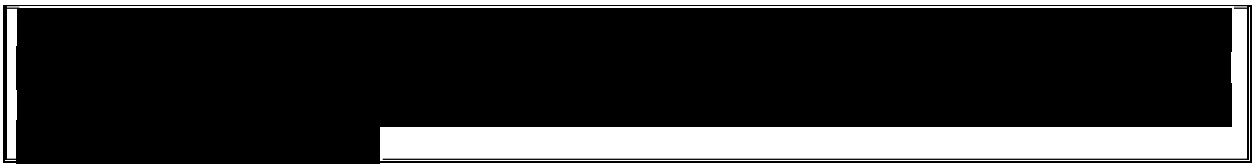
IND Number: [redacted] Regeneron Pharmaceuticals, Inc.
EudraCT number: 2017-000350-19

Clinical Study Protocol

AN OPEN-LABEL, RANDOMIZED, PHASE 3 CLINICAL TRIAL OF REGN2810 VERSUS INVESTIGATOR'S CHOICE OF CHEMOTHERAPY IN RECURRENT OR METASTATIC CERVICAL CARCINOMA

Compound:	REGN2810 (Cemiplimab)
Clinical Phase:	3
Protocol Number:	R2810-ONC-1676/GOG-3016 (CVP1601) ENGOT-cx9
Protocol Version:	R2810-ONC-1676/GOG-3016 (CVP1601) ENGOT-cx9 Amendment 7
Amendment 7 Date of Issue	*See appended electronic signature page*
Amendment 6 Date of Issue	26 May 2020
Amendment 5 Date of Issue	08 Mar 2019
Amendment 4 Date of Issue	16 Aug 2018
Amendment 3JP Date of Issue	27 Apr 2018
Amendment 3 Date of Issue	21 Mar 2018
Amendment 2 Date of Issue:	03 Nov 2017
Amendment 1 Date of Issue:	14 Jul 2017
Original Date of Issue:	13 Apr 2017
Scientific/Medical Monitors:	[redacted] Regeneron Pharmaceuticals, Inc. 777 Old Saw Mill River Road Tarrytown, NY 10591 [redacted]

[redacted]



AMENDMENT HISTORY

Amendment 7

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

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

Patients currently receiving IC chemotherapy (pemetrexed, gemcitabine, topotecan, irinotecan, or vinorelbine) may continue to be treated as long as, in the opinion of the investigator, they are continuing to derive benefit from the assigned treatment.

As of Amendment 7 retreatment is no longer an option. As of Amendment 7, follow-up visits are no longer required.

Detailed changes are in the following table:

Description of Change	Brief Rationale	Section # and Name
Added a cemiplimab Extension Phase so that patients previously randomized to the IC chemotherapy arm can receive cemiplimab 350 mg Q3W up to 96 weeks. Added language stating that patients currently on cemiplimab will also transition to the cemiplimab Extension Phase with pared-down assessments up to 96 weeks (inclusive of previous cemiplimab therapy).	This is due to the observed superiority of OS in patients receiving cemiplimab as compared to IC chemotherapy at the second interim analysis. Cemiplimab continues to demonstrate a safety profile consistent in class.	Clinical Study Protocol Synopsis: Study Design Section 5.1 Study Description and Duration Section 5.1.2 End of Study Definition Section 7.1.7 Note Regarding IDMC Interim Analysis 2 (new section) Section 7.1.7.1 Cemiplimab Extension Phase of the Study (new section) Table 3 Schedule of Events for Cemiplimab Extension Phase (new table) Section 7.1.7.2 Footnotes for the Schedule of Events Table 3 for the

Description of Change	Brief Rationale	Section # and Name
		Cemiplimab Extension Phase (new section) Section 15 Protocol Amendments
Added language to remove option for retreatment upon disease progression for patients entering the cemiplimab Extension Phase.	Based on limited data, the benefit of retreating patients with cemiplimab after progression on cemiplimab during the follow-up phase can't be confirmed.	Section 7.1.7 Note Regarding IDMC Interim Analysis 2 (new section)
Added language to remove follow-up visits for patients entering the cemiplimab Extension Phase.	This is due to the observed superiority of OS in patients receiving cemiplimab as compared to IC chemotherapy at the second interim analysis. Cemiplimab continues to demonstrate a safety profile consistent in class.	Section 7.1.7 Note Regarding IDMC Interim Analysis 2 (new section)
MedDRA Dictionary-Derived Preferred Terms for Potential immune-related adverse events (irAEs) list updated as per MedDRA version 23.0.	The list was updated since the last amendment.	Appendix 3 MedDRA Dictionary-Derived Preferred Terms for Potential irAEs

Amendment 6

Change and Rationale for Change	Sections Changed
Added European Network for Gynaecological Oncological Trial groups (ENGOT) number to Protocol Number and Protocol Version.	Protocol Number Protocol Version
Added 2 interim analyses to provide early efficacy assessment in this unmet-need population, and increased sample size to maintain 90% power with 2 interim analyses. Interim efficacy analyses will be reviewed by Independent Data Monitoring Committee (IDMC).	Clinical Study Protocol Synopsis: Study Design, Population, Statistical Plan Section 3.2.1 Rationale for Patient Population and Study Design Section 5.1 Study Description and Duration

Change and Rationale for Change	Sections Changed
	Figure 2 Study Design Schematic Section 5.1.2 End of Study Definition Section 5.2 Planned Interim Analysis Section 5.3.1. Independent Data Monitoring Committee Section 6.1 Number of Patients Planned Section 7.1.5 Footnotes for the Schedule of Events Table for Post-Treatment Follow-up, footnote #2 Section 8.8 Method of Treatment Assignment Section 10.2 Justification of Sample Size Section 10.4.5.1 Primary Efficacy Analysis Section 10.5 Interim Analysis Table 15 Alpha Spending in Group Sequential Design Using Lan-DeMets (O'Brien Fleming) Spending Function Section 10.6 Additional Statistical Data Handling Conventions
Added language to meet a requirement under the guidance that has come out in the [redacted] to address considerations related to conduct of a study during the COVID-19 pandemic, including statistical analysis language.	Section 5.4 Study Conduct in Response to COVID-19 (new) Section 7.1.1 COVID-19 Adaptation (new) Section 10 Statistical Plan
Corrected typo regarding lymph nodes to have Inclusion Criteria #3 consistent with Appendix 1. Changed >15 mmto ≥15 mm.	Section 6.2.1 Inclusion Criteria, #3
Added language to clarify that peripheral blood mononuclear cell (PBMC) collection is optional and will only be done for patients receiving cemiplimab and who have signed the PBMC consent.	Section 7.1.5 Footnotes for the Schedule of Events Table for Post-Treatment Follow-up, footnote #6
Corrected typo in Appendix 1 to make consistent with Response Evaluation Criteria in Solid Tumors (RECIST) guidelines.	Appendix 1.RESPONSE EVALUATION CRITERIA IN SOLID TUMORS: RECIST GUIDELINE (VERSION 1.1)

Amendment 5

Change and Rationale for Change	Sections Changed
Updated background information on cemiplimab, including information regarding FDA approval in 2018, to keep this section current.	Section 1 Introduction
Updated study population to cap enrollment of patients with adenocarcinoma histology and increase enrollment of patients with squamous cell histology (SCC) based on emerging internal data and early data from other oncology studies that PD-1/PD-L1 blockade is efficacious in squamous histology, and added a rationale for this change. Increased enrollment to approximately 534 in order to accommodate the new target enrollment of 436 patients with SCC histology. Updated the statistical plan to prioritize analysis of SCC over all histologies of cervical cancer.	Clinical Study Protocol Synopsis: Objectives Clinical Study Protocol Synopsis: Study Design Clinical Study Protocol Synopsis: Population Clinical Study Protocol Synopsis: Statistical Plan Section 2.1 Primary Objective Section 2.2 Secondary Objectives Section 3.1 Hypothesis Section 3.2.1 Rationale for Patient Population and Study Design Section 5.1 Study Description and Duration Figure Study Design Schematic Section 6.1 Number of Patients Planned Section 6.2 Study Population Section 6.2.1 Inclusion Criteria, #1 Section 7.2.1 Procedures Performed at the Screening Visit Section 8.8 Method of Treatment Assignment Section 10.2 Justification of Sample Size Section 10.4.5.1 Primary Efficacy Analysis Section 10.4.5.2 Secondary Efficacy Analysis Section 10.4.5.5 Subgroup Analyses Section 10.4.6 Safety Analysis

Change and Rationale for Change	Sections Changed
Updated the total duration of study to accommodate increased enrollment needed to enroll 436 patients with SCC histology.	Section 5.1.2 End or Study Definition
Removed interim futility rule because the overall survival benefit of immune checkpoint blockers in oncology studies may not be evident in an early event analysis. As clinical safety and efficacy of cemiplimab has been demonstrated in a variety of tumor types, including cutaneous squamous cell carcinoma (Migden 2018) and the clinical efficacy of PD-1 blockade in cervical carcinoma has recently been described (Chung 2018), an interim futility analysis is not warranted.	Clinical Study Protocol Synopsis: Statistical Plan Section 5.2 Planned Interim Analysis Section 10.5 Interim Analysis
Updated definitions of treatment and post-treatment periods to align with updated company protocol template.	Section 9.4.1 Adverse Events Section 9.4.2 Serious Adverse Events Section 10.4.6.1 Adverse Events
Removed the text on sample size consideration and subgroup analyses of patients from Japan, as the Japan-specific information will be provided separately.	Clinical Study Protocol Synopsis: Statistical Plan Section 10.2 Justification of Sample Size Section 10.4.5.1 Primary Efficacy Analysis
Added statement that death due to disease progression will not be considered an adverse event but will be reported in efficacy endpoints such as PFS and OS, for consistency with updated company protocol template.	Section 10.4.6.1 Adverse Events
Added description of Trial Steering Committee	Section 5.3.2 Trial Steering Committee (Section Added)
Added statements to clarify that peripheral blood mononuclear cell (PBMC) collection is optional and will only be done for patients receiving cemiplimab.	Table 1 Schedule of Events: Screening and Treatment Period Section 7.1.2 Footnotes for the Schedule of Events Table for Screening and Treatment, footnote 14 Table 2 Schedule of Events, Post-Treatment Follow-Up Section 7.1.5 Footnotes for the Schedule of Events Table for Post-treatment Follow-up, footnote 6

Change and Rationale for Change	Sections Changed
	Section 7.2.7.3 Peripheral Blood Mononuclear Cells (optional)
Added guidance stating "patients who fail screening may be screened one additional time and an ICF will need to be signed at re-screen. Some procedures may not need to be repeated if they were previously completed within 28 days prior to cycle 1 day 1."	Table 1 Schedule of Events: Screening and Treatment Period Section 7.1.2 Footnotes for the Schedule of Events Table for Screening and Treatment, footnote 1 (footnote added) Section 7.2.1 Procedures Performed at the Screening Visit
Added clarifying language to the definition of "further progression after resumption of treatment."	Section 8.6 Treatment Beyond Progression in the Cemiplimab Treatment Group
Updated definition of ORR from overall response rate to objective response rate to align with other protocols in the cemiplimab program.	Clinical Study Protocol Synopsis: Objectives Section 2.2 Secondary Objectives
Added language to clarify that dose modification recommendations pertain to treatment related adverse events (AEs) only.	Section 8.3.1 Dose Modification
Removed confirmatory scans at progressive disease, because per RECIST 1.1, progressive disease does not require confirmation.	Appendix 1 Response Evaluation Criteria in Solid Tumors: RECIST Guideline (Version 1.1)
Added a time point for vital sign check on day 15 of each cycle of irinotecan, as standard of care dictates that vitals should be taken prior to administering each weekly infusion.	Table 1 Schedule of Events: Screening and Treatment Period
Updated footnotes to schedule of events to remove PK and ADA sample collection time points at the end of treatment and during follow-up.	Section 7.1.2 Footnotes for the Schedule of Events Table for Screening and Treatment, footnotes 11 and 12
Updated footnote to schedule of events describing ADA sample collection to include PK sample collection as well.	Section 7.1.5 Footnotes for the Schedule of Events Table for Post-treatment Follow-up, footnote 4
Removed statement that triplicate ECGs are not required.	Section 7.2.5.3 Electrocardiogram
Updated "follow up visit 2" to "end of study" in the Schedule of Events to clarify that survival follow-up starts after the end of study and that follow-up is quarterly.	Section 7.1.5 Footnotes for the Schedule of Events Table for Post-treatment Follow-up, footnote 2

Change and Rationale for Change	Sections Changed
Minor language clarifications	Section 4.2.1 Primary Endpoint
Administrative changes	Title Page: Scientific/Medical Monitor
"REGN2810 (cemiplimab)" replaced with cemiplimab	Throughout

Amendment 4

Amendment 4 incorporates all changes made for Amendment 3 JP, which were changes that were required to conduct the study in Japan. In addition, the following changes were made in this amendment:

Change	Sections Changed
Removed the requirement that patients must be platinum-refractory, which was defined as progression of disease within 6 months of last dose of platinum therapy. Therefore, the term 'platinum-refractory' used to describe the patient population was removed from the protocol.	Face Page- Title Synopsis - Title Synopsis – Objectives Synopsis – Study Design Section 2.1 Primary Objective Section 3.2.1 Rationale for Patient Population and Study Design Section 5.1 Study Description and Duration Figure 2: Study Design Schematic
Revised inclusion requiring platinum-therapy. Patients must have had disease progression after prior platinum therapy in recurrent or metastatic disease setting, but without the requirement for progression within 6 months of last dose.	Clinical Study Protocol Synopsis – Study Population Section 3.1 Hypothesis Section 6.2.1. Inclusion Criteria #2
Revised and shortened the summary of prior studies regarding discussion of platinum-free interval.	Section 3.2.1 Rationale for Patient Population and Study Design
Deleted statement that follow-up will occur until death or study completion. Replaced with clarification that patients will be followed for survival after the follow-up period.	Clinical Study Synopsis – Study Design Section 5.1 Study Description and Duration
Added clarification that patients who only received prior platinum-based therapy concurrently with radiation therapy for localized disease are not eligible.	Clinical Study Protocol Synopsis – Study Population Section 6.2.1 Inclusion Criteria – Criterion #2

Change	Sections Changed
Increased the duration of which the investigator is required to report a pregnancy, from 'within 90 days' to 'within 6 months,' of the last dose of study drug. This change was made to ensure consistency with Exclusion criterion #16 (Section 6.2.2) to exclude women of childbearing potential who are unwilling to practice highly effective contraception for at least 6 months after the last dose of study drug.	Section 9.4.3 Other Events that Require Accelerated Reporting to Sponsor
Added the description of patient population, to the appropriate section in the protocol body, for consistency with the corresponding section in the Clinical Study Protocol Synopsis	Section 6.2 Study Population
Added clarification that for patients who experience toxicity with a dose increase from 100 mg/m^2 to 125 mg/m^2, the recommended first dose reduction should be to 100 mg/m^2.	Section 8.4.3 Irinotecan Dose Modifications
Added clarification of the Dose Modification and Study Treatment Discontinuation Rules for Investigator's Choice Chemotherapy that for other chemotherapy-related AEs that are not specifically addressed in these sections, the general approach for ≥ grade 3 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.	Section 8.4 Dose Modification and Study Treatment Discontinuation Rules for Investigator's Choice Chemotherapy
Added language regarding selection of Investigator's Choice Chemotherapy when prescribing chemotherapy to patients on the control arm to give preference to regimens allowed by local regulations. This addition was requested by the [redacted].	Section 8.1 Investigational and Reference Treatments
Added clarification that the EORTC QLQ-C30 assessment may be performed at any subsequent visit if the assessment is not performed on day 1.	Table 1: Schedule of Events: Screening and Treatment Period Section 7.1.2 Footnotes for the Schedule of Events Table for Screening and Treatment – Footnote #14
Added a subgroup analysis by number of prior lines of systemic therapy for recurrent or metastatic disease (1 line or >1 line), which will	Section 10.4.5.5 Subgroup Analysis

Change	Sections Changed
be performed for the primary and key secondary endpoints. This planned analysis was in response to a request by the Independent Data Monitoring Committee.	

Change	Sections Changed
Updated synopsis for consistency with Amendment 3 Japan, with addition of 'for patients enrolling in Japan, there will be at least 14 days of rest before subsequent irinotecan administration.'	Clinical Study Protocol Synopsis - Treatments
Removed details on drug supply packaging and withdrawable volume and referred to the pharmacy manual	Section 8.1.1 Experimental Group Treatment (REGN2810 [Cemiplimab])
Added clarification that laboratory assessment of glucose may be performed either fasting or non-fasting	Section 7.2.5.4 Laboratory Testing
Clarified that the treatment days for gemcitabine dose reduction guidelines for myelosuppression refer to a 3-week treatment cycle	Section 8.4.4 Gemcitabine Dose Modifications
Revised text to simply state that Exclusion Criterion #10 was deleted in Amendment 3	Section 6.2.2. Exclusion Criteria - Criterion #10
Removed placeholder for footnote 1 of Table 1, which was deleted in Amendment 3	Section 7.1.2 Footnotes for the Schedule of Events Table for Screening and Treatment- footnote 1 (deleted)
Editorial revisions and corrections	Clinical Study Protocol Synopsis – Site Locations Section 3.2.2 Rationale for REGN2810 (Cemiplimab) Dose Selection Section 4.2.3 Other Secondary Endpoints Section 6.1 Number of Patients Planned Section 6.2.1 Inclusion Criteria – Criterion #3 Section 7.2.5.4 Laboratory Testing Section 8.1 Investigational and Reference Treatments Section 8.8 Method of Treatment Assignment

Amendment 3 JP

These changes apply to studies conducted in Japan

Change	**Sections Changed**
Inclusion criterion #5 clarified to include the following statement: For patients enrolling in Japan who are ≥18 and <20 years old, both the patient and parent/legal representative must provide signed informed consent.	Section 6.2.1 Inclusion Criteria - Criterion #5
Per standard of care in Japan, for patients enrolling in Japan, there will be at least 14 days of rest before subsequent irinotecan administration.	Section 8.1.2 Control Group Treatments (Investigator's Choice) Section 8.1.2.3 Irinotecan
Good Clinical Practice Statement section clarified to include the following text: The clinical study will be conducted in compliance with Pharmaceutical and Medical Device Act, Japanese GCP, and other relevant laws in Japan.	Section 14.1 Good Clinical Practice Statement

Amendment 3

Change	Sections Changed
The protocol is being amended to update the monitoring needed for investigators choice chemotherapy of vinorelbine treatment. These changes align with the standard of care.	Table 1 Schedule of Events: Screening and Treatment Period - hematology row under laboratory testing for day 8 and day 29 in all cycles
Figure 2 revised to include ECOG stratification to align with the written text.	Figure 2 Study Design Schematic
The end of treatment definition was added in the text and deleted from Table 1 The end of study definition was updated.	Section 5.1.1 End of Treatment Definition Section 5.1.2 End of Study Definition
Concomitant medications will be assessed on day 42	Table 1 Schedule of Events: Screening and Treatment Period
Study drug indicates REGN2810 (cemiplimab) or investigators choice of chemotherapy	Section 6.2.2 Exclusion Criteria #4, #5, #8, #11, and #19 and throughout the protocol
Exclusion criterion of known allergy to doxycycline or tetracycline was removed from the list of criteria – number of exclusion criterion kept in the list for formatting purposes	Section 6.2.2 Exclusion Criteria, #10
Following text added: All other "days" in the protocol refer to calendar days. Missed doses of study drug or visits will not be made up. In the case of missed doses, response assessments should still follow original schedule. If a patient is unable to undergo scans within the window due to logistical or medical reasons, response assessment will be obtained at the next available date and before subsequent study treatment.	Section 7.1 Schedule of Events

Change	Sections Changed
Footnote #1 was deleted. Footnote #3 updated as follows: 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 . Following text was added to Footnote #10: If surgical procedure for sterility was done ≤30 days prior to signing ICF, serum pregnancy test must still be performed. Footnote #12 updated the ADA sample collection	Section 7.1.2 Footnotes for the Schedule of Events Tables for Screening and Treatment, Footnote 3, 10, and 12
Footnote #1 revised as follows: 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 REGN2810 (cemiplimab) or IC of chemotherapy. Follow-up visit 2 occurs approximately 90 days (±10 days) after follow-up visit 1.	Section 7.1.5 Footnotes for the Schedule of Events Table for Post-treatment Follow-up
Survival status check deleted from Follow-up Visits 1 and 2	Table 2 Schedule of Events Post-Treatment Follow-Up
Any treatment administered, other than anti-cancer therapy, from the time of informed consent until 90 days after the last study treatment will be considered concomitant treatment.	Section 8.10 Concomitant Medications and Procedures
Following text are added for statistical considerations regarding enrollment of patients from Japan:	Section 10.2 Justification of Sample Size

