CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761097Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NME
Application Number(s)	BLA 761097
Priority or Standard	Priority
Submit Date(s)	February 28, 2018
Received Date(s)	February 28, 2018
PDUFA Goal Date	October 28, 2018
Division/Office	DOP2/OHOP
Established Name	Cemiplimab-rwlc (Cemiplimab)
(Proposed) Trade Name	LIBTAYO™
Pharmacologic Class	PD-1 blocking antibody
Code name	REGN2810
Applicant	Regeneron Pharmaceuticals, Inc.
Formulation(s)	Injection: 350 mg/7 mL (50 mg/mL) solution in a single-dose vial
Dosing Regimen	350 mg as an intravenous infusion over 30 minutes every 3 weeks
Applicant Proposed Indication(s)/Population(s)	Treatment of patients with metastatic cutaneous squamous cell carcinoma or patients with locally advanced cutaneous squamous cell carcinoma who are not candidates for surgery
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	LIBTAYO is indicated 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

Table of Contents

Reviewers of Multi-Disciplinary Review and Evaluation....8

Additional Reviewers of Application....8

Glossary....9

1 Executive Summary....11
1.1. Product Introduction....11
1.2. Conclusions on the Substantial Evidence of Effectiveness....11
1.3. Benefit-Risk Assessment....14
1.4. Patient Experience Data....17

2 Therapeutic Context....19
2.1. Analysis of Condition....19
2.2. Analysis of Current Treatment Options....19

3 Regulatory Background....22
3.1. U.S. Regulatory Actions and Marketing History....22
3.2. Summary of Presubmission/Submission Regulatory Activity....22

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety....26
4.1. Office of Scientific Investigations (OSI)....26
4.2. Product Quality....26
4.3. Clinical Microbiology....26
4.4. Devices and Companion Diagnostic Issues....26

5 Nonclinical Pharmacology/Toxicology....27
5.1. Executive Summary....27
5.2. Referenced NDAs, BLAs, DMFs....30
5.3. Pharmacology....30
5.4. ADME/PK....36
5.5. Toxicology....36
5.5.1. General Toxicology....36
5.5.2. Genetic Toxicology....41
5.5.3. Carcinogenicity....41

5.5.4. Reproductive and Developmental Toxicology 41
5.5.5. Other Toxicology Studies 45

6 Clinical Pharmacology 47
6.1. Executive Summary 47
6.2. Summary of Clinical Pharmacology Assessment 47
6.2.1. Pharmacology and Clinical Pharmacokinetics 48
6.2.2. General Dosing and Therapeutic Individualization 49
6.3. Comprehensive Clinical Pharmacology Review 49
6.3.1. General Pharmacology and Pharmacokinetic Characteristics 49
6.3.2. Clinical Pharmacology Questions 51

7 Sources of Clinical Data and Review Strategy 62
7.1. Table of Clinical Studies 62
7.2. Review Strategy 64

8 Statistical and Clinical and Evaluation 65
8.1. Review of Relevant Individual Trials Used to Support Efficacy 65
8.1.1. Studies R2810-ONC-1423 and R2810-ONC-1540 65
8.1.2. Study Results 68
8.1.3. Integrated Assessment of Effectiveness 87
8.2. Review of Safety 87
8.2.1. Safety Review Approach 87
8.2.2. Review of the Safety Database 88
8.2.3. Adequacy of Applicant's Clinical Safety Assessments 90
8.2.4. Safety Results 91
8.2.5. Analysis of Submission-Specific Safety Issues 110
8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability 126
8.2.7. Safety Analyses by Demographic Subgroups 126
8.2.8. Specific Safety Studies/Clinical Trials 127
8.2.9. Additional Safety Explorations 127
8.2.10. Safety in the Postmarket Setting 127
8.2.11. Integrated Assessment of Safety 129

SUMMARY AND CONCLUSIONS 130

8.3. Statistical Issues 130
8.4. Conclusions and Recommendations 130
9 Advisory Committee Meeting and Other External Consultations 133
10 Pediatrics 134
11 Labeling Recommendations 134
11.1. Prescription Drug Labeling 134
12 Risk Evaluation and Mitigation Strategies (REMS) 137
13 Postmarketing Requirements and Commitment 138
14 Division Director (DHOT) 139
15 Division Director (OCP) 140
16 Division Director (OB) 141
17 Division Director (Clinical) 142
18 Office Director (or designated signatory authority) 143
19 Appendices 144
19.1. References 144
19.2. Financial Disclosure 146
19.3. OCP Appendices (Technical documents supporting OCP recommendations) 148
19.3.1. Summary of Bioanalytical Method Validation and Performance 148
19.3.2. Pharmacometric Review 150

Table of Tables

Table 1: Summary of Treatments Relevant to Proposed Indication....20
Table 2: In Vitro Binding and Blocking Activity of Cemiplimab....30
Table 3: Percent of Tumor-Free Mice on Day 21....35
Table 4: Histopathological Findings in the 26-Week Monkey Study....39
Table 5. Summary of integrated efficacy analyses for mCSCC, laCSCC and CSCC combined....51
Table 6.Single Dose (Cycle 1) and Steady State (observed on Cycle 3, Day 1) PK Parameters of Cemiplimab as a monotherapy, in combination with Radiation and/or Cyclophosphamide, or in all patients with solid tumors....53
Table 7. Single Dose (Cycle 1) and Steady State (observed on Cycle 3, Day 1) PK Parameters of Cemiplimab monotherapy in CSCC patients....53
Table 8. Comparison of Model Simulated 350 mg Q3W Exposure vs. 3 mg/kg Q2W at Population Level and Body Weight Stratified Subgroups....55
Table 9. Summary of Treatment-Emergent Adverse Events in Study 1540 at 90-Day Safety Update....56
Table 10. Summary of the ADA Status, Category, Maximum Titer, and NAb Status in All Patients With Solid Tumors by Dose (Study 1423 and Study 1540)....59
Table 11. Listing of Clinical Trials Relevant to this BLA....63
Table 12. Patient disposition, Advanced CSCC Population....70
Table 13: Major Protocol Deviations during Study 1540....71
Table 14. Demographic characteristics at baseline....73
Table 15. Patient clinical and disease characteristics at baseline....74
Table 16. Results of objective response rate by central review....74
Table 17. Results of objective response rate by central review by study....75
Table 18. Subgroup analysis of objective response rate in metastatic CSCC....77
Table 19. Subgroup analysis of objective response rate in locally advanced CSCC....77
Table 20. Subgroup analysis of objective response rate in combined CSCC....78
Table 21. Clinical Response Criteria, Locally Advanced CSCC....82
Table 22. Composite Response Criteria: Locally Advanced CSCC....83
Table 23.Characteristics of Response in Patients with Locally Advanced CSCC....83
Table 24. Exposure Summary....89
Table 25. Deaths Due to Causes other than Disease Progression: Pool 1....91
Table 26. Treatment-Related SAEs, Pool 1....97
Table 27. AEs Leading to Discontinuation of Cemiplimab, Pool 1....100
Table 28. Grade 3-4 Adverse Events, Pool 1....101
Table 29: Adverse Events by SOC, Pool 1....102
Table 30. TEAEs in at least 5% of patients, Pool 1....103
Table 31. Laboratory Abnormalities Occurring in ≥10% of Patients, Pool 1....106
Table 32. Laboratory Abnormalities, Pools 1, 2 and 3....107
Table 33. Overview of imARs, Pools 1, 2 and 3....111
Table 34. Identified ImARs by Composite/Preferred Term and Grade, Pools 1, 2 and 3....113
Table 35. Identified ImARs by Composite/Preferred Term and Grade, Pool 3....114

Table 36. Serious imARs by PT and Grade, Pool 3 115
Table 37. MedDRA Query for IRR Diagnoses and Symptoms 125
Table 38. Summary of IRRs, Pools 1 and 3.....125
Table 39. AEs by age subgroups, Pool 1 126
Table 40. Summary of Significant Labeling Changes 134
Table 41: Summary of Studies Included in Pop PK Analysis 151
Table 42: Sponsor's Parameter Estimates of the Final Model (LN900) 154
Table 43: Parameter comparison between sponsor's final Pop-PK model and FDA's final Pop-PK model.....155
Table 44: Comparison of Model Simulated 350 mg Q3W Exposure vs. 3 mg/kg Q2W at Population Level and Body Weight Stratified Subgroups.....157
Table 45: Estimated Parameters in logistic regression for ER relationship for efficacy 159
Table 46: 90-Day Safety Update of Cemiplimab at Dosing Level of 350 mg Q3W.....161

Table of Figures

Figure 1: Effect of Cemiplimab on T-Cell Receptor Signaling in a First-Generation Bioassay Using Jurkat/PD-1-CD300a/AP-1-Luc Cells and Raji Cells With or Without PD-L1 31
Figure 2: Effect of Cemiplimab on T-Cell Receptor Signaling in a Second-Generation Bioassay Using Jurkat/PD-1/AP-1-Luc Cells and HEK293/mIgE Cells With or Without PD-L1 31
Figure 3: Effect of Cemiplimab on Human CD4+ T Cell Proliferation Following Incubation with HEK293/hCD20/hPD-L1 cells 32
Figure 4: Effect of Cemiplimab on Human CD4+ T Cell Proliferation in a Primary Human T Cell/Immuno-Bead Bioassay 33
Figure 5: Effect of Cemiplimab on Human CD8+ T Cell Proliferation Following Incubation with HEK293 Cells Engineered to Express anti-CD3 or anti-CD3 and FcγR1 34
Figure 6: Effect of Cemiplimab on MC38.Ova Colon Cancer Xenografts in huPD-1 Mice.....35
Figure 7: Activity of Cemiplimab in a TDAR Assay in Cynomolgus Monkeys 40
Figure 8: Decreased Survival, Increased Bacterial Proliferation and Increased Inflammation in PD-1-deficient Mice Infected with M. tuberculosis 46
Figure 9. Preliminary efficacy data for Study 1540 Group 3 at 350 mg Q3W: Waterfall Plot per RECIST 1.1 by Investigator Assessment (Patients who had at Least One Post Baseline Scan Available within the Data Cutoff) 52
Figure 10. Best Percentage Change From Baseline in Target Lesions by Patient Over Time by Independent Central Reviewer - mCSCC (blue) and laCSCC (red) – FAS (Study 1423) 54
Figure 11. Percent Change From Baseline in Target Lesions by Patient Over Time by Independent Central Review - mCSCC (blue) and laCSCC (red) – FAS (Study 1540).....54
Figure 12. Comparison of Model Simulated 350 mg Q3W (Blue) vs. 3mg/kg Q2W (Red).....55
Figure 13. Exposure response for efficacy by logistic regression 57
Figure 14. Exposure Response Relationship for First Cycle Cmax versus Incident Rate of >Gr3 AE and SAE 57
Figure 15. Forest Plot of Covariates and Their Effect on Model Parameters, Estimated by the Full Model, Relative to the Parameter Values of a Reference Patients 58
Figure 16. Individual Cemiplimab Concentrations (Log Scale) vs. Actual Time by ADA Category and NAb Status in Patients with Solid Tumors at 1 mg/kg Q2W in Combination Therapy (Study R2810-ONC-1423).....60
Figure 17. Individual Cemiplimab Concentrations (Log Scale) vs. Actual Time by ADA Category and NAb Status for all Patients at 3 mg/kg Q2W in Monotherapy (Study R2810-ONC-1423) 60
Figure 18. Individual Cemiplimab Concentrations (Log Scale) vs. Actual Time by ADA Category and NAb Status for Patients at 3 mg/kg Q2W in (Study R2810-ONC-1423) 60
Figure 1. Mean global health status/QOL over time, by study arm.....79
Figure 2. Mean pain (subscale) over time, by study arm.....80

Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Missiratch (Mimi) Biable
Nonclinical Reviewer	Emily Wearne
Nonclinical Team Leader	Whitney Helms
Office of Clinical Pharmacology Reviewer(s)	Xiling Jiang, Yuan Xu
Office of Clinical Pharmacology Team Leader(s)	Hong Zhao, Jiang Liu
Clinical Reviewer	Denise Casey
Clinical Team Leader	Suzanne Demko
Statistical Reviewer	Mallorie Fiero
Statistical Team Leader	Pallavi Mishra-Kalyani
Cross-Disciplinary Team Leader	Suzanne Demko
Division Director (DHOT)	John K Leighton
Division Director (OCP)	Nam Atiqur Rahman
Division Director (OB)	Rajeshwari Sridhara
Division Director (OHOP)	Steven Lemery
Office Director (or designated signatory authority)	Richard Pazdur

Additional Reviewers of Application

OPQ	Willie Wilson, DS OBP, Jens Fricke, DP OBP
Microbiology	Max Van Tassell, DS and Aimee Cunningham, DP
OPDP	Nicholas Senior
OSI	Navid Homayouni
OSE/DEPI	Carolyn McCloske
OSE/DMEPA	Janine Stewart
OSE/DRISK	Joyce Weaver
Other	Ruth Lidoshore, Patient Labeling

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science

OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Regeneron Pharmaceuticals, Inc. (Regeneron) submitted a Biologics License Application (BLA) for cemiplimab (Libtayo™, REGN2810), a new molecular entity (NME), pursuant to the regulations under 21 CFR 601. The BLA was submitted under rolling review with the initial modules of the application submitted on November 30, 2017, and the final modules submitted on February 28, 2018, which started the review clock under the Prescription Drug User Fee Act (PDUFA). A safety update report was submitted to the application on May 29, 2018.

