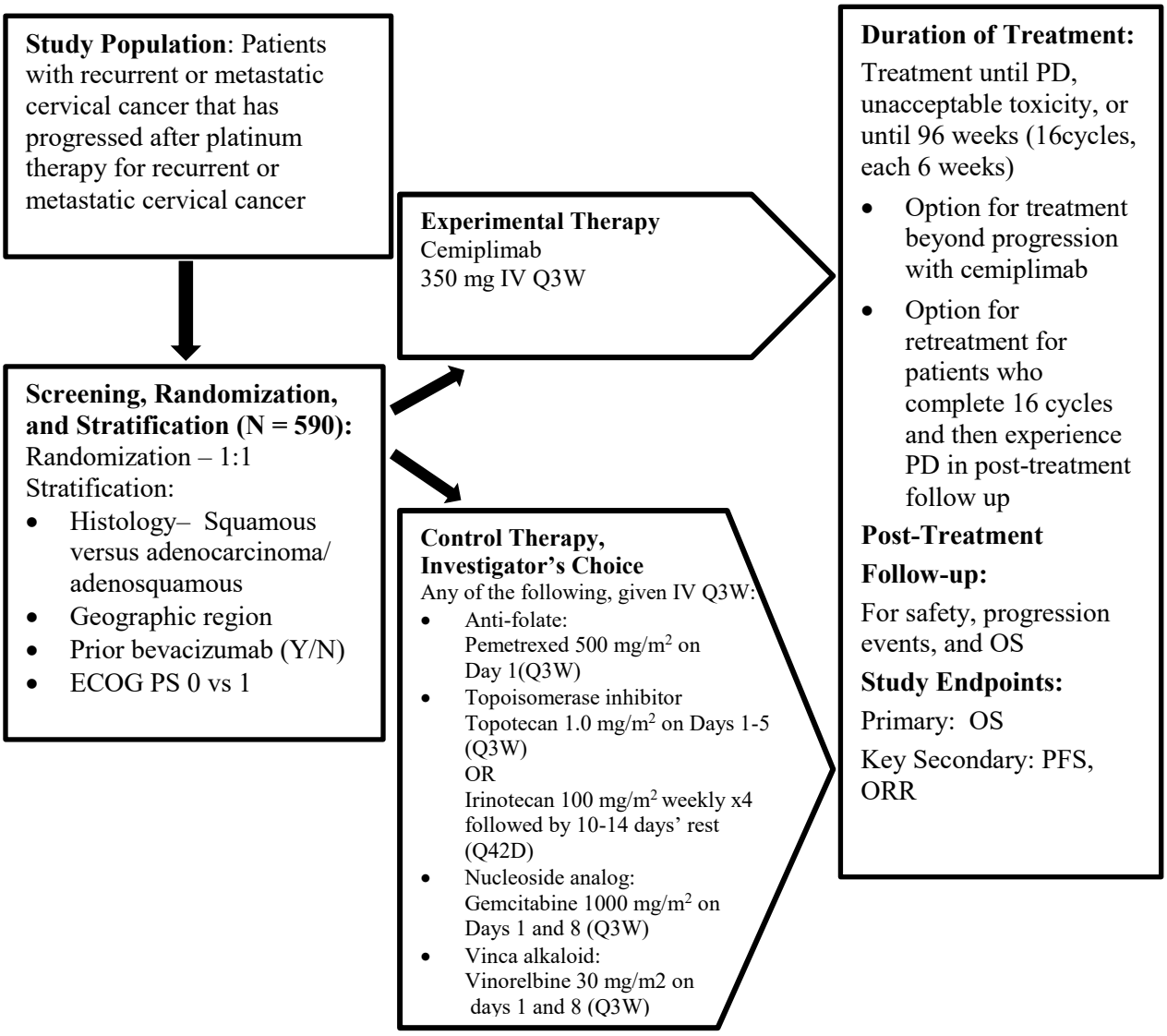
Relationships between efficacy endpoints and candidate biomarkers in tumor and peripheral blood will be described.

5. STUDY DESIGN

5.1. Study Description and Duration

This is an open-label, randomized, multi-center, phase 3 trial comparing cemiplimab versus IC of chemotherapy in patients with recurrent or metastatic cervical cancer. Approximately 590 patients will be randomized to either the experimental cemiplimab treatment arm or the IC of chemotherapy control treatment arm. In the experimental group, cemiplimab will be administered as a flat dose of 350 mg Q3W. In the control group, IC chemotherapy options are in 4 classes: (1) antifolate - pemetrexed, (2) topoisomerase 1 inhibitor – topotecan or irinotecan, (3) nucleoside analogue – gemcitabine, and (4) vinca alkaloid - vinorelbine. A schematic diagram of the study design is presented in Figure 2. The only chemotherapy treatments allowed in the control arm are any of the 5 drugs that are listed as IC options. Other agents in these classes are not permitted in this study.

Figure 2: Study Design Schematic



Q42D=every 42 days

Table 1: Schedule of Events: Screening and Treatment Period

		Cycles 1 through 16 (cycle length = 6 weeks)					
Study Procedure	**Screening Visit X**	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 29**	**Day 42**
Screening[1]							
Inclusion/exclusion	X						
Informed consent[2]	X						
Genomics sub-study informed consent (optional)	X						
Medical history and demographics	X						
Electrocardiogram	X						
Performance status	X						
Tumor tissue sample	X						
Randomization	X						
Treatment:							
Cemiplimab (experimental)		X[3]			X		
Pemetrexed		X[3]			X		
Topotecan		Days 1-5[3]			Days 22-26		
Irinotecan		X[3]	X	X	X		
Gemcitabine		X[3]	X		X	X	
Vinorelbine		X[3]	X		X	X	
Concomitant medications	X	X	X	X	X	X	X
Efficacy (Radiologic):							
CT scan and/or MRI	X						X (cycles 1-4, 6, 8, 10, 12, 14, and 16)
Safety:							
Vital signs[4]	X	X	Only for gemcitabine, irinotecan, and vinorelbine	Only for irinotecan	X	Only for gemcitabine and vinorelbine	
Weight and height (height at screening only)[5]	X	X[6]					
Complete physical examination[7]	X						
Limited physical examination[8]		X			X		

12. The ADA samples for immunogenicity are collected pre-infusion on day 1 of cycle 1, 3, 7, 11, and 15. The ADA samples for immunogenicity are to be obtained only from patients randomized to receive cemiplimab.
13. The biomarker samples are collected pre-infusion on day 1 of cycles 1 through 8.
14. Peripheral blood mononuclear cell (PBMC) collection is optional. If pre-treatment PBMC is not collected on day 1/cycle 1, PBMC should not be collected at future dates. If PBMC are collected, this sample should be collected prior to treatment on day 1 of cycles 1 through 3. Samples are to be obtained only from patients randomized to receive cemiplimab.
15. The EORTC QLQ-C30 assessment may be performed at any subsequent visit within the same treatment cycle if the assessment is not performed on day 1.

7.1.3. 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.

7.1.4. Post-Treatment Follow-Up

Table 2: Schedule of Events, Post-Treatment Follow-Up

Study Procedure	Follow-up Visits 1 and 2[1]	Survival Follow-Up Assessments[2]
Survival status		X
Limited physical exam[3]	X	
Concomitant medications	X	
Vital signs	X	
Electrocardiogram	X	
Adverse events	X	
Laboratory Testing		
Hematology	X	
Blood chemistry	X	
Pregnancy test for WOCBP	X	
TSH (with reflex T3, free T4)	X	
ADA	X[4]	
PK	X[4]	
Soluble biomarkers (serum/plasma)	X	
PBMC (optional)	X[6]	
Quality of Life		
EORTC QLQ-C30	X	
Efficacy (Radiology)		
CT and/or MRI[5]	X	X

7.1.5. Footnotes for the Schedule of Events Table for Post-Treatment Follow-up

1. Post-treatment follow-up pertains to all patients (both treatment groups). This pertains to patients who completed all 16 cycles of planned treatment, and to patients who discontinue treatment prior to the completion of 16 cycles. Follow-up visit 1 occurs approximately 30 days (±10 days) from last dose of cemiplimab or IC of chemotherapy. Follow-up visit 2 occurs approximately 90 days (±10 days) after follow-up visit 1.