Change	Sections Changed
Based on "Method 2" described in "Basic Principles on Global Clinical Trials" (Ministry of Health, Japan, 2007), the probability of observing a consistent trend across 2 regions (Japan vs. outside of Japan) is calculated. Assume the true treatment effect is uniform across the 2 regions and the natural logarithm of HR is normally distributed. Per method of Kawai (Kawai, 2008), 33 OS events from Japan, or 10% of total 330 OS events, and approximately 44 Japanese patients are required for the primary analysis to yield a probability of 84.6% to observe an HR <1 from both regions for the comparison of REGN2810 (cemiplimab) versus the IC chemotherapy options.	
Subgroup analyses of patients from Japan are included.	Clinical Study Protocol Synopsis: Statistical Plan Section 10.4.5.1 Primary Efficacy Analysis Section 10.4.5.5 Subgroup Analyses
MedDRA Dictionary-Derived Preferred Terms for Potential irAEs list updated as per MedDRA version 20.1	Appendix 3 MedDRA Dictionary-Derived Preferred Terms for Potential irAEs
Minor editorial changes	Throughout the protocol

Amendment 2

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

Change	Sections Changed
Updated anti-drug antibody wording to be consistent with current practice	Section 4.3.2 Anti-Dug Antibody Variables Section 7.1.2 Footnotes for the Schedule of Events Table for Screening and Treatment (footnote #12)
Revised exclusion criteria per request from the [redacted]	Section 6.2.2 Exclusion Criteria (#6, 7, 19, and 20)
Added a window between randomization and start of treatment, to try to provide some flexibility	Protocol Synopsis (Study Design) Section 5.1 Study Description and Duration Table 1 Schedule of Events (footnote reference #3) Section 7.1.2 Footnotes for the Schedule of Events Table for Screening and Treatment (added footnote #3) (new)
Corrected length of study accrual and follow-up for consistency with other sections	Section 5.1.1 End of Study Definition
Clarified that some assessments didn't need to be performed at cycle 1/day 1 if it was within 72 hours of screening, in order to decrease site and patient burden	Table 1 Schedule of Events (footnote reference #6) Section 7.1.2 Footnotes for the Schedule of Events Table for Screening and Treatment (added footnote #6) (new)
Reduced sampling of peripheral blood mononuclear cells, to minimize blood volume collection and to focus exploratory research in the earlier cycles	Section 7.1.2 Footnotes for the Schedule of Events Table for Screening and Treatment (footnote #14 [was previously #11])
Corrected number of planned cycles to be consistent across protocol	Section 7.1.6 Option for Retreatment
Revised wording to provide a window for a drug-free period during irinotecan dosing	Protocol Synopsis (Treatments) Section 8.1.2.3 Irinotecan Section 8.4.3 Irinotecan Dose Modifications
Added Eastern Cooperative Oncology Group (ECOG) performance status as a stratification factor for randomization to	Section 8.8 Method of Treatment Assignment

Change	Sections Changed
balance treatment assignment, per request from the [redacted] The ECOG performance status will not be included in the primary analysis model for efficacy.	
Revised the alternate statistical hypothesis at the request of [redacted]	Section 10.1 Statistical Hypothesis
Updated sections to be consistent with the current protocol template	Section 6.2.2 Exclusion Criteria (#21, new) Section 14.3 Patient Confidentiality and Data Protection (new section)
Made minor editorial changes	Section 5.1.1 End of Study Definition Section 7.1 Schedule of Events Section 7.1.2 Footnotes for the Schedule of Events Table for Screening and Treatment Section 7.1.5 Footnotes for the Schedule of Events Table for Post-treatment Follow-up Section 7.1.6 Option for Retreatment Section 8.1.2 Control Group Treatments (Investigator's Choice) Section 8.1.2.5 Vinorelbine Section 8.5.1.1 Reasons for Permanent Discontinuation of Study Treatment Section 9.4.1 Adverse Events Section 9.4.3 Other Events that Require Accelerated Reporting to Sponsor Section 9.4.4 Reporting Adverse Events Leading to Withdrawal from the Study Appendix 2 Recommended Dose Modification or Discontinuation and Supportive Care Guidelines for Specific Study Drug Related Adverse Events

Amendment 1

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

Change	Sections Changed
An exclusion criterion has been added for the following reason: Patients who have previously been treated with idelalisib will be excluded from treatment with REGN2810 as a result of the safety findings for 3 patients with indolent lymphoma previously treated with idelalisib, a phosphatidylinositol 3-kinase (PI 3-K) inhibitor, in study R1979-ONC-1504. Following a single dose of REGN2810 monotherapy in each case, 2 patients experienced severe stomatitis and/or skin reactions. The third patient experienced myositis and myasthenia gravis after 2 doses of REGN2810.	Section 6.2.2 Exclusion Criteria #18
Additional safety guidance language added for the management of patients developing stomatitis or mucositis	Section 8.5.1 Study Drug Discontinuation
An adverse event of special interest (AESI) has been added to the list of AESIs: An irAE of any grade in a patient previously treated with a PI 3-K inhibitor.	Section 9.4.3 Other Events that Require Accelerated Reporting to Sponsor

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

CLINICAL STUDY PROTOCOL SYNOPSIS

Title	An Open-Label, Randomized, Phase 3 Clinical Trial of REGN2810 Versus Investigator's Choice of Chemotherapy in Recurrent or Metastatic Cervical Carcinoma
Site Location(s)	Patients will be enrolled at approximately 100 sites globally.
Principal Investigator	The Principal Investigator is to be determined.
Objectives	The primary objective is to compare overall survival (OS) for patients with recurrent or metastatic cervical cancer who have histology of squamous cell carcinoma (SCC) and who have any eligible histology, treated with either REGN2810 (cemiplimab) or investigator's choice (IC) chemotherapy. The secondary objectives performed among SCC patients and among all eligible histologies (SCC and adenocarcinoma/adenosquamous carcinoma [AC]) are: • To compare progression-free survival (PFS) of cemiplimab versus IC chemotherapy • To compare objective response rate (ORR) (partial response [PR] + complete response [CR]) of cemiplimab versus IC chemotherapy per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 • To compare the duration of response (DOR) of cemiplimab versus IC chemotherapy • 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 the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30)
Study Design	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 intravenously (IV) as a flat dose of 350 mg every 3 weeks (Q3W). In the control group, IC chemotherapy options are 4 classes: (1) antifolate - pemetrexed, (2) topoisomerase 1 inhibitor - topotecan or irinotecan, (3) nucleoside analogue – gemcitabine, and (4) vinca alkaloid - vinorelbine. 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.

	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

	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)

- Peripheral blood mononuclear cells
- Quality of life assessments

Statistical Plan

The primary OS endpoint will be tested in patients with SCC first. If the null hypothesis is rejected in the 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 first interim efficacy analysis will be performed after observing approximately 238 OS events (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 (85% of total OS events). It is projected that an 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. 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. 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.

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, 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 approximately 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 + 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%.

The primary endpoint of OS will be analyzed in patients with SCC first by stratified log-rank test using geographic region (North America versus Asia versus Rest of World [ROW]) as a stratification factor. The HR and its 95% confidence interval (CI) will be estimated by a stratified Cox regression model using the treatment as covariate.

If the final analysis of OS is statistically significant in the SCC patients, then the analysis of OS will be performed in the overall population by stratified log-rank test using histology and geographic region. If statistically significant, the secondary endpoints PFS and ORR will be tested using a hierarchical procedure. The order of hierarchical testing for secondary endpoints will be specified in the statistical analysis plan (SAP) before database lock (DBL).

Analysis of PFS and ORR will be performed at the time of OS analysis. The PFS will be analyzed using the same statistical method as the analysis of OS. The ORR will be analyzed using Cochran-Mantel-Haenszel test stratified by the same stratification factors used in analysis of OS. An associated odds ratio and 95% CI will be calculated. Objective response rate and the corresponding 95% exact CI will be calculated by the Clopper-Pearson method for each treatment arm.

The change in EORTC QLQ-C30 scores from baseline to the end of the study will be summarized descriptively at each post-baseline time point and compared using a mixed effect model, if appropriate.

Safety observations and measurements including drug exposure, AEs, laboratory data, vital signs, and Eastern Cooperative Oncology Group performance status will be summarized and presented in tables and listings.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition of Term
AC	Adenosquamous carcinoma
ADA	Anti-drug antibody
ADL	Activities of Daily Living
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
βHCG	β-human chorionic gonadotropin
BUN	Blood urea nitrogen
CI	Confidence interval
COVID-19	Coronavirus Disease 2019
CR	Complete response
CRF	Case report form (electronic or paper)
CSCC	Cutaneous squamous cell carcinoma
CT	Computed tomography
DOR	Duration of response
DBL	Database Lock
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
EMA	European Medicines Agency
ENGOT	European Network for Gynaecological Oncological Trial
EORTC QLQ30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
FAS	Full analysis set
FDA	Food and Drug Administration
FFPE	Formalin-fixed, paraffin-embedded
FIH	First-in-human
GCP	Good Clinical Practice
GOG	Gynecologic Oncology Group

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

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

1. INTRODUCTION

The global annual incidence of cervical cancer is approximately 527 000 cases per year, and there are approximately 265 000 deaths (Torre 2015). The highest incidence rates are in the Caribbean, Africa, Eastern Europe, and South America (Forman 2012). In the United States (US), there are approximately 13000 new cases and 4100 deaths annually (Siegel 2016). In most cases, causation is due to infection with human papillomavirus (HPV). Although vaccination against high risk strains of HPV is projected to gradually decrease the global incidence of cervical cancer in the next 15 years, the burden of this disease remains profound (Bray 2012).

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

After progression on first line platinum-taxane based chemotherapy for recurrent or metastatic disease, there is no standard of care. Non-randomized phase 2 trials have demonstrated survival times of 7.4 to 8.1 months (N = 29 and 43 patients, respectively) with single agent pemetrexed monotherapy (Lorusso 2010) (Miller 2008). Gemcitabine monotherapy yielded median overall survival (OS) of 6.5 months in a phase 2 study of women (N = 22 patients) with previously treated cervical cancer (Schilder 2005). In a phase 2 study (N = 45 patients) of topotecan in which most patients had received prior platinum, median OS was 6.6 months (Bookman 2000). In phase 2 studies of vinorelbine for patients who could have received 1 prior chemotherapy regimen for squamous or non-squamous advanced cervical cancer, observed response rates were 13% (6/44 patients) and 7% (2/28 patients), respectively (Muggia 2004) (Muggia 2005). Weekly dosing of irinotecan yielded a response rate of 13% (6/45 patients) in a phase 2 study for women with recurrent squamous cervical cancer in the US (Look 1998), and a response rate of 24% (13/55 patients) in a phase 2 study for women with cervical cancer in Japan (Takeuchi 1991). New systemic therapy options are needed for this patient population.

Cemiplimab (the INN for REGN2810) is a hinge-stabilized IgG4P anti-PD-1 (programmed cell death 1) monoclonal antibody that has demonstrated encouraging efficacy and favorable tolerability in a phase 1 study that is now enrolling patients in multiple expansion cohorts (Papadopoulos 2016) (NCT02383212). Cemiplimab is also being evaluated in various clinical trials and indications globally. On 28 September 2018, cemiplimab was approved in the US by the Food and Drug Administration (FDA) as LIBTAYO® (cemiplimab-rwlc) for the treatment of patients with metastatic cutaneous squamous cell carcinoma (CSCC) or locally advanced CSCC who are not candidates for curative surgery or curative radiation.

The current study seeks to evaluate the clinical efficacy of cemiplimab in patients with recurrent or metastatic cervical cancer that has progressed after platinum-based therapy. Programmed cell death 1 is expressed on activated T-cells, and binding of PD-1 to its ligands, PD-L1 and PD-L2, imparts inhibition of cytotoxic T-cell activity (Francisco 2010). Upregulated expression of PD-1/PD-L1 checkpoint signaling in the tumor microenvironment plays a role in resistance to antitumor immune responses (Zou 2008). The clinical study of cemiplimab in cervical cancer is supported by both preclinical and clinical observations regarding the role of PD-1/PD-L1

checkpoint signaling in the suppression of anti-tumor immune responses against this and other HPV-associated cancers.

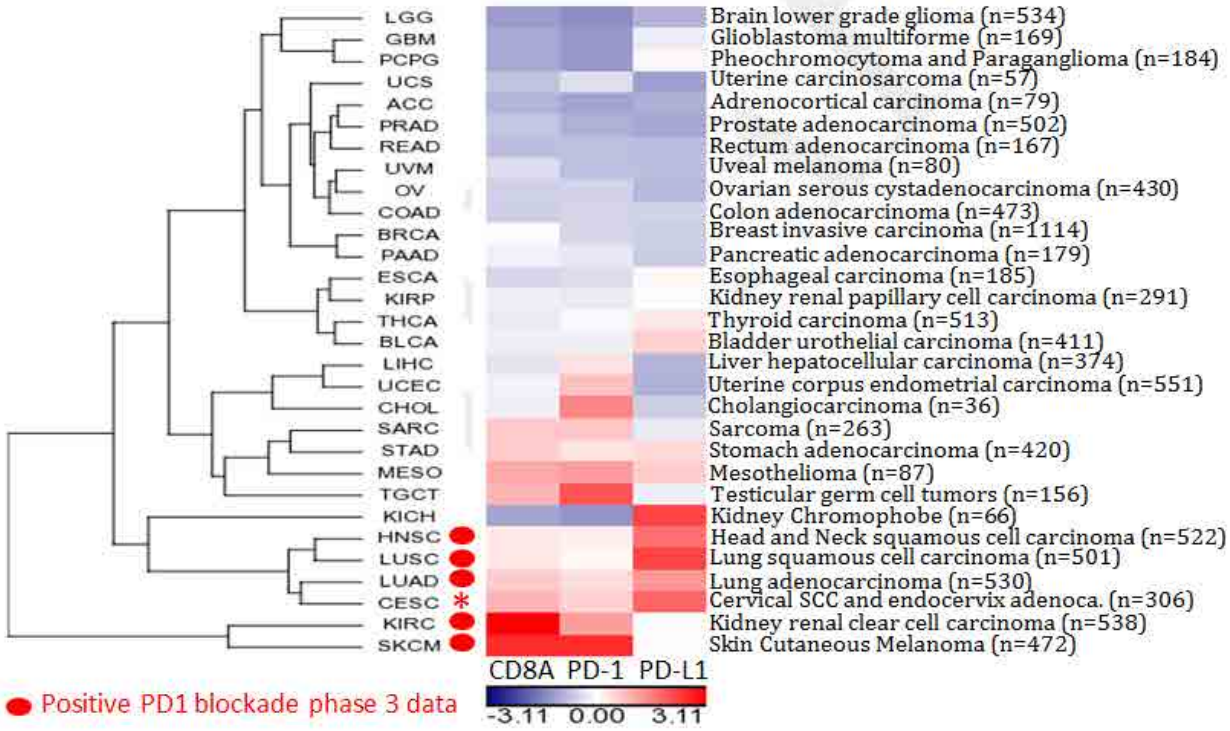
First, almost all cervical squamous cell carcinomas are associated with high risk strains of HPV (The Cancer Genome Atlas Research Network). Tumors that express viral antigen appear to be responsive to PD-1 blockade as a strategy to enhance the antitumor immune response, as demonstrated by positive clinical trial results in patients with HPV-associated head and neck squamous cell carcinoma and in polyomavirus-associated Merkel Cell carcinoma, with nivolumab and pembrolizumab, respectively (Gillison 2016) (Nghiem 2016). Secondly, cervical squamous carcinomas may evade immune response by expression of PD-L1 ligand, which was detectable by immunohistochemistry (>5% staining) in 54% (83/154) of squamous tumors, and in 14% (7/49) of adenocarcinomas (Heeren 2016).

Thirdly, preliminary clinical data demonstrate efficacy of PD-1 blockade against cervical cancer. In a cohort of 24 cervical cancer patients with PD-L1+ recurrent or metastatic cervical cancer treated with pembrolizumab, objective responses were observed in 17% (4/24) of patients and median OS was 9 months (95% confidence interval [CI]: 4 to 12 months) (Frenel 2016). In the first-in-human (FIH) study of cemiplimab, 3 patients with cervical squamous cancer were enrolled in dose escalation cohorts to receive cemiplimab plus hypofractionated radiation therapy (9 gray [Gy] X 3 fractions or 6 Gy X 5 fractions) (Papadopoulos 2016). Two of these patients have experienced durable responses. Radiation therapy was administered in week 2, and cemiplimab was administered intravenously (IV) every 2 weeks (Q2W) for up to 48 weeks or until progression of disease or unacceptable toxicity. Non-radiated lesions were evaluated for response. One patient has experienced a radiologic complete response (CR), and another has experienced an overall partial response (CR in target lesions, with a non-target lesion that persisted). Both patients completed 48 weeks of treatment, and entered post-treatment follow up. The cervical cancer patient with partial response experienced progressive disease (PD) with an enlarging supraclavicular node after approximately 8 months of post-treatment follow up, and this was biopsy-proven. This patient resumed treatment with cemiplimab monotherapy (no radiation) and experienced a partial response at the first response assessment (8 weeks) after resuming treatment.

Fourth, analysis of gene expression data in The Cancer Genome Atlas (TCGA) (The Cancer Genome Atlas Research Network) demonstrates similarities between cervical cancer and other tumor types for which anti-PD-1 therapy achieves therapeutic advantage. Briefly, average expression of 3 genes (CD8A, PD-1, and PD-L1) in each tumor type is normalized to standard distribution across all tumor types. Tumors are organized according to Z-scores using hierarchical clustering (Figure 1). Cervical cancer clusters with non-small cell lung cancer, melanoma, renal clear cell carcinoma, and head and neck squamous cell carcinoma. Programmed cell death 1 blockade improved OS in each of these tumor types in randomized phase 3 studies (Ferris 2016) (Motzer 2015) (Trivedi 2015).

Taken together, these observations suggest that a prospective randomized trial of PD-1 inhibition with cemiplimab is warranted for patients with recurrent/metastatic cervical cancer to potentially improve OS.

Figure 1: TCGA Immune Signatures Using CD8A/PD-1/PD-L1 Expression



Source: Regeneron Molecular Profiling analysis of TCGA RNA-Seq data.
Color key of z value is shown.

Additional background information on the study drug and development program can be found in the Investigator's Brochure.

2. STUDY OBJECTIVES

2.1. Primary Objective

To compare OS for patients with recurrent or metastatic cervical cancer who have histology of squamous cell carcinoma (SCC) and who have any eligible histology, treated with either cemiplimab or investigator's choice (IC) chemotherapy.

2.2. Secondary Objectives

The secondary objectives of the study performed among SCC patients and among all eligible histologies (SCC and adenocarcinoma/adenosquamous carcinoma [AC]) are:

- To compare progression-free survival (PFS) of cemiplimab versus IC chemotherapy
- To compare objective response rate (ORR) (partial response [PR] + CR) of cemiplimab versus IC chemotherapy per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 (Appendix 1)
- To compare the duration of response (DOR) of cemiplimab versus IC chemotherapy

- 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

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

advantage in this patient population, and the IC option in this study comprises a group of treatments that are commonly used in clinical practice as monotherapy options.

In a phase 2 study of pemetrexed (900 mg/m^2 every 21 days), patients (N = 27) who had 1 prior chemotherapy regimen for recurrent or metastatic cervical cancer had an ORR of 15% and a median OS of 7.4 months (Miller 2008). In another phase 2 trial of pemetrexed (500 mg/m^2 every 21 days) for patients (N = 43) with recurrent or metastatic cervical cancer that had been previously treated with 1 prior chemotherapy regimen in any setting (including concurrent chemoradiation), ORR was 14% and median OS was 8 months (Lorusso 2010). The dose and schedule of pemetrexed (500 mg/m^2 IV every 21 days with folic acid and vitamin B_{12} support) that is used in the current protocol is the same pemetrexed monotherapy regimen that has been approved by the FDA for non-small cell lung cancer (Hanna 2004).

Topotecan is an FDA-approved agent for the treatment of cervical cancer when given in combination with cisplatin. Topotecan plus cisplatin, compared to cisplatin alone, improved OS for women with stage IVB, recurrent, or persistent cervical cancer that was not amenable to curative treatment with surgery or radiation therapy in GOG179 (Long 2005). A phase 2 study evaluated topotecan monotherapy for patients with recurrent or metastatic cervical cancer who had received no more than 1 prior chemotherapy regimen for metastatic disease. The regimen was topotecan 1.5 mg/m^2 per day for 5 consecutive days of a 21-day cycle. Of 41 evaluable patients, 34 had received prior chemotherapy, generally including cisplatin. The ORR was 12.5% and the median OS was 6.6 months (Bookman 2000). The 21-day topotecan monotherapy regimen (topotecan 1.5 mg/m^2 per day for 5 consecutive days of a 21-day cycle) was subsequently approved in small cell lung cancer (von Pawel 1999) and in ovarian cancer (ten Bokkel Huinink 2004). Topotecan monotherapy is recognized as a palliative option for patients with recurrent or metastatic cervical cancer (NCCN 2017).

However, in cervical cancer patients who have received prior platinum-based chemotherapy, the topotecan regimen of 1.5 mg/m^2 per day for 5 consecutive days is associated with unacceptable hematologic toxicity, including 68% and 39% incidence rates of grade 4 neutropenia and grade 4 thrombocytopenia, respectively (Bookman 2000). Even among patients who had not received prior systemic therapy for recurrent, persistent, or metastatic cervical cancer, the incidence rates of grade 4 neutropenia and grade 4 thrombocytopenia with this regimen were 68% and 18%, respectively (Muderspach 2001). To optimize patient safety, the starting topotecan dose and schedule in this protocol is 1 mg/m^2 per day for 5 consecutive days, which is acceptable in routine clinical practice.