Cemiplimab is a recombinant human IgG4 monoclonal antibody that targets the programmed death-1 receptor (PD-1) and is part of the pharmacologic class of programmed death receptor-1 (PD-1) blocking antibodies. PD-1 is expressed on activated T and B cells, natural killer cells, and myeloid lineage cells. Binding of PD-1 to its ligands, programmed death-ligand 1 (PD-L1) and PD-L2, inhibits T-cell activity, T-cell proliferation, and cytokine production. In the tumor microenvironment, PD-1 signaling contributes to the inhibition of T cell-mediated immune surveillance of tumors. Blockade of PD-1 signaling in the tumor microenvironment is intended to enhance tumor immunosurveillance and anti-tumor immune responses, which is the mechanism of action for cemiplimab.

The action date for this application under PDUFA is October 28, 2018. The proposed indication for cemiplimab is: “For the treatment of patients with metastatic cutaneous squamous cell carcinoma (CSCC) or patients with locally advanced CSCC who are not candidates for surgery.” Data from two trials were submitted to support the safety and effectiveness of cemiplimab for the proposed indication. Study R2810-ONC-1423 (Study 1423) was an open-label, multi-center, non-randomized, dose-finding, expansion trial in patients with advanced solid tumors, including metastatic CSCC and locally regionally advanced CSCC, and Study R2810-ONC-1540 (Study 1540) was an open-label, multi-center, non-randomized, multicohort trial in patients with metastatic CSCC and locally advanced unresectable CSCC.

1.2. Conclusions on the Substantial Evidence of Effectiveness

All interdisciplinary scientific review teams recommend approval of the cemiplimab BLA under 21 CFR 601 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. I concur with these recommendations.

Evidence for the effectiveness of cemiplimab for patients with advanced CSCC, including patients with metastatic CSCC and patients with locally advanced CSCC who are not candidates for surgical resection or radiation, is derived from the pooled results of patients with metastatic and locally advanced CSCC treated with single agent cemiplimab in Study 1423 and Study 1540. There are data for 75 patients with metastatic CSCC who had at least six months of follow-up from accrual using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 to assess disease status. The data demonstrated a confirmed, centrally reviewed overall response rate (ORR) of 47% (95% CI: 35, 59); four patients (5%) experienced a complete response (CR) and 31 patients (41%) a partial response (PR). Among the 35 responding patients, the median duration of response (DOR) was not reached (range 2.8 to > 15.2 months) and 80% of patients (28/35) had ongoing responses at the data cutoff. Sixty percent (21/35) of responding patients maintained responses for $\geq$ 6 months. The majority of responding patients experienced objective responses at the first response assessment (Week 8) and the median time to response was 1.9 months.

There are also data from 33 patients with locally advanced CSCC (N=33) who had been followed for at least nine months after accrual. These data demonstrated a confirmed, centrally reviewed ORR of 49% (95% CI: 31, 67). Among the 16 responding patients, the median DOR was not reached (range 1 to > 12.9 months) and 81% of patients (13/16) had ongoing responses at the data cutoff. Sixty-three percent (10/16) of responding patients maintained responses of $\geq$ 6 months. The median time to response was 3.7 months with more than 80% of responders experiencing response at the first or second response evaluation (Week 8 or 16).

Data from exploratory subgroup analyses demonstrated that efficacy was consistent across relevant subgroups consisting of those patients who had or did not have prior systemic or radiotherapy, and those with nodal or distant metastases. For the small subset of patients who had PD-L1 expression results for their tumors, patients experienced durable responses regardless of whether the tumors tested positive or negative for PD-L1 expression.

The recommended dose of cemiplimab is 350 mg intravenously every 3 weeks. The dose was selected based on similar exposures between the weight-based 3 mg/kg every 2-week dose and the flat dose of 350 mg every 3 weeks that were evaluated during the cemiplimab development program. Although there is less clinical experience with the flat dose regimen for patients with CSCC (n=35), the Applicant provided population PK modeling and simulation results and additional safety and efficacy data for the flat dose in the 90 Day safety update. Based on these data and modeling, the 350 mg every 3-week regimen resulted in similar steady-state exposure compared to the 3mg/kg every 2-week regimen to allow for bridging the safety and efficacy data between the two regimens and conclude that the recommended dose is both safe and effective.

For patients with metastatic CSCC and patients with locally advanced CSCC who are not candidates for surgery or curative radiation, durable objective response rate of sufficient

magnitude is an acceptable endpoint that represents a direct clinical benefit for patients with an advanced cancer that will shorten their lives. Durable tumor shrinkage as a primary endpoint to support regular approval for drugs treating malignancies with primary skin involvement is also not without precedent. In the cemiplimab development program, radiographic response rate correlated with visible improvement of baseline disfiguring lesions during treatment, as demonstrated in the photographic data submitted in the application for the group of responding patients in Study 1540. In some cases, there was near complete resolution of cosmetically deforming lesions that had been refractory to multiple prior local and systemic treatments. Clinically meaningful shrinkage of disfiguring lesions located in highly visible areas such as the face, scalp, neck, or extremities is also a direct clinical benefit for patients.

Regeneron has successfully demonstrated that cemiplimab is effective for the treatment of patients with metastatic CSCC or patients with locally advanced CSCC who are not candidates for curative surgery or radiation, at a dose of 350 mg IV every 3 weeks. The data submitted in support of this application are statistically robust, clinically meaningful, and include confirmed durable ORR based upon independent central review as well as correlative substantial shrinkage of disfiguring cutaneous tumors. These results represent clinical benefit to patients with metastatic or locally advanced CSCC.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The pooled safety population supporting the BLA included 534 patients with various advanced solid tumors who were enrolled in Study 1423 and Study 1540 and received at least one dose of cemiplimab, including 163 patients with advanced CSCC.

Serious adverse reactions were experienced by 28% of patients. Serious adverse reactions that occurred in at least 2% of patients were cellulitis, sepsis, pneumonia, pneumonitis and urinary tract infection. The most common toxicities experienced by patients treated with cemiplimab that occurred in at least 20% of patients were fatigue, rash, and diarrhea.

Of the pooled population, 17% of patients experienced at least one immune-related adverse reaction (imAR). The most common imARs occurring in more than 2% of patients were hypothyroidism, pneumonitis and hepatitis. Eight percent of all immune-mediated events were Grade 3 or 4. Serious imARs observed at a lower frequency across the development program included autoimmune myocarditis, encephalomyelitis, hypophysitis, pemphigoid and paraneoplastic encephalomyelitis. The frequency and types of imARs in patients treated with cemiplimab are consistent with the safety profiles of other approved PD-1 and PD-L1 antibodies. ImARs were usually manageable with corticosteroids and hormone replacement therapy. Dose-modification and management guidelines for imARs are included in product labeling.

Infusion-related reactions (IRRs) during cemiplimab treatment were mostly low-grade in severity and led to permanent discontinuation in two (0.4%) patients. IRRs were managed with temporary interruptions, infusion rate reductions and administration of symptomatic treatments including antihistamines and corticosteroids. Management guidelines for IRRs are also included in the product label.

The safety profile of cemiplimab is consistent with other anti-PD-1/PD-L1 monoclonal antibodies, is favorable when compared to available cytotoxic chemotherapy regimens that have been used for this disease and is acceptable in view of the serious and life-threatening nature of metastatic or locally advanced CSCC.

Given the demonstrated effectiveness described previously in this review, the ratio of benefit: risk weighs in favor of the benefit of cemiplimab, at the recommended dose and regimen, for the treatment of patients with metastatic CSCC or patients with locally advanced CSCC who are not candidates for curative surgery or radiation.

Dimension	Evidence and Uncertainties	Conclusions and Reasons

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• CSCC has an estimated annual incidence of 700,000 cases in the US. • Second most common skin cancer • Precise incidences of overall disease, high-risk disease, and survival outcomes are not available as these cancers are grouped with other nonmelanoma skin cancers for reporting purposes • Most cases are localized and amenable to curative resection, approximately 8% of patients will experience a local recurrence, 5% will develop nodal metastases, and an estimated 2% will die from their disease • CSCC causes significant functional morbidities and cosmetic deformities as tumors commonly arise in the head and neck region and invade blood vessels, nerves, and vital organs • Patients with recurrence of disease after primary tumor resection develop local or distant metastases 25% of the time • Ten-year survival rates are less than 20% for patients with regional lymph-node involvement • Patients with distant metastases have a median survival time estimated to be less than two years	**The population treated in the studies supporting this application represent patients having a serious and life-threatening disease**
Current Treatment Options	• Standard of care for locoregional CSCC is complete surgical resection • For nodal involvement, a regional lymph node dissection is recommended • Adjuvant radiation therapy is utilized in most cases • (b) (4) • There are case reports of various epithelial growth factor receptor (EGFR) inhibitors and single arm, prospective studies of cetuximab and gefitinib in patients with high-risk CSCC that have reported	**There are no FDA-approved systemic therapies for patients with locally advanced and unresectable or metastatic CSCC and chemotherapy regimens tried to date have not been successful in providing meaningful outcomes for patients.**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	objective responses; (b) (4) • In addition, panitumumab and pembrolizumab are being studied as treatments for this disease	
Benefit	• The data supporting clinical benefit are derived from two studies and were pooled • For the 75 patients with metastatic CSCC, the data demonstrated a confirmed, centrally reviewed ORR of 47% (95% CI: 35, 59); there were four CRs (5%) and 31 PRs (41%). DOR was not reached (range 2.8 to > 15.2 months) and 80% of patients (28/35) had ongoing responses at the data cutoff. Sixty percent (21/35) of responding patients maintained responses for ≥ 6 months. • For the 33 patients with locally advanced CSCC, the data demonstrated a confirmed, centrally reviewed ORR of 49% (95% CI: 31, 67). The median DOR was not reached (range 1 to > 12.9 months) and 81% of patients (13/16) had ongoing responses at the data cutoff. Sixty-three percent (10/16) of responding patients maintained responses of ≥ 6 months.	**Durable objective response rate of sufficient magnitude, in the appropriate context, can represent a direct clinical benefit for patients with an advanced cancer that will shorten their lives. Durable tumor shrinkage as a primary endpoint to support regular approval for drugs treating malignancies with primary skin involvement is also not without precedent. Radiographic response rate correlated with visible improvement of baseline disfiguring lesions during treatment, as demonstrated in the photographic data submitted in the application for a group of responding patients. Clinically meaningful shrinkage of disfiguring lesions located in highly visible areas such as the face, scalp, neck or extremities, is also a direct clinical benefit for patients.**
Risk and Risk Management	• Serious risks of cemiplimab are like those of other monoclonal antibodies acting in the PD -1/PD-L1 pathway including serious and fatal imARs and IRRs. • Among 534 patients treated with cemiplimab, 17% (92/534) experienced at least one imAR during treatment.	**Overall, the safety profile of cemiplimab is consistent with that expected for immunologically-mediated anticancer therapies. The safety data submitted in the BLA do not change the favorable benefit: risk**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Four percent of patients required permanent discontinuation and 7% required temporary interruption of cemiplimab for imARs. • ImARs were rarely fatal and generally manageable with corticosteroid administration. • IRRs occurred in 9% of patients in Pool 3, and all were grade 1-2 except for one patient who experienced one Grade 3 IRR. • Two patients required permanent discontinuation of cemiplimab due to an IRR. IRRs were manageable with temporary interruptions, infusion rate reductions and administration of symptomatic treatments including antihistamines and corticosteroids.	**assessment for cemiplimab for the treatment of patients with advanced CSCC.**

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	The patient experience data that was submitted as part of the application, include:				Section where discussed, if applicable
	□	Clinical outcome assessment (COA) data, such as			[e.g., Section 6.1 Study endpoints]
			X	Patient reported outcome (PRO) EORTC QLQ-C30 (descriptive data only)	8.2.6
			□	Observer reported outcome (ObsRO)	
			□	Clinician reported outcome (ClinRO)	
			□	Performance outcome (PerfO)	

	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Section 2.1 Analysis of Condition]
	□	Observational survey studies designed to capture patient experience data	
	□	Natural history studies	
	□	Patient preference studies (e.g., submitted studies or scientific publications)	
	□	Other: (Please specify)	
□	Patient experience data that was not submitted in the application, but was considered in this review.		