2. After the end of study, survival follow-up assessments will occur every 90 days (±10 days) until death or study termination per sponsor and GOG. It is preferable for survival follow-up assessments to occur in the clinic, but telephone assessments are acceptable. Regeneron may request that survival data be collected on all randomized participants outside of the 90-day specified window. At the time of this request, each participant will be contacted to determine their survival status unless the patient has withdrawn consent for all contact.
3. Limited physical exam includes heart, lung, abdomen, and skin.
4. During the follow-up period, after end of treatment of cemiplimab, PK and ADA samples are collected at follow-up 1 visit. PK and ADA samples may be collected at follow-up visit 2 (approximately 4 months post last treatment of cemiplimab). In response to adverse events of special interest (AESIs), such as anaphylaxis or hypersensitivity, ADA samples may be collected closer to the event, based on the judgment of the investigator and/or medical monitor.
5. Radiologic imaging in the post-treatment follow-up period is only required for patients who have not experienced prior PD. Tumor assessments should occur every 90 days (±10 days) until PD.
6. PBMC samples are to be obtained only from patients randomized to receive cemiplimab and have signed optional PBMC consent.

7.1.6. Option for Retreatment

Patients who complete 16 cycles of treatment (Table 1) enter the follow up period (Table 2). If they have not experienced PD during the study, radiologic assessments will continue until PD, as per Table 2. If a patient experiences PD during the follow-up period, retreatment with the same drug that was given during the treatment period is an option. A patient who was initially randomized to receive cemiplimab may be considered for resumption of cemiplimab. A patient who was initially randomized to IC of chemotherapy may be considered for resumption of the same chemotherapy that they received in the treatment period. Resumption of treatment due to PD during the follow-up period may be allowed if:

- The patient received no other anticancer systemic therapy during the follow-up period.
- The reason for discontinuation of study treatment was the completion of 16 planned cycles, not for toxicity.
- The patient provides written informed consent prior to initiating retreatment by signing the current version of the ICF (eg, the patient repeats the written informed consent process that was performed prior to study enrollment).
- All screening period assessments (with the exception of providing tumor pathology material) are repeated, and the patient meets all study eligibility criteria (with the exception of the exclusion regarding prior anti-PD-1 therapy if the patient was randomized to cemiplimab).

Patients who resume study treatment will follow the schedule of events in Table 1, for up to 8 cycles total with the same treatment to which they were originally randomized. Cycles will be counted as 17 through 24. However, PK, ADA, research blood samples, and PBMC samples are

- Documentation of pathologic confirmation of cervical cancer (SCC or adenocarcinoma/AC prior to Amendment 5; squamous cell histology only starting with Amendment 5)
- Pathology material (formalin-fixed, paraffin-embedded [FFPE] block or 20 slides from the sample in the submitted pathology report). This material will be used for correlative science studies (Section 7.2.7).
- Patients who fail screening may be screened one additional time and an ICF will need to be signed at the re-screen. Some procedures may not need to be repeated if they were previously completed within 28 days prior to cycle 1 day 1.

7.2.2. Efficacy Procedures

For all patients, disease will be measured radiologically according to RECIST 1.1 criteria (Appendix 1; Eisenhauer 2009). The CT or MRI for tumor assessment will be performed in screening, during treatment, and during follow-up, as detailed in Table 1 and Table 2. During the treatment period, tumor response assessments are performed at end of cycles 1 through 4, 6, 8, 10, 12, 14, and 16 (Table 1). During follow-up, tumor response assessments are performed at follow-up visits 1 and 2 (Table 2). The choice of whether the imaging is by CT or MRI is an investigator decision. Once the choice of CT scan or MRI has been made, subsequent assessments should be made using the same modality whenever possible.

- Whole-body (chest/abdomen/pelvis) imaging is performed at the baseline assessment and is strongly recommended at each response assessment. A CT or MRI of the neck should be performed in patients with metastases to neck. At a minimum, all radiologically measurable target lesions (RECIST 1.1) should be imaged at each response assessment. The same radiologic imaging modality should be used at each response assessment.
- Brain imaging – MRI brain with gadolinium (or CT brain with contrast, if MRI is not feasible) will be performed in the screening period for patients with history of brain metastases, or for whom there is clinical suspicion of brain metastases. Patients with brain metastases that are "not active" (see Section 6.2.2) who are enrolled on the study should have brain imaging at each response assessment, or sooner if there is clinical suspicion of worsening brain metastases during treatment.

All radiological scans will be submitted to central depository and may be reviewed centrally.

7.2.3. Survival Data Collection

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. 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 being alive.

7.2.4. Quality of Life Questionnaires

Patient-reported outcomes will be measured at a frequency indicated in Table 1 and Table 2 using the validated patient self-administered EORTC QLQ-C30 questionnaire. Patients will be asked to

complete these questionnaires prior to any study procedures being performed at a given study visit (during the on-study/treatment and follow-up periods).

7.2.5. Safety Procedures

7.2.5.1. Vital Signs

Vital signs, including temperature, resting blood pressure, pulse, and respiration, will be collected at time points according to Table 1 and Table 2.

> **NOTE**: blood pressure should be measured after the patient has been resting quietly for at least 5 minutes.

Only for patients assigned to cemiplimab: At cycle 1 day 1 and cycle 1 day 22, vital signs will be collected prior to infusion, and approximately 30 minutes after the completion of the infusion. For all other cemiplimab infusions, vital signs are collected prior to infusion, and approximately 15 minutes after the completion of the infusion. The allowable window for each specified time point is ±10 minutes.

7.2.5.2. Physical Examination

A thorough complete or limited physical examination will be performed at visits specified in Table 1 and 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, lymph nodes, extremities, and skin. A brief neurologic examination also should be performed.

Limited physical examination will include lungs, heart, abdomen, and skin.

7.2.5.3. Electrocardiogram

A 12-lead electrocardiogram (ECG) should be performed during the screening period.

The patient should be relaxed and in a recumbent or semi-recumbent position at least 5 minutes before recording an ECG. The ECG strips or reports will be retained with the source. The ECG will be reviewed by the investigator (paper or electronic tracing) and will be available for comparison with subsequent ECGs by the investigator. The following will be recorded on the CRF:

- PR interval (msec)
- QRS interval (msec)
- QT interval (msec)
- Heart rate (beats per minute; recorded from the ventricular rate)

There is not a required time window for ECGs; they may be performed at any time on the study days according to Table 1 and Table 2 (±3 days).

7.2.7. Biomarker Procedures

7.2.7.1. Tumor Samples

On-treatment tumor biopsies for correlative science research purposes do not occur in this study. However, for all study patients, a pretreatment tumor sample (preferably a recent FFPE tissue block, or alternatively, 20 unstained FFPE slides) is required. This should be provided in central lab in the screening period, but a patient's enrollment would not be delayed if sample is not received in screening period. An archived tumor sample may satisfy this requirement. Tumor samples should be of sufficient size to ensure an adequate amount of tissue for analysis (excisional, incisional, or core needle; fine needle aspirates are not acceptable). If sufficient archived material is not available, fresh biopsy (excisional, incisional, or core needle) should be performed in the screening period to obtain adequate tumor material (preferably an FFPE tissue block, or alternatively, 20 unstained FFPE slides) if the investigator deems the biopsy can be safely performed. Invasive procedures that require general anesthesia should not be performed to satisfy the biopsy requirement. However, if surgery is performed for a clinical indication, excess tumor material from the surgical procedure could be used to satisfy the required for pretreatment tumor material. Complete instructions on the collection, processing, handling, and shipment of all samples will be provided in the laboratory manual.

Candidate biomarkers will be analyzed in archived (pretreatment) tumor samples. Immunohistochemistry (IHC) will be performed to determine PD-L1 expression levels in archived tumor specimens. This approach may provide a better understanding of the performance of PD-L1 expression level as a predictive biomarker of response to cemiplimab. Of special interest is PD-L1 expression across different cell types including tumor cells, stroma cells, and infiltrating immune cells. After completion of PD-L1 expression analysis, the remaining tumor tissue may be used to study candidate biomarkers associated with clinical response to cemiplimab, including characterization of expression of other immune-related or cervical cancer-related genes (DNA, RNA and/or protein), tumor-infiltrating lymphocytes and other immune cell populations, HPV status and subtype, human leukocyte antigen variants and antigen processing components, tumor genetic mutation profile, and T cell receptor repertoire. Methodologies that may be employed include, but are not limited to, IHC, RNA sequencing, RNAscope®, fluorescence in situ hybridization, and whole exome DNA sequencing.