A phase 2 study of gemcitabine administered over a 28-day treatment course (800 mg/m^2, 3 weeks on, 1 week rest) enrolled 22 patients who had received 1 prior regimen for metastatic, persistent, or recurrent cervical cancer (Schilder 2005). The ORR was 4.5% and median OS was 6.5 months. In the current protocol, the IC regimen for gemcitabine is 1000 mg/m^2 on days 1 and 8 of a 21-day treatment course, which is the FDA-approved dose and schedule for gemcitabine in combination with carboplatin in ovarian cancer (Pfisterer 2006). Gemcitabine also has monotherapy activity in ovarian cancer (Mutch 2007). The FDA approval in ovarian cancer provides toxicity management guidelines that are specific for this dose and schedule of gemcitabine (see Section 8.4.3). Over 12 weeks, this 21-day treatment course provides similar exposure to gemcitabine (8000 mg) as the 28-day treatment course in the Schilder study (7200 mg). Gemcitabine monotherapy is

recommended as a palliative treatment option in recurrent or metastatic cervical cancer (NCCN 2017).

Vinorelbine monotherapy (30 mg/m^2 days 1 and 8, every 21 days) has been evaluated in two phase 2 studies for women with advanced cervical cancer (recurrent or persistent) who could have received one prior systemic therapy. Among 44 patients with squamous histology, the observed response rate was 13% (5 partial responses, 1 complete response). Grade 3 or 4 neutropenia occurred in 41% of patients (Muggia 2004). Among 22 patients with nonsquamous histology, the observed response rate was 7% (2 partial responses), and grade 3 or 4 neutropenia occurred in 32% of subjects (Muggia 2005). Neither vinorelbine study presented survival data, but the 6 squamous responders received a median of 24 weeks (range, 12 to 30 weeks) of treatment (Muggia 2004), and the 2 nonsquamous responders received 18 weeks of therapy before progression (Muggia 2005). The weekly dosing schedule (days 1 and 8, every 21 days) facilitates safe administration for this regimen as regards neutropenia and other potential drug-related AEs.

Irinotecan (CPT-11) monotherapy has been studied in several phase 2 clinical trials in advanced cervical cancer (Look 1998) (Takeuchi 1991) (Irvin 1998) (Verschraegen 1997). A phase 2 study evaluated weekly dosing (125 mg/m^2 x 4 weeks, followed by 2 rest weeks) among women with recurrent cervical cancer who could have only received prior chemotherapy as a radiosensitizer (Look 1998). Response rate was 13% (6/45 evaluable patients). Survival data was not presented, but duration of response was 8.8 months in 1 patient with complete response and median duration of response was 4.8 months (range, 3.2 to 12+ months) among 5 patients with partial responses. Grade 3 or 4 gastrointestinal toxicity occurred in 39% of patients. In a phase 2 study that evaluated the same regimen in cervical cancer patients who could have received 1 prior chemotherapy for recurrent or metastatic disease, response rate was 21% (9/42) and overall median survival was 6.4 months. Dose reduction was required in 77% of patients (Verschraegen 1997).

In a Japanese phase 2 study of CPT-11 in cervical cancer and ovarian cancer, the observed response rate was 24% (13/55 patients) in the cervical cancer group, including 5 complete responses. Two regimens were used in the study, but no significant differences were observed between the regimens of 100 mg/m^2 weekly dosing or 150 mg/m^2 every 2 week dosing (Takeuchi 1991). The regimen of irinotecan 100 mg/m^2 (weekly for 4 weeks, followed by 2 weeks rest) is approved in Japan for women with recurrent and metastatic cervical cancer. Because the patient population in this protocol will include patients who may have received more than 1 prior line of therapy, this 100 mg/m^2 weekly dosing regimen (weekly x 4, followed by 2 rest weeks) is selected as the starting dose for this IC option to optimize patient safety.

In clinical practice, other possible monotherapy options exist for palliation of advanced cervical cancer, including paclitaxel, bevacizumab, ifosfamide, mitomycin, and 5-fluorouracil (NCCN 2017). Paclitaxel or other taxane is not included as an IC chemotherapy option in this protocol because it is anticipated that most study patients will have received prior paclitaxel in the context of prior first-line therapy for recurrent, persistent, or metastatic cervical cancer with cisplatin plus paclitaxel ± bevacizumab as per the GOG240 regimen (Tewari 2014). Most patients with access to bevacizumab will also have received it as part of the GOG240 regimen. Because no survival advantage has been established in this setting for any monotherapy option, the IC options in this protocol (pemetrexed, topotecan, irinotecan, gemcitabine, and vinorelbine) were selected based on relatively favorable safety profiles and the Gynecologic Oncology Group's

(GOG) impression that the older agents (ifosfamide, mitomycin, and 5-fluoruracil) are less commonly used in contemporary practice for cervical cancer.

4. STUDY VARIABLES

4.1. Demographic and Baseline Characteristics

Baseline characteristics will include standard demography (eg, age, race, weight, and height) and disease characteristics, tumor histology (squamous versus adenocarcinoma/adenosquamous), and geographic region, as well as medical and oncology history. Oncologic history will include prior treatments with platinum agents, paclitaxel, and bevacizumab (or reason why paclitaxel or bevacizumab was not given previously).

4.2. Primary and Secondary Endpoints

4.2.1. Primary Endpoint

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.

4.2.2. Secondary Endpoints

The key secondary endpoints are PFS and ORR.

Progression-free survival will be defined as the time from randomization to the date of the first documented tumor progression using RECIST 1.1, or death due to any cause. Patients will be censored according to rules listed below:

1. Patients who do not have a documented tumor progression or death will be censored on the date of their last evaluable tumor assessment.
2. Patients who do not have any evaluable tumor assessments after randomization and do not die will be censored on the date of randomization.

Overall response rate will be defined as the number of patients with a best overall response of confirmed CR or PR divided by the number of patients in the efficacy analysis set. Best overall response will be defined as the best overall response between the date of randomization and the date of the first objectively documented progression or the date of subsequent anti-cancer therapy, whichever comes first.

4.2.3. Other Secondary Endpoints

Other secondary endpoints will include DOR and QOL. Duration of response will be defined as the time between the date of first response (CR or PR) to the date of the first documented tumor progression (per RECIST 1.1) or death due to any cause. Quality of life will be measured by the EORTC QLQ-C30.

Other secondary endpoints will also include the safety and tolerability of cemiplimab. To evaluate the safety and tolerability of cemiplimab IC chemotherapy, the incidence of AEs, serious adverse events (SAEs), deaths, and laboratory abnormalities will be assessed.

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

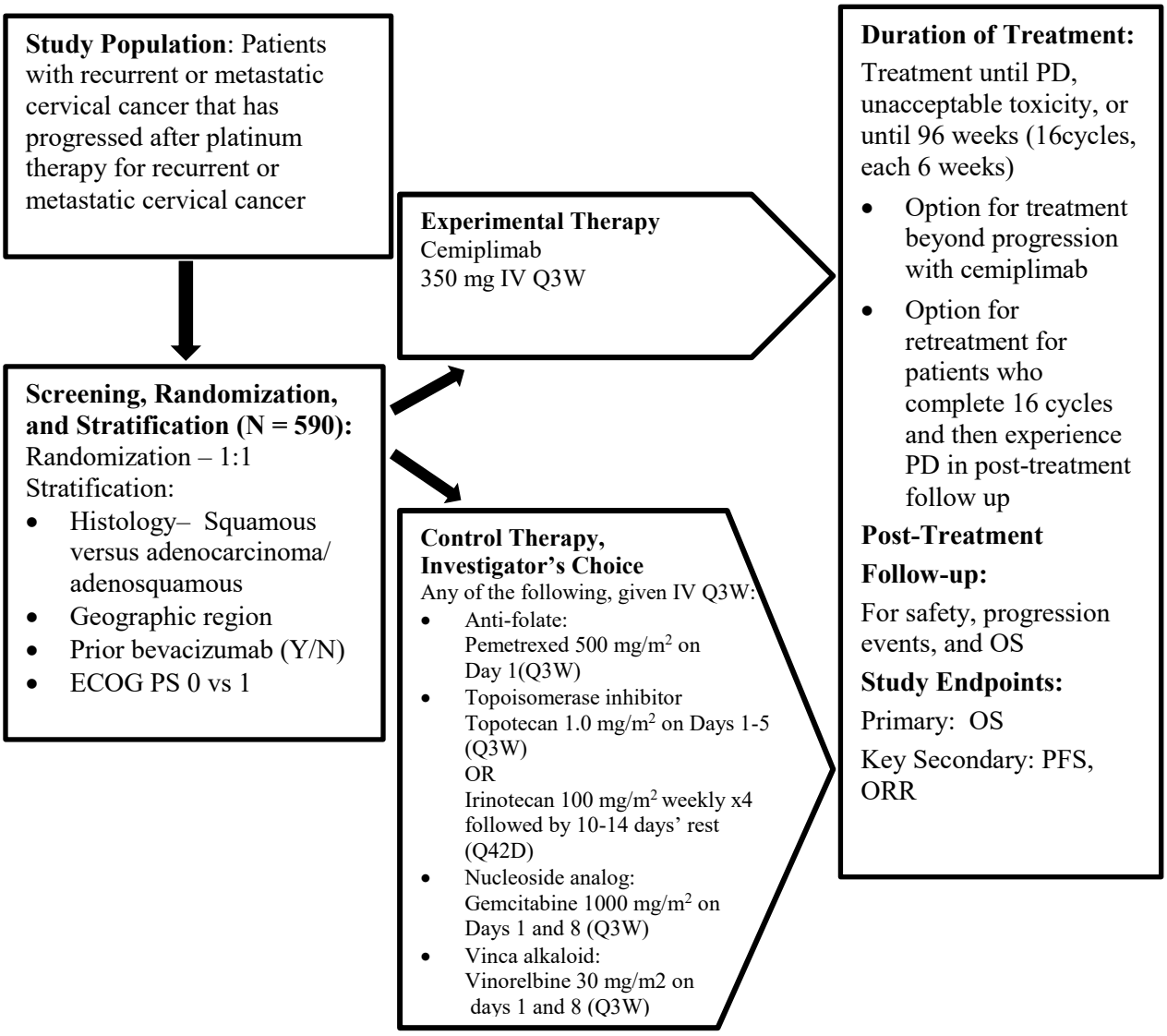
Relationships between efficacy endpoints and candidate biomarkers in tumor and peripheral blood will be described.

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

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

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).

a. Patients with acceptable histologies (squamous carcinoma, adenocarcinoma, and AC) will be enrolled from the original protocol through protocol Amendment 4. For the purpose of this study, AC will be stratified as adenocarcinoma.
b. Starting with protocol Amendment 5, only patients with squamous cell histology are eligible to enroll.

2. Tumor progression or recurrence after treatment with platinum therapy (must have been used to treat metastatic, persistent, or recurrent cervical cancer).

   NOTE: Platinum-therapy given in other settings (eg, concurrent with radiation therapy as part of curative-intent therapy, after radiation [or chemoradiation] as adjuvant treatment in a patient with no evidence of disease) does not satisfy the eligibility requirement regarding prior platinum therapy.

3. Patient must have measurable disease as defined by RECIST 1.1. Measurable disease is defined as at least one lesion that can be accurately measured in at least 1 dimension (longest dimension to be recorded). Each lesion must be ≥10 mm when measured by computed tomography (CT), magnetic resonance imaging (MRI), or caliper measurement by clinical exam or must be ≥20 mm when measured by chest x-ray. Lymph nodes must be ≥15 mm in short axis when measured by CT or MRI.

   Tumors within a previously irradiated field will be designated as non-measurable lesions unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy.

4. Eastern Cooperative Oncology Group (ECOG) performance status ≤1

5. ≥18 years old

   NOTE: For patients enrolling in Japan who are ≥18 and <20 years old, both the patients and parent/legal representative must provide signed informed consent.

6. Hepatic function:

   a. Total bilirubin ≤1.5x upper limit of normal (ULN; if liver metastases ≤3x ULN). Patients with Gilbert's Disease and total bilirubin up to 3x ULN may be eligible after communication with and approval from the medical monitor.
   b. Transaminases ≤3x ULN (or ≤5.0x ULN, if liver metastases)
   c. Alkaline phosphatase ≤2.5x ULN (or ≤5.0x ULN, if liver or bone metastases)

   NOTE: For patients with hepatic metastases**,** if transaminase levels (aspartate aminotransferase [AST] and/or alanine aminotransferase [ALT]) >3x but ≤5x ULN, total bilirubin must be ≤1.5x ULN. If total bilirubin >1.5x but ≤3x ULN, both transaminases (AST and ALT) must be ≤3x ULN.

7. Renal function: Serum creatinine ≤1.5x ULN or estimated creatinine clearance >45 mL/min

8. Bone marrow function:

   a. Hemoglobin ≥9.0 g/dL
   b. Absolute neutrophil count (ANC) ≥1.5x 10^9/L
   c. Platelet count ≥75 x 10^9/L

9. Anticipated life expectancy >12 weeks
10. Willing and able to comply with clinic visits and study-related procedures
11. Provide signed informed consent
12. Able to understand and complete study-related questionnaires
13. Patients must meet at least one of the following criteria regarding prior bevacizumab therapy:
    a. Received prior bevacizumab-containing therapy, which was discontinued due to progression of disease
    b. Received prior bevacizumab-containing therapy, which was discontinued due to toxicity
    c. Was deemed unsuitable for prior bevacizumab therapy for one of the following reasons: (i) unacceptable risk of fistula formation, (ii) poorly controlled hypertension, (iii) "low risk" disease according to the Moore Criteria (Tewari 2015)
    d. Refused prior bevacizumab therapy
    e. Did not have access to bevacizumab therapy due to logistical reasons (eg, lived in a region in which bevacizumab was not commercially available for patients with cervical cancer, or did not have insurance coverage for bevacizumab)
14. Patients must meet at least one of the following criteria regarding prior paclitaxel therapy:
    a. Received prior paclitaxel-containing therapy, which was discontinued due to progression of disease
    b. Received prior paclitaxel-containing therapy, which was discontinued due to toxicity
    c. Was deemed unsuitable for prior paclitaxel therapy for one of the following reasons: (i) neuropathy (ii) allergy to paclitaxel or its components
    d. Refused prior paclitaxel therapy

6.2.2. Exclusion Criteria

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

1. Ongoing or recent (within 5 years) evidence of significant autoimmune disease that required treatment with systemic immunosuppressive treatments, which may suggest higher risk for severe irAEs. The following are not exclusionary: vitiligo, childhood asthma that has resolved, type 1 diabetes, residual hypothyroidism that required only hormone replacement, or psoriasis that does not require systemic treatment.
2. Prior treatment with an agent that blocks the PD-1/PD-L1 pathway.
3. Prior treatment with other systemic immune-modulating agents that was (a) within fewer than 4 weeks (28 days) of the enrollment date, or (b) associated with irAEs of any grade within 90 days prior to enrollment, or (c) associated with toxicity that resulted in discontinuation of the immune-modulating agent. Examples of immune-modulating include therapeutic vaccines, cytokine treatments (other than granulocyte colony stimulating factor or erythropoietin), or agents that target cytotoxic T-lymphocyte antigen 4 (CTLA-4), 4-1BB (CD137), PI 3-K-delta, LAG3, or OX-40.
4. Known history of brain metastasis(es) that may be considered active (screening imaging of brain is not required unless there is clinical suspicion of brain metastases). Patients with

previously treated brain metastases may participate provided that the lesions are stable (without evidence of progression for at least 6 weeks on imaging obtained during the screening period), there is no evidence of new or enlarging brain metastases, and the patient does not require any immunosuppressive doses of systemic corticosteroids for management of brain metastases within 4 weeks of the first dose of study drug (cemiplimab or IC chemo).

5. Immunosuppressive corticosteroid doses (>10 mg prednisone daily or equivalent) within 4 weeks prior to the first dose of study drug (cemiplimab or IC chemo).

   NOTE: Patients who require brief courses of steroids (eg, as prophylaxis for imaging studies due to hypersensitivity to contrast agents) are not excluded.

6. Active bacterial, viral, fungal or mycobacterial infection requiring therapy, including known infection with human immunodeficiency virus (HIV), or active infection with hepatitis B virus (HBV) or hepatitis C virus (HCV).

   NOTE: Active infection with HBV is defined as having positive surface antigen.

7. History of pneumonitis within the last 5 years.

   NOTE: Pneumonitis is inclusive of interstitial pneumonitis and active, non-infectious pneumonia, including interstitial lung disease.

8. Any anticancer treatment (chemotherapy, targeted systemic therapy, photodynamic therapy), investigational, or standard of care, within 30 days of the initial administration of study drug (cemiplimab or IC chemo) or planned to occur during the study period (patients receiving bisphosphonates or denosumab are not excluded).

   NOTE: Any radiation therapy must be discontinued at least 14 days prior to initial administration of study drug (cemiplimab or IC chemo).

9. History of documented allergic reactions or acute hypersensitivity reaction attributed to antibody treatments.

10. Criterion deleted in Amendment 3.

11. Concurrent malignancy other than cervical cancer and/or history of malignancy other than cervical cancer within 3 years of date of first planned dose of study drug (cemiplimab or IC chemo), except for tumors with negligible risk of metastasis or death, such as adequately treated cutaneous squamous cell carcinoma or basal cell carcinoma of the skin or ductal carcinoma in situ of the breast. Patients with hematologic malignancies (eg, chronic lymphocytic leukemia) are excluded.

12. Any acute or chronic psychiatric problems that, in the opinion of the investigator, make the patient ineligible for participation.

13. Patients with a history of solid organ transplant (patients with prior corneal transplant(s) may be allowed to enroll after discussion with and approval from the medical monitor).

14. Any medical co-morbidity, physical examination finding, or metabolic dysfunction, or clinical laboratory abnormality that, in the opinion of the investigator, renders the patient unsuitable for participation in a clinical trial due to high safety risks and/or potential to affect interpretation of results of the study.

15. Pregnant or breastfeeding women.
16. Women of childbearing potential* who are unwilling to practice highly effective contraception prior to the initial study drug treatment, during the study, and for at least 6 months after the last dose. Highly effective contraceptive measures include stable use of combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening; intrauterine device; intrauterine hormone-releasing system; bilateral tubal ligation; vasectomized partner; and or sexual abstinence†, ‡.

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

    † Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

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

17. Patients committed to an institution by virtue of an order issued by either the judicial or the administrative authorities will be excluded from this study.
18. Prior treatment with idelalisib.
19. Prior treatment with live vaccines within 30 days of initial administration of study drug (cemiplimab or IC chemo). Patients must not be treated with live vaccines during the study and up to 5 half-lives following the last dose of study drug.
20. Patients with prior treatment on any clinical trial within 30 days of the initial administration of study drug. Non-interventional and observational trials are acceptable.
21. Member of the clinical site study team and/or his or her immediate family.

6.3. Premature Withdrawal from the Study

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

The investigator and/or sponsor have the right to withdraw a patient from the study if it is no longer in the interest of the patient to continue in the study, or if the patient's continuation in the study places the scientific outcome of the study at risk (eg, if a patient does not or cannot follow study procedures). An excessive rate of withdrawals would render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided.

Patients who are withdrawn prematurely from the study will be asked to complete study assessments, as described in Section 7.1.4. Patients who discontinue study drug will, as feasible, remain in the study, to complete the follow-up procedures (Section 7.1.4). When patients

withdraw from the study (eg, to pursue treatment options not allowed in the study), they should be encouraged to provide consent for OS follow-up. Patients who specifically withdraw consent for follow-up should notify the investigator of this decision in writing whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, and should include whether it is from further treatment only, or also from study procedures and follow-up. It should also be entered in the appropriate case report form (CRF) page. If survival is being assessed, use of publicly available information should only be in accordance with local law.

Rules for discontinuation of study treatment (permanent or temporary) are discussed in Section 8.5.

6.4. Replacement of Patients

Patients prematurely discontinued from the study will not be replaced.

7. STUDY SCHEDULE OF EVENTS AND PROCEDURES

7.1. Schedule of Events

Study assessments and procedures are presented by study period and visit in Table 1 and Table 2. The allowable window for all visit days and assessments is ±3 business days (excluding weekends and holidays), unless otherwise stated in the protocol. All other "days" in the protocol refer to calendar days. For response assessments (CT or MRI), the window is ±7 days from planned scan dates (day 42 of cycles 1-4, 6, 8, 10, 12, 14, and 16).

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

7.1.1. COVID-19 Adaptation

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

Table 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		

		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]					

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. 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

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

Phase is approximately 6 weeks, corresponding to two Q3W cemiplimab treatments (+/- 3-day treatment window). The principle of "time marches on" applies in the Extension Phase: Treatment not administered in the treatment window will not be made up. Treatment beyond progression is allowed in the cemiplimab Extension Phase if the conditions set forth in Section 8.6 are met.

Table 3: Schedule of Events for Cemiplimab Extension Phase

	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]**
Inclusion//Exclusion	X				
Informed Consent[1]	X				
Serious Adverse Events	X	X	X	X	
Cemiplimab 350 mg IV		X	X		
Complete Physical Examination	X	After the Screening Period, these assessments should be done as clinically appropriate.			
ECOG PS	X				
Limited Physical Exam					
Vital Signs	X				
Hematology	X				
Blood Chemistry	X				
Pregnancy Test for WOCBP	X				
TSH (with reflex T3, free T4)	X				
CT and/or MRI	X				
Concomitant Medications	X				
Concomitant Procedures	X				

	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

- 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).