COA analyses to inform long term tolerability were not conducted by the Applicant.

Suzanne G. Demko, P.A.-C.
Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1 Analysis of Condition

Cutaneous squamous cell carcinoma (CSCC) is the second most common human cancer in the United States, with an estimated annual incidence of 700,000 cases (Karia et al. 2013). While most cases are localized tumors amenable to curative resection, approximately 8% of patients will experience a local recurrence, 5% of patients will develop nodal metastases, and an estimated 2% of patients will die from their disease (Thompson et al. 2016). In addition to being a life-threatening disease, CSCC causes significant functional morbidities and cosmetic deformities based on tumors commonly arising in the head and neck region and invading blood vessels, nerves and vital organs such as the eye or ear (Kauver et al. 2015).

Precise incidences of overall disease, high-risk disease, and survival outcomes are not available because these cancers are grouped with other nonmelanoma skin cancers (NMSC) in the Surveillance, Epidemiology, and End Results (SEER) database. High-risk patients are those who have recurrent disease or who are at high risk for recurrence, lymph node metastases, or distant metastases. Patients who have recurrence of disease after having a primary tumor resection will develop local or distant metastases 25% of the time (Kauver et al. 2015). Factors associated with recurrence and poor prognosis in CSCC include tumor size > 2 cm, tumor depth > 2 mm (Breslow thickness), perineural invasion, host immunosuppression, poorly differentiated histology and location on the ear, temple, or lip (Thompson et al. 2016, Kauver et al. 2015). Ten-year survival rates are less than 20% for patients with regional lymph-node involvement. For those patients who develop distant metastases, the median survival time is estimated to be less than two years (Stratigos et al. 2015).

2.2. Analysis of Current Treatment Options

The standard of care for locoregional CSCC is complete surgical resection with a minimum margin of 5 mm for low risk tumors and 10 mm for high risk tumors. If there is nodal involvement, a regional lymph node dissection is recommended, and adjuvant radiation therapy is utilized in most cases (Stratigos et al. 2015; NCCN Guidelines, VI.2017).

Treatment options are limited for the small subset of patients with CSCC who develop local recurrences, unresectable disease, or distant metastatic disease. Radiation as the definitive treatment may be considered in some patients with unresectable locally advanced disease based on the durable response rates and disease-free survival described in retrospective studies (Samstein et al. 2014; Veness et al. 2008).

There are no FDA-approved systemic therapies for patients with locally advanced and unresectable or metastatic CSCC (b) (4) . Additionally, there are case reports of various epithelial growth factor receptor (EGFR) inhibitors and single arm, prospective studies of cetuximab and gefitinib in patients with high-risk CSCC that have reported objective responses; (b) (4) (Lewis et al. 2012; Jarkowski et al. 2014). In one of the largest clinical studies of cetuximab in 36 patients with advanced CSCC, the median overall survival from diagnosis of advanced CSCC was 8.1 months (Maubec et al. 2011).

Table 1 summarizes agents that have been or are currently being evaluated in clinical studies in patients with CSCC with advanced disease. The table does not include topical agents, cytotoxic chemotherapeutics, or drugs being evaluated in refractory all-comer cancer populations. Note that the studies below may have used different response criteria or responses were not evaluated per independent review. Furthermore, some studies (e.g., gefitinib) evaluated different patient populations.

Table 1: Summary of Treatments Relevant to Proposed Indication

Product	Mechanism of Action	Reference	Comments
Cetuximab	EGFR TKI	Maubec et al. 2011	Completed. 36 patients with unresectable CSCC (three patients with metastatic disease). ORR 28%. DOR not reported. Median OS 8.1 months.
Gefitinib	EGFR TKI	Lewis et al. 2012	Completed. 22 patients with aggressive or recurrent local CSCC. Patients with distant metastases excluded. Neoadjuvant gefitinib for 2 cycles followed by standard of care local control. ORR (b) (4) %.
Panitumumab	MAB to EGFR	Foote et al. 2014	Completed. 16 patients with incurable advanced CSCC (two patients had metastatic disease). ORR per RECIST was 31% (95 CI: 11-59). DOR not reported. Median OS 11 months.

Product	Mechanism of Action	Reference	Comments
Pembrolizumab	MAB to PD-1	Ragini et al. 2018	Ongoing. Metastatic CSCC. Interim analysis demonstrated ORR 40% in first 10 patients enrolled. DOR not reported.
Pembrolizumab	MAB to PD-1	NCT03284424	Ongoing. Metastatic or inoperable locally advanced CSCC. Preliminary results unavailable. Estimated sample size=120.

MAB monoclonal antibody; TKI tyrosine kinase inhibitor

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Cemiplimab is an NME and is not currently marketed in the U.S. Cemiplimab is not currently approved by any foreign regulatory agency.

3.2. Summary of Presubmission/Submission Regulatory Activity

On December 22, 2014, IND 123950 for REGN2810 was submitted to the Division of Oncology Products 1 (DOP 1). The IND included the clinical protocol for Study R2810-ONC-1423 entitled, "A First-in-Human (FIH) Study of Repeat Dosing with REGN2810, a Monoclonal, Fully Human Antibody to Programmed Death -1 (PD-1), as Single Therapy and in Combination with Other Anti-Cancer Therapies in Patients with Advanced Malignancies."

On September 10, 2015, a pre-IND meeting was held with DOP2 to discuss the development program for REGN2810 in CSCC based on preliminary efficacy data from the CSCC expansion cohorts of Study 1423. The following items summarize key agreements and recommendations discussed at this meeting:

- FDA agreed to the enrollment of patients without a requirement for prior systemic therapy if the Applicant agreed to provide analyses of confirmed ORR based on subgroups defined by extent of prior systemic therapy.
- FDA agreed to the enrollment of patients with metastatic CSCC without a requirement for prior radiation therapy; however, for patients with locally advanced CSCC, FDA recommended that an individualized benefit: risk assessment be performed by a multidisciplinary team consisting of a medical oncologist with expertise in cutaneous malignancies or a dermato-oncologist and a radiation oncologist prior to enrollment in the proposed study. FDA also stated that the case report form (CRF) for patients with locally advanced CSCC should capture the reasons for enrollment in the study including why the patient with locally advanced CSCC was not a candidate for surgical resection or for radiation therapy.
- FDA recommended that pre-specified subgroup analyses of patients with locally advanced and metastatic disease be outlined in the statistical analysis plan. FDA also stated that since a different treatment effect may be observed in patients with metastatic disease as compared to patients with locally advanced disease, there must be an adequate sample size to demonstrate direct clinical benefit in both populations.
- FDA stated that the eligibility criteria should require that the most recent biopsy of the lesion be reviewed centrally by an independent dermatopathologist to assure that the lesions are CSCC without the presence of other malignant components.

- FDA agreed that a primary endpoint of confirmed ORR may be acceptable provided ORR is shown to be clinically meaningful in magnitude and duration, with an acceptable safety profile for REGN2810 in this patient population. For patients with locally advanced CSCC, a (generally) non-life-threatening disease, FDA advised the Applicant to provide justification that the observed reduction in tumor size provides clearly defined, direct clinical benefit.
- FDA recommended independently reviewed objective response and duration of response data for the efficacy analyses to reduce potential reader bias and measurement variability. For patients with locally advanced disease, FDA recommended independent review of all radiology, photography, and biopsy results by a blinded central review committee to determine the overall response for each patient based on an integration of these assessment modalities for the proposed composite endpoint.
- FDA stated that the Applicant must provide a detailed, study-specific response guideline in the protocol submitted to the IND. The response assessment criteria should address issues of measurement of scar, fibrosis, ulceration, protuberance formation, and palpable subcutaneous components that may not be visible or evident in photography. The procedures for choosing baseline target and non-target lesions and the methods for obtaining serial measurements using color photography should be well-described. The guideline should outline the methods for obtaining tumor biopsies, the time points for biopsy assessments and the number and location of the biopsies that will be taken depending on the size of the target lesion. FDA recommended that the modified response criteria include a provision that all patients considered to have a complete response will be biopsied with central pathologic review to confirm absence of tumor; otherwise response assessment will be considered as PR.

On December 7, 2015, IND 127100 was submitted and contained the protocol for Study R2810-ONC-1540 (1540), entitled “A Phase 2 Study of REGN2810, a Fully Human Monoclonal Antibody to Programmed Death – 1 (PD-1), in Patients with Advanced Cutaneous Squamous Cell Carcinoma.” The proposed study was an open-label, non-randomized, multicenter study of REGN2810 administered at a dose of 3 mg/kg every two weeks to patients with metastatic CSCC or patients with locally advanced CSCC who were not candidates for surgery or radiation.

On October 17, 2016, a CMC meeting was held to gain agreement with FDA on the

(b) (4)

On December 16, 2016, the Applicant requested Preliminary Breakthrough Therapy Designation Request (BTDR) Advice. A teleconference with FDA was held on January 25, 2017. During this teleconference, FDA stated that while the proposed data from 25 patients who received cemiplimab may be adequate for a breakthrough request in a rare disease, the determination of breakthrough designation will depend on the magnitude of the treatment effect on both

response rate and duration of response. FDA recommended that the Applicant seek a second preliminary breakthrough designation request discussion after all patients included in the dataset had been followed for a minimum of four months after the onset of response, that there be an independent review of all responses, and that available medical photographs be submitted for patients enrolled in the study if an improvement in disfiguring lesions is considered clinical benefit in this disease.

On June 27, 2017, a follow-up teleconference was held with the FDA, to review the updated data on the same 25 patient cohort. During the teleconference, FDA recommended that Regeneron provide a more recent data cutoff which could provide more mature DOR results and would only minimally delay a BTDR.

On July 18, 2017, Regeneron submitted a BTDR for cemiplimab for patients with advanced CSCC supported by summary response and duration of response data from 26 patients treated in Study 1423.

On July 26, 2017, a Type B pre-BLA meeting was held between FDA and Regeneron to discuss and reach agreement on the content and presentation of data for the planned BLA for REGN2810 for advanced CSCC. Regeneron requested guidance on approval pathways and whether the results of Study 1423 would support an accelerated approval.

- FDA acknowledged that the reported Study 1423 ORR results were suggestive of a treatment effect; however, FDA requested that Regeneron rely on additional data from Study 1540 given the small sample sizes for metastatic and locally advanced disease cohorts from Study 1423.
- FDA agreed that the complete data from Group 1 in Study 1540 in addition to data from Study 1423 could support a marketing authorization for REGN2810 for the treatment of CSCC in patients with metastatic disease if the effect size on independently assessed ORR and duration of response was of sufficient magnitude. Whether the data would support regular approval or accelerated approval would depend on the results observed. FDA stated that Regeneron would need to provide justification for the proposed effect size and duration of effect to be considered evidence of direct benefit or likely to predict clinical benefit based on a lower limit of the confidence interval observed around the response rate.
- FDA stated that whether both indications (metastatic CSCC and locally advanced CSCC) are sought or granted for a marketing application will depend on the continued enrollment and results of Study 1540. FDA stated no objection to filing an application based on a single indication (i.e., metastatic CSCC) while the data in patients with locally advanced disease was maturing, but also inquired about the status of Group 2 enrollment in Study 1540. Regeneron asked whether they could perform an interim assessment of the data from patients with locally advanced CSCC (Group 2) with sufficient follow-up. FDA agreed to an interim analysis of Group 2 and recommended that Regeneron select the number of patients in Group 2 who will have had their responses followed for at least six months (e.g.,

patients who have initiated treatment nine months prior to the cut-off date) when conducting the analysis.