7.2.7.2. Serum/Plasma Samples

Serum/plasma samples will be collected from all patients enrolled in this study at multiple time points to study the potential pharmacodynamics or predictive biomarkers of response to cemiplimab (refer to the laboratory manual).

7.2.7.3. Peripheral Blood Mononuclear Cells (optional)

Peripheral blood mononuclear cells 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.

investigators distinguish irAEs from non-immune AEs. These case definitions pertain to the more commonly reported irAEs associated with PD-1 inhibition (Weber 2015) (Naidoo 2015), and is not exhaustive of all possible irAEs. Clinical presentations of less common irAEs, including neurologic, musculoskeletal, cardiac, renal, and ocular events (Zimmer 2016) (Hofmann 2016), should be reviewed in patients with concerning presentations.

The case definitions below have not been validated, and are intended only as guidance for investigators to help distinguish irAEs from non-immune AEs. Investigators' clinical judgment may include other factors when determining immune-relatedness. The case definitions for irAEs may evolve as clinical experience increases with cemiplimab and other antibodies targeting the PD-1/PD-L1 axis.

a. **Immune-related rash**: Skin examination demonstrates a rash that is usually maculopapular, but other presentations may occur, including papulopustular, follicular, or urticarial dermatitis. Consider dermatologic consultation and biopsy for atypical presentations. Exclude other cause such as virally-induced rash or contact dermatitis.
b. **Immune-related diarrhea/colitis**: These events are on a continuum, with diarrhea defined as increased stool frequency, and colitis involves abdominal pain and/or radiologic evidence of colonic inflammation (Naidoo 2015). Onset at 4 to 6 weeks is common (Weber 2015). A CT scan usually demonstrates diffuse colitis (Tirumani 2015). Exclude *Clostridium difficile* or other infectious etiologies and exclude laxative misuse.
c. **Immune-related hepatitis**: Laboratory studies are notable for elevated ALT and/or AST that is usually asymptomatic. Viral or other drug-induced hepatitis is excluded. Exclude alcohol-related liver toxicity. If clinically appropriate, consider radiologic imaging to exclude malignant causes. If clinically appropriate, exclude worsening of underlying cirrhosis.
d. **Immune-related hypothyroidism**: Laboratory studies are notable for elevated TSH associated with low serum free thyroxine (free T4). If elevated TSH is detected, it is recommended that free T4 level also be tested. Elevated TSH with low free T4 establishes the diagnosis of hypothyroidism. Hypothyroidism may be asymptomatic or associated with symptoms such as fatigue, constipation, cold intolerance, dry skin, weight gain, and/or bradycardia. Exclude other causes of hypothyroidism, such as prior radiation therapy to the neck. In patients with prior history of hypothyroidism, exclude noncompliance with thyroid replacement medication.
e. **Immune-related hyperthyroidism**: Hyperthyroidism should be managed with standard antithyroid pharmacotherapy, and consultation with an endocrinologist is recommended.
f. **Immune-related pneumonitis**: Pneumonitis, defined as inflammation of the lung parenchyma, may present as shortness of breath, cough, fever, and/or chest pain. Median time from start of anti-PD-1 therapy to onset of pneumonitis is 2.6 months (Nishino 2016), but delayed onset of pneumonitis has been reported. The most common radiologic pattern on CT chest has been described as cryptogenic organizing pneumonia, but other radiographic patterns may occur (Nishino 2016). If performed, biopsy may demonstrate lymphocyte-predominant interstitial pneumonitis with areas of organizing pneumonia (Nishino 2016). Exclude infectious causes of pneumonitis.

Adverse events that meet the criteria above should be entered using the appropriate terms (see Appendix 3 for terms corresponding to common potential irAEs), and attributing them as related to cemiplimab. Such related events will be assumed to be irAEs in the database (unless

(United States Package Insert for pemetrexed, gemcitabine, vinorelbine, irinotecan, and topotecan) will be considered as unexpected.

In addition, the sponsor will report all other SAEs to the health authorities, according to local regulations.

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

9.3. Definitions

9.3.1. 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.

An AE also includes any worsening (ie, any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug.

Progression of underlying malignancy will not be considered an AE if it is clearly consistent with the typical progression pattern of the underlying cancer (including time course, affected organs, etc.). Similarly, death due to progression of malignancy will be considered a study endpoint but not an AE. Clinical symptoms of progression may be reported as AEs if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy, or does not fit the expected pattern of progression for the disease under study.

If there is any uncertainty about an AE being due only to progression of the underlying malignancy, it should be reported as an AE or SAE as outlined in Section 9.4.

9.3.2. 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 admission to a hospital or an emergency room 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.

9.3.3. Adverse Events of Special Interest

An AESI (serious or non-serious) is one of scientific and medical concern 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. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (eg, regulators) might also be warranted (Section 9.4.3).

9.3.4. Infusion Reactions

Infusion reactions are defined as any AE that occurs during the infusion or within 2 hours after the infusion is completed. All infusion reactions must be reported as AEs (see Section 9.4.1) and graded using the grading scale as instructed in Section 9.5.1.

9.4. Recording and Reporting Adverse Events

9.4.1. 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, pemetrexed, gemcitabine, vinorelbine, irinotecan, and topotecan.

Information on follow-up for AEs is provided in Section 9.4.6. Laboratory, vital signs, or ECG abnormalities are to be recorded as AEs as outlined in Section 9.4.5.

9.4.2. 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.

9.4.3. 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 9.4.2. 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 reaction
- Grade ≥3 irAEs (see Section 8.3.2)
- An irAE of any grade in a patient previously treated with a PI 3-K inhibitor

NOTE (Applicable to cemiplimab only): An irAE 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 irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an AE as an irAE.

9.4.3.1. Immune-Related Adverse Events

Detailed guidance of management of irAEs is provided in Section 8.3.2 and Appendix 2.

NOTE: Regarding irAEs, 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 irAE by the investigator, the sponsor may request additional information.

9.4.4. 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.

9.4.5. 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 9.5.1.

9.4.6. Follow-up

Information for any non-SAE that starts during the treatment period or within 90 days after last treatment will be collected from the time of the event until resolution of the event, or until the patient's last study visit, whichever comes first.

Serious adverse event information will be collected until the event is considered chronic and/or stable.

9.5. Evaluation of Severity and Causality

9.5.1. Evaluation of Severity

The severity of AEs (including test findings classified as AEs) will be graded using the current version of the NCI-CTCAE grading system. Adverse events not listed in the NCI-CTCAE will be graded according to the following scale:

1 (Mild): Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

2 (Moderate): Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL)*.

3 (Severe): Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.

4 (Life–threatening): Life-threatening consequences; urgent intervention indicated.

5 (Death): Death related to AE

* Instrumental Activities of Daily Living (ADL) refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

If a laboratory value is considered an AE, its severity should be based on the degree of physiological impairment the value indicates.

9.5.2. Evaluation of Causality

Relationship of Adverse Events to Study Drug:

The relationship of AEs or SAEs to study drug will be assessed by the investigator, and will be a clinical decision based on all available information. The following question will be addressed:

Is there a reasonable possibility that the AE or SAE may have been caused by the study drug?

The possible answers are:

Not Related: There is no reasonable possibility that the event may have been caused by the study drug

Related: There is a reasonable possibility that the event may have been caused by the study drug

A list of factors to consider when assessing the relationship of AEs or SAEs to study drug is provided in Appendix 4.

The investigator should justify the causality assessment of each SAE.

Relationship of Adverse Events to Study Conduct:

The relationship of AEs or SAEs to study conduct will be assessed by the investigator, and will be a clinical decision based on all available information. The following question will be addressed:

Is there a reasonable possibility that the AE or SAE may have been caused by study conduct?

The possible answers are:

Not Related: There is no reasonable possibility that the event may have been caused by study conduct

Related: There is a reasonable possibility that the event may have been caused by study conduct

A list of factors to consider when assessing the relationship of AEs or SAEs to study conduct is provided in Appendix 4.

The investigator should justify the causality assessment of each SAE.

9.6. 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 monitor will have primary responsibility for the emerging safety profile of the compound, but will be supported by other departments (eg, Pharmacovigilance and 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.

9.7. Investigator Alert Notification

Regeneron (or designee) will inform all investigators participating in this clinical trial, as well as in any other clinical trial using the same investigational drug, of any SAE that meets the relevant requirements for expedited reporting (an AE that is serious, unexpected based on the Investigator's Brochure or this protocol, and has a reasonable suspected causal relationship to the medicinal/study drug).