7.2.5.4. 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

Urinalysis (Dipstick)

Glucose	pH	Ketones
Blood	Specific gravity	Spot urine protein

Other Laboratory Tests

- Prothrombin time, Activated partial thromboplastin time
- HBV, HCV, HIV testing
- Serum β-HCG
- Thyroid-stimulating hormone (TSH) (+ reflex T3 and free T4). Thyroid-stimulating hormone will be analyzed by the site's local laboratory. If TSH is abnormal, a T3 and free T4 should be measured at the investigative site's local laboratory.

Abnormal Laboratory Values and Laboratory Adverse Events

- All laboratory values must be reviewed by the investigator or authorized designee.
- Significantly abnormal test results that occur after start of treatment must be repeated to confirm the nature and degree of the abnormality. When necessary, appropriate ancillary investigations should be initiated. If the abnormality fails to resolve or cannot be explained by events or conditions unrelated to the study medication or its administration, the medical monitor must be consulted.
- The clinical significance of an abnormal test value, within the context of the disease under study, must be determined by the investigator.

Criteria for reporting laboratory values as AEs are provided in Section 9.4.5.

7.2.5.5. Anti-Drug Antibody Measurements and Samples

Samples for ADA assessment will be collected prior to dosing at time points shown in Table 1 and during the follow-up period as shown in Table 2. Any unused samples collected for ADA assessment may be used for exploratory research or to investigate unexpected AEs.

7.2.5.6. Pharmacokinetic Samples

Samples for PK assessment will be collected prior to dosing and at end of infusion (or within 10 minutes of the end of infusion) at time points shown in Table 1 and during the follow-up period as shown in Table 2. Any unused samples collected for PK assessment may be used for exploratory research or to investigate unexpected AEs.

7.2.6. Quality of Life Procedures

Quality of life questionnaires (EORTC QLQ-C30) will be collected according to the time points shown in Table 1 and Table 2.

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.

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.

Regeneron will provide cemiplimab. Investigator's choice chemotherapy (pemetrexed, topotecan, irinotecan, gemcitabine, and vinorelbine) should be procured by investigative sites as local commercial product, where allowed by local regulations. In countries in which local regulations do not allow IC chemotherapy to be procured as local commercial product for the study, Regeneron may provide the chemotherapy to the study sites. The sites will also procure any supplies needed for administration of investigational product, including IV bags, diluents, lines, and filters. Investigational product will be stored in a secure area according to local regulations.

8.1.1. Experimental Group Treatment (Cemiplimab)

Open-label cemiplimab will be supplied as a liquid in sterile, single-use vials. Each vial will contain cemiplimab at a concentration of 50 mg/mL. Instructions on dose preparation are provided in the pharmacy manual.

Open-label cemiplimab will be administered in an outpatient setting as a 30-minute IV infusion. Each patient's dose will be administered as a flat dose of 350 mg Q3W.

A pharmacist or other qualified individual will be identified at each site to prepare cemiplimab for administration. The prepared infusion bag should be kept no more than 6 hours at room temperature, or no more than 24 hours at 2°C to 8°C. Detailed preparation and administration instructions will be provided to the sites in the pharmacy manual.

8.1.2. Control Group Treatments (Investigator's Choice)

Patients assigned to the control arm will receive one of the Investigator's Choice chemotherapy options, as follows:

- Antifolate: Pemetrexed, 500 mg/m^2 IV every 21 days, for up to 96 weeks of treatment. Vitamin B_{12} and folate support will be provided according to standard of care with pemetrexed (Lorusso 2010)
- Topoisomerase 1 inhibitor: Topotecan, 1 mg/m^2 daily IV for 5 days, every 21 days, for up to 96 weeks of treatment (Bookman 2000); or irinotecan 100 mg/m^2 IV weekly x 4, followed by 10 to 14 days' rest, for up to 96 weeks of treatment (Look 1998) (Takeuchi 1991). For patients enrolling in Japan, there will be at least 14 days of rest before subsequent irinotecan administration

  NOTE: For patients without significant toxicity during the first 21-day course of topotecan, subsequent courses may be increased to 1.25 mg/m^2 x 5 days, every 21 days.

  NOTE: For patients without significant toxicity during the first 42-day course of irinotecan, subsequent courses may be increased to 125 mg/m^2 IV weekly x 4, followed by 2 weeks rest
- Nucleoside analogue: Gemcitabine, 1000 mg/m^2 IV on days 1 and 8 and every 21 days, for up to 96 weeks of treatment (Mutch 2007) (Schilder 2005)
- Vinca alkaloid: Vinorelbine 30 mg/m^2 IV on days 1 and 8 and every 21 days, for up to 96 weeks of treatment (Muggia 2004) (Muggia 2005)

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.

See Section 3.2.3 for rationale regarding doses and schedules for Investigator's Choice options.

For pemetrexed, topotecan, irinotecan, gemcitabine, and vinorelbine, instructions for storage, handling, and administration are to be found in the appropriate Summary of Product Characteristics or package insert or pharmacy reference sheets.

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 1weight 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.

8.1.2.1. Pemetrexed, Alimta®

Drug Class and Mechanism of Action

Pemetrexed is a folate analogue that inhibits multiple enzymes involved in both purine and pyrimidine synthesis, including thymidylate synthase, dihydrofolate reductases, and glycinamide ribonucleotide formyl transferase. Pemetrexed is not metabolized to an appreciable extent, and is primarily eliminated in the urine.

Supplier/How Handled

See pharmacy manual.

Solution Preparation

See pharmacy manual.

Storage/Stability

See pharmacy manual.

Administration

Pemetrexed will be administered at a dose of 500 mg/m^2 as an IV infusion over 10 minutes (±5 minutes) on day 1 of each 21-day cycle (Lorusso 2010) for up to 96 weeks of treatment. See Section 3.2.3 for rationale in support of IC chemotherapy regimens.

To reduce toxicity, patients treated with pemetrexed must be instructed to take a low dose oral folic acid preparation or multivitamin with folic acid on a daily basis (usual dose, 400 µg/day; range, 350 µg/day to 1000 µg/day). At least 5 daily doses of folic acid must be taken in the 7-day period preceding the first dose of pemetrexed. Daily folic acid dosing should continue during the entire period of pemetrexed treatment and for 21 days after the last dose of pemetrexed. Patients must also receive 1 intramuscular injection of 1000 µg vitamin B_{12} in the week preceding the first dose of pemetrexed, and with every third pemetrexed dose thereafter (every 9 weeks, if no delays in pemetrexed dosing). Subsequent 1000 µg vitamin B_{12} injections may be given on the same day as pemetrexed infusions.

Adverse Effects

See FDA/European Medicines Agency (EMA)-approved (or local equivalent) pemetrexed prescribing information for a comprehensive list of AEs associated with pemetrexed.

8.1.2.2. Topotecan

Drug Class and Mechanism of Action

Topotecan is a cell cycle-specific inhibitor of the nuclear enzyme topoisomerase I. It has a mean half-life of approximately 3 hours. Topotecan's metabolism and clearance are complex but it is estimated that approximately 40% of the drug undergoes renal clearance.

Supplier/How Supplied

See pharmacy manual.

Solution Preparation

See pharmacy manual.

Storage/Stability

See pharmacy manual.

Administration

Topotecan 1 mg/m^2 will be administered by IV infusion over 30 minutes (±10 minutes) daily for 5 consecutive days, starting on day 1 of a 21-day course (Bookman 2000) for up to 96 weeks of treatment. See Section 3.2.3 for rationale in support of IC chemotherapy regimens. For patients who do not experience significant toxicity with the first course of topotecan, subsequent courses may be increased to topotecan 1.25 mg/m^2 daily x 5 days, every 21 days.

Adverse effects

See FDA/EMA-approved (or local equivalent) topotecan prescribing information for a comprehensive list of AEs associated with topotecan.

8.1.2.3. Irinotecan

Drug Class and Mechanism of Action

Irinotecan is a derivative of camptothecin. Camptothecins interact specifically with the enzyme topoisomerase 1, which relieves torsional strain in DNA by inducing reversible single-strand breaks. Irinotecan and its active metabolite SN-38 bind to the topoisomerase 1-DNA complex and prevent relegation of these single strand breaks. Cytotoxicity of irinotecan is thought be due to double-stranded damage during DNA synthesis when replication enzymes interaction with ternary complex formed by DNA/topoisomerase 1/irinotecan or SN-38. Mammalian cells cannot efficient repair these double-strand breaks.

Supplier/How Supplied

See pharmacy manual.

Stability/Storage

See pharmacy manual.

Preparation

See pharmacy manual.

Administration

Irinotecan 100 mg/m^2 will be administered IV over approximately 90 minutes (±15 minutes) 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. See Section 3.2.3 for rationale for dose and schedule of IC chemotherapy regimens.

For patients who do not experience significant toxicity with the first course of irinotecan, subsequent courses may be increased to irinotecan 125 mg/m^2 on days 1, 8, 15, and 22, followed by 10 to 14 days of rest. For patients enrolling in Japan, there will be at least 14 days of rest before subsequent irinotecan administration.

Adverse Effects

See FDA/EMA-approved (or local equivalent) irinotecan prescribing information for a comprehensive list of AEs associated with irinotecan.

8.1.2.4. Gemcitabine, Gemzar®

Drug Class and Mechanism of Action

Gemcitabine HCl is a nucleoside analog that exhibits anti-tumor activity. Gemcitabine is a pyrimidine antimetabolite that is anabolized into a diphosphate form, which inhibits ribonucleotide reductase, and a triphosphate form, which is incorporated into DNA resulting in chain termination.

Supplier/How Supplied

See pharmacy manual.

Stability/Storage

See pharmacy manual.

Preparation

See pharmacy manual.

Administration

Gemcitabine 1000 mg/m^2 will be administered IV over approximately 30 minutes (±10 minutes) on days 1 and 8 and every 21 days, for up to 96 weeks of treatment. See Section 3.2.3 for rationale for dose and schedule of IC chemotherapy regimens.

Adverse effects

See FDA/EMA-approved (or local equivalent) gemcitabine prescribing information for a comprehensive list of AEs associated with gemcitabine.

8.1.2.5. Vinorelbine

Drug Class and Mechanism of Action

Vinorelbine is a vinca alkaloid compound that interferes with microtubule assembly.

Supplier/How Supplied

See pharmacy manual.

Stability/Storage

See pharmacy manual.

Preparation

See pharmacy manual.

Administration

Vinorelbine 30 mg/m^2 will be administered IV over approximately 6 to 10 minutes (±5 minutes) on days 1 and 8, every 21 days, for up to 96 weeks of treatment. See Section 3.2.3 for rationale for dose and schedule of IC chemotherapy regimens.

Adverse Events

See FDA/EMA-approved (or local equivalent) vinorelbine prescribing information for a comprehensive list of AEs associated with vinorelbine.

8.2. Pretreatments

No premedications are to be administered for the first dose of cemiplimab. If needed, premedication will be allowed for subsequent doses of cemiplimab to manage any observed low-grade infusion reactions.

For the IC chemotherapy options, appropriate premedication for study treatments may be administered at the investigator's discretion as per usual clinical practice and in accordance with institutional guidelines. Premedications should be procured by the investigative sites where allowed by local regulations. In countries in which local regulations do not allow premedications to be procured as local commercial product for the study, Regeneron may provide the premedications to the study sites.

For patients who receive pemetrexed, premedications should include folate and vitamin B_{12}, per manufacturer's instructions. At least 5 daily doses of folic acid (usual dose, 400 µg/day; range, 350 µg/day to 1000 µg/day) must be taken in the 7-day period preceding the first dose of pemetrexed. Patients must also receive 1 intramuscular injection of 1000 µg vitamin B_{12} in the week preceding the first dose of pemetrexed. Skin rashes have been reported to be more severe in patients not pretreated with corticosteroid prior to pemetrexed. Pretreatment with dexamethasone (or equivalent) reduces the incidence and severity of cutaneous reaction to pemetrexed. Dexamethasone 4 mg (or equivalent) should be given twice daily on the day before, the day of, and the day after pemetrexed infusion.

8.3. Dose Modification and Study Treatment Discontinuation Rules for Cemiplimab

Adverse events are to be reported according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03.

8.3.1. Dose Modification

The general approach regarding missed doses of cemiplimab (eg, due to AEs) is "time marches on." Missed doses of systemic therapy will not be made up, unless ≤3 business days from the scheduled date.

The planned dose and schedule is a 350 mg flat dose of cemiplimab IV over approximately 30 minutes (±10 minutes) Q3W. Patients will generally remain on the assigned dosage of cemiplimab throughout the course of study treatment. The general approach to cemiplimab toxicity management is dose interruption rather than dose modification. Cemiplimab treatment may be held at any time upon occurrence of a treatment-related AE. General guidelines for cemiplimab treatment modifications due to treatment-related AEs and irAEs are provided in Table 4 and Table 5. These recommendations should be seen as guidelines, and the treating physician should exercise clinical judgment based on the symptoms and condition of the individual patient. For additional information regarding irAEs, reference Section 8.3.2 and Appendix 2. Acute infusion reactions to cemiplimab are discussed separately in Section 8.7.

Table 4: General Guidelines for Cemiplimab Treatment Modifications or Discontinuations Due to Adverse Events

Toxicity	Grade	Hold Treatment?	Restarting Criteria	Discontinuation Criteria
Hematological Toxicity (other than grade 3 thrombocytopenia greater than 7 days or associated with bleeding)	1, 2, 3	No	N/A	N/A
	4	Yes	Toxicity resolves to grade ≤1 or baseline	Toxicity does not resolve within 84 days of last infusion *Permanent discontinuation should be considered for any severe or life-threatening event*
Grade 3 thrombocytopenia greater than 7 days or associated with bleeding	3	Yes	Toxicity resolves to grade ≤1 or baseline	Toxicity does not resolve within 84 days of last infusion *Permanent discontinuation should be considered for any severe or life-threatening event*
Nonhematological Toxicity NOTE: Exceptions to be treated as for Grade 1 toxicity: • Grade 2 alopecia • Grade 2 fatigue • Clinically insignificant lab abnormality not meeting AE criteria	1	No	N/A	N/A
	2	Consider withholding for persistent symptoms	Toxicity resolves to grade 0–1 or baseline	Toxicity does not resolve within 84 days of last infusion
	3	Yes	Toxicity resolves to grade 0–1 or baseline	Toxicity does not resolve within 84 days of last infusion
	4	Yes	N/A	Patient must be discontinued

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

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

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.

Table 7: Dose Reductions for Pemetrexed: Hematologic Toxicity

Toxicity	Dose Modification
Nadir ANC <500/mm^3 and nadir platelets ≥50,000/mm^3	75% of previous dose
Nadir platelets <50,000/mm^3 without bleeding regardless of nadir ANC	75% of previous dose
Nadir platelets <50,000/mm^3 with bleeding regardless of nadir ANC	50% of previous dose

If patients develop nonhematologic toxicity ≥grade 3, treatment should be held until resolution to less than or equal to the patient's pretherapy value. Treatment should be resumed according to the guidelines in Table 8.

Table 8: Dose Reductions for Pemetrexed: Nonhematologic Toxicity

Toxicity	Dose Modification
Any grade 3[a] or 4 toxicities except mucositis	75% of previous dose
Any diarrhea requiring hospitalization (regardless of grade) or grade 3 or 4 diarrhea	75% of previous dose
Grade 3 or 4 mucositis	50% of previous dose

[a] Excluding grade 3 transaminase elevation, for which no dose modification is required

Pemetrexed therapy should be discontinued if patient experiences any hematologic or nonhematologic grade 3 or 4 toxicity (except transaminase elevations) after 2 dose reductions, and immediately for grade 3 or 4 neurologic toxicity at any time.

Renally impaired patients: In clinical studies, patients with creatinine clearance ≥45 mL/min required no dose adjustments other than those required for all patients. Insufficient numbers of patients with creatinine clearance <45 mL/min have been treated to make dosage recommendations for this group. Therefore, pemetrexed should not be administered to patients with creatinine clearance <45 mL/min using the standard Cockcroft and Gault formula. Caution should be used in administering pemetrexed concurrently with nonsteroidal anti-inflammatory drugs to patients with creatinine clearance <80 mL/min.

Cockcroft and Gault Formula:

Creatinine Clearance, Males (mL/min) = [140 – Age in years] * [Actual Body Weight in kg]/ 72 * [Serum Creatinine, mg/dL]

Creatinine Clearance, Females (mL/min) = estimate creatinine clearance for males * 0.85

8.4.2. Topotecan Dose Modifications

The dose reduction guidelines for topotecan are in Table 9.

Table 9: Dose Reductions for Topotecan

Toxicity	Dose Modification
ANC ≤1000/mm^3 **or** Platelet count of ≤100,000/mm^3 **or** Hemoglobin <9.0 g/dL **or** Serum creatinine >1.5 mg/dL	Delay next cycle of topotecan until hematologic or renal recovery. No dose reduction unless criteria below are met.
ANC <500/mm^3 in preceding cycle	Permanently reduce topotecan dose to 0.75 mg/m^2 or administer prophylactic granulocyte colony-stimulating factor during subsequent cycles
Platelets <25,000/mm^3 in preceding cycle	Permanently reduce topotecan dose to 0.75 mg/m^2
Creatinine clearance 20 mL/min to 39 mL/min in preceding cycle	Permanently reduce topotecan dose to 0.75 mg/m^2

Special safety considerations for topotecan:

- Topotecan-induced neutropenia can lead to neutropenic colitis, which can be fatal. In patients presenting with neutropenia, fever, and a compatible pattern of abdominal pain, consider the possibility of neutropenic colitis.
- For patients for whom dose was increased to 1.25 mg/m^2 after the first course and then experienced any toxicity requiring dose reduction, the recommended first dose reduction is to 1.0 mg/m^2.
- Topotecan can cause interstitial lung disease (ILD), which can be fatal. Monitor patients for symptoms indicative of interstitial lung disease (cough, fever, dyspnea, or/or hypoxia), and discontinue topotecan if a new diagnosis of ILD is confirmed.

8.4.3. Irinotecan Dose Modifications

The starting dose for irinotecan is 100 mg/m^2 weekly x 4, followed by 10 to 14 days of rest. Patients who experience toxicity at 100 mg/m^2 will undergo a first dose reduction (dose level -1) to 75 mg/m^2. Patients who experience toxicity at 75 mg/m^2 will undergo a second dose reduction to dose level -2) of 50 mg/m^2.

For patients who experience toxicity with 125 mg/m^2 after an increase from the starting dose of 100 mg/m^2 (described in Section 8.1.2.3), the recommended first dose reduction is to 100 mg/m^2.

A new cycle of therapy should not begin until the granulocyte count has recovered to ≥1500/mm^3, and the platelet count has recovered to ≥100,000/mm^3, and treatment-related diarrhea has fully resolved. Treatment should be delayed for 1 to 2 weeks to allow for recovery of irinotecan-related toxicities. If the patient has not recovered after a 2-week delay, consideration should be given to discontinuing irinotecan. Dose modifications of irinotecan for specific toxicities are provided in Table 10.

Table 10: Recommended Dose Modifications for Irinotecan Monotherapy[a]

Worst Toxicity, NCI Grade[b]	During a Cycle of Therapy	At Start of Next Cycle of Therapy (after adequate recovery), Compared with the Starting Dose of the Previous Cycle
Neutropenia		
1 (1500 – 1999/mm^3)	Maintain dose level	Maintain dose level
2 (1000 – 1499/mm^3)	↓ 25 mg/m^2	Maintain dose level
3 (500 – 999/mm^3)	Omit dose level until resolved to ≤ grade 2, then ↓ 25 mg/m^2	↓ 25 mg/m^2
4 (<500/mm^3)	Omit dose level until resolved to ≤ grade 2, then ↓ 50 mg/m^2	↓ 50 mg/m^2
Neutropenic Fever	Omit dose level until resolved, then ↓ 50 mg/m^2	↓ 50 mg/m^2
Other Hematologic Toxicities	Dose modifications for leucopenia, thrombocytopenia, and anemia during a cycle of therapy and at the start of subsequent cycles of therapy are also based on NCI toxicity criteria and are the same as those recommended for neutropenia above	
Diarrhea		
1 (2 – 3 stools/day)[c]	Maintain dose level	Maintain dose level
2 (4 – 6 stools/day)[c]	↓ 25 mg/m^2	Maintain dose level
3 (7 – 9 stools/day)[c]	Omit dose level unit resolved to ≤ grade 2, then ↓ 25 mg/m^2	↓ 25 mg/m^2
4 (≥10 stools/day)[c]	Omit dose level until resolved to ≤ grade 2, then ↓ 50 mg/m^2	↓ 50 mg/m^2
Other nonhematologic toxicities[d]		
1	Maintain dose level	Maintain dose level
2	↓ 25 mg/m^2	Maintain dose level
3	Omit dose level until resolved to ≤ grade 2, then ↓ 25 mg/m^2	↓ 25 mg/m^2
4	Omit dose level until resolved to ≤ grade 2, then ↓ 50 mg/m^2	↓ 50 mg/m^2

[a] All dose modifications should be made based on the worst preceding toxicity.
[b] National Cancer Institute Common Toxicity Criteria (version 4.0)
[c] All numbers refer to increase over number of pre-treatment number of stools/day
[d] Excludes anorexia, alopecia, fatigue, asthenia, and laboratory abnormalities that are not felt to be clinically significant

8.4.4. Gemcitabine Dose Modifications

The dose reduction guidelines for myelosuppression on days 1 and 8 (of a 3-week treatment course of gemcitabine) are in Table 11.