- FDA stated that discussion of the approvability of the 350 mg Q3W flat dose of REGN2810 based on the PK modeling was premature. The adequacy of the dosage regimen for REGN2810 would be determined upon review of the BLA.
- FDA agreed to the proposed pooling strategy for safety across Studies 1423 and 1540. FDA also agreed with the proposed presentation of data by disease subtypes for the metastatic and locally advanced populations of CSCC and in total. FDA recommended including side-by-side comparison tables in the Summary of Clinical Safety and Summary of Clinical Efficacy.
- FDA recommended that Regeneron propose case definitions for classifying adverse events of infusion reactions and immune-mediated adverse reactions (imARs).

On September 6, 2017, REGN2810 (cemiplimab) was granted Breakthrough Therapy Designation for the treatment of adults with metastatic cutaneous squamous cell carcinoma (CSCC) and with locally advanced and unresectable CSCC based on demonstration of durable objective responses in Study 1423.

On November 29, 2017, a Type C meeting was held to further discuss the content and format of the cemiplimab BLA for the treatment of patients with metastatic CSCC, or with locally advanced CSCC who are not candidates for surgery. FDA agreed to the proposed case definitions for infusion reactions and imARs and to the overall plans for the presentation of safety and efficacy results in the BLA.

On November 30, 2017, the first part of the rolling BLA was submitted: Module 4 (Nonclinical Study Reports).

On February 28, 2018, the final portion of the BLA was submitted and included Module 5 (Clinical), Module 2.2 (Introduction), Module 2.3 (Quality Overall Summary), Module 2.4 (Nonclinical Overview), Module 2.5 (Clinical Overview), Module 2.6 (Nonclinical written and tabulated summaries), Module 2.7 (Clinical Summary), and Module 1 (administrative).

The following summarizes the important clinical post submission regulatory activity for the cemiplimab application:

On April 2, 2018, an Applicant Orientation meeting was held at FDA.

On May 29, 2018, the Applicant submitted the 90-day Safety Update Report and datasets including cumulative safety data through the data cut-off date of January 20, 2018.

On June 8, 2018, the Midcycle Communication teleconference was held with the Applicant. FDA stated that no significant nonclinical or clinical review issues and no major safety concerns had been identified to date. FDA stated that the 90-day safety update and the additional data to

support the proposed flat dosing strategy versus the body weight-based dosage regimen was under review. Important CMC review issues were discussed including pending responses for FDA informational requests. See CMC review for details.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

DOP2 consulted the Office of Scientific Investigation (OSI) on March 18, 2018, to perform an audit of four clinical trial sites and the Applicant site. The Division, in consultation with OSI, selected clinical sites for inspection using the Center for Drug Evaluation and Research (CDER) risk-based Site Selection Tool and a manual assessment of the trends in screening and enrollment characteristics, patterns of protocol violations reported for the sites, patterns of efficacy reporting, and patterns of serious adverse event (SAE) reporting.

The OSI inspections identified one serious violation at one clinical site regarding a dosing error for two patients enrolled in Group 2 of Study 1540 (each patient received the other patient's dose). The investigator submitted details of the error and risk mitigation plans and the site received an inspection classification of Voluntary Action Indicated (or VAI). No serious violations were identified at the other three sites. Overall, OSI did not identify significant issues that could affect the quality and interpretation of the data submitted in the application

See OSI review for additional details regarding site inspections and findings.

4.2. Product Quality

Please see FDA CMC reviews by Willie Wilson (drug substance) and Jens Fricke (drug product) for details regarding cemiplimab quality and manufacturing.

4.3. Clinical Microbiology

Please see FDA product quality microbiology reviews by Max Van Tassell (drug substance reviewer) and Aimee Cunningham (drug product reviewer) for details regarding microbiology.

4.4. Devices and Companion Diagnostic Issues

There is no device or companion diagnostic test for review in support of this BLA.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Cemiplimab is a hinge-stabilized human IgG4 monoclonal antibody that targets the programmed death-1 receptor (PD-1); its established pharmacologic class is programmed death receptor-1 (PD-1) blocking antibody. PD-1 is expressed on activated T and B cells, natural killer cells, and myeloid lineage cells. Binding of PD-1 to its ligands programmed death-ligand 1 (PD-L1) and PD-L2 inhibits T-cell activity, T-cell proliferation, and cytokine production. In the tumor microenvironment, PD-1 signaling contributes to the inhibition of T cell-mediated immune surveillance of tumors. Thus, blockade of PD-1 signaling in the tumor microenvironment is intended to enhance tumor immunosurveillance and anti-tumor immune responses.

In in vitro studies, cemiplimab (REGN2810) bound to human and cynomolgus monkey PD-1 with similar affinity, but did not bind rodent PD-1, supporting the use of cynomolgus monkeys as the single pharmacologically relevant species for toxicity assessment. Cemiplimab also blocked the binding of human and cynomolgus monkey PD-1 to human PD-L1 and PD-L2. In cell-based PD-1 bioassays, incubation with cemiplimab blocked the PD-1/PD-L1 interaction, thereby increasing T-cell activation. Following incubation with a CD3 x CD20 T cell activating bispecific antibody and HEK293 cells engineered to express human CD20 and full-length human PD-L1, cemiplimab induced a dose-dependent increase in human CD4+ T-cell proliferation compared to isotype control. In contrast, in the presence of increasing amounts of anti-CD28 and in the absence of PD-L1, incubation with anti-CD3 and cemiplimab coated beads resulted in slightly reduced human CD4+ T-cell proliferation compared to beads coated with anti-CD3 and isotype control. Further, incubation with soluble or cross-linked cemiplimab did not enhance anti-CD3-induced human CD8+ T-cell proliferation or cytokine release compared to isotype control. Overall, these data suggest that cemiplimab does not directly activate T cells or have significant effects in the absence of PD-L1 mediated inhibition.

Given that cemiplimab does not bind mouse PD-1, the Applicant investigated the in vivo anti-tumor activity of cemiplimab in immunocompetent mice genetically engineered to express a human/mouse PD-1 chimeric receptor (huPD-1 mice). Intraperitoneal administration of cemiplimab at dose levels ≥2.5 mg/kg on Days 3, 7, 10, 13/14, and 17 resulted in inhibition of syngeneic colorectal cancer xenograft growth in huPD-1 mice.

As expected for an IgG4 antibody, cemiplimab did not induce in vitro antibody-dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) activity against PD-1-positive or PD-1-negative cells. Cemiplimab did not form circulating immune complexes in the presence of soluble recombinant human PD-1 capable of binding to C1q. Thus, induction of ADCC and CDC activity do not appear to play significant roles in the in vivo activity of cemiplimab.

The Applicant evaluated the safety of cemiplimab in cynomolgus monkeys in GLP-compliant repeat-dose toxicology studies of up to 26 weeks duration. In the 26-week study, monkeys received once weekly intravenous (I.V.) administration of cemiplimab at doses up to 50 mg/kg, which resulted in exposures approximately 21 times higher based on AUC than the steady-state $AUC_{0\text{-}3w}$ of 1900 µg/mL*day at the human dose of 350 mg once every 3 weeks, though anti-drug antibody (ADA) responses seen in 53% of cemiplimab-treated monkeys resulted in variable exposure. There were two mortalities, one each at the 10 and 50 mg/kg dose levels, attributed to pulmonary hemorrhage and edema that were considered secondary to immunogenicity. Findings in all surviving animals were generally minimal to mild and, consistent with its mechanism of action, consisted primarily of an increase in the incidence and/or severity of histologic mononuclear cell infiltration in numerous tissues, which often persisted or developed during the 12-week recovery period. One high dose female exhibited an enlarged spleen correlating with an increase in spleen weight and in the number/size of lymphoid follicles. Histologic findings observed only following 12 weeks of recovery included adrenal gland mineralization, colon congestion, and corneal hyperkeratosis in the eye. Cemiplimab was still detected in 50% of cemiplimab-treated monkeys alive at the end of the recovery period. Based on clinical trials done to support the approval of cemiplimab in the proposed patient population, toxicities associated with cemiplimab are primarily immune-mediated adverse reactions, such as pneumonitis, that are predicted by its mechanism of action.

Since the PD-1/PD-L1 signaling pathway has been implicated in T-cell exhaustion and the maintenance of chronic infection (Barber et al. 2006), inhibition of this pathway may lead to increases in the primary immune response as well as secondary responses to infection. To evaluate the effect of cemiplimab on primary and recall antibody responses to antigen challenge, the Applicant included a T-cell-dependent antigen response (TDAR) assay in the 4-week repeat-dose toxicology study in monkeys. Administration of cemiplimab at the 2 mg/kg and 50 mg/kg dose levels resulted in increased anti-keyhole limpet hemocyanin (KLH) IgG memory responses compared to controls after secondary immunization with KLH emulsified in incomplete Freund's adjuvant (IFA). Once weekly I.V. administration of cemiplimab also induced dose-independent and reversible increases in proliferating T-lymphocytes, T-helper lymphocytes, and T-cytotoxic lymphocytes in the 4-week toxicology study.

Based on its mechanism of action and data from the literature, there is the potential for inappropriate or enhanced immune responses to infection following treatment with cemiplimab. PD-1 deficient mice (C57BL/6) infected with *M. tuberculosis* exhibited decreased survival compared to wild-type mice, which correlated with uncontrolled bacterial proliferation and an increased inflammatory response in the lungs. It is unclear whether decreased survival resulted from an inability to mount an appropriate antibacterial response or a failure to control the immune response leading to normal tissue destruction and organ failure (Lazar-Molnar, et al. 2010). Further, in mouse models of lymphocytic choriomeningitis virus (LCMV) infection, the absence of PD-1 pathway signaling led to fatal CD8+ T cell-mediated killing of virally infected vascular endothelial cells, systemic vascular leakage, and ultimately cardiovascular collapse (Frebel et al. 2012; Mueller et al. 2010). Similarly, PD-L1 deficient mice died early after chronic

systemic LCMV infection (Barber et al. 2006). A brief description of these data was included in Section 13.2 of the label to convey these potential risks to prescribers.

While fertility assessments are not generally needed to support the approval of products intended for the treatment of patients with advanced cancer, early uncertainty regarding the definition of the intended treatment population led to advice to include sexually mature animals in the long term general toxicology study to assess fertility parameters and to evaluate the male and female reproductive tracts, consistent with recommendations in ICH S6(R1). Subsequently, the Applicant conducted a separate 13-week toxicology study in sexually mature cynomolgus monkeys. There were no clear drug-related effects on fertility parameters including menstrual cycle determination, semen analysis, orchidometry, or evaluation of reproductive organs at doses up to the high dose level of 50 mg/kg (approximately 5.5 to 25.5 times the human exposure by AUC at the human dose of 350 mg once every 3 weeks).

Embryo-fetal developmental toxicology studies were not conducted with cemiplimab. Rather, consistent with the alternative approach to providing information on the potential for reproductive toxicity described in ICH S6(R1) and ICH S9, the Applicant provided a literature-based assessment of the potential reproductive toxicity of cemiplimab. Data from the literature demonstrate that the PD-1/PD-L1 pathway plays a critical role in maintaining maternal immunological tolerance to the fetus during pregnancy. In allogeneic mouse models of pregnancy, blockade of PD-1/PD-L1 signaling resulted in an increased incidence of fetal loss but no fetal malformations. There are no reports of fetal malformations associated with PD-1 deficiency in mice, however, late onset autoimmunity can occur in these animals. Based on these findings, potential risks of administering cemiplimab during pregnancy include increased rates of abortion or stillbirth and an increased risk in offspring of developing immune-related disorders or altering the normal immune response. As a result, the pharmacology/toxicology team recommends a warning for embryo-fetal toxicity in the label for LIBTAYO. Based on a half-life of cemiplimab of approximately 19 days, females of reproductive potential are advised to use effective contraception during treatment with LIBTAYO and for at least 4 months (rounded up due to patient variability) after the final dose. The Applicant did not evaluate transfer of cemiplimab to the fetus or milk, but IgG antibodies can be present in milk. Because of potential adverse effects of LIBTAYO on a breastfeeding infant, the review team recommends the inclusion in the label of advice not to breastfeed during treatment with LIBTAYO and for 4 months after the final dose. Neither genetic toxicology or carcinogenicity studies were conducted or required to support the use of an antibody in the currently proposed indication. There are no outstanding issues from a pharmacology/toxicology perspective that would prevent the approval of LIBTAYO for the treatment of patients with metastatic or locally advanced cutaneous squamous cell carcinoma (CSCC) who are not candidates for surgery or radiation.