10. STATISTICAL PLAN

This section provides the basis for the statistical analysis plan (SAP) for the study. The SAP may be revised during the study to accommodate amendments to the clinical study protocol and to make changes to adapt to unexpected issues in study execution and data that may affect the planned analyses. The final SAP will be issued before the database is locked.

Analysis variables are listed in Section 4.

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.

10.1. Statistical Hypothesis

The primary analysis of OS will be performed for the following null (H0) and alternative hypotheses (H1):

- H_0: The survival curve of OS for cemiplimab is the same as that for IC chemotherapy

10.4.6.1. 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 treatment period is defined as the day from first dose of study drug to the day of the last dose of study drug plus 90 days, or to the day before the patient commences another anticancer systemic therapy, whichever comes first.
- The post-treatment period is defined as the time starting one day after the treatment period ends.

Treatment-emergent adverse events (TEAEs) are defined as those that are not present at baseline or represent the exacerbation of a pre-existing condition during the on-treatment period. In addition, the study drug related AEs occurring anytime are considered as TEAEs.

Analysis

All AEs reported in this study will be coded using the currently available version of the Medical Dictionary for Regulatory Activities (MedDRA®). Coding will be to lowest level terms. The verbatim text, the PT, and the primary SOC will be listed.

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 (according to the grading scale outlined in Section 9.5.1), presented by SOC and PT
- TEAEs by relationship to treatment (related, not related), presented by SOC and PT
- Treatment-emergent AESIs (defined with a PT or a prespecified grouping)

Deaths and other SAEs will be listed and summarized by treatment group. Death due to disease progression will not be considered an AE, but will be reported in efficacy endpoints such as PFS and OS.

Treatment-emergent adverse events leading to permanent treatment discontinuation will be listed and summarized by treatment group.

10.4.6.2. 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 at any post randomization time point 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.

Listings will be provided with flags indicating the out of range laboratory values.

10.4.6.3. Treatment Exposure

Treatment duration, dose intensity, and number of cycles administered will be summarized by treatment group.

10.4.6.4. Treatment Compliance

Treatment compliance, which is defined as (number of doses patients received X scheduled dose interval)/divided by total duration of study drug X 100%, will be summarized by treatment group.

10.4.7. Analysis of Drug Concentration Data

No formal statistical analysis will be performed. Descriptive statistics are planned, with least square mean analysis for concentration at steady state. See Section 4.3 for PK variables.

10.4.8. Analysis of Anti-Drug Antibody Data

The ADA variables described in Section 4.3.2 will be summarized using descriptive statistics in the ADA analysis set of the experimental therapy (cemiplimab-treated) group. Frequency tables of the proportion of patients with treatment-emergent, treatment-boosted, persistent ADA response, neutralizing antibody status in the neutralizing antibody assay, and titers will be presented as absolute occurrence (n) and percent of patients (%),in the experimental therapy (cemiplimab treated) group. Listings of all ADA peak titer levels and neutralizing antibody status will be provided for patients positive in the ADA assay.

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

10.4.9. Analysis of Biomarker Data

Biomarker analyses in this study will be exploratory in nature and results will be summarized in a separate report. Detailed description of statistical methods that will be used for biomarker data analyses will be provided in a separate biomarker statistical analytical plan.

10.5. Interim Analysis

Two interim efficacy analyses are planned using Lan-DeMets (O'Brien-Fleming) spending function at 70% and 85% of the total OS events in SCC patients, respectively. The first interim efficacy analysis will be performed after observing approximately 238 OS events in SCC patients (70% of total OS events). It is projected that an observed HR of 0.729 or lower would result in a statistically significant improvement in OS at the 1-sided nominal type I error of 0.0074 at the first interim efficacy analysis. The second interim efficacy analysis will be performed after observing approximately 289 OS events in SCC patients (85% of total OS events). It is projected that an

		Cycles 1 through 16 (cycle length = 6 weeks)					
Study Procedure	**Screening Visit X**	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 29**	**Day 42**
Adverse events		←	←	←	Continuous Monitoring for Adverse Events →	→	→
Laboratory Testing:							
Hematology	X	X[6, 9]	Only for gemcitabine and vinorelbine	Only for irinotecan	X	Only for gemcitabine and vinorelbine	
Blood chemistry	X	X[6, 9]		Only for irinotecan	X		
Prothrombin time, Activated partial thromboplastin time	X						
TSH (with reflex T3, free T4)	X						
HBV, HCV, HIV	X						
Pregnancy test for WOCBP[10]	X	X[6]					
Urinalysis	X						
PK, ADA, Biomarkers	PK, ADA, soluble biomarkers, and PBMC are collected from patients randomized to cemiplimab						
PK		X[11]					
ADA sample		X[12]					
Soluble biomarkers (serum/plasma)[13]		X					
PBMC only for cemiplimab arm (optional)		X[14]					
Genomic DNA sample (optional sub-study)		X					
Quality of Life							
EORTC QLQ-C30	X	X[6, 15]					

	Screening Period for Extension Phase (28 days) [1,2]	**Extension Cycle 1/Day 1 (EC1D1)**	**Every 3 weeks, ±3 days (EC1D22 through EC16D22)**	**End of Extension Phase (up to 96 weeks)[3] 30 days ±7 days after last dose of cemiplimab**	**Survival Follow-Up[4]**
CT=computed tomography; ECOG PS=Eastern Cooperative Oncology Group Performance Status; IV=intravenous; MRI=magnetic resonance imaging; TSH=thyroid stimulating hormone; WOCBP=women of childbearing potential					

7.1.7.2. Footnotes for the Schedule of Events Table 3 for the Cemiplimab Extension Phase

1. Written informed re-consent for the cemiplimab Extension Phase must be provided prior to the initiation of screening procedures and must be obtained within 45 days prior to first dose of cemiplimab in the Extension Phase of the study. All screening assessments must be performed within 28 days prior to first dose of cemiplimab in the Extension Phase. 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 do not need to be repeated for eligibility.
2. Patients who are currently receiving cemiplimab will transition to the cemiplimab Extension Phase. Their Extension Phase treatment day should correspond to their current treatment day, such that they may receive up to 96 weeks of total cemiplimab therapy (inclusive of cemiplimab received prior to the cemiplimab Extension Phase). These patients do not need to repeat screening procedures.
3. Total duration of cemiplimab therapy is up to 96 weeks, or PD, or unacceptable toxicity.
4. After the end of treatment, survival follow-up assessments will occur every 90 days (±10 days) until death or study termination per sponsor. Telephone assessments are acceptable. Regeneron may request that survival data be collected on all randomized participants outside of the 90-day specified window. At the time of this request, each participant will be contacted to determine their survival status unless the patient has withdrawn consent for all contact.

7.2. Study Procedures

7.2.1. Procedures Performed at the Screening Visit

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

- Serum β-HCG (result must be ≤72 hours before first dose)
- HBV, HCV, and HIV screening: hepatitis B surface antigen, hepatitis C positive RNA (positive hepatitis C antibody test will require hepatitis C RNA test to rule out active infection), HIV-1, or HIV-2 serum antibody

Table 5: General Treatment Hold Guidelines for Immune Related Adverse Events

Severity	Withhold/Discontinue Treatment?	Supportive Care
Grade 1	No action	Provide symptomatic treatment
Grade 2	May withhold treatment	Consider systemic corticosteroids in addition to appropriate symptomatic treatment
Grade 3 Grade 4	Withhold treatment Discontinue if unable to reduce corticosteroid dose to <10 mg per day prednisone equivalent within 12 weeks of toxicity	Systemic corticosteroids are indicated in addition to appropriate symptomatic treatment. May utilize 1 to 2 mg/kg prednisone or equivalent per day. Steroid taper should be considered once symptoms improve to Grade 1 or less and tapered over at least 4 weeks. For any severe (grade 3-4) irAE, if symptoms worsen or do not improve on adequate corticosteroids within 48 to 72 hours, consider adding additional immunosuppressive agents (to be selected from agents such as infliximab, cyclophosphamide, cyclosporine, mycophenolate mofetil). Referral of the patient to a specialized unit for assessment and treatment should be considered.

In the limited circumstances in which cemiplimab dose modifications are called for in the toxicity management guidelines, the dose reductions will be as per Table 6. The medical monitor should be notified of dose reductions.