Table 11: Dose Modifications for Gemcitabine for Myelosuppression on Day of Treatment

Treatment Day	Absolute Neutrophil Count ($X 10^6$/L)		Platelet Count ($X 10^6$/L)	% of Full Dose
Day 1	≥1500 <1500	And Or	≥100 000 <100 000	100% Hold
Day 8	≥1500 1000-1499 <1000	And Or Or	≥100 000 75000-99999 <75000	100% 50% Hold

The dose reduction guidelines for myelosuppression (of a 3-week treatment course of gemcitabine) on in the preceding cycle are in Table 12.

Table 12: Gemcitabine Dose Modifications for Myelosuppression in Preceding Cycle

Occurrence	Myelosuppression During Treatment Cycle	Dose Modification
Initial Occurrence	ANC <500 x 10^6/L for more than 5 days ANC <100 x 10^6/L for more than 3 days Febrile Neutropenia Platelets <25000 x 10^6/L Cycle delay >1 week due to toxicity	Permanently reduce gemcitabine to 800 mg/m^2 on days 1 and 8
Subsequent Occurrence	If any of the above toxicities occurred after the initial dose reduction	Permanently reduce gemcitabine to 800 mg/m^2 on day 1 only

Permanently discontinue gemcitabine for any of the following:

- Unexplained dyspnea or other evidence of severe pulmonary toxicity
- Severe hepatic toxicity
- Hemolytic-Uremic Syndrome
- Capillary Leak Syndrome
- Posterior reversible encephalopathy syndrome

Withhold gemcitabine or reduce dose by 50% for other severe (grade 3 or 4) nonhematologic toxicity until resolved. No dose modifications are recommended for alopecia, nausea, or vomiting.

8.4.5. Vinorelbine Dose Modifications

Hematologic Toxicity

Hold or decrease the dose of vinorelbine in patients with decreased neutrophil counts using the schema in Table 13.

Table 13: Vinorelbine Dose Modifications for Neutropenia

Neutrophils on Day of Treatment (cells/mm^3)	Percentage of Starting Dose of Vinorelbine
≥1500	100%
1000 - 1499	50%
<1000	Do not administer vinorelbine. Repeat neutrophil count in 1 week. If 3 consecutive weekly doses are held because neutrophil count is <1000/mm^3, discontinue vinorelbine
NOTE: For patients who experience fever and/or sepsis while neutrophil count is <1500 or had 2 consecutive weekly doses held due to neutropenia, subsequent doses of vinorelbine should be:	
≥1500	75%
1000 - 1499	37.5%
<1000	Do not administer vinorelbine. Repeat neutrophil count in 1 week.

Hepatic Impairment/Toxicity

Reduce vinorelbine dose in patients with elevated serum total bilirubin concentration according to the schema in Table 14.

Table 14: Vinorelbine Dose Modifications for Elevated Bilirubin

Serum total bilirubin concentration (mg/ml)	Percentage of starting dose of vinorelbine
≤2.0	100%
2.1 to 3.0	50%
>3.0	25%

Concurrent Hematologic Toxicity with Hepatic Impairment

In patients with both hematologic toxicity and hepatic impairment, administer the lower of the doses based on the corresponding starting dose of vinorelbine determined from the respective schemas in Table 13 and Table 14.

Neurologic Toxicity

Discontinue vinorelbine for NCI CTCAE grade 2 or higher peripheral neuropathy or autonomic neuropathy causing constipation.

8.5. Study Treatment Discontinuation Rules, General Guidance

Guidelines for discontinuation of cemiplimab or IC chemotherapy due to AEs are provided in Sections 8.3 and 8.4, respectively. This section provides general guidance on protocol requirements after discontinuation of either cemiplimab or IC chemotherapy.

8.5.1. Study Drug Discontinuation

Patients who permanently discontinue from study drug and who do not withdraw from the study will be asked to return to the clinic for all remaining study visits per the visit schedule.

Patients who permanently discontinue from study drug and who opt to withdraw from the study will be asked to complete study assessments, per Section 7.1.4.

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

8.5.1.1. Reasons for Permanent Discontinuation of Study Treatment

Reasons for permanent discontinuation of study treatment may include, but are not limited to:

- An infusion reaction of grade ≥3 severity during or directly following infusion
- Patient withdrawal of consent at any time
- Any medical condition that the investigator or sponsor determines may jeopardize the patient's safety if he or she continues in the study or continues treatment with study drug
- The investigator or sponsor determines it is in the best interest of the patient
- Patient noncompliance (eg, not complying with protocol required visits, assessments, and dosing instructions)
- Evidence of pregnancy
- Progression of disease
- Unacceptable toxicity
- Treatment delay of ≥84 consecutive days from last dose of cemiplimab or IC of chemotherapy due to toxicity

8.6. Treatment Beyond Progression in the Cemiplimab Treatment Group

For a small percentage of cancer patients treated with anti-PD-1 therapy, unconventional responses may occur in which radiologic evidence of progression on therapy occurs before subsequent radiologic response. To account for this possibility in the cemiplimab treatment group, treatment beyond progression may be allowed after consultation with the medical monitor at Regeneron if the following conditions are met:

- The patient has stable performance status
- The patient does not have rapid progression of disease
- The patient has not experienced adverse events that would require permanent discontinuation of cemiplimab
- The patient provides written informed consent prior to resuming treatment by signing the current version of the ICF (eg, the patient repeats the written informed consent that was done prior to initial study enrollment).
- It is understood that, if there is further progression after resumption of treatment (≥30% increase in tumor burden from the time of initial progressive disease by RECIST criteria; this includes an increase in the sum of all target lesions and/or the development of new lesions), that cemiplimab will be discontinued.

8.7. Management of Acute Reactions

8.7.1. Acute Infusion Reactions

Acute infusion reactions are defined as any AE that occurs during the infusion or within 2 hours after the infusion is completed. Emergency equipment and medication for the treatment of infusion reactions must be available for immediate use. All infusion reactions must be reported as AEs (as defined in Section 9.4.1) and graded using the grading scales as instructed in Section 9.5.1.

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

To assist investigators in identifying cemiplimab-related infusion reactions, the following case definition is provided:

- Typical symptoms may include fever, chills, rigors, skin flushing, dyspnea, back pain, abdominal pain, and nausea
- Infusion reactions usually occur either during the infusion or within 2 hours after the infusion is completed
- Vital signs may be notable for hypotension and/or tachycardia

The investigator's clinical judgment may include other factors when evaluating a possible cemiplimab-related infusion reaction. For example, rarely, an infusion reaction may occur up to 24 hours after initiation of the infusion.

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

Patients who experience grade ≥3 acute infusion reactions to IC chemotherapy should discontinue treatment.

8.7.1.1. Interruption of the Infusion

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

- cough
- rigors/chills
- rash, pruritus (itching)
- urticaria (hives, welts, wheals)
- diaphoresis (sweating)
- hypotension
- dyspnea (shortness of breath)
- vomiting
- flushing

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

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

For patients who experience infusion-related hypersensitivity reactions that are less than grade 3 and who plan to continue treatment, premedication will be required for re-treatment.

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

For grade 2 symptoms (moderate reaction that requires therapy or infusion interruption, but for which symptoms resolve promptly with appropriate treatment such as antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, corticosteroids, and/or IV fluids; prophylactic medications indicated ≤24 hours), the following prophylactic medications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 mg to 1000 mg at least 30 minutes prior to subsequent cemiplimab infusions. If necessary, corticosteroids (up to 25 mg of hydrocortisone or equivalent) may be used.

8.7.1.2. Termination of the Infusion

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

- anaphylaxis
- laryngeal/pharyngeal edema
- severe bronchospasm
- chest pain

- seizure
- severe hypotension
- other neurological symptoms (confusion, loss of consciousness, paresthesia, paralysis, etc.)
- any other symptom or sign that, in the opinion of the investigator, warrants discontinuation of the infusion

8.8. Method of Treatment Assignment

Approximately 590 patients will be randomized in a 1:1 ratio to receive either cemiplimab or IC of chemotherapy, according to a central randomization scheme provided by an interactive voice response system (IVRS)/interactive web response system (IWRS) to the designated study pharmacist (or qualified designee). Randomization will be stratified according to:

1. Histology (squamous cell carcinoma versus adenocarcinoma). Adenosquamous histology be considered adenocarcinoma for purposes of stratification.
2. Geographic Region: North America versus Asia versus Rest of World (ROW)
3. Prior bevacizumab (yes/no)
4. ECOG performance status (0,1)

The stratification factors of "prior bevacizumab use" and "ECOG performance status" are used for balancing treatment assignment only and will not be included in the statistical model for analysis of the primary endpoint.

After it is confirmed that the patient meets all eligibility criteria, she will be enrolled in IVRS. The following information must be provided at time of enrollment, prior to randomization:

- Patient number
- Date of birth
- Histology (squamous cell carcinoma versus adenocarcinoma). Adenosquamous histology will be considered adenocarcinoma for purposes of stratification and analysis. Starting with Amendment 5, only squamous cell patients will be enrolled
- Geographic region
- Prior bevacizumab (yes/no)
- ECOG performance status (0,1)
- Choice of Investigator's Choice treatment

After a patient is enrolled in IWRS with this information, she will be randomized (1:1) to either cemiplimab or Investigator's Choice of chemotherapy.

8.8.1. Blinding

Not applicable.

8.9. Treatment Logistics and Accountability

8.9.1. Packaging, Labeling, and Storage

Open-label study drug will display the product lot number on the label.

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

8.9.2. Supply and Disposition of Treatments

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

8.9.3. Treatment Accountability

All drug accountability records must be kept current.

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

- dispensed to each patient,
- returned from each patient (if applicable), and
- disposed of at the site or returned to the sponsor or designee

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

8.9.4. Treatment Compliance

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

8.10. Concomitant Medications and Procedures

Any treatment administered, other than anti-cancer therapy, from the time of informed consent until 90 days after the last study treatment will be considered concomitant treatment. This includes medications and other therapies for which administration started before the study and will continue during the study, as well as any therapies started in the follow-up period to treat a study drug-related AE. All concomitant treatments must be recorded in the study CRF with the generic name, dose, dose unit, frequency, indication, and start/stop date, as appropriate.

8.10.1. Prohibited Medications and Procedures

While participating in this study, a patient may not receive any anti-cancer treatment other than the treatment assigned at randomization: cemiplimab or IC of chemotherapy. Patients must not receive live vaccines during the study and for up to 5 half-lives after the last dose of study drug. Any other medication which is considered necessary for the patient's welfare, and which is not

expected to interfere with the evaluation of the assigned treatment (cemiplimab or IC of chemotherapy), may be given at the discretion of the investigator.

Patients using immunosuppressive doses (>10 mg per day of prednisone or equivalent) of systemic corticosteroids other than for corticosteroid replacement will not be eligible for the study. For patients on the cemiplimab arm, it is recommended that patients do not receive systemic corticosteroids such as hydrocortisone, prednisone, prednisolone (Solu-Medrol®) or dexamethasone (Decadron®) at any time throughout the study except in the case of a life-threatening emergency and/or to treat an irAE.

NOTE: Bisphosphonates and denosumab are not prohibited.

8.10.2. Permitted Medications and Procedures

Physiologic replacement doses of systemic corticosteroids are permitted, even if >10 mg/day prednisone equivalents. A brief course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by contact allergen) is permitted.

NOTE: Bisphosphonates and denosumab are not prohibited.

Radiation therapy is not part of the study regimen in either the experimental group or the control group. Patients for whom radiation therapy is planned are not eligible. If, during the course of the study, a patient develops a symptomatic lesion for which palliative radiation therapy is deemed appropriate by the investigator, this will be deemed PD, and generally, the patient would be removed form study. Palliative radiation therapy may be allowed in certain circumstances in patients who have been on study for at least 24 weeks. Palliative radiation is only allowed to a non-target lesion in this study.

If the investigator feels that palliative radiation therapy to a non-target lesion, followed by resumption of the assigned treatment (cemiplimab or IC of chemotherapy) after radiation is in the best interest of the patient, such cases must be discussed with and approved by the medical monitor prior to initiation of palliative radiation therapy. The patient will be deemed to have experienced PD if radiation therapy is instituted, but will be followed for OS.

9. SAFETY DEFINITIONS, REPORTING, AND MONITORING

9.1. Obligations of Investigator

The investigator must promptly report to the Institutional Review Board (IRB)/Ethics Committee (EC) all unanticipated problems involving risks to patients according to local regulations.

9.2. Obligations of Sponsor

During the course of the study, the sponsor will report in an expedited manner all SAEs that are both unexpected and at least reasonably related to the study drug (suspected unexpected serious adverse reaction), to the health authorities, IRBs/ECs as appropriate, and to the investigators.

Any AE not listed as an expected event in the Reference Safety Information section of the cemiplimab Investigator's Brochure or in the reference safety document for the IC chemotherapy

(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

- 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.

10.3.3. Other Analysis Sets

The PK population includes all randomized patients (safety population) who received cemiplimab and who had at least 1 non-missing cemiplimab concentration following the first dose of cemiplimab up to the end of the study.

The ADA analysis set includes all treated patients who received any study drug and had at least 1 non-missing post-baseline ADA assay result following the first dose of study drug.

The biomarker analysis set includes all treated patients who had at least 1 sample assayed.

10.4. Statistical Methods

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

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

The descriptive summary of time-to-event data will include median time to event and its 95% CI using the Kaplan-Meier method.

10.4.1. Patient Disposition

The following will be provided:

- The total number of screened patients: met the inclusion criteria regarding the target indication and signed the ICF
- The total number of randomized subjects: received a randomization number
- The total number of patients in the FAS
- The total number of patients in the SAF
- The total number of patients who discontinued treatment and the reasons for treatment discontinuation
- The total number of patients who discontinued the study and the reasons for discontinuation
- A listing of patients treated but not randomized, patients randomized but not treated, and patients randomized but not treated as randomized
- A listing of patients prematurely discontinued from treatment and study, along with reasons for discontinuation

10.4.2. Demography and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group and by all patients combined.

10.4.3. Medical History

Medical history will be summarized by primary system organ class (SOC) and preferred term (PT) for each treatment group, with the table sorted by decreasing frequency of SOC, followed by PT based on the overall incidence between treatment groups.

10.4.4. Prior Medications/Concomitant Medications

Number and proportion of patients taking prior/concomitant medication will be summarized by decreasing frequency of anatomical therapeutic chemical (ATC) level 2 and ATC level 4 according to the current version of the World Health Organization Drug Dictionary, based on the overall incidence between treatment groups.

Listings of pretreatment medication and concomitant medications include generic name, ATC levels 2 and 4, indication, study day onset, the study end date (defined similarly as for study onset day), ongoing status, dose, frequency, and route.

For medications started before treatment, the study day onset is defined as date of medication start - date of the first dose; for medications started on or after treatment, the study day onset is defined as the date of medication start - date of the first dose + 1.

10.4.5. Efficacy Analyses

10.4.5.1. Primary Efficacy Analysis

The primary analysis of OS will be implemented after the pre-specified numbers (Table 15) of OS events have been reported in patients with SCC. The analyses will include all survival information available at the time.

The primary endpoint of OS will be analyzed in SCC patients first by stratified log-rank test using geographic region (North America versus Asia-Pacific versus ROW) as a stratification factor.

The HR and its 95% CI will be estimated by a stratified Cox regression model using the treatment as covariate.

If the analysis of OS is statistically significant in the SCC patients, then the analysis of OS will be performed in the overall population by stratified log-rank test using the following stratification factors:

1. Histology: SCC versus adenocarcinoma. Adenosquamous histology will be considered adenocarcinoma for the purpose of stratification.
2. Geographic Region: North America versus Asia Pacific versus ROW.

The HR and its 95% CI will be estimated by a stratified Cox regression model using the treatment as covariate.

10.4.5.2. Secondary Efficacy Analysis

The multiplicity is controlled by a hierarchical testing procedure as follows: The primary endpoint OS will be tested in SCC patients first. If statistically significant, OS will be tested in the overall population. If statistically significant, the secondary endpoints PFS and ORR will be tested. The

order for hierarchical testing in secondary endpoints will be specified in the SAP before database lock (DBL).

Analysis of PFS and ORR will be performed at the time of OS analysis. The PFS will be analyzed using the same statistical method as the analysis of OS. The ORR will be analyzed using the Cochran-Mantel-Haenszel test stratified by the same stratification factors used in analysis of OS. An associated odds ratio and 95% CI will be calculated. Objective response rate and the corresponding 95% exact CI will be calculated by Clopper-Pearson method for each treatment arm.

10.4.5.3. Quality of Life Analysis

The change in EORTC QLQ-C30 scores from first assessment to the end of the study will be summarized descriptively at each post-baseline time point and compared using a mixed effect model, if appropriate.

10.4.5.4. Exploratory Efficacy Endpoint Analysis

Relationships between efficacy endpoints and candidate biomarkers will be described.

10.4.5.5. Subgroup Analyses

To determine the consistency of treatment effect across various demographic and baseline subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the primary and key secondary endpoints will be estimated and plotted within each category of the following subgroup variables:

- Age category (≤65 years, >65 years)
- Choice of IC chemotherapy: (1) Antifolate - pemetrexed, (2) Topoisomerase 1 inhibitor - topotecan or irinotecan, (3) Nucleoside analogue - gemcitabine, or (4) Vinca alkaloid - vinorelbine
- Race (white, non-white)
- ECOG status (0, 1)
- Histology adenocarcinoma/adenosquamous
- Geographic region (North America, Asia, ROW)
- Geographic region (Japan, outside of Japan)
- Prior bevacizumab use(Y/N)
- Number of prior lines of systemic therapy for recurrent or metastatic disease (1 line or >1 line)

10.4.6. Safety Analysis

Safety will be assessed in the overall population. Safety observations and measurements including drug exposure, AEs, laboratory data, vital signs, and ECOG performance status will be summarized and presented in tables and listings.

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

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:

- 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

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

addition, representatives of the sponsor may observe the conduct of any aspect of the clinical study or its supporting activities both within and outside of the investigator's institution. In all instances, the confidentiality of the data must be respected.

14. ETHICAL AND REGULATORY CONSIDERATIONS

14.1. Good Clinical Practice Statement

It is the responsibility of both the sponsor and the investigator(s) to ensure that this clinical study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the ICH guidelines for GCP and applicable regulatory requirements. The clinical study will be conducted in compliance with Pharmaceutical and Medical Device Act, Japanese GCP, and other relevant laws in Japan.

14.2. Informed Consent

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

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

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

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

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

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

14.3. Patient Confidentiality and Data Protection

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

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

14.4. Institutional Review Board/Ethics Committee

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

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

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

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

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

15. PROTOCOL AMENDMENTS

The sponsor may not implement a change in the design of the protocol or ICF without an IRB/EC-approved amendment or formal notification from the sponsor in the event of recommendations from the IDMC.

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

16.1. Premature Termination of the Study

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

16.2. Close-out of a Site

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

Investigator's Decision

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

Sponsor's Decision

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

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

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

17. STUDY DOCUMENTATION

17.1. Certification of Accuracy of Data

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

17.2. Retention of Records

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

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

18. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

19. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

20. PUBLICATION POLICY

The publication policy is provided as a separate agreement.

21. REFERENCES

Appleby P, Beral V, Berrington de Gonzalez A, Colin D, Franceschi S, et al. Carcinoma of the cervix and tobacco smoking: collaborative reanalysis of individual data on 13,541 women with carcinoma of the cervix and 23,017 women without carcinoma of the cervix from 23 epidemiological studies. Int J Cancer 2006; 118(6):1481-95.

Bookman MA, Blessing JA, Hanjani P, et al. Topotecan in squamous cell carcinoma of the cervix: a phase II trial of the gynecologic oncology group. Gynecol Oncol 2000;77:446-449.

Bray FB, Jemal A, Grey N, et al. Global cancer transitions according to the Human Development Index (2008-2030): a population-based study. Lancet Oncol 2012;13:790-801.

Chung HC, Schellens JHM, Delord J-P, Perets R, Italiano A, Schapira-Frommer R, et al. 2018. Pembrolizumab Treatment of Advanced Cervical Cancer: Updated Results from the Phase 2 KEYNOTE-158 Study. American Society of Clinical Oncology Annual Meeting. Chicago, IL.

Donoghue M, Lemery SJ, Yuwan W, et al. Eribulin mesylate for the treatment of patients with refractory metastatic breast cancer: use of a "physician's choice" control arm in a randomized approval trial. Clin Canc Res 2012;18:1496-1505.

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45:228–247.

Ferris RL, Blumenschein G, Fayette J, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. New Engl J Med 2016; Oct 8 [Epub ahead of print].

Forman D, de Martel C, Lacey CJ, et al. Global burden of human papillomavirus and related diseases. Vaccine 2012; 30 Suppl 5:F12-F23.

Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. Immunol Rev 2010; 236:219–242.

Frenel J-S, Le Torneau C, O'Neil BH, et al. Pembrolizumab in patients with advanced cervical squamous cell cancer: preliminary results from the Keynote-028 phase 1b study. ASCO 2016 Annual Meeting, Abstract 5515.