5.2. Referenced NDAs, BLAs, DMFs

None

5.3. Pharmacology

Primary pharmacology

A. In Vitro Studies

The Applicant determined the binding affinities of REGN2810 (cemiplimab) for human, cynomolgus monkey, rat, and mouse PD-1 using surface plasmon resonance (SPR-Biacore; Study # REGN2810-MX-14078-SR-01V1). REGN2810 exhibited similar binding affinity for human and cynomolgus monkey PD-1 (see Table 2), but did not bind mouse or rat PD-1, supporting the use of cynomolgus monkeys as a pharmacologically relevant species for toxicity assessment. As assessed by enzyme-linked immunosorbent assay (ELISA), REGN2810 blocked the binding of human and cynomolgus monkey PD-1 to plate-bound human PD-L1 and PD-L2 (see Table 2; Study # REGN2810-MX-14079-SR-01V1).

Table 2: In Vitro Binding and Blocking Activity of Cemiplimab

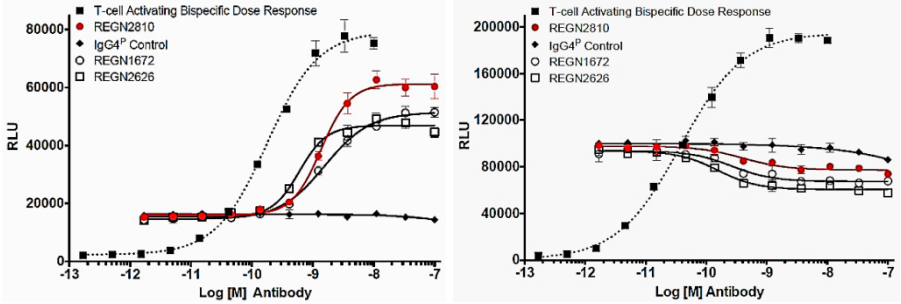
	K_D or IC_{50}		Method
	Human	Cynomolgus	
Binding to myc-myc-hexahistidine-tagged monomeric form of PD-1	5.61 nM	7.61 nM	SPR-Biacore
Binding to dimeric Fc-fusion of PD-1	577 pM	499 pM	SPR-Biacore
Blockade of binding of PD-1 to plate-coated human PD-L1	0.6 nM	0.97 nM	ELISA
Blockade of binding of PD-1 to plate-coated human PD-L2	0.13 nM	0.22 nM	ELISA
Blockade of binding of biotin-labeled PD-1 to plate-coated human PD-L1	85 pM	NT	ELISA

NT = Not tested; (Reviewer generated table based on results from Study # REGN2810-MX-14078-SR-01V1 and # REGN2810-MX-14079-SR-01V1)

The Applicant tested REGN2810 in two versions of a cell-based PD-1 bioassay. In the first-generation bioassay, CD3-expressing Jurkat cells transduced with the AP-1-Luc reporter gene and a human PD-1-CD300a chimeric receptor (Jurkat/PD-1-CD300a/AP-1-Luc cells) were used as effector cells and human B-lymphocyte CD20-expressing Raji cells were used as antigen-presenting cells (APCs). The Applicant also utilized Raji cells transduced with human PD-L1 to assess whether the inclusion of REGN2810 could prevent PD-1 pathway mediated inhibition of T cells in this system. Jurkat/PD-1-CD300a/AP-1-Luc cells were incubated with Raji cells or PD-L1-expressing Raji cells at a 1:1 ratio in the presence of 30 pM of a CD3 x CD20 T cell activating bispecific protein (REGN2281) to activate T-cell receptor (TCR)/AP-1 signaling. Investigators then added 1.7 pM to 100 nM of REGN2810, comparator anti-PD1 antibodies (REGN1672, REGN2626), or the IgG4 isotype control antibody REGN1945 to these cultures for 5 hours in order to measure the ability of cemiplimab to block PD-1-mediated signaling. In the presence of PD-L1 expressing cells, the addition of REGN2810 blocked the PD-1/PD-L1 interaction, thereby increasing TCR activation (EC_{50} = 1.37 nM) compared to the isotype control (Figure 1, left panel). Similar results were seen with the PD-1 comparator antibodies although the maximum RLU (relative luciferase units) seen with REGN2810 was ~15% higher than that seen with the comparators. In the absence of PD-1 pathway inhibition (native Raji cells), incubation with the

CD3-CD20 bispecific resulted in strong activation which neither REGN2810 or the other anti-PD-1 comparator antibodies could further enhance (Figure 1, right panel). Incubation with anti-PD-1 antibodies actually caused mild decreases in TCR signaling in the PD-L1 negative setting (~11 to 29% compared to the isotype control), which were hypothesized to be an artifact of assay and not observed in all instances.

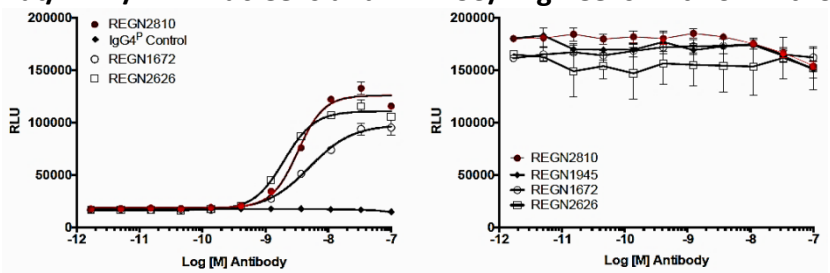
Figure 1: Effect of Cemiplimab on T-Cell Receptor Signaling in a First-Generation Bioassay Using Jurkat/PD-1-CD300a/AP-1-Luc Cells and Raji Cells With or Without PD-L1



Left: Raji/PD-L1 cells; Right: PD-L1-negative Raji cells; Solid black square = REGN2281; REGN2810 = cemiplimab
(Applicant Figures reproduced from Study # REGN2810-MX-14079-SR-01V1)

The Applicant subsequently developed a second-generation PD-1 bioassay. In this assay, Jurkat cells transduced with the AP-1-Luc reporter gene and full length PD-1 (Jurkat/PD-1/AP-1-Luc cells) were used as effector cells and HEK293 cells transduced with a membrane bound IgE (mIgE) with anti-CD3 variable domains either with or without PD-L1 (HEK293/mIgE and HEK293/mIgE/PD-L1) were used as APC-like cells. Jurkat/PD-1/AP-1-Luc cells were incubated with HEK293/mIgE cells or HEK293/mIgE/PD-L1 cells in the presence of 1.7 pM to 100 nM of REGN2810, comparator PD-1 antibodies, or an isotype control for 5 hours. As determined by reporter-driven luciferase activity, incubation with REGN2810 in the presence of HEK293/mIgE/PD-L1 cells blocked the PD-1/PD-L1 interaction, increasing TCR activation (EC_{50} = 3.3 nM) compared to the isotype control (Figure 2, left panel). Conversely, in the presence of PD-L1-negative HEK293/mIgE cells, REGN2810 did not substantially affect TCR signaling. In conclusion, REGN2810-mediated blockade of the PD-1/PD-L1 interaction resulted in increased TCR activation in two different PD-1 bioassays.

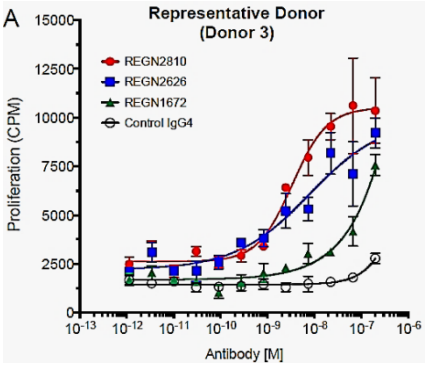
Figure 2: Effect of Cemiplimab on T-Cell Receptor Signaling in a Second-Generation Bioassay Using Jurkat/PD-1/AP-1-Luc Cells and HEK293/mIgE Cells With or Without PD-L1



Left: HEK293/mIgE/PD-L1 cells; Right: PD-L1-negative HEK293/mIgE cells; REGN2810 = cemiplimab
(Applicant Figure reproduced from Study # REGN2810-MX-14079-SR-01V1)

The Applicant also investigated the effect of REGN2810 on PD-1/PD-L1 signaling using primary human T cell-based PD-1 bioassays (Study # REGN2810-MX-14082-SR-01V1). Primary human CD4+ T cells isolated from human peripheral blood mononuclear cells (PBMCs) from eight human donors were pre-activated to induce PD-1 expression. HEK293 cells engineered to express human CD20 and full-length human PD-L1 (HEK293/hCD20/hPD-L1 cells) were incubated with primary human CD4+ T cells at a 1:2 ratio in the presence of 2 nM of the CD3 x CD20 T cell activating bispecific antibody REGN1979 plus serial dilutions (3.4 pM to 200 nM) of REGN2810, comparator PD-1 antibodies (REGN1672, REGN2626) or the isotype control antibody REGN1945 for 72 hours. As measured by tritiated thymidine incorporation, REGN2810 induced a dose-dependent increase in T-cell proliferation (EC_{50}~ 2nM) compared to the isotype control. Relatively similar results were seen with the comparator PD-1 antibodies.

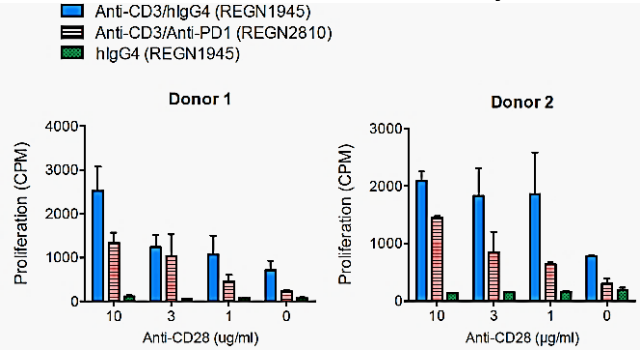
Figure 3: Effect of Cemiplimab on Human CD4+ T Cell Proliferation Following Incubation with HEK293/hCD20/hPD-L1 cells



REGN2810 = cemiplimab; (Applicant Figure reproduced from Study # REGN2810-MX-14082-SR-01V1)

To further determine the effects of immobilized REGN2810 on T cell activation, immuno-beads coated with anti-CD3 (UCHTI) and REGN2810, anti-CD3 and REGN1945, or REGN1945 alone were incubated with primary human CD4+ T cells isolated from two human donors at a bead:CD4 ratio of 1:1 in the presence of increasing concentrations of soluble anti-CD28 antibody for 72 hours. As measured by tritiated thymidine incorporation, anti-CD28 enhanced T cell proliferation induced by anti-CD3, whereas the presence of REGN2810 on anti-CD3-coated beads slightly reduced anti-CD28-enhanced T-cell proliferation compared to beads coated with anti-CD3 and REGN1945.