Table 6: Cemiplimab Dose Reductions

Dose Level	Reduction Order	Dose
Dose Level -1	First dose reduction	120 mg flat dose cemiplimab Q3W
Dose Level -2	Second dose reduction	60 mg flat dose cemiplimab Q3W

A patient who requires dose reduction below dose level -2 will be permanently discontinued from the study.

8.3.2. Immune-Related Adverse Events (irAEs)

Investigators must be extremely vigilant and be ready to intervene early in the management of irAEs, as the onset of symptoms of irAEs (eg, pneumonitis) may be subtle. Detailed guidance of management of irAEs is provided in Appendix 2. In the event of irAEs that are not addressed in Appendix 2, general guidance is provided in Table 5. The recommendations in Table 5 and Appendix 2 should be seen as guidelines, and the treating physician should exercise clinical judgment based on the symptoms and condition of the individual patient.

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

Based on the emerging safety profile of cemiplimab and other antibodies targeting the PD-1/PD-L1 axis (Weber 2015) (Naidoo 2015), the following working case definitions are provided to help

- Assessments taken outside of protocol allowable windows will be displayed according to the CRF assessment recorded by the investigator.

Unscheduled assessments:

- Extra assessments (laboratory data or vital signs associated with non-protocol-defined clinical visits or obtained in the course of investigating or managing AEs) will be included in listings, but not by visit summaries. If more than 1 laboratory value is available for a given visit, the first observation will be used in summaries, and all observations will be presented in listings.

10.7. 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 16.1.

11. DATA MANAGEMENT AND ELECTRONIC SYSTEMS

11.1. Data Management

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

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

The CRF data for this study will be collected with an electronic data capture (EDC) tool. User training must be documented before the user is granted access to the EDC system.

11.2. Electronic Systems

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

- IVRS/IWRS system – randomization, study drug supply
- EDC system – data capture
- Statistical Analysis System – statistical review, analysis, and reporting
- Pharmacovigilance safety database

The study includes 3 periods: screening, treatment, and follow-up. The screening period begins with the signing of the informed consent form (ICF). The screening period ends when the patient has been confirmed as fully eligible for the study and is randomized, or with confirmation that the patient is ineligible and is a screen failure. The treatment period begins within 5 days of randomization to 1 of the treatment arms. Cycle length is 6 weeks, and tumor imaging is planned to be conducted on day 42 (±7 days) of cycles 1-4, 6, 8, 10, 12, 14, and 16. Planned treatment is for up to 96 weeks. The treatment phase ends when the patient discontinues study therapy. There is no cross-over during this study. After completion of the treatment period, patients enter the follow-up period. After the follow-up period, patients will be followed for survival.

Study closeout procedures will be implemented after last patient last visit of the cemiplimab Extension Phase (Section 7.1.7.1).

5.1.1. End of Treatment Definition

There is an end of treatment disposition point for each patient, as reflected by treatment completion/discontinuation case report form (CRF). The end of treatment occurs for each individual patient after the patient completes or discontinues from the treatment (Table 1), but before follow-up visits 1 and 2 (Table 2).

5.1.2. End of Study Definition

The end of study for the study as a whole is planned to occur when approximately 340 deaths have occurred in squamous cell patients, as per Section 10.2. The total duration of study from start of randomization to final analysis of OS is expected to be approximately 42 months (33 months of accrual plus 11 months of follow-up). There is an end of study disposition point for each patient, as reflected by study completion/discontinuation CRF. The end of study occurs for each individual patient after the patient completes or discontinues from the treatment (Table 1) and/or follow-up visit 1 and 2 portion of Table 2, but before the survival follow-up portion of Table 2.

Due to survival benefit, for patients on the cemiplimab arm on second interim analysis, a cemiplimab Extension Phase was added (Section Section 7.1.7). Therefore, end of study is now planned to occur after last patient last visit of the cemiplimab Extension Phase.

5.2. Planned Interim Analysis

Two interim efficacy analyses are planned using Lan-DeMets (O'Brien-Fleming) spending function. The first interim efficacy analysis will be performed after observing approximately 238 OS events (70% of total OS events). The second interim efficacy analysis will be performed after observing approximately 289 OS events (85% of total OS events). The details are provided in Section 10.5.

5.3. Study Committees

5.3.1. Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) composed of members who are independent from the sponsor and the study investigators will monitor patient safety by conducting formal reviews of accumulated safety data and available efficacy data. The IDMC will also monitor and

sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

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

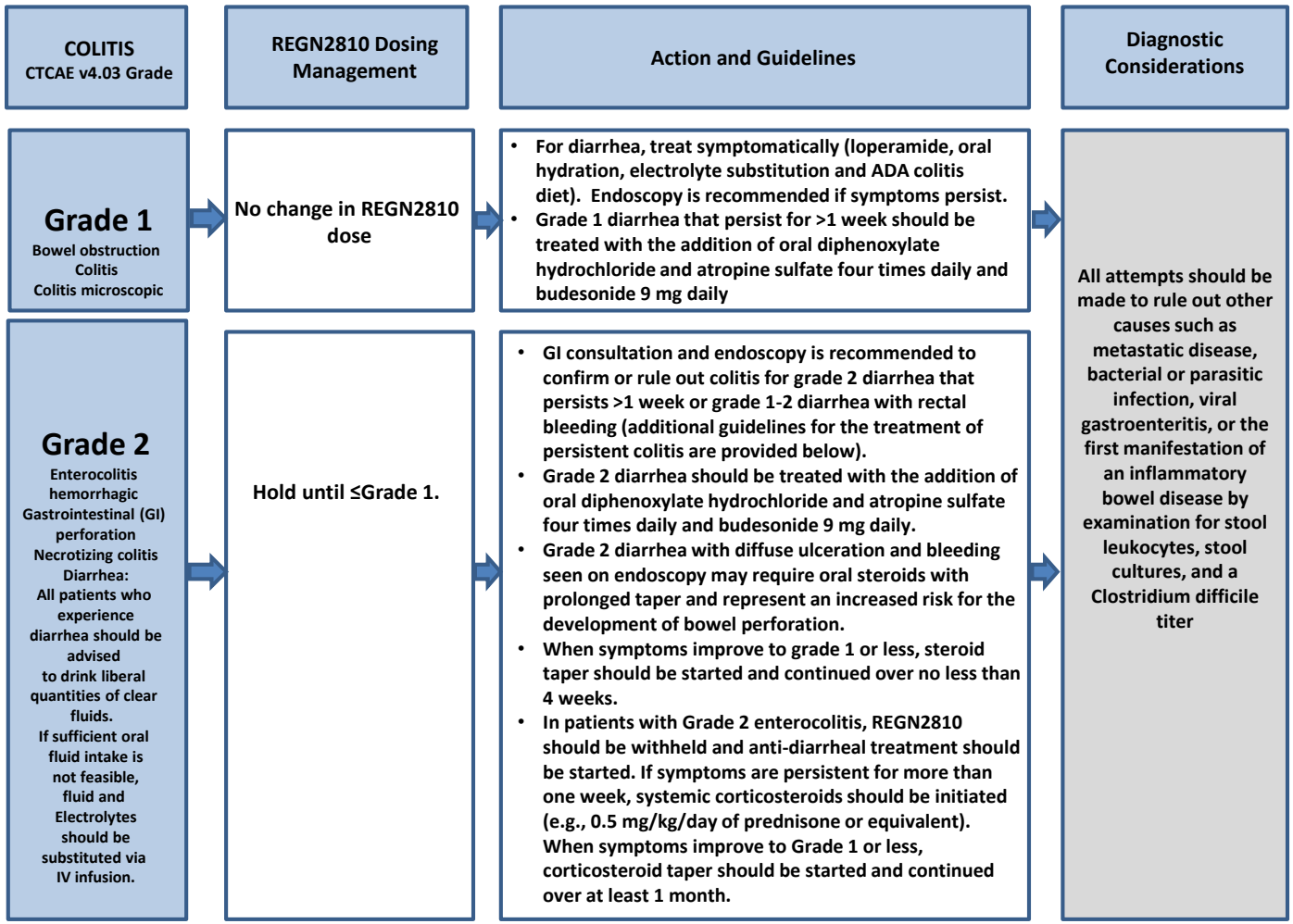
Methods for Evaluation of Measurable Disease

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

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

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

Colitis Adverse Event Management



SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS

(Scientific/Medical Monitor, Regulatory Representative, Clinical Study Team Lead, and Biostatistician)