Gillison ML, Blumenschein G, Fayette J, et al. Nivolumab versus investigator's choice (IC) for recurrent or metastatic (R/M) head and neck squamous cell carcinoma (SCCHN): CheckMate-141. AACR 2016 Annual Meeting, Abstract CT099.

Hanna N, Shepherd FA, Fosella FV, et al. Randomized Phase III Trial of Pemetrexed Versus Docetaxel in Patients With Non–Small-Cell Lung Cancer Previously Treated With Chemotherapy. J Clin Oncol 2004;22:1589-1597.

Heeren AM, Punt S, Bleeker MCG, Gaarenstroom KN, van der Velen J, Kenter GG, et al. Prognostic effect of different PD-L1 expression patterns in squamous cell carcinoma and adenocarcinoma of the cervix. Mod Pathol 2016; 29(7)753-63.

Hofmann L, Forschner A, Loquai C, et al. Cutaneous, gastrointestinal, hepatic, endocrine, and renal side-effects of anti-PD-1 therapy. Eur J Cancer 2016;60 190e209.

Irvin WP, Price FV, Bailey H, et al. A Phase II Study of irinotecan (CPT-11) in Patients with Advanced Squamous Cell Carcinoma of the Cervix. Cancer 1998; volume 82,number 2.

KEYTRUDA (pembrolizumab) [package insert]. Whitehouse Station (NJ): Merck Sharp & Dohme Corp; 2018.

Look KY, Blessing JA, Levenback C, et al. A Phase II Trial of CPT-11 in Recurrent Squamous Carcinoma of the Cervix: A Gynecologic Oncology Group Study. Gynecologic Oncology 1998;70, 334–338.

Long III HJ, Bundy BN, Grendys Jr EC, et al. Randomized Phase III Trial of Cisplatin With or Without Topotecan in Carcinoma of the Uterine Cervix: A Gynecologic Oncology Group Study. J Clin Oncol 2005;23:4626-4633.

Lorusso D, Ferrandina G, Pignata S, et al. Evaluation of pemetrexed (Alimta, LY231514) as second-line chemotherapy in persistent or recurrent carcinoma of the cervix: the CERVIX 1 study of the MITO (Multicentre Italian Trials in Ovarian Cancer and Gynecologic Malignancies) Group. Ann Oncol 2010;. 21.

McLachlan J, Boussios S, Okines A, et al. The Impact of Systemic Therapy Beyond First-line Treatment for Advanced Cervical Cancer. Clinical Oncology (2016), http://dx.doi.org/10.1016/j.clon.2016.10.002.

Migden MR, Rischin D, Schmults CD, Guminski A, Hauschild A, Lewis KD, et al. PD-1 Blockade with Cemiplimab in Advanced Cutaneous Squamous-Cell Carcinoma. N Engl J Med 2018; 379(4):341-51.

Miller DS, Blessing JA, Bodurka DC, et al. Evaluation of pemetrexed (Alimta, LY231514) as second line therapy in persistent or recurrent carcinoma of the cervix: a phase 2 study of the Gynecologic Oncology Group. Gynecol Oncol 2008; 110:65-70.

Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med 2015;373:1803-13.

Muderspach LI, Blessing JA, Levenback C, et al. A Phase II Study of Topotecan in Patients with Squamous Cell Carcinoma of the Cervix: A Gynecologic Oncology Group Study. Gynecologic Oncology 2001;81, 213–215.

Muggia FM, Blessing JA, Method M, et al. Evaluation of vinorelbine in persistent or recurrent squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. Gynecologic Oncology 2004;92: 639–643.

Muggia FM, Blessing JA, Waggoner S, et al. Evaluation of vinorelbine in persistent or recurrent nonsquamous carcinoma of the cervix: a Gynecologic Oncology Group Study. Gynecologic Oncology 2005;96:108–111.

Mutch DG, Orlando M, Goss T, et al. Randomized phase III trial of gemcitabine compared with pegylated liposomal doxorubicin in patients with platinum-resistant ovarian cancer. J Clin Oncol 2007;25:2811-2818.

Naidoo J, Page DB, Li BT, et al. Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. Annals of Oncology 2015;26: 2375–2391.

National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. Cervical Cancer. Version 1.2017 – October 10, 2016. NCCN.org.

Nghiem PT, Bhatia S, Lipson EJ, et al. PD-1 blockade with pembrolizumab in advanced Merkel cell carcinoma. N Engl J Med 2016;374:2542-2552.

Nishino M, Ramaiya NH, Awad MM, et al. PD-1 inhibitor-related pneumonitis in advanced cancer patients: Radiographic patterns and clinical course. Clin Cancer Res. 2016 Aug 17. pii: clincanres.1320.2016. [Epub ahead of print].

Papadopoulos KP, Crittenden M, Johnson, M, et al. A first-in-human study of REGN2810, a fully human monoclonal antibody against programmed death-1 (PD-1) in combination with immunomodulators including hypofractionated radiotherapy (hfRT). J Clin Oncol 2016;34:(suppl.1abstr 3024).

Pfisterer J, Plante M, Vergote I, et al. Gemcitabine Plus Carboplatin Compared With Carboplatin in Patients With Platinum-Sensitive Recurrent Ovarian Cancer: An Intergroup Trial of the AGO-OVAR, the NCIC CTG, and the EORTC GCG. J Clin Oncol 2006;24:4699-4707.

Rischin D, Gil-Martin M, Gonzalez-Martin A, Brana I, Hou JY, Cho D, et al. 2018. Cemiplimab, a Human PD-1 Monoclonal Antibody, in Patients with Recurrent or Metastatic Cervical Cancer: Interim Data from Phase 1 Cohorts. European Society for Medical Oncology Congress. Munich, Germany.

Schilder RJ, Blessing J, Cohn DE. Evaluation of gemcitabine in previously treated patients with non-squamous cell carcinoma of the cervix: a phase II study of the Gynecologic Oncology Group. Gynecol Oncol 2005;96:103-107.

Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2016. CA Cancer J Clin. 66:7-30.

Takeuchi S, Dobashi K, Fujimoto S, et al. A late phase study of CPT-11 on uterine cervical cancer and ovarian cancer. Research Groups of CPT-11 in Gynecologic Cancers. Gan To Kagaku Ryoho 1991 Aug;18(10):1681-9.

Tanioka M, Katsumata N, Yonemori K, et al. Second platinum therapy in patients with uterine cervical cancer previously treated with platinum chemotherapy. Cancer Chemother Pharmacol (2011) 68:337–342.

ten Bokkel Huinink W, Lane SR, Ross GA, et al. Long-term survival in a phase III, randomised study of topotecan versus paclitaxel in advanced epithelial ovarian carcinoma. Annals of Oncology 2004;15: 100–103.

Tewari KS, Sill MW, Monk BJ, et al. Prospective Validation of Pooled Prognostic Factors in Women with Advanced Cervical Cancer Treated with Chemotherapy with/without Bevacizumab: NRG Oncology/GOG Study. Clin Cancer Res 2015; 21(24)

Tewari KS, Sill MW, Long HJ, et al. Improved survival with bevacizumab in advanced cervical cancer. N Engl J Med 2014;370:734-743.

The Cancer Genome Atlas Research Network. Integrated genomic and molecular characterization of cervical cancer. Nature http://dx.doi.org/10.1038/nature21386 (2017).

Tirumani SH, Ramaiya NH, Keraliya A, et al. Radiographic Profiling of Immune-Related Adverse Events in Advanced Melanoma Patients Treated with Ipilimumab. Cancer Immunol Res 2015 Oct;3(10):1185-92.

Torre LS, Bray FB, Siegel RL, et al. Global Cancer Statistics, 2012. CA Cancer J Clin 2015;65:87-108.

Trivedi MS, Hoffner B, Winkelmann JL, et al. Programmed Death 1 Immune Checkpoint Inhibitors. Clinical Advances in Hematology & Oncology 2015;Volume 13, Issue 12.

Verschraegen CF, Levy T, Kudelka AP, et al. Phase II Study of Irinotecan in Prior Chemotherapy-Treated Squamous Cell Carcinoma of the Cervix. J Clin Oncol 1997;15:625-631.

von Pawel J, Schiller JH, Shepherd FA, et al. Topotecan Versus Cyclophosphamide, Doxorubicin, and Vincristine for the Treatment of Recurrent Small-Cell Lung Cancer. Journal of Clin Oncol 1999;Vol 17, No 2 (February): pp 658-667.

Weber JS, Yang JC, Atkins MB, et al. Toxicities of Immunotherapy for the Practitioner. J Clin Oncol 2015;33:2092-2099.

Zimmer L, Goldinger SM, Hofmann L, et al. Neurological, respiratory, musculoskeletal, cardiac and ocular side-effects of anti-PD-1 therapy. Eur J Cancer 2016;60 210e225.

Zou W and Chen L. Inhibitory B7-family molecules in the tumour microenvironment. Nat Rev Immunol 2008;8:467–477.

22. INVESTIGATOR'S AGREEMENT

I have read the attached protocol, "An Open-Label, Randomized, Phase 3 Clinical Trial of REGN2810 Versus Investigator's Choice of Chemotherapy in Recurrent or Metastatic Cervical Carcinoma," and agree to abide by all provisions set forth therein.

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

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

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

_____ _____

(Signature of Investigator) (Date)

_____

(Printed Name)

APPENDIX 1. RESPONSE EVALUATION CRITERIA IN SOLID TUMORS: RECIST GUIDELINE (VERSION 1.1)

For the purposes of this study, patients should be re-evaluated for response at day 42 (±7 days) in cycles 1 through 4, 6, 8, 10, 12, 14, and 16. Confirmatory scans should also be obtained 4 weeks following initial documentation of objective response.

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

Selection of Lesions

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

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

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

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

Methods for Evaluation of Measurable Disease

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

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

- **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

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.

Response Criteria

Evaluation of Target Lesions

- **Complete Response (CR):** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (<1 cm).
- **Partial Response (PR):** At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive Disease (PD):** At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (0.5 cm).

NOTE: the appearance of one or more new lesions is also considered progressions).

- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Evaluation of Non-Target Lesions

- **Complete Response (CR):** Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis).

NOTE: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

- **Non-CR/Non-PD:** Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- **Progressive Disease (PD):** Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

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

Evaluation of Overall Response Criteria

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

Response According to Revised Response Evaluation Criteria in Solid Tumors (Version 1.1)

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

CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease.
[a]. In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as PD.

Missing Assessments and Inevaluable Designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of progressive disease. For example, if a patient had a baseline sum of 50 mm with 3 measured lesions and at follow-up only 2 lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved progressive disease status, regardless of the contribution of the missing lesion.

Best Overall Response: All Time Points

The best overall response is determined once all the data for the patient is known. Best response determination in trials where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and progressive disease on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, progressive disease at second and does not meet minimum duration for SD, will have a best response of progressive disease. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

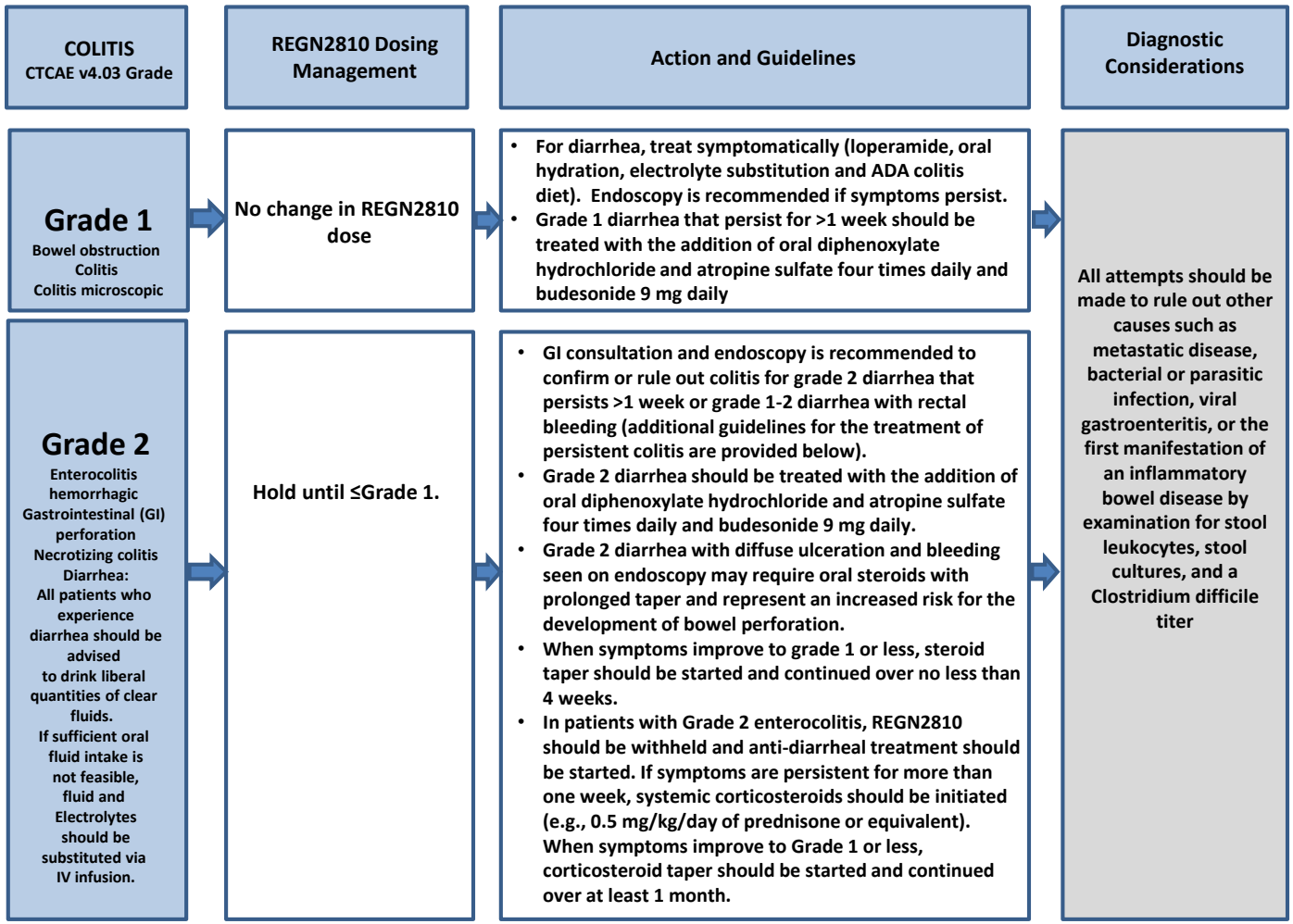
Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study). The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

APPENDIX 2. RECOMMENDED DOSE MODIFICATION OR DISCONTINUATION AND SUPPORTIVE CARE GUIDELINES FOR SPECIFIC CEMIPLIMAB RELATED ADVERSE EVENTS

Section 8.3 provides the dose level reductions.