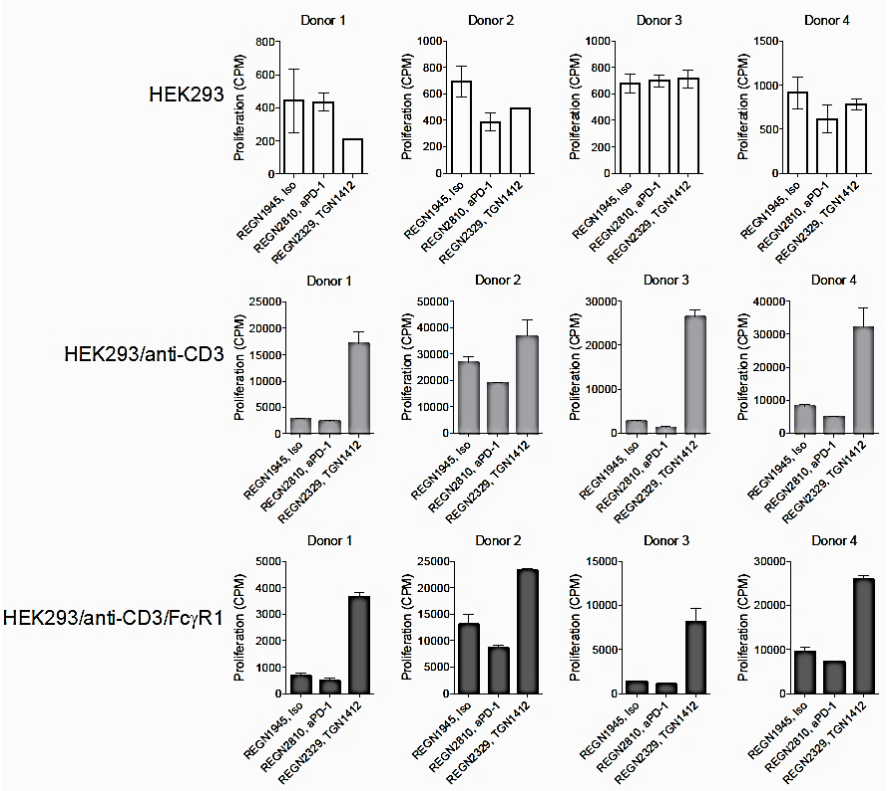
Figure 4: Effect of Cemiplimab on Human CD4+ T Cell Proliferation in a Primary Human T Cell/Immuno-Bead Bioassay



REGN2810 = cemiplimab; (Applicant Figure reproduced from Study # REGN2810-MX-14082-SR-01V1)

To investigate the effect of REGN2810 cross-linking, HEK293 cells were engineered to express membrane bound anti-CD3 to activate T cells and FcγR1 to cross-link REGN2810 via its Fc receptors. Primary human CD8+ T cells isolated from four human donors were incubated with HEK293 cells, HEK293 cells expressing anti-CD3, or HEK293 cells expressing anti-CD3 and FcγR1 at a 1:2 (T-cell: HEK293) ratio in the presence of 2 nM REGN2810, anti-CD28 (REGN2329; amino acid sequence identical to TGN1412), or the isotype control REGN1945 for 72 hours. As measured by tritiated thymidine incorporation, incubation with the positive control REGN2329 enhanced anti-CD3-induced CD8+ T cell proliferation in HEK293 cells expressing anti-CD3 and anti-CD3/FcγR1; however, incubation with soluble or cross-linked REGN2810 did not enhance CD8+ T-cell proliferation compared to REGN1945 in any of the cell lines tested, suggesting REGN2810 does not provide co-stimulatory signals. Overall, these data indicate that REGN2810 is unlikely to induce nonspecific activation of human T cells.

Figure 5: Effect of Cemiplimab on Human CD8+ T Cell Proliferation Following Incubation with HEK293 Cells Engineered to Express anti-CD3 or anti-CD3 and FcγR1



REGN2810 = cemiplimab; (Applicant Figure reproduced from Study # REGN2810-MX-14082-SR-01V1)

The Applicant next evaluated the ability of REGN2810 to induce in vitro cytokine release from human PBMCs isolated from 12 healthy human donors. PBMCs were incubated for 18 hours with 0.4, 1.1, 3.3, and 10 µg/mL REGN2810 immobilized onto 96-well plates using the air-drying method. Anti-CD3 (OKT3) and anti-CD28 (REGN2329) antibodies were included as positive controls, and REGN1945 was included as an isotype negative control. Incubation with up to 10 µg/mL REGN2810 did not substantially induce IFN-γ, IL-2, IL-4, IL-13, or IL-10 secretion from human PBMCs compared to REGN1945.

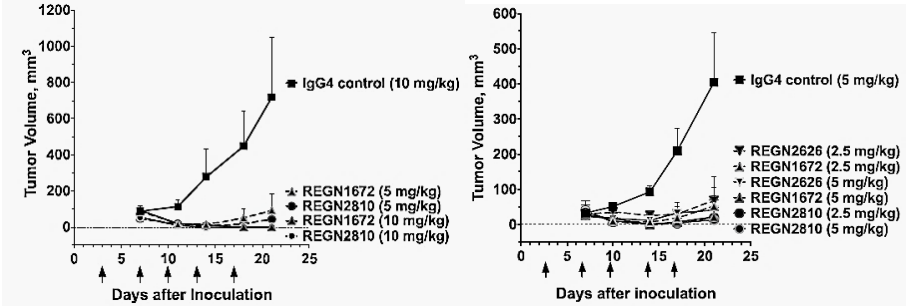
The Applicant evaluated the ability of REGN2810 to induce in vitro ADCC and CDC activity by human PBMCs against cell lines expressing varying levels of PD-1 as target cells (Study #REGN2810-MX-14080-SR-01V1). Cell death was measured by luminescence in the presence of CytoTox-Glo™ Reagent. Incubation of human PBMCs with REGN2810 or isotype control REGN1945 for 4 hours did not induce in vitro ADCC activity against Jurkat cells (low PD-1 expression), Jurkat cells stimulated with anti-CD3/CD28 (moderate PD-1 expression), HEK293/PD-1 cells (high PD-1 expression), or PD-1-negative HEK293 cells at concentrations up to 250 nM using an effector: target (E:T) ratio of 25:1. In contrast, the positive control anti-EGFR antibody REGN171 induced dose-dependent ADCC activity against EGFR-positive A431 cells.

In the CDC assay, PD-1 positive and negative target cell lines were incubated with REGN2810 or REGN1945 +/- 5% normal human serum (NHS) for 3.5 hours. Neither REGN2810 nor REGN1945 induced in vitro CDC by human PBMCs against Jurkat cells, Jurkat cells stimulated with anti-CD3/CD28, HEK293/PD-1 cells, or HEK293 cells at concentrations up to 500 nM in the presence or absence of NHS. In contrast, the positive control anti-CD20 antibody rituximab induced dose-dependent CDC activity against CD20-positive Raji cells. Thus, there is a relatively low potential for REGN2810 to induce ADCC and CDC activity in vivo. The Applicant also investigated the ability of REGN2810 to form circulating immune complexes (CIC) in the presence of soluble recombinant human PD-1 tagged with a myc-myc-hexahistidine tag (hPD-1.mmH) at molar antibody:PD-1 ratios of 1:1 and 1:2. As assessed by ELISA, incubation with 10 or 50 nM REGN2810 or REGN1945 and human PD-1 for 30 minutes did result in the formation of CIC capable of binding to C1q, the first step in the complement cascade.

B. In Vivo Studies

Since REGN2810 does not bind mouse PD-1, mice were genetically engineered to express a human/mouse PD-1 chimeric receptor (huPD-1 mice); these mice have a functional human PD-1 with expression regulated by the mouse PD-1 promoter. The Applicant investigated the in vivo anti-tumor activity of REGN2810 in huPD-1 mice bearing syngeneic colorectal cancer xenografts (Study #REGN2810-MX-14081-SR-01V1). Five to seven mice/group were subcutaneously implanted on Day 0 with 1 x 10^6 MC38.Ova mouse colon adenocarcinoma cells engineered to express chicken ovalbumin. Across two experiments, intraperitoneal administration of ≥2.5 mg/kg REGN2810 on Days 3, 7, 10, 13/14, and 17 resulted in statistically significant ($P < 0.05$) inhibition of MC38.Ova xenograft growth compared to isotype control REGN1945 (Figure 6 and Table 3). REGN2810 exhibited similar in vivo anti-tumor activity as comparator anti-PD-1 antibodies. The Applicant did not assess body weight or tolerability in these experiments.

Figure 6: Effect of Cemiplimab on MC38.Ova Colon Cancer Xenografts in huPD-1 Mice



Left: Experiment #1; Right: Experiment #2; Arrows denote treatment days; REGN2810 = cemiplimab
(Applicant Figure reproduced from Study # REGN2810-MX-14081-SR-01V1)

Table 3: Percent of Tumor-Free Mice on Day 21

Antibody	Experiment #1		Experiment #2	
	Rx: Days 3, 7, 10, 13, and 17		Rx: Days 3, 7, 10, 14, and 17	
	5 mg/kg	10 mg/kg	2.5 mg/mg	5 mg/kg
REGN1945 (isotype)	NT	1/5 (20%)	NT	0/7 (0%)
REGN2810	4/5 (80%)	5/5 (100%)	6/7 (85.7%)	6/7 (85.7%)

Antibody	Experiment #1		Experiment #2	
	Rx: Days 3, 7, 10, 13, and 17		Rx: Days 3, 7, 10, 14, and 17	
	5 mg/kg	10 mg/kg	2.5 mg/mg	5 mg/kg
REGN1672	4/5 (80%)	5/5 (100%)	6/7 (85.7%)	6/7 (85.7%)
REGN2626	NT	NT	6/7 (85.7%)	6/7 (85.7%)

Rx = Treatment; NT = Not tested; (Reviewer generated table based on results from Study # REGN2810-MX-14081-SR-01V1)

5.4. ADME/PK

A pharmacokinetics and local tolerability study evaluating single subcutaneous injection of cemiplimab to female cynomolgus monkeys was not reviewed because cemiplimab is administered intravenously to patients. Traditional distribution, metabolism, and excretion studies were not conducted with cemiplimab because it is a monoclonal antibody; however, consistent with ICH S6(R1), the Applicant did include a tissue cross reactivity assay to assess distribution of the target (See 5.5.5).

Type of Study	Major Findings
Absorption REGN2810: A Single Dose Intravenous Pharmacokinetic Study in Female Cynomolgus Monkeys, Study #REGN2810-PK-14065	*Dose proportionality:* C_{max} increased dose proportionally; AUC_{last} increased greater than dose proportionally *Anti-drug antibody (ADA):* Detected in all monkeys dosed with REGN2810.

Dose (mg/kg)	C_{max} (µg/mL)	AUC_{last} (day·µg/mL)	t_{max} (hour)	CL (mL/day/kg)	Vss (mL/kg)	$t_{1/2}$ (day)
1	33.3	168	3.13	5.99	37.3	1.19
5	121	1100	1.13	4.56	63.4	2.02
15	355	3950	2 35	3.68	65.6	9.85

CL = clearance; Vss = Volume of distribution at steady-state; ADA-impacted concentrations were excluded from PK calculations

5.5. Toxicology

5.5.1. General Toxicology

Study title/ number: A 26-Week Intravenous Toxicology Study in Cynomolgus Monkeys with a 12-Week Recovery Period/ REGN2810-TX-14153

Key Study Findings

- There was one mortality each after multiple injections at the 10 mg/kg and 50 mg/kg dose levels attributed to pulmonary hemorrhage and edema considered to be secondary to immunogenicity. The high dose preterm decedent also exhibited histologic hemorrhage and/or edema in the kidney, skin, urinary bladder, cecum, stomach, and liver.
- REGN2810 induced an increase in the incidence and/or severity of multi-organ mononuclear cell infiltration
- Other potential target organs included the spleen, eye (corneal hyperkeratosis), and cecum (erosion and mixed cell inflammation)

Conducting laboratory and location:
(b) (4)
GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 2, 10, and 50 mg/kg once weekly for 26 weeks
Route of administration:	I.V. infusion over approximately 30 minutes
Formulation/Vehicle:	10 mM histidine pH 6.0, 10% sucrose, 0.1% polysorbate 80
Species/Strain:	Cynomolgus monkey
Number/Sex/Group:	4/sex/group (main) 2/sex/group (12-week recovery period)
Age:	2-5 years old
Satellite groups/ unique design:	None/ immunogenicity, immunophenotyping, respiratory rates, pulse oximetry, body temperature, blood pressure, neurologic exam
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters	Major findings
Mortality	There were five mortalities; three (2 control and one MD monkey) were not drug-related. The other two are described below. **10 mg/kg: 1 MD female (#3503)** exhibiting lethargy, weakness, dyspnea, decreased activity, dilated pupils, pale gums, and vomitus was euthanized on Day 36 (dosing day) after the 6th dose. Exhibited fluid accumulation in the lung correlating histologically with hemorrhage and edema. ADA were detected on Day 36 correlating with reduced REGN2810 exposure. The cause of death was considered pulmonary hemorrhage and edema secondary to immunogenicity. **50 mg/kg: 1 HD male (#4006)** exhibiting decreased activity, loss of consciousness, lying on side, reduced appetite, decreased respiratory rate, and uncoordination was found dead on Day 94 two days after the 14th dose on Day 92. ADA were detected on Day 86+ correlating with reduced REGN2810 exposure. The cause of death was considered pulmonary hemorrhage and edema secondary to immunogenicity.
Clinical Signs	See clinical signs in preterm decedents above. There was a dose-related increase in the incidence of red skin beginning at the LD, including facial redness beginning by Day 22. **2 mg/kg:** Retching, dry/flaking skin, red feces **10 mg/kg:** Decreased activity, pink skin, pale gums/face **50 mg/kg:** Decreased activity (no dose response), prepuce swelling, liquid/mucoid feces, vomitus
Body Weights	Unremarkable
Ophthalmoscopy	Unremarkable