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

Study Title:	An Open-Label, Randomized, Phase 3 Clinical Trial of REGN2810 versus Investigator's Choice of Chemotherapy in Recurrent or Metastatic Cervical Carcinoma
Protocol Number:	R2810-ONC-1676/GOG-3016 (CVP1601) ENGOT-cx9
Protocol Version:	R2810-ONC-1676/GOG-3016 (CVP1601) ENGOT cx9 Amendment 7

See appended electronic signature page

Sponsor's Responsible Scientific/Medical Monitor

See appended electronic signature page

Sponsor's Responsible Regulatory Representative

See appended electronic signature page

Sponsor's Responsible Clinical Study Team Lead

See appended electronic signature page

Sponsor's Responsible Biostatistician

	therapy for localized disease are not eligible. Starting with Amendment 5, only patients with squamous histology will be enrolled.
Treatments	
Cemiplimab Dose/Route/Schedule:	Cemiplimab will be administered IV as a flat dose of 350 mg Q3W, for up to 96 weeks of treatment
IC chemotherapy Dose/Route/Schedule:	Pemetrexed will be administered IV at a dose of 500 mg/m^2 Q3W, for up to 96 weeks of treatment
IC chemotherapy Dose/Route/Schedule:	Topotecan will be administered IV at a dose of 1 mg/m^2 daily for 5 days, every 21 days, for up to 96 weeks of treatment
IC chemotherapy Dose/Route/Schedule:	Irinotecan will be administered IV at a dose of 100 mg/m^2 on days 1, 8, 15, and 22, followed by 10 to 14 days of rest, for a 42-day (6-week cycle), for up to 96 weeks of treatment. For patients enrolling in Japan, there will be at least 14 days of rest before subsequent irinotecan administration
IC chemotherapy Dose/Route/Schedule:	Vinorelbine will be administered IV at a dose of 30 mg/m^2 on days 1 and 8, every 21 days, for up to 96 weeks of treatment.
IC chemotherapy Dose/Route/Schedule:	Gemcitabine will be administered IV at a dose of 1000 mg/m^2 on days 1 and 8, every 21 days, for up to 96 weeks of treatment
Endpoints	
Primary:	The primary endpoint is OS, defined as the time from randomization to the date of death. A patient who has not died will be censored at the last known date of contact.
Secondary:	The key secondary endpoints are PFS and ORR. Other secondary endpoints will include DOR, QOL, and the safety and tolerability of cemiplimab.
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 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 • Biomarkers (serum, plasma, tumor tissue)

Abbreviation	Definition of Term
PT	Preferred term
Q2W	Every 2 weeks
Q3W	Every 3 weeks
QOL	Quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
Regeneron	Regeneron Pharmaceuticals, Inc.
ROW	Rest of world
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SCC	Squamous cell carcinoma
SD	Stable disease
SOC	System organ class
TCGA	The Cancer Genome Atlas
TEAE	Treatment-emergent adverse event
TSC	Trial Steering Committee
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WOCBP	Women of child-bearing potential

squamous histology. The accelerated approval of pembrolizumab for cervical cancer patients in the US was based on a data set (N = 77 patients) in which 92% of the patients had squamous histology (KEYTRUDA 2018). The observation in cervical cancer that PD-L1 expression is higher in squamous cell histology than in adenocarcinoma histology may partially account for the observed association of anti-PD-1 efficacy with histology in this disease (Heeren 2016).

These observations support a protocol amendment to improve the ability of the study to test for efficacy in the squamous population, and also to increase the probability that the proportion of patients with squamous histology in the total study population will be consistent with the global proportions of histologies in cervical cancer. As such, Amendment 5 sets forth that enrollment will only be allowed for patients with squamous histology and that enrollment will continue until 460 patients with squamous histology are enrolled per Amendment 6. Based on current and projected enrollment trends and anticipated time to implementation of Amendments 5 and 6 at study sites, total enrollment to the study will be approximately 590 patients, and approximately 80% of patients will have squamous histology. This is consistent with global distribution of cervical cancer histologies described above (Appleby 2006).

See Section 10 for details regarding statistical analysis considerations regarding histology.

3.2.2. Rationale for Cemiplimab Dose Selection

In this phase 3 clinical study in cervical cancer, cemiplimab monotherapy at a dose of 350 mg every 3 weeks (Q3W) is being proposed, to allow for compatibility with many standard chemotherapeutic regimens that are dosed on a Q3W schedule, and to improve patient convenience. This cemiplimab dose of 350mg Q3W was chosen based on the safety and preliminary anti-tumor activity observed in the ongoing FIH study R2810-ONC-1423 (NCT02383212), and was supported by modeling of cemiplimab exposure in serum based on data collected in the FIH study.

Simulations of cemiplimab exposure in 1000 patients using population PK analyses indicated that 1) the variability in cemiplimab exposure (CV%) was similar with body-weight adjusted as compared to fixed doses, therefore supporting the fixed dose selection, and 2) that a 350 mg Q3W dose resulted in similar (≤20% difference) C_{trough}, AUC_{12W} and C_{max} as compared to a 3 mg/kg Q2W dose, used in the FIH study. cemiplimab concentrations exceeded those observed at 1 mg/kg Q2W dose, which demonstrated clinical efficacy in the FIH study and C_{trough} values exceeded concentrations of approximately 5 mg/L to 20 mg/L above which saturation of PD-1 target occupancy is expected to occur, based on animal data. The 350 mg Q3W dose of cemiplimab is therefore being proposed as the optimal dose in the phase 3 studies in patients with cervical cancer and across the cemiplimab program.

3.2.3. Rationale for Investigator's Choice Chemotherapy Options

The IC chemotherapy agents in this study are in 4 classes: (1) antifolate - pemetrexed, (2) topoisomerase 1 inhibitor – topotecan or irinotecan, (3) nucleoside analogue – gemcitabine, and (4) vinca alkaloid - vinorelbine. These agents have all been evaluated as monotherapies in single arm, non-randomized, phase 2 studies, and are included as possible treatment options in the National Comprehensive Cancer Network (NCCN) Guidelines for recurrent or metastatic cervical cancer (NCCN 2017). No systemic treatment agents have been associated with a survival

not required for these patients during retreatment. In response to AESIs like anaphylaxis or hypersensitivity, ADA samples closer to the event may be collected and analyzed, based on the judgement of the medical investigator and/or medical monitor.

There is no treatment crossover in this study.

7.1.7. Note Regarding IDMC Interim Analysis 2

The Independent Data Monitoring Committee (IDMC) convened on 8 March 2021 to evaluate the data from a planned formal interim analysis of OS. The IDMC declared superiority of OS in subjects receiving cemiplimab as compared to IC chemotherapy. As a result of the assessment, Protocol Amendment 7 is being implemented to provide a mechanism for eligible subjects randomized to chemotherapy to receive subsequent cemiplimab as part of the cemiplimab Extension Phase (Section 7.1.7.1).

Patients randomized to IC chemotherapy may screen to receive cemiplimab in the cemiplimab Extension Phase up to and including 30 June 2021. Patients previously on IC chemotherapy may receive up to 96 weeks on cemiplimab as per the Schedule of Events for the cemiplimab Extension Phase as per Table 3.

All patients currently on cemiplimab may continue treatment up to 96 weeks. All patients receiving cemiplimab will do so as per the Schedule of Events for the cemiplimab Extension Phase as per Table 3.

Subjects currently receiving IC chemotherapy (pemetrexed, gemcitabine, topotecan, irinotecan, or vinorelbine) may continue to be treated with IC as long as, in the opinion of the investigator, they are continuing to derive benefit from the assigned treatment. Patients who opt to continue receiving IC chemotherapy will do so as per routine clinical practice.

As of Amendment 7, retreatment is no longer an option (Section 7.1.6). As of Amendment 7, follow-up visits are no longer required (Section 7.1.4).

7.1.7.1. Cemiplimab Extension Phase of the Study

All patients currently on cemiplimab will transition to cemiplimab Extension Phase (Table 3) as of Amendment 7.

This section also provides a mechanism for patients randomized to the IC chemotherapy arm to receive cemiplimab 350 mg Q3W.

All patients randomized to IC chemotherapy are eligible for crossover to receive cemiplimab in the cemiplimab Extension Phase of the study, as long as eligibility criteria (Section 6.2) are met. Patients with squamous histology or adenocarcinoma/adenosquamous histology may be eligible for the cemiplimab Extension Phase. The following criteria are not exclusionary for patients to enter the cemiplimab Extension Phase of the study:

- Exclusion criteria #5: Steroids applied as supportive medications for IC chemotherapy will not be exclusionary.
- Exclusion criteria #20: Patients currently enrolled in R2810-ONC-1676 are not excluded.