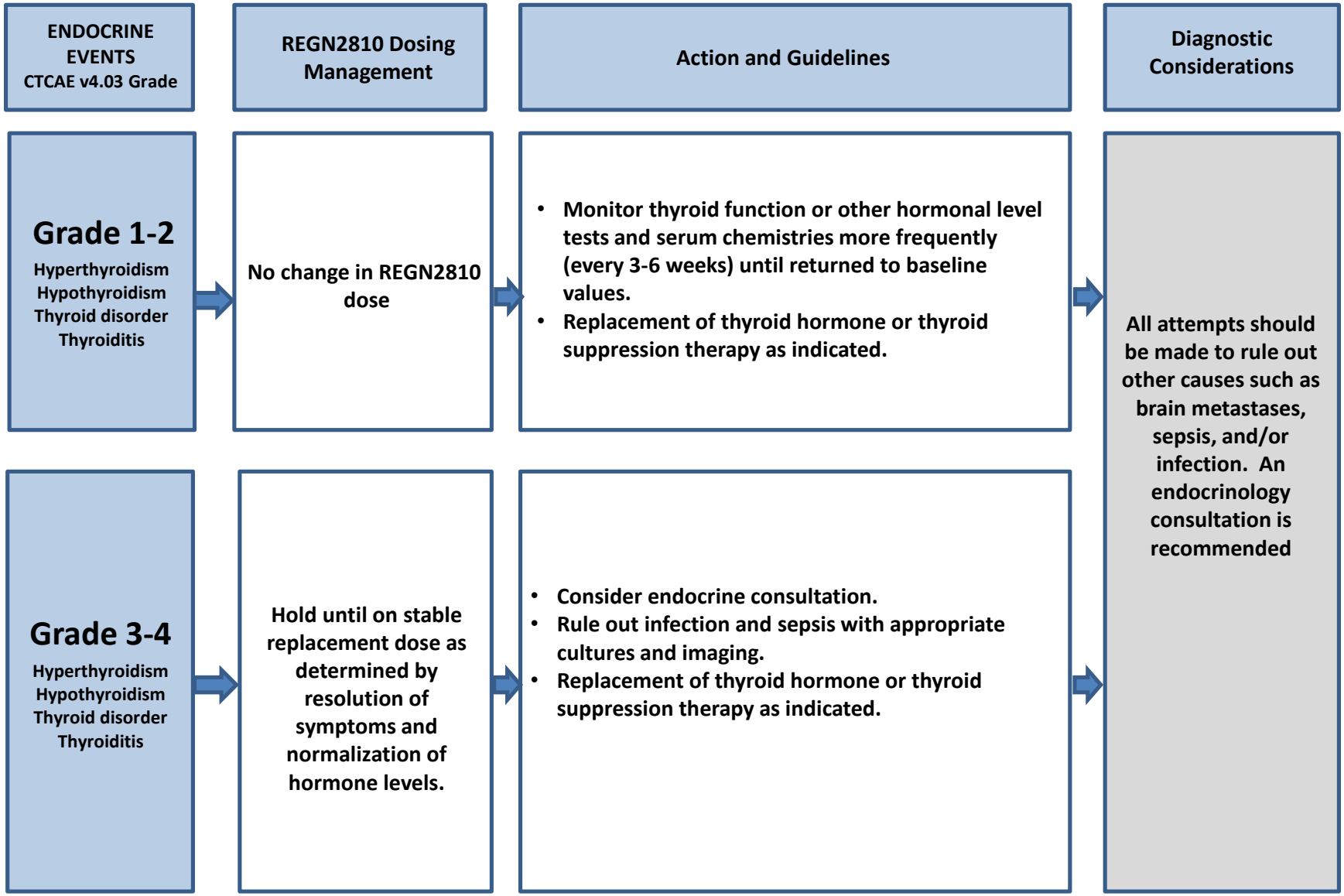
Colitis Adverse Event Management



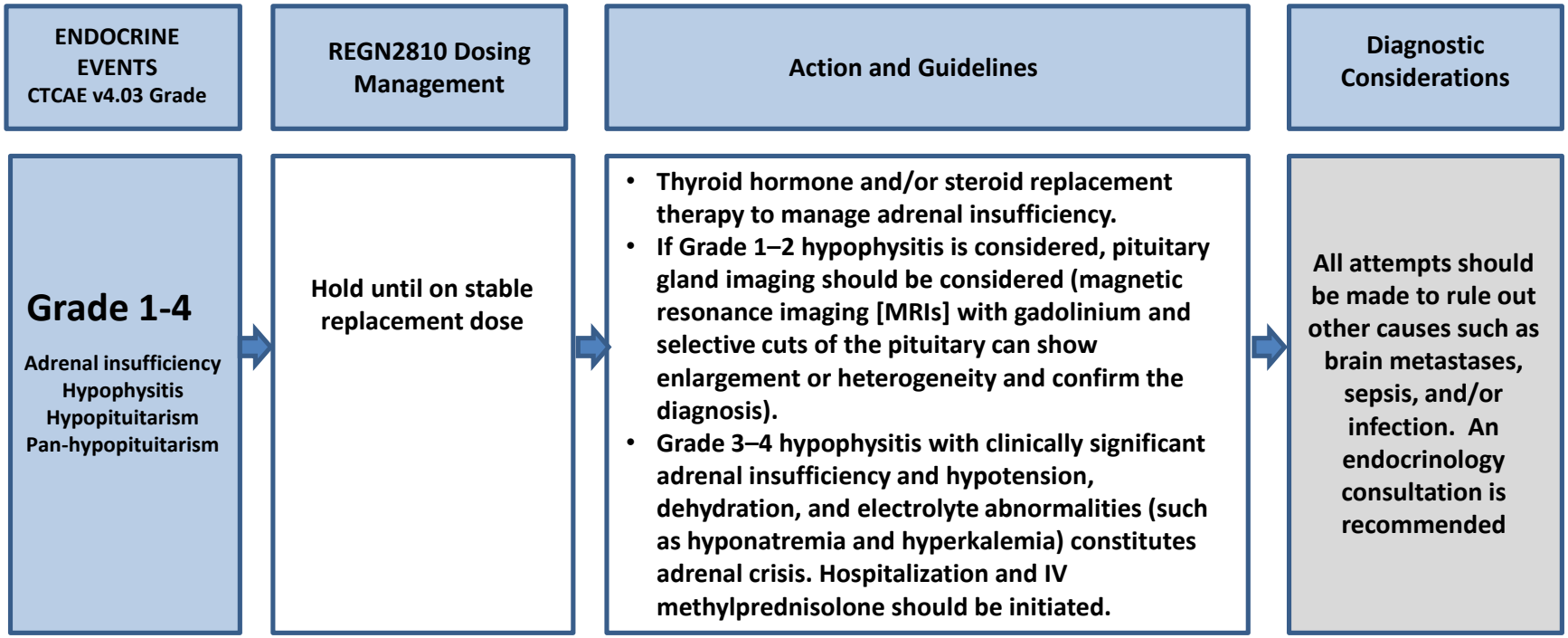
Colitis Adverse Event Management

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

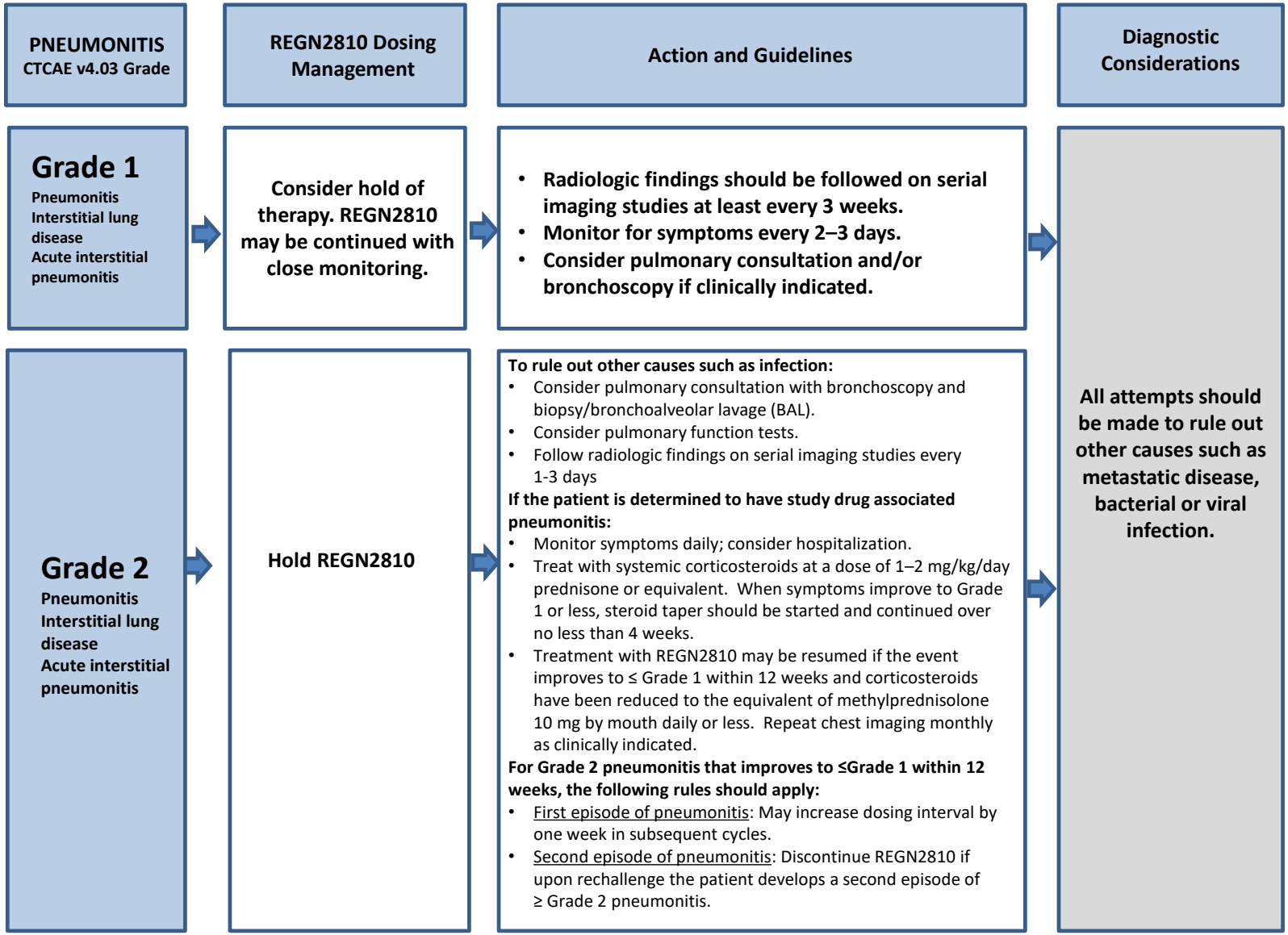
Endocrine Adverse Event Management



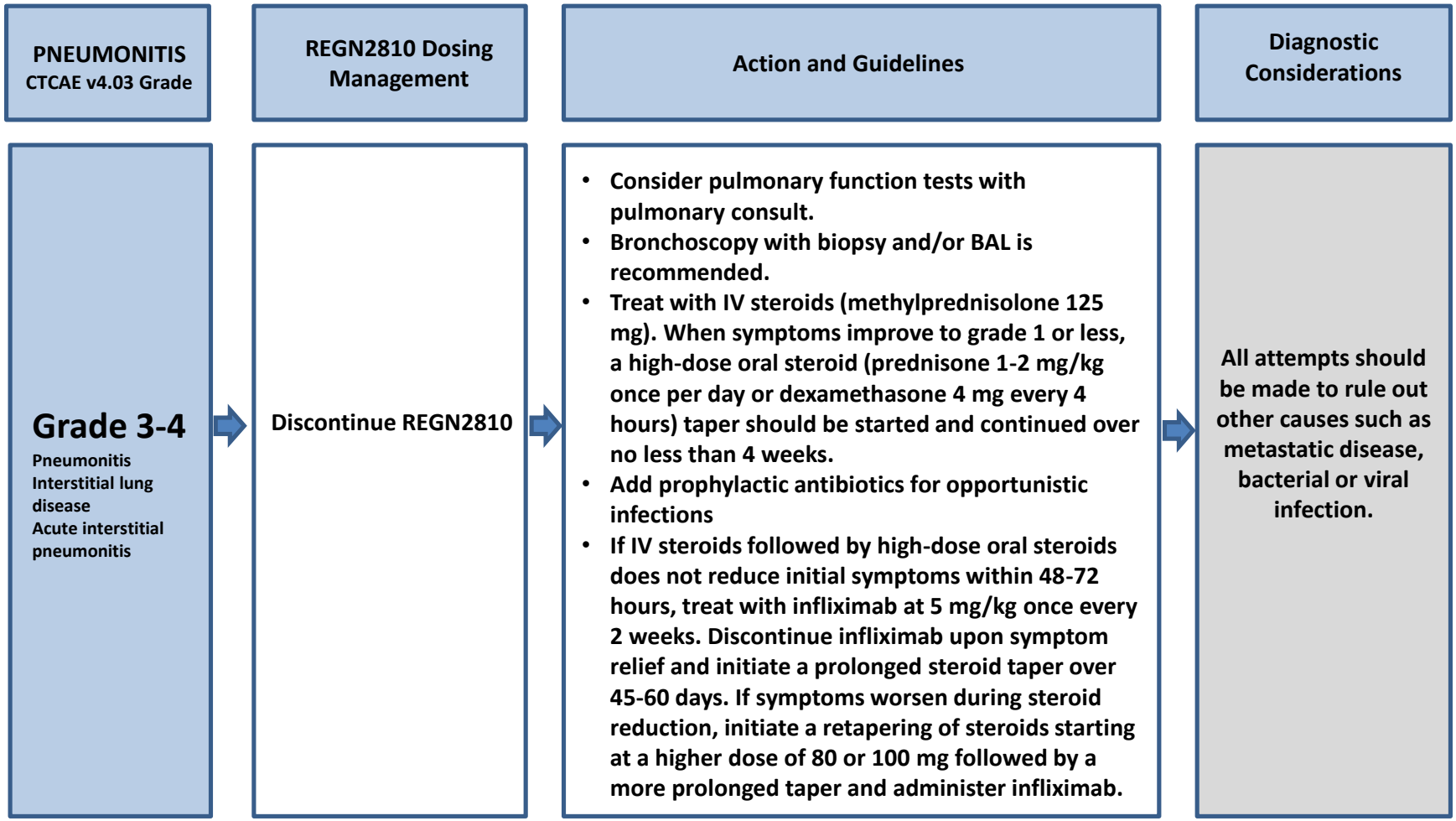
Endocrine Adverse Event Management (Cont)



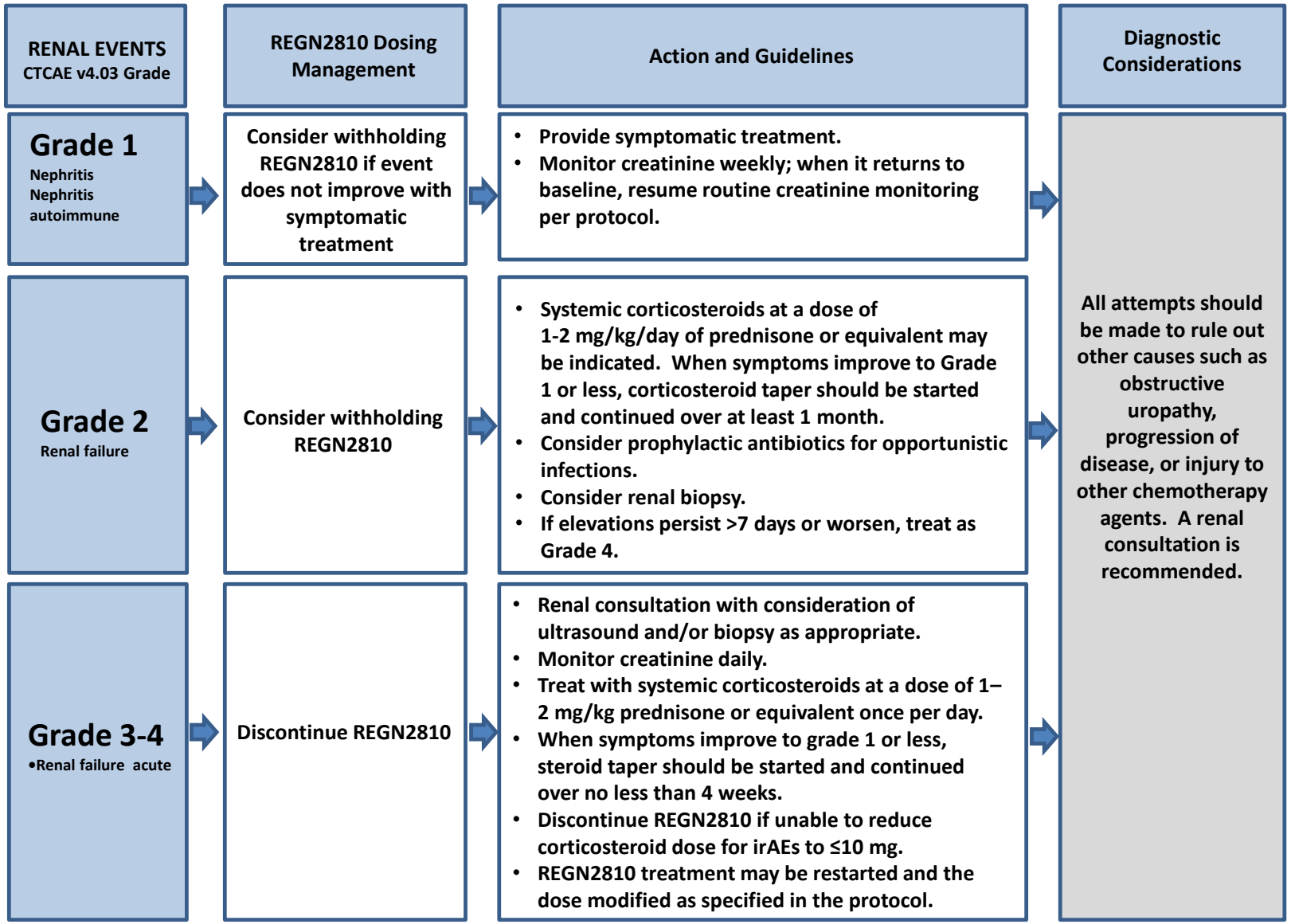
Pneumonitis Adverse Event Management



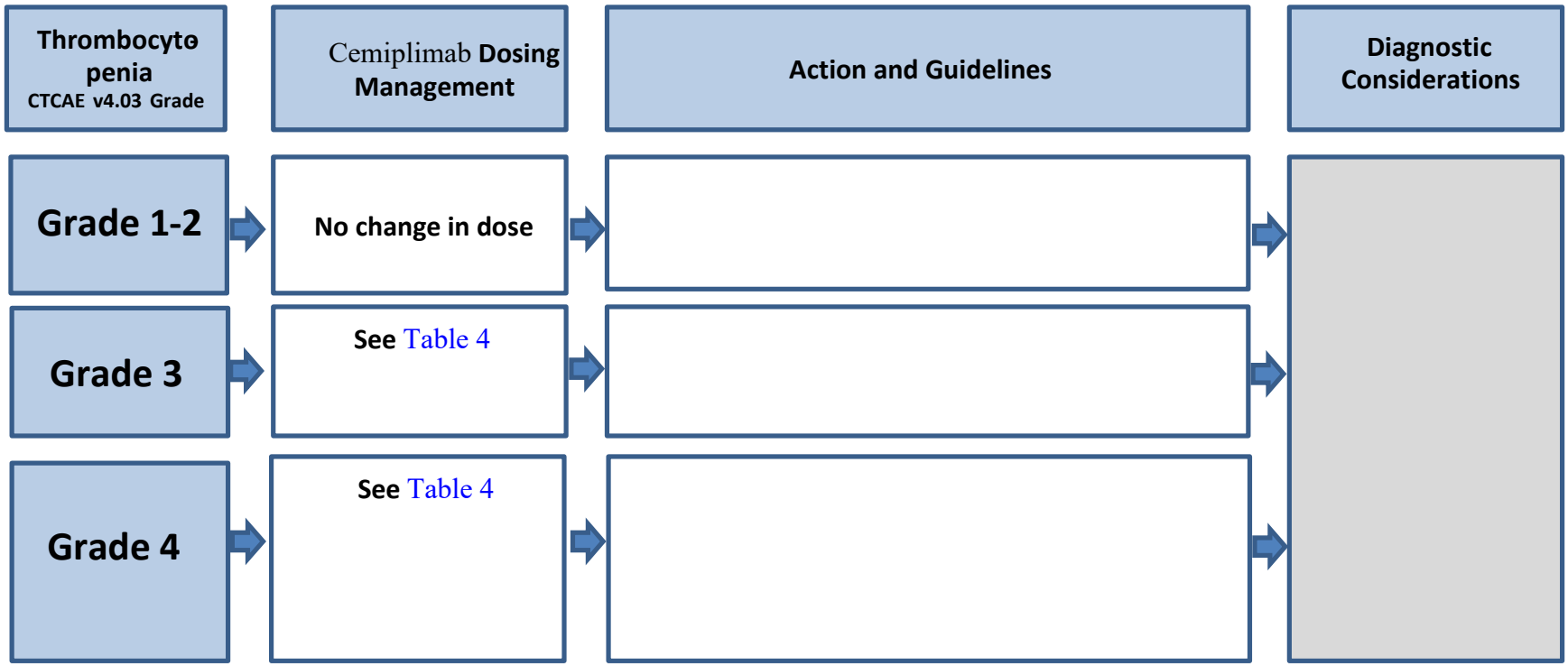
Pneumonitis Adverse Event Management (Cont)