<table>
<tr><td>ECG, blood pressure, and automated heart rate</td><td>Unremarkable</td></tr>
<tr><td>Respiratory Rate/Pulse Oximetry</td><td>Unremarkable</td></tr>
<tr><td>Body Temperature</td><td>Unremarkable</td></tr>
<tr><td>Neurologic Examination</td><td>Unremarkable</td></tr>
<tr><td>Hematology</td><td>Unremarkable</td></tr>
<tr><td>Clinical Chemistry</td><td>Statistically significant 38% increase in mean bilirubin on Day 92 in HD females.</td></tr>
<tr><td>Urinalysis</td><td>Unremarkable</td></tr>
<tr><td>Gross Pathology</td><td>2 mg/kg: Dark red focus in stomach (fundus) in 1 male monkey (#2001)
50 mg/kg: Enlarged spleen in 1 female monkey (#4502)</td></tr>
<tr><td>Organ Weights</td><td>Increase in spleen weight (absolute and relative to body and brain weight) in 1 HD female monkey (#4502) up to 314%.</td></tr>
<tr><td>Histopathology
Adequate battery: Yes</td><td>See Table 4. In addition to these findings, there was an increased incidence and/or severity of multi-organ (including the brain) mononuclear cell infiltration up to mild at the HD.</td></tr>
<tr><td>Immunophenotyping</td><td>Unremarkable; no drug-related effects on absolute or percent T-lymphocytes, T-cytotoxic lymphocytes, T-helper lymphocytes, monocytes, B-lymphocytes, or natural killer cells</td></tr>
<tr><td>Reversibility</td><td>There was a statistically significant transient decrease (≤25%) in mean heart rate at an ECG timepoint scheduled within one week of the recovery necropsy in monkeys dosed with ≥2 mg/kg REGN2810 compared to controls; this decrease was observed 4 hrs. into the 24 hr. monitoring period and showed evidence of recovery.

In general, all findings trended towards recovery or were similar to controls except for the recovery cohort findings in Table 4, some of which developed during the recovery period.
Minimal mononuclear cell infiltration was still present in the brain (MD-HD), esophagus (HD), salivary gland (LD-HD), kidney (LD-HD), and urinary bladder (LD-MD) and also developed in the optic nerve in one HD monkey during the recovery period.</td></tr>
<tr><td>Immunogenicity</td><td>ADAs were detected in 19/36 (53%) monkeys dosed with REGN2810 including 11/12 (92%), 4/12 (33%), and 4/12 (33%) monkeys dosed with 2, 10, and 50 mg/kg REGN2810, respectively. ADAs generally resulted in lower REGN2810 concentrations. Given the drug tolerance limit (DTL) of ~1284 µg/mL in the validated ADA assay, ADA formation at the HD was likely masked by high REGN2810 concentrations.</td></tr>
<tr><td>Toxicokinetics</td><td>$T_{1/2}$: 13.5-19.3 days; T_{max}: ~0.583 hours
Dose proportionality: C_{max} and AUC_{tau} generally increased dose proportionally
Accumulation: Yes, based on C_{max} and AUC_{tau} (≤4-fold and ≤5-fold on Day 176 and Day 92 compared to Day 1, respectively)
Sex differences: No significant differences
On Day 176, AUC_{tau} was only calculated in 2 and 3 monkeys dosed with 10 mg/kg and 50 mg/kg REGN2810, respectively, due to ADAs

<table>
<tr><th rowspan="2">Day/ Dose</th><th rowspan="2">Dose (mg/kg)</th><th colspan="2">C_{max} (µg/mL)</th><th colspan="2">AUC_{tau} (µg·day/mL)</th><th colspan="2">$T_{1/2}$ (days)</th></tr>
<tr><th>M</th><th>F</th><th>M</th><th>F</th><th>M</th><th>F</th></tr>
<tr><td>1/1</td><td>2</td><td>45.5</td><td>51</td><td>166</td><td>190</td><td>NC</td><td>NC</td></tr>
</table></td></tr>
</table>

	10	181	251	659	844	NC	NC
	50	1650	1340	5580	5240	NC	NC
92/14	2	219	N/A	714	N/A	NC	NC
	10	698	511	3180	2560	NC	NC
	50	2400	2660	11800	14800	NC	NC
176/26	2	98	126	N/A	N/A	N/A	N/A
	10	679	537	2750	3100	13.5	19.3
	50	2470	3030	8800	14000	9.01	17.6

ADA-impacted concentrations were excluded from TK calculations
AUC_{tau}: Area under the concentration-time curve calculated during the dosing interval; N/A: Not Applicable; NC: Not Calculated

LD: low dose (2 mg/kg); MD: mid dose (10 mg/kg); HD: high dose (50 mg/kg); ADA: anti-drug antibody

Table 4: Histopathological Findings in the 26-Week Monkey Study

Dose (mg/kg)		0		2		10		50	
Sex		M	F	M	F	M	F	M	F
# of monkeys examined		4,2R	3,1R	4,2R	4,2R	4,2R	3,1R	4,1R	4,2R
Brain	Gliosis, Min						1		
Epididymis	Hypospermia, bilateral Marked					1			
Eye	Hyperkeratosis, corneal, Min								1R
Adrenal gland	Mineralization, Min			1R	1R				
Thyroid gland	Cyst Ectopia Increased colloid, Mild	1	1	1,1R 2,1R	1,1R	2	1 1	1R	
Kidney	Hemorrhage, tubular, Min Regeneration, tubular, Min					1 1R	1		
Cecum	Erosion, Min Mixed cell inflammation, Mild							1R 1R	
Colon	Congestion, Min					1R			
Liver	Mixed cell inflammation, Mild Degeneration/necrosis, hepatocellular, Min					1 1			
Axillary lymph node	Erythrocytosis, sinus, Min					1			
Skeletal muscle	Degeneration Min Mild Mononuclear cell inflammation, Mild			 1 1					1
Ovary	Cyst				1,1R				
Pancreas	Congestion, islet, Min Mononuclear cell inflammation, Mild				1		1		
Spleen	Increased number/size, lymphoid follicle Min Mild	1R	1	1R 1		1R		1R	 1
Spinal cord, cervical	Mononuclear cell inflammation, Min								1
Stomach	Congestion/hemorrhage, Min			1					

Dose (mg/kg)		0		2		10		50	
Sex		M	F	M	F	M	F	M	F
# of monkeys examined		4,2R	3,1R	4,2R	4,2R	4,2R	3,1R	4,1R	4,2R
Testis	Decreased spermatogenesis, bilateral, Marked					1			
	Hypospermatogenesis								
	Min	1		1					
	Mild			1R					
Thymus	Decreased lymphocytes								
	Min	1		1		1R		1,1R	
	Mild					1			

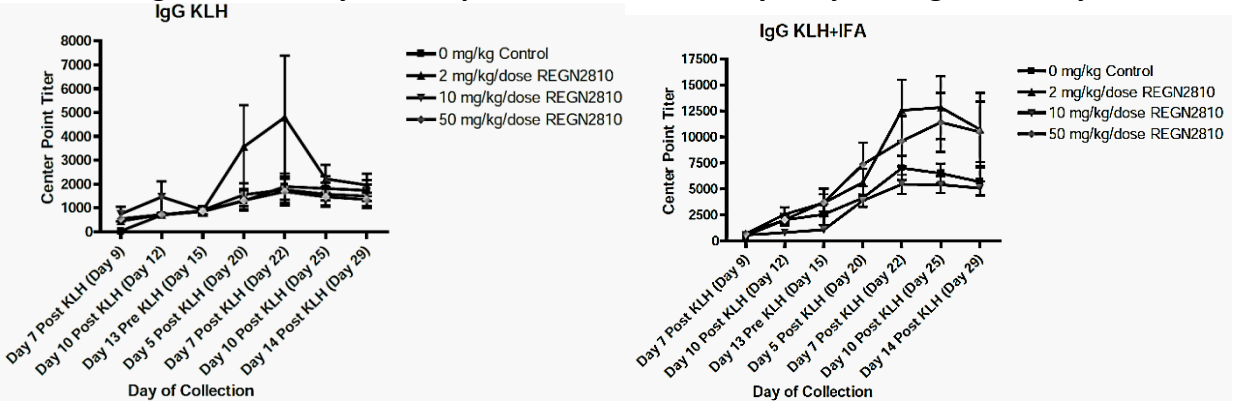
R: Recovery Group

General toxicology; additional studies

REGN2810: 4-Week Intravenous Toxicology Study in Cynomolgus Monkeys with an 8-Week Recovery Period / REGN2810-TX-14059

REGN2810 was administered intravenously once weekly at dose levels of 2, 10, or 50 mg/kg for 4 weeks to cynomolgus monkeys. There were no mortalities. ADAs were detected in 23/30 (77%) monkeys dosed with REGN2810 including 10/10 (100%), 7/10 (70%), and 6/10 (60%) monkeys dosed with 2, 10, and 50 mg/kg REGN2810, respectively. There was evidence of immune complex deposition, and histologic findings were seen in the adrenal gland, spleen, liver, mandibular lymph node, and axillary lymph node. As determined by flow cytometry for Ki67, REGN2810 induced dose-independent increases in the absolute counts of proliferating T-lymphocytes, T-helper lymphocytes, and T-cytotoxic lymphocytes on Day 9 which generally showed evidence of recovery by Day 50. There were no REGN2810-related increases in the proliferation of isolated PBMCs activated ex vivo or in C1q-CIC or C3d-CIC formation. In a T-cell-dependent antigen response (TDAR) assay, administration of REGN2810 at the 2 mg/kg and 50 mg/kg dose levels increased anti-keyhole limpet hemocyanin (KLH) IgG memory responses compared to control after secondary immunization on Day 15 with KLH emulsified in incomplete Freund's adjuvant (IFA; Figure 7). Administration of REGN2810 at the 2 mg/kg dose level increased KLH IgG memory responses after secondary immunization with KLH without IFA in individual female monkeys, particularly monkey #2505.

Figure 7: Activity of Cemiplimab in a TDAR Assay in Cynomolgus Monkeys



REGN2810 = cemiplimab; (Applicant Figure reproduced from Study # REGN2810-TX-14059)

5.5.2. Genetic Toxicology

Not conducted per ICH S6.

5.5.3. Carcinogenicity

Carcinogenicity studies were not conducted or required to support the use of an antibody in the currently proposed indication per ICH S9.

5.5.4. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

Standard fertility and early embryonic development studies were not conducted with cemiplimab. While, consistent with the ICH S9 guidance, fertility assessments are not typically expected for products intended for the treatment of patients with cancer, early uncertainty regarding the definition of the intended treatment population led to advice to include sexually mature animals in the long term general toxicology study in order to assess fertility parameters and to evaluate the male and female reproductive tracts, consistent with recommendations in ICH S6(R1). Rather than include sexually mature animals in the long term chronic toxicology study, the Applicant evaluated the reproductive tract of sexually mature cynomolgus monkeys in a separate 13-week toxicology study that included endpoints consistent with the recommendations on fertility assessment discussed in the ICH S6 guidance.