Patients must complete screening assessments as set forth in Table 3, including signing the ICF. Patients will follow the Schedule of Events in Table 3. Cycle length in the cemiplimab Extension

7.2.5.4. Laboratory Testing

Hematology, blood chemistry, urinalysis, and pregnancy testing samples will be collected at time points according to Table 1 and Table 2, and will be analyzed by the site's local laboratory.

Detailed instructions for blood sample collection are in the laboratory manual provided to study sites.

Blood Chemistry

Sodium	Total protein, serum	Aspartate aminotransferase (AST)
Potassium	Creatinine	Alanine aminotransferase (ALT)
Chloride	Blood urea nitrogen (BUN)*	Alkaline phosphatase
Carbon dioxide (bicarbonate)**	Total bilirubin	
Calcium	Albumin	
Glucose (fasting or non-fasting)		

* At ex-US centers at which a urea assay is performed instead of BUN, the urea assay will be acceptable.

** At ex-US centers at which the bicarbonate assays is not performed as part of the routine chemistry panel, it may be omitted.

Hematology

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

7.2.8. Future Biomedical Research

The biomarker samples unused 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 of cervical cancer and other diseases. No additional samples will be collected for future biomedical research. After 15 years, any residual samples will be destroyed.

7.2.8.1. Genomics Sub-study - Optional

Patients who agree to participate in the genomics sub-study will be required to sign a separate genomics sub-study ICF before collection of the samples. Patients are not required to participate in the genomics sub-study in order to enroll in the primary study. Samples for DNA extraction should be collected on cycle 1 day 1 (baseline/predose) but may be collected at any study visit.

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

8. STUDY TREATMENTS

8.1. Investigational and Reference Treatments

The term "investigational product" (study drug) includes the experimental treatment cemiplimab (REGN2810) and the IC chemotherapy treatments. In this protocol, the investigational products (study drugs) are:

- Cemiplimab (experimental group)
- Antifolate: Pemetrexed (an IC option in the control group)
- Topoisomerase inhibitor: Topotecan or irinotecan (IC options in the control group)
- Nucleoside analogue: Gemcitabine (an IC option in the control group)
- Vinca alkaloid: Vinorelbine (an IC option in the control group)

The only chemotherapy treatments allowed in the control arm are any of the 5 drugs that are listed as IC options. Other agents in these classes are not permitted in this study. Preference should be given to regimens that are allowed by local regulations.

medical review of data raises questions regarding the attribution and are queried). If AEs corresponding to the common terms are attributed as NOT related to (cemiplimab), additional information should be provided substantiating 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.

8.3.3. Resumption of Cemiplimab After Treatment Hold, or Discontinuation

Resumption of cemiplimab after resolution of adverse event to ≤grade 1 (or baseline) is allowed at the discretion of the investigator in accordance with the toxicity management guidelines in this protocol if resumption of treatment is thought to be in best interest of the patient. Treatment after an AE may resume, at the discretion of the investigator, if the AE is felt to be manageable through supportive/medical therapy (eg, grade 3 hypertension that can be controlled with the addition of a second anti-hypertensive agent). However, cemiplimab treatment resumption is not allowed in the following circumstances:

- Patients with events that require cemiplimab to be permanently discontinued or held for more than 84 days from last scheduled dose
- Patients with ≥grade 2 uveitis. Patients with grade 2 uveitis will generally be discontinued from cemiplimab treatment, unless there is resolution to ≤grade 1 AND approval from the medical monitor at the sponsor prior to resumption of treatment.

Patients who permanently discontinue from study drug and who do not withdraw from the study should continue follow-up in the study without additional treatment until PD, completion of all study assessments, or closure of the study (Section 6.3). After PD, all patients should be followed for survival.

8.4. Dose Modification and Study Treatment Discontinuation Rules for Investigator's Choice Chemotherapy

Adverse events are to be reported according to the NCI-CTCAE version 4.03. Dose adjustments at the start of a subsequent cycle should be based on nadir observed hematologic counts or maximum nonhematologic toxicity from the preceding cycle of therapy. Treatment may be delayed to allow sufficient time for recovery. Upon recovery, patients should be retreated using guidelines in the following subsections. The general approach regarding missed doses of IC chemotherapy (eg, due to AEs) is "time marches on." Missed doses of IC chemotherapy will not be made up, unless ≤3 business days from the scheduled date.

The following section provides toxicity management guidelines for selected AEs that are characteristic for the IC agents, pemetrexed, topotecan, irinotecan, gemcitabine, and vinorelbine. For other chemotherapy-related AEs that are not specifically addressed in the following sections, the general approach for ≥ grade 3 chemotherapy treatment-related AEs is to hold chemotherapy until resolution of the event to ≤ grade 1 or baseline, and to reduce by one dose level on resumption of treatment.

8.4.1. Pemetrexed Dose Modifications

The dose reduction guidelines for hematologic toxicity are in Table 7.

- H_1: The survival curve of OS for cemiplimab is superior to that for IC chemotherapy.

10.2. Justification of Sample Size

The primary endpoint will be overall survival among patients treated with cemiplimab versus IC of chemotherapy. After progression on platinum-taxane based chemotherapy, there is no standard of care. The median OS has been reported in range of 6.5 months to 8.1 months in the phase 2 setting (Lorusso 2010) (Miller 2008) (Schilder 2005) (Bookman 2000).

The primary OS endpoint will be tested in patients with SCC first. If the null hypothesis is rejected in SCC patients, then OS will be tested in the overall population. The sample size and power are calculated using East® version 6.4.1 statistical software.

The sponsor assumes a median OS of 7 months for SCC patients treated with IC chemotherapy and a median OS of 10 months for SCC patients treated with cemiplimab. The assumptions correspond to an approximately 42.8% increase in median OS and a hazard ratio (HR) of 0.7 if OS is distributed exponentially in both treatment groups.

Two interim efficacy analyses are planned using Lan-DeMets (O'Brien-Fleming) spending function at 70% and 85% of the total OS events, respectively. A total of 340 OS events in SCC patients will yield approximately 90% power to detect an HR of 0.7 with an overall type I error of 0.025 (1-sided). The details of alpha spending at interim and final analyses based on the planned number of OS events are provided in Section 10.5.

Considering the enrollment rate (2 patients/month for months 1 to 5, 9 patients/month for months 6 to 16, 20 patients/month for months 17 to 23, and 22 patients/month for month 24 and beyond) and 10% dropout rate per year, enrollment of 460 randomized SCC patients will yield 340 OS events for analysis of OS around 42 months after the first SCC patient is randomized.

At the time when 460 SCC patients are enrolled in the study, a total enrollment in the study of approximately 590 patients is projected (SCC plus non-SCC). The actual number of patients to be enrolled will depend on the proportion of adenocarcinoma patients in the patient population and the time when Amendment 5 is implemented at each of the study sites. If the HR is 0.7, the power for testing OS in the overall population will be higher than 90%.

10.3. Analysis Sets

10.3.1. Efficacy Analysis Sets

The full analysis set (FAS) includes all randomized patients. This is the intention to treat population. The FAS is based on the treatment allocated (as randomized). All efficacy endpoints will be analyzed using the FAS.

10.3.2. Safety Analysis Set

The safety analysis set (SAF) includes all randomized patients who received any study drug. This population is based on the treatment received (as treated). Treatment compliance/administration and all clinical safety variables will be analyzed using the SAF.

observed HR of 0.769 or lower would result in a statistically significant improvement in OS at the 1-sided nominal type I error of 0.0129 at the second interim efficacy analysis. The final efficacy analysis will be performed after observing approximately 340 OS events in SCC patients. It is projected that an observed HR of 0.801 or lower would result in a statistically significant improvement in OS at the 1-sided nominal type I error of 0.0202 at the final analysis. Table 15 summarizes the alpha spending for interim and final analyses based on planned number of OS events. The actual alpha spending will be based on the actual number of OS events included in the analyses and determined by the O'Brien-Fleming spending function at the time of interim and final analyses.