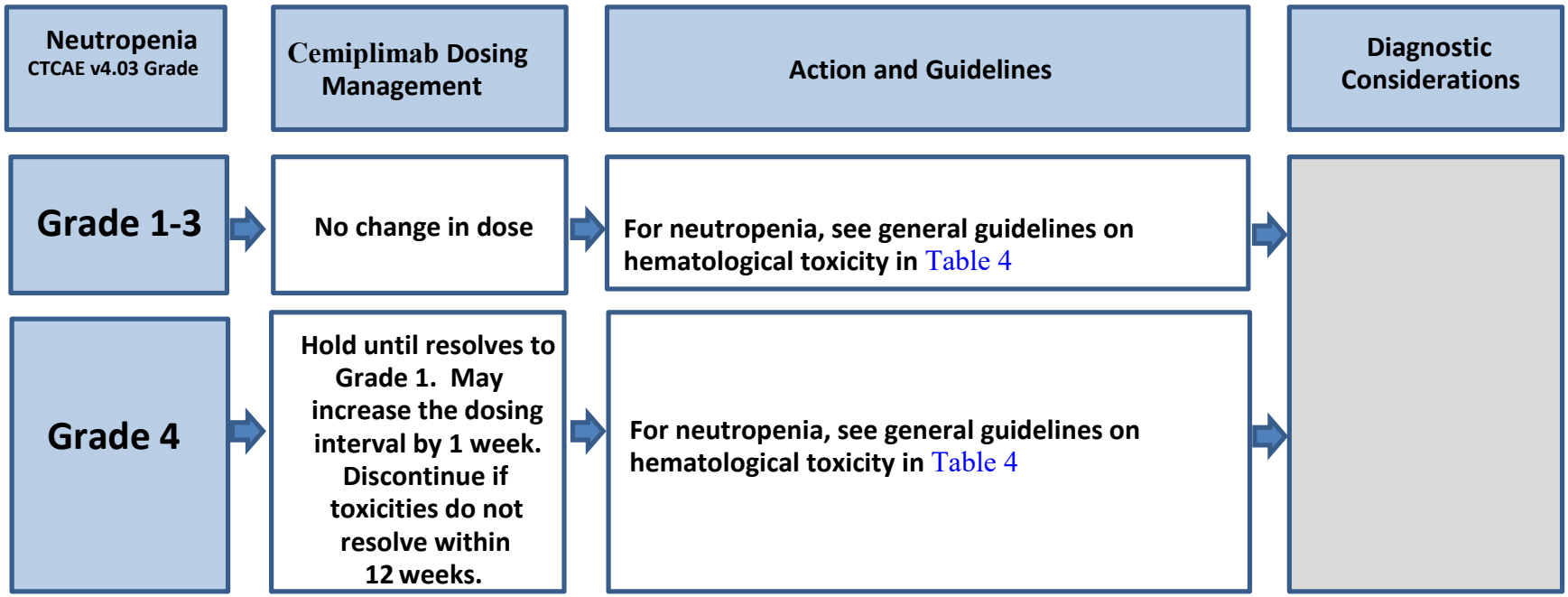
Renal Adverse Event Management



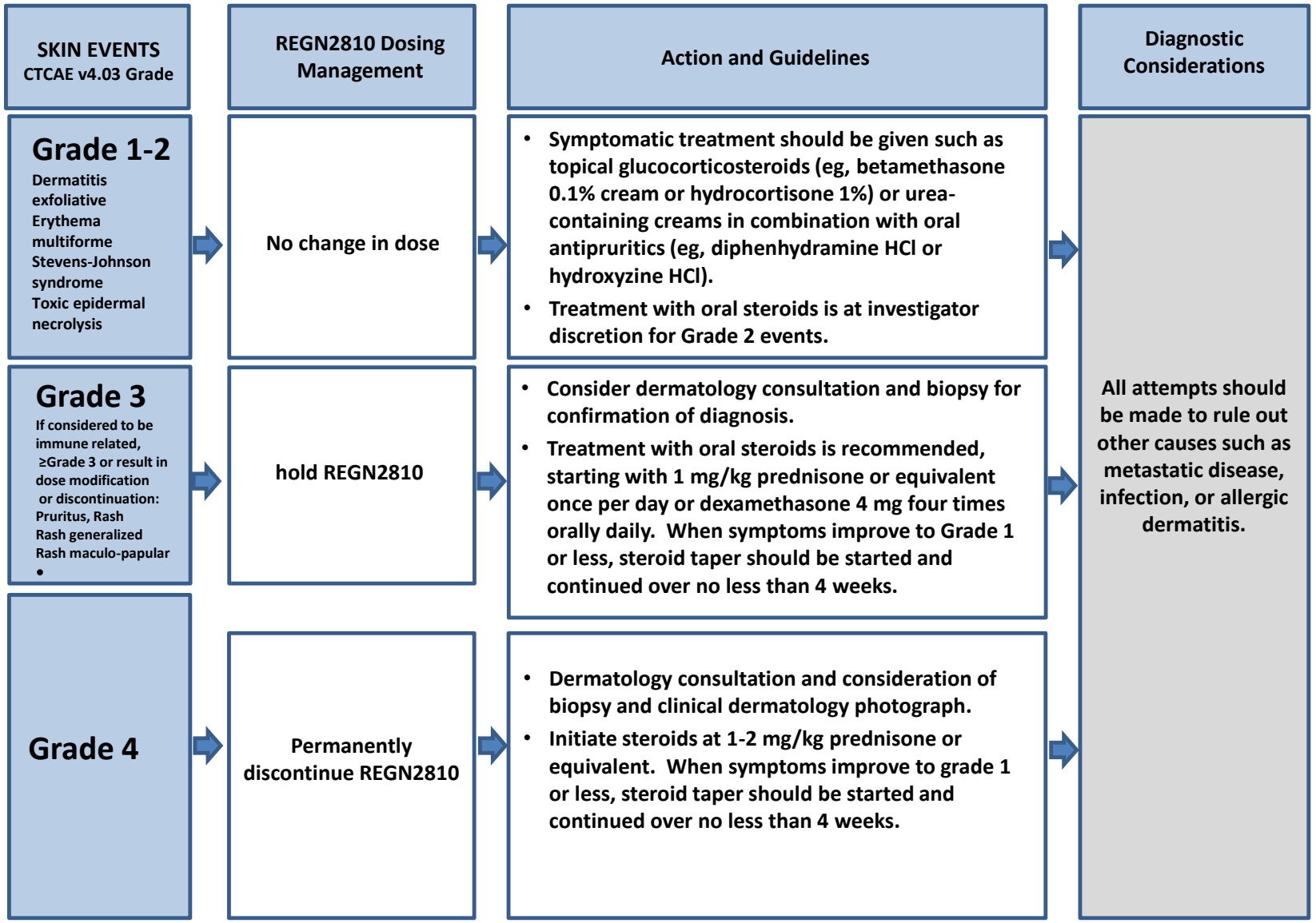
Hematologic Adverse Event Management



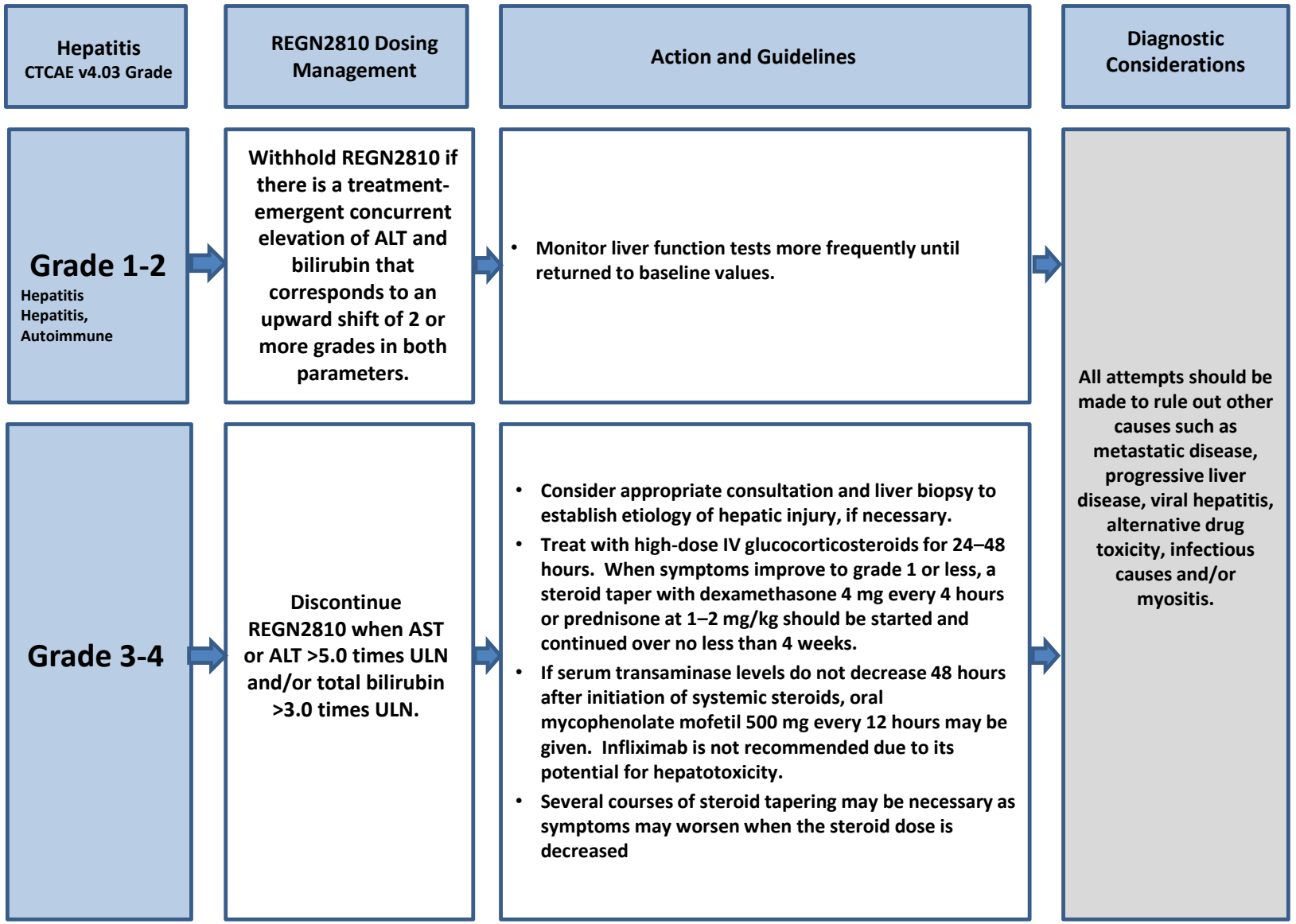
Hematologic Adverse Event Management (Cont.)



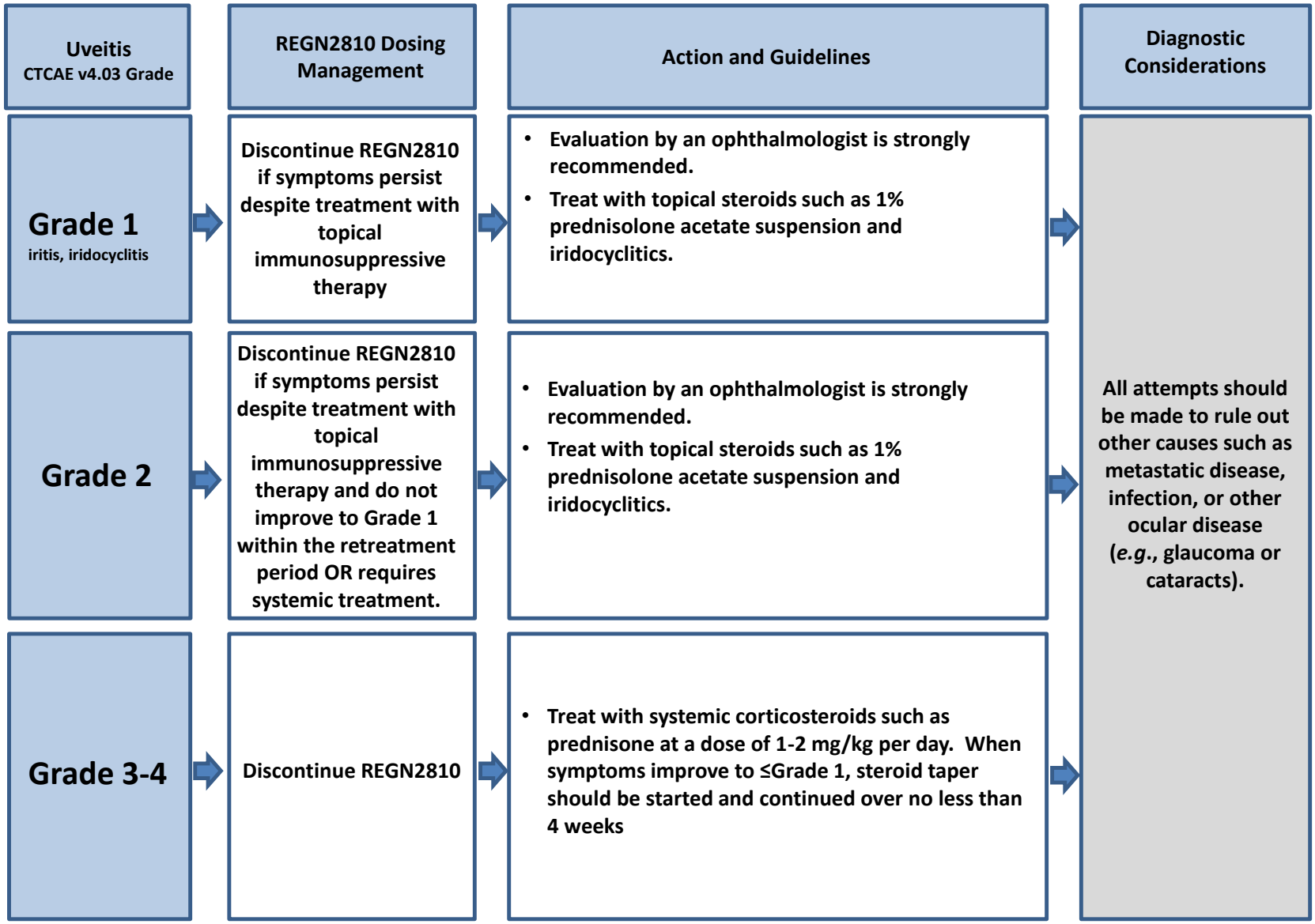
Dermatologic Adverse Event Management



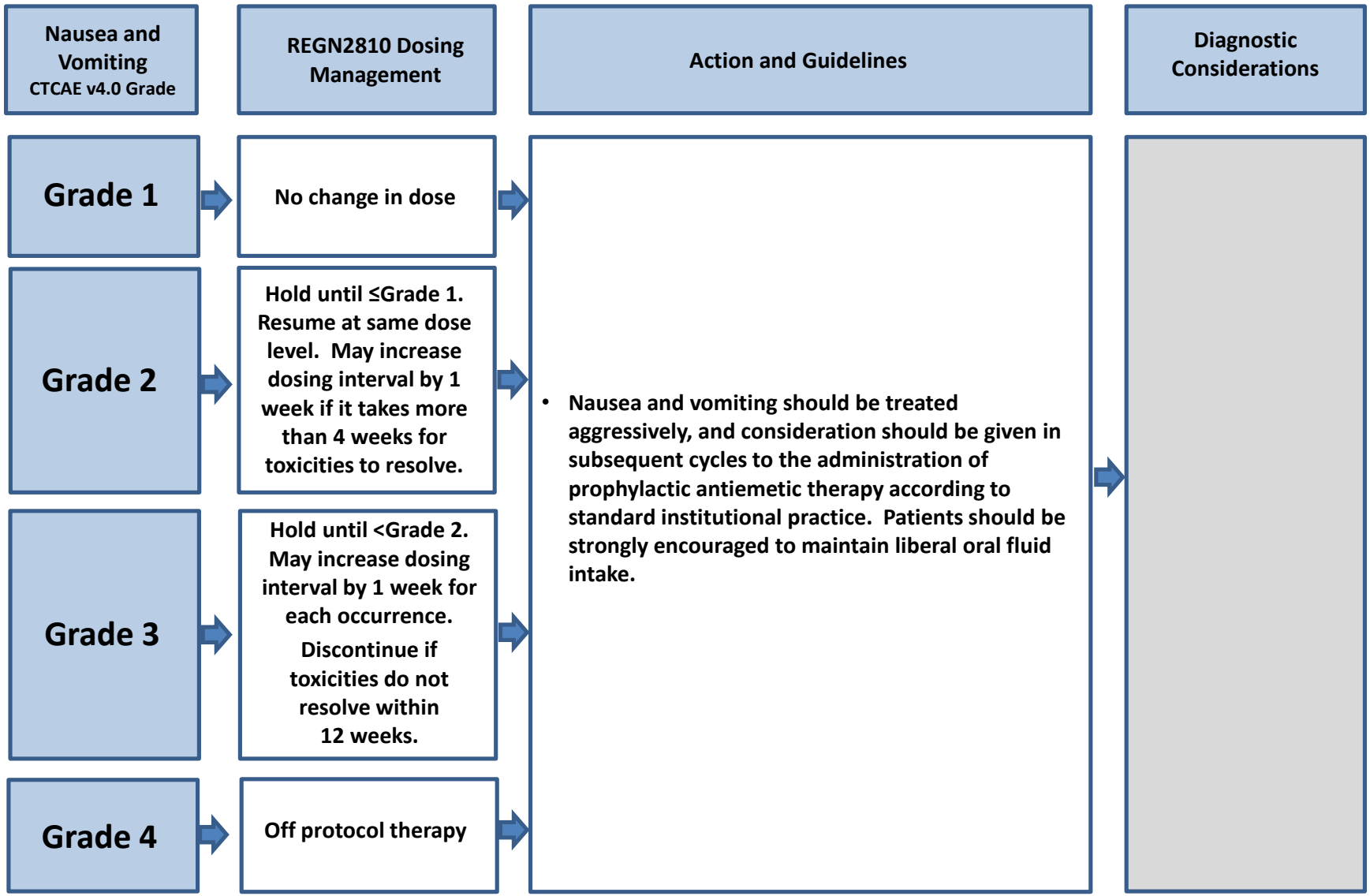
Hepatitis Adverse Event Management



Ophthalmologic (Uveitis) Adverse Event Management



Nausea and Vomiting Adverse Event Management



APPENDIX 3. MEDDRA DICTIONARY-DERIVED PREFERRED TERMS FOR POTENTIAL IRAES

MedDRA v23.0 Preferred Terms (N=267)
Addison's disease
Adrenal androgen deficiency
Adrenal atrophy
Adrenal insufficiency
Adrenal suppression
Adrenocortical insufficiency acute
Glucocorticoid deficiency
Hypoaldosteronism
Mineralocorticoid deficiency
Primary adrenal insufficiency
Secondary adrenocortical insufficiency
Antinuclear antibody increased
Antinuclear antibody positive
Arthralgia
Arthritis
Autoimmune arthritis
Immune-mediated arthritis
Polyarthritis
Rheumatoid arthritis
Autoimmune demyelinating disease
Axonal neuropathy

Chronic inflammatory demyelinating polyradiculoneuropathy
Demyelinating polyneuropathy
Demyelination
Autoimmune disorder
Autoimmune eye disorder
Blood alkaline phosphatase increased
Blood creatine phosphokinase increased
Blood thyroid stimulating hormone decreased
Blood thyroid stimulating hormone increased
Cardiac amyloidosis
Central nervous system inflammation
Chronic gastritis
Cutaneous vasculitis
Duodenitis
Encephalitis
Encephalomyelitis
Encephalitis allergic
Encephalitis autoimmune
Immune-mediated encephalitis
Noninfective encephalitis
Noninfective encephalomyelitis
Autoimmune encephalopathy
Encephalopathy
Immune-mediated endocrinopathy

Autoimmune endocrine disorder
Episcleritis
Gastrointestinal perforation
Guillain-Barre syndrome
Hepatic amyloidosis
Basedow's disease
Hyperthyroidism
Immune-mediated hyperthyroidism
Marine Lenhart syndrome
Primary hyperthyroidism
Secondary hyperthyroidism
Thyrotoxic crisis
Thyrotoxic periodic paralysis
Toxic goitre
Toxic nodular goitre
Hypoglossal nerve paralysis
Hypophysitis
Lymphocytic hypophysitis
Hypopituitarism
Autoimmune hypothyroidism
Hypothyroidic goitre
Hypothyroidism
Immune-mediated hypothyroidism
Myxoedema

Primary hypothyroidism
Secondary hypothyroidism
Tertiary hypothyroidism
Immune-mediated adverse reaction
Autoimmune anaemia
Autoimmune aplastic anaemia
Autoimmune haemolytic anaemia
Acute haemorrhagic ulcerative colitis
Allergic colitis
Autoimmune colitis
Autoimmune enteropathy
Colitis
Colitis erosive
Colitis ischaemic
Colitis microscopic
Colitis ulcerative
Crohn's disease
Diarrhoea
Diarrhoea haemorrhagic
Enterocolitis
Enterocolitis haemorrhagic
Eosinophilic colitis
Immune-mediated enterocolitis
Inflammatory bowel disease

Necrotising colitis
Neutropenic colitis
Acute hepatic failure
Autoimmune cholangitis
Autoimmune hepatitis
Hepatic failure
Hepatic function abnormal
Hepatitis
Hepatitis acute
Hepatotoxicity
Hyperbilirubinaemia
Immune-mediated cholangitis
Immune-mediated hepatic disorder
Immune-mediated hepatitis
Jaundice
Liver injury
Alanine aminotransferase increased
Aspartate aminotransferase increased
Blood bilirubin increased
Gamma-glutamyltransferase increased
Hepatic enzyme increased
Liver function test abnormal
Transaminases increased
Autoimmune hyperlipidaemia

Autoimmune inner ear disease
Blood creatinine increased
Glomerular filtration rate decreased
Acute kidney injury
Autoimmune nephritis
Chronic autoimmune glomerulonephritis
Immune-mediated nephritis
Immune-mediated renal disorder
Lupus nephritis
Nephritis
Nephritis haemorrhagic
Perinephritis
Renal failure
Renal impairment
Tubulointerstitial nephritis
Tubulointerstitial nephritis and uveitis syndrome
Autoimmune neutropenia
Autoimmune pancytopenia
Immune-mediated pancytopenia
Acute interstitial pneumonitis
Autoimmune lung disease
Immune-mediated pneumonitis
Interstitial lung disease
Pneumonitis

Autoimmune retinopathy
Rash pustular
Perineal rash
Acute generalised exanthematous pustulosis
Autoimmune blistering disease
Autoimmune dermatitis
Dermatitis
Dermatitis acneiform
Dermatitis bullous
Dermatitis exfoliative
Dermatitis exfoliative generalised
Dermatitis herpetiformis
Drug eruption
Drug reaction with eosinophilia and systemic symptoms
Dyshidrotic eczema
Erythema
Erythema multiforme
Erythema nodosum
Exfoliative rash
Immune-mediated dermatitis
Lichen planus
Oculomucocutaneous syndrome
Palmoplantar keratoderma
Parapsoriasis

Pemphigoid
Pemphigus
Psoriasis
Rash
Rash erythematous
Rash generalised
Rash macular
Rash maculo-papular
Rash maculovesicular
Rash morbilliform
Rash papular
Rash pruritic
Rash rubelliform
Rash scarlatiniform
Rash vesicular
Skin reaction
Stevens-Johnson syndrome
Toxic epidermal necrolysis
Toxic skin eruption
Autoimmune heparin-induced thrombocytopenia
Heparin-induced thrombocytopenia
Immune thrombocytopenia
Immune thrombocytopenic purpura
Insulin autoimmune syndrome

Iridocyclitis
Iritis
Keratitis
Ulcerative keratitis
Meningitis
Meningitis aseptic
Motor dysfunction
Mucosal inflammation
Muscular weakness
Myalgia
Ocular myasthenia
Myasthenia gravis
Myasthenia gravis crisis
Myasthenic syndrome
Myelitis
Noninfectious myelitis
Myelitis transverse
Autoimmune myocarditis
Immune-mediated myocarditis
Myocarditis
Blood creatine phosphokinase MB increased
Troponin increased
Autoimmune myositis
Immune-mediated myositis

Myositis
Polymyositis
Dermatomyositis
Autoimmune neuropathy
Immune-mediated neuropathy
Neuritis
Neuropathy peripheral
Peripheral sensory neuropathy
Polyneuropathy
Oral lichen planus
Autoimmune pancreatitis
Immune-mediated pancreatitis
Pancreatitis
Pancreatitis acute
Paraneoplastic encephalomyelitis
Autoimmune pericarditis
Pericarditis
Polymyalgia rheumatica
Pruritus
Pruritus allergic
Pruritus generalised
Pseudopolyposis
Psoriatic arthropathy
Idiopathic pulmonary fibrosis

Pulmonary fibrosis
Raynaud's phenomenon
Sarcoidosis
Pulmonary sarcoidosis
Sjogren's syndrome
Epidermal necrosis
Skin necrosis
Stomatitis
Systemic inflammatory response syndrome
Thyroid dermatopathy
Autoimmune thyroid disorder
Thyroid disorder
Autoimmune thyroiditis
Immune-mediated thyroiditis
Thyroiditis
Thyroiditis acute
Thyroiditis chronic
Thyroiditis fibrous chronic
Thyroiditis subacute
Trigeminal nerve paresis
Diabetes mellitus
Diabetic ketoacidosis
Latent autoimmune diabetes in adults
Type 1 diabetes mellitus

Autoimmune uveitis
Immune-mediated uveitis
Uveitis
Vasculitis
Vitiligo
Vocal cord paralysis

APPENDIX 4. FACTORS TO CONSIDER IN ASSESSING THE RELATIONSHIP OF ADVERSE EVENTS TO STUDY DRUG, STUDY CONDUCT, INFUSION PROCEDURE, OR STUDY PROCEDURE

Is there a reasonable possibility that the event may have been caused by the study drug, study conduct, infusion procedure, or study procedure?

No:

- due to external causes such as environmental factors or other treatment(s) being administered
- due to the patient's disease state or clinical condition
- do not follow a reasonable temporal sequence following the time of administration of the dose of study drug
- do not reappear or worsen when dosing with study drug or study procedure resumed
- are not a suspected response to the study drug or study procedure based upon preclinical data or prior clinical data

Yes:

- could not be explained by environmental factors or other treatment(s) being administered
- could not be explained by the patient's disease state or clinical condition
- follow a reasonable temporal sequence following the time of administration of the dose of study drug or study procedure
- resolve or improve after discontinuation of study drug or study procedure
- reappear or worsen when dosing with study drug or study procedure is resumed
- are known or suspected to be a response to the study drug or study procedure based upon preclinical data or prior clinical data

NOTE: This list is not exhaustive.

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

Signature Page for VV-RIM-00146791 v1.0

ESig Approval	[redacted]000
ESig Approval	[redacted]21 14:14:43 GMT+0000
ESig Approval	[redacted]1-2021 14:35:22 GMT+0000
ESig Approval	[redacted]-2021 14:46:23 GMT+0000
ESig Approval	[redacted]-2021 16:10:37 GMT+0000

Signature Page for VV-RIM-00146791 v1.0 Approved