Table 15: Alpha Spending in Group Sequential Design Using Lan-DeMets (O'Brien-Fleming) Spending Function

1st Interim Efficacy Analysis		2nd Interim Efficacy Analysis		Final Efficacy Analysis	
# Events needed	1-sided Nominal Alpha	# Events needed	1-sided Nominal Alpha	# Events needed	1-sided Nominal Alpha
238 (70%)	0.0074	289 (85%)	0.0129	340 (100%)	0.0202

In the event the primary endpoint is met during interim or final analysis, all pre-specified endpoints will be analyzed at that time at all remaining alpha.

10.6. Additional Statistical Data Handling Conventions

The following analysis and data conventions will be followed:

Definition of baseline:

- Unless otherwise specified, the last assessment before the initial administration of cemiplimab will be considered the baseline evaluation for safety measurements. And the last assessment before the randomization will be considered the baseline evaluation for efficacy measurements.

General rules for handling missing data:

- Unless otherwise specified, there will be no imputations for the missing data.
- The pattern of missing data and potential prognostic factors for missing data (QOL, clinical neurologic assessment, and mental status) will be examined to guide the use of proper statistical models.
- If the start date of an AE or concomitant medication is incomplete or missing, it will be assumed to have occurred on or after the intake of study drug except if an incomplete date (eg, month and year) clearly indicates that the event started prior to treatment. If the partial date indicates the same month or year of the intake of study drug date, then the start date by the study drug intake date will be imputed; otherwise, the missing day or month by the first day or the first month will be imputed.

Visit windows:

7.1.2. Footnotes for the Schedule of Events Table for Screening and Treatment

1. Patients who fail screening may be screened one additional time and an ICF will need to be signed at the re-screen. Some procedures may not need to be repeated if they were previously completed within 28 days prior to cycle 1 day 1.
2. 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. 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.
3. The first dose should be administered no later than 5 days after randomization (except for patient assigned to pemetrexed, for whom the first dose of pemetrexed may be given no later than 10 days after randomization due to need for folate premedication for at least 5 days in the 7 day period preceding the first dose of pemetrexed, as per Section 8.1.2.1).
4. Only for patients assigned to cemiplimab: At cycle 1 day 1 and cycle 1 day 22, vital signs will be collected prior to infusion, and approximately 30 minutes after the completion of the infusion. For all other cemiplimab infusions, vital signs are collected prior to infusion, and approximately 15 minutes after the completion of the infusion. The allowable window for each specified time point is ±10 minutes.
5. For the IC options, doses are weight-based. For cycle 1/day 1, the investigator should use screening height and weight to calculate dose, but cycle 1/day 1 weight is also allowed to be used, per investigator discretion. Weight is measured at start of each cycle. If there is a ≥10% change in weight, the IC chemotherapy dose should be re-calculated.
6. If cycle 1/day 1 is within 72 hours of screening, this assessment does not need to be repeated at cycle 1/day 1.
7. Complete physical examination includes head and neck, lungs, heart, abdomen, lymph nodes, extremities, and skin. A brief neurologic examination should also be performed. The exam (and measurement of weight) may be performed ≤72 hours prior to study treatment.
8. Limited physical exam includes lungs, heart, abdomen, and skin. The exam (and easement of weight) may be performed ≤72 hours prior to study treatment.
9. Hematology and chemistry samples may be obtained ≤72 hours prior to study treatment.
10. Pre-dose serum β-human chorionic gonadotropin (HCG) at screening up to 72 hours prior to first administration. Subsequent predose pregnancy tests (up to 72 hours before the dose) may be urine β-HCG. Serum pregnancy test and urine pregnancy test are requirements for women of child bearing potential only. If surgical procedure for sterility was done ≤30 days prior to signing ICF, serum pregnancy test must still be performed.
11. The PK samples are collected predose (pre-infusion) and at the end of infusion on day 1 of cycle 1. PK samples are collected at pre-infusion and at the end of infusion on day 1 of cycles 2 through 6, 7, 9, 11, 13, and 15. The PK samples are to be obtained only from patients randomized to receive cemiplimab. "End of infusion" includes up to within 10 minutes after completion of the infusion.

12. STUDY MONITORING

12.1. Monitoring of Study Sites

The study monitor and/or designee (eg, contract research organization monitor) will visit each site prior to enrollment of the first patient, and periodically during the study.

12.2. Source Document Requirements

Investigators are required to prepare and maintain adequate and accurate patient records (source documents).

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.

12.3. Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded on electronic CRFs within the EDC system by trained site personnel. All required CRFs must be completed for each patient enrolled in the study. 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.

13. 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

review the interim efficacy analyses for OS. If requested, the IDMC may have access to the treatment allocation code or any other requested data for the purposes of a risk-benefit assessment.

The IDMC will provide the sponsor with appropriate recommendations on the conduct of the clinical study to ensure the protection and safety of the patients enrolled in the study. The IDMC will also institute any measures that may be required for ensuring the integrity of the study results during the study execution. The IDMC will act in an advisory capacity to Regeneron. Regeneron will have responsibility for the overall design and conduct of the study including communication of the data.

All activities and responsibilities of the IDMC are described in the IDMC charter.

5.3.2. Trial Steering Committee

All activities of the Trial Steering Committee (TSC) are described in the TSC charter.

5.4. Study Conduct in Response to COVID-19

Included in amendment 6 of the protocol are measures to account for the "Coronavirus Disease 2019" (COVID-19) pandemic and to minimize the risks to the patients in the study as well as healthcare providers.

6. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

6.1. Number of Patients Planned

Approximately 460 SCC patients will be randomized 1:1 (230 per treatment arm) at approximately 100 sites globally. Approximately 590 patients in the overall population are projected to have accrued when the enrollment for SCC patients is completed. However, the actual number of patients in the overall population depends on the proportion of adenocarcinoma patients in the patient population and the time when Amendment 5 is implemented at each of the study sites.

6.2. Study Population

The study will enroll women ≥18 years old with recurrent, persistent, and/or metastatic cervical cancer that has progressed after platinum-containing chemotherapy given to treat recurrent or metastatic cervical cancer. Patients who have only received prior platinum-based therapy concurrently with radiation therapy for localized disease are not eligible. Starting with Amendment 5, only patients with squamous histology will be enrolled.

6.2.1. Inclusion Criteria

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

1. Recurrent, persistent, and/or metastatic cervical cancer with squamous cell histology, for which there is not a curative-intent option (surgery or radiation therapy with or without chemotherapy).

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

- **Endoscopy, Laparoscopy**. The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following CR or surgical resection is an endpoint.
- **Tumor markers**. Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
- **Cytology, Histology**. These techniques can be used to differentiate between partial responses (PR) and CR in rare cases (eg, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease

- **^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET)**. While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

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

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

Colitis Adverse Event Management

COLITIS CTCAE v4.03 Grade	REGN2810 Dosing Management	Action and Guidelines	Diagnostic Considerations
Grade 3-4	Withhold REGN2810 Discontinue if unable to reduce corticosteroid dose to <10 mg per day prednisone equivalent within 12 weeks of toxicity	• Patients with Grade 3 enterocolitis, drug will be permanently discontinued and treatment with systemic corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month. For Grade 3-4 diarrhea (or Grade 2 diarrhea that persists after initial steroid treatment), • Rule out bowel perforation. Imaging with plain films or computed tomography (CT) can be useful. • Consider consultation with gastroenterologist and confirmation biopsy with endoscopy. • Treat with intravenous (IV) steroids (methylprednisolone 125 mg) followed by high-dose oral steroids (prednisone 1-2 mg/kg once per day or dexamethasone 4 mg every 4 hours). When symptoms improve to grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Taper over 6-8 weeks in patients with diffuse and severe ulceration and/or bleeding. • If IV steroids followed by high-dose oral steroids does not reduce initial symptoms within 48-72 hours, consider treatment with infliximab at 5 mg/kg once every 2 weeks. Discontinue infliximab upon symptom relief and initiate a prolonged steroid taper over 45-60 days. If symptoms worsen during steroid reduction, initiate a retapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer infliximab. CAUTION: infliximab is contraindicated in patients with bowel perforation or sepsis. • If symptoms persist despite the above treatment a surgical consult should be obtained.	All attempts should be made to rule out other causes such as metastatic disease, bacterial or parasitic infection, viral gastroenteritis, or the first manifestation of an inflammatory bowel disease by examination for stool leukocytes, stool cultures, and a Clostridium difficile titer If symptoms are persistent And/or severe, endoscopic evaluation should be considered

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ESig Approval	[redacted]-2021 14:46:23 GMT+0000
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