Study title/ number: REGN2810: A 13-Week Intravenous Toxicology Fertility Assessment Study in Sexually Mature Cynomolgus Monkeys With a 12-Week Recovery Period/ REGN2810-TX-15151

Key Study Findings

- There was a slight increase in the severity of tubular hypoplasia/atrophy in the testis of one low dose recovery cohort male monkey compared to controls
- One low dose female monkey exhibited an extended menstrual cycle during the dosing phase compared to the pre-dosing phase and one high dose female monkey exhibited amenorrhea in the dosing phase. These menstrual cycle irregularities did not correlate with any histologic findings and are not clearly drug-related.
- There were no substantial drug-related effects on fertility parameters or the reproductive tract at any of the dose levels tested

Conducting laboratory and location	(b) (4)
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	0, 10, and 50 mg/kg once weekly for 13 weeks

Route of administration:	I.V. infusion over approximately 30 minutes
Formulation/Vehicle:	10 mM histidine, 5% sucrose, 0.1% polysorbate 80, pH 6.0
Species/Strain:	Sexually mature cynomolgus monkey
Number/Sex/Group:	4/sex/group; 2/sex/group for a 12-week recovery period
Satellite groups:	None
Study design:	Performed fertility assessments on sexually mature monkeys including menstrual cycle determination, semen analysis, orchidometry (testicular measurements), and evaluation of reproductive organs (histologic, macroscopic, and weight)
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters	**Major findings**
Mortality	None
Clinical Signs	One LD male monkey (#I13508) exhibited ecchymotic hemorrhage in the scrotum and legs on Day 44, which was attributed to a possible antigen/antibody reaction. Black feces were observed at the HD on Day 90.
Body Weights	Unremarkable
Hematology	10 mg/kg: -15% neutrophils (male and female) 50 mg/kg: -26% (male) and -43%* (female) neutrophils
Clinical Chemistry	Unremarkable
Urinalysis	Unremarkable
Gross Pathology	Unremarkable
Organ Weights	Statistically significant increase in mean lung weight (absolute and relative to body and brain weight) in HD male monkeys up to 44%
Histopathology **Adequate battery:** Yes for this study (reproductive tract tissues only)	

Dose (mg/kg)		0		10		50	
Sex		M	F	M	F	M	F
# of monkeys examined		4,2R	4,2R	4,2R	4,2R	4,2R	4,2R
Epididymis	Mononuclear cell infiltrate						
	Min	1R		1,1R		2,1R	
	Cytoplasmic alteration, eosinophilic, Slight					1R	
Ovary	Corpus luteum, involuting		2,2R		3,1R		3,2R
	Cyst, inclusion				1		
	Cyst, corpus luteum						1R
Prostate	Mononuclear cell infiltrate						
	Min	1,1R		2,1R		2,1R	
	Slight					1R	
Seminal vesicle	Mononuclear cell infiltrate						
	Min					1R	
Testis	Stasis, sperm	2		1,1R		1R	
	Hypoplasia/atrophy, tubular						
	Min	2		1		1,2R	
	Moderate	1					
	Marked			1R			
Uterus	Atopic tissue						1

R: Recovery Group

<table>
<tr><th>Parameters</th><th>Major findings</th></tr>
<tr><td>Menstrual Cycle analysis</td><td>One LD female (#I13526) exhibited one long menstrual cycle in the dosing phase (83 days) compared to two shorter cycles in the pre-dosing phase (mean = 36 days). One HD female (#I13531) exhibited menstrual bleeding during the first half of the pre-dose phase followed by amenorrhea during the dosing phase. Recovery was not assessed in this animal. These menstrual cycle irregularities did not correlate with any histologic findings in female reproductive organs. Given the lack of dose dependence and histologic correlates, as well as the high variability of the menstrual cycle data, these findings were not considered to be drug-related.</td></tr>
<tr><td>Semen analysis</td><td>Unremarkable. There were no drug-related findings in semen sample weight, sperm density/morphology, total sperm count, or percent sperm motility.</td></tr>
<tr><td>Testicular measurements</td><td>Unremarkable</td></tr>
<tr><td>Reversibility</td><td>Findings trended towards recovery or were similar to controls except for the recovery cohort findings shown in the histopathology table above, some of which developed during the recovery period. There was an increase in the severity of tubular hypoplasia/atrophy in the testis of one LD recovery cohort monkey (marked) compared to controls in the dosing phase (up to moderate).</td></tr>
<tr><td>Immunogenicity</td><td>ADAs were detected in 8/24 (33%) monkeys dosed with REGN2810 including 6/12 and 2/12 monkeys dosed with 10 and 50 mg/kg REGN2810, respectively. ADA formation generally resulted in lower REGN2810 concentrations, was more prevalent in male monkeys, and was likely masked at the HD by high REGN2810 concentrations.</td></tr>
<tr><td>Toxicokinetics</td><td>$T_{1/2}$: 12.2-17.7 days; T_{max}: ~0.583 hours
AUC_{last} (Day 13; M/F; mean; day·µg/mL):
10 mg/kg: Not calculated / 13900
50 mg/kg: 38300 / 66500
Dose proportionality: C_{max} and AUC_{tau} generally increased dose proportionally
Accumulation: Yes, based on C_{max} (≤2.4-fold) and AUC_{tau} (≤3.5-fold) after the 13th dose compared to the 1st dose
Sex differences: No significant differences

<table>
<tr><th rowspan="2">Dose #</th><th rowspan="2">Dose (mg/kg)</th><th colspan="2">C_{max} (µg/mL)</th><th colspan="2">AUC_{tau} (day·µg/mL)</th><th colspan="2">$T_{1/2}$ (days)</th></tr>
<tr><th>M</th><th>F</th><th>M</th><th>F</th><th>M</th><th>F</th></tr>
<tr><td rowspan="2">1</td><td>10</td><td>335</td><td>263</td><td>1270</td><td>904</td><td>NC</td><td>NC</td></tr>
<tr><td>50</td><td>1510</td><td>1330</td><td>5350</td><td>4280</td><td>NC</td><td>NC</td></tr>
<tr><td rowspan="2">7</td><td>10</td><td>551</td><td>525</td><td>2680</td><td>2620</td><td>NC</td><td>NC</td></tr>
<tr><td>50</td><td>3240</td><td>2650</td><td>16200</td><td>13200</td><td>NC</td><td>NC</td></tr>
<tr><td rowspan="2">13</td><td>10</td><td>745</td><td>569</td><td>4080</td><td>2920</td><td>NC</td><td>17.7</td></tr>
<tr><td>50</td><td>3680</td><td>2850</td><td>18700</td><td>13600</td><td>12.2</td><td>17.1</td></tr>
</table>
ADA-impacted concentrations were excluded from TK calculations
AUC_{tau}: Area under the concentration-time curve calculated during the dosing interval; N/C: Not Applicable; NC: Not Calculated</td></tr>
</table>

LD: low dose (10 mg/kg); HD: high dose (50 mg/kg); -: indicates reduction in parameters compared to control; +: indicates increase in parameters compared to control; *, P ≤ 0.05 vs. controls; ADA: anti-drug antibody

Embryo-Fetal Development

Embryo-fetal development studies were not conducted with cemiplimab. Rather, the Applicant provided a scientific literature review and assessment of the reproductive toxicity potential of cemiplimab. FDA agreed in September 2015 that this approach appeared reasonable.

Studies in the literature demonstrate that the PD-1/PD-L1 pathway plays a critical role in maintaining maternal immunological tolerance to the fetus during pregnancy. PD-L1 is expressed in the human placenta throughout pregnancy and at the maternal-fetal interface in human fetal villous syncytiotrophoblasts and cytotrophoblasts (Petroff et al. 2003). In an allogeneic mouse model of pregnancy (CBA x C57BL/6), PD-L1 expression was detected at the utero-placental interface of the placenta as early as 10.5 days post-conception (Guleria et al. 2005). Intraperitoneal administration of 250-500 µg of a murine anti-PD-L1 monoclonal antibody to allogeneic pregnant mice on 6.5, 8.5, 10.5, and 12.5 days post-conception resulted in an increased incidence of abortions and pregnancy loss (86%) compared to isotype control (18%). Allogenic fetal rejection was T-cell dependent in this experiment. In addition, increased rates of abortion occurred in female PD-L1 homozygous knockout (PD-L1 -/-) mice compared to female PD-L1 heterozygous knockout mice. Pregnant PD-L1 -/- mice as well as mice administered an anti-PD-L1 antibody exhibited an increase in IFN-γ-producing Th1 cells at the maternal-fetal interface compared to appropriate controls (Guleria et al. 2005).

In other preclinical studies, depletion of regulatory T cells (Tregs) abrogated the effect of PD-L1 blockade on fetal resorption and survival in pregnant C57BL/6 mice, whereas adoptive transfer of Tregs from wild-type mice to PD-L1 -/- mice improved fetal survival (Habicht et al. 2007), suggesting that PD-L1-expressing Tregs are responsible for tolerance to fetal alloantigens. Conversely, in a CBA/J x DBA/2J mouse model of pregnancy, blockade of PD-1 abrogated the protective effects of Tregs, resulting in a higher rate of abortion compared to controls (Wafula et al. 2009). Notably, blockade of PD-1/PD-L1 signaling in PD-L1 -/- mice or via an anti-PD-1/PD-L1 antibody did not result in overt malformations in offspring (Guleria et al. 2005; Habicht et al. 2007; Wafula et al. 2009). The maternal-fetal interface of mice is similar to that of humans, suggesting that findings from mouse models of allogeneic pregnancy are applicable to humans.

Thus, based on its mechanism of action and findings from murine models of pregnancy, administration of cemiplimab is likely to disrupt the maintenance of normal pregnancy. Potential risks associated with administration of cemiplimab during pregnancy include increased rates of abortion and stillbirth. Further, since PD-1 -/- mice develop late onset autoimmune phenotypes (Okazaki and Honjo 2007), fetal exposure to cemiplimab may alter the normal immune response or increase the risk of developing immune-related disorders. As a result, a warning for embryofetal toxicity is recommended for LIBTAYO. Based on a half-life of approximately 19 days, females of reproductive potential are advised to use effective contraception during treatment with LIBTAYO and for at least 4 months after the final dose of LIBTAYO.

Prenatal and Postnatal Development
Not requested due to the reproductive toxicity assessment indicating effects of the drug on maintenance of pregnancy. In addition, as the final intended patient population appears more consistent with the scope of ICH S9 (see 5.5.3), no additional studies are warranted at this time, consistent with that guidance.

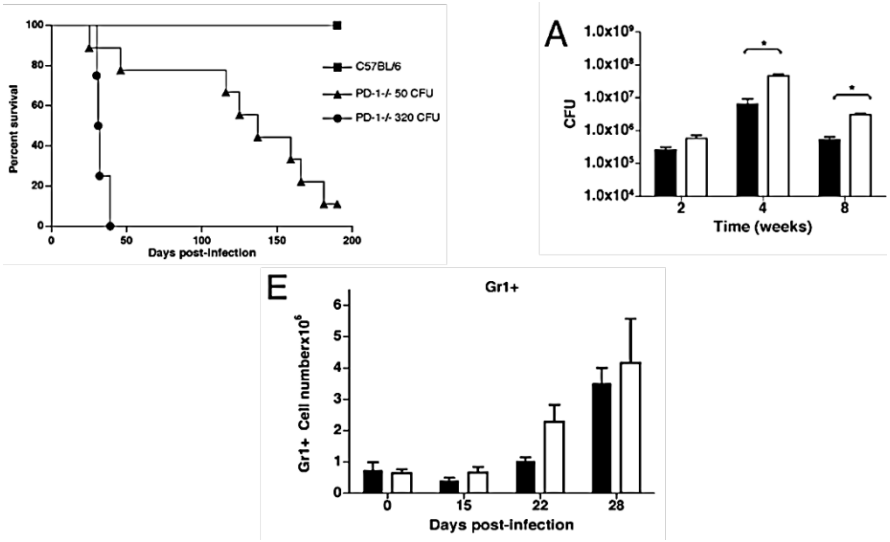
5.5.5. Other Toxicology Studies

A Tissue Cross-Reactivity Study of Biotinylated REGN2810 in Normal Human and Cynomolgus Monkey Tissues / REGN2810-TX-14073
The Applicant conducted a GLP-compliant tissue cross-reactivity study with normal human and cynomolgus monkey tissues (three donors/tissue) using 15 µg/mL and 2 µg/mL biotinylated REGN2810 (REGN2810-Bio). REGN2810-Bio stained the plasma membrane of human mononuclear leucocytes in the lymph node, spleen, and tonsil; cytoplasmic elements of human mononuclear leucocytes in the kidney, lymph node, spleen, thymus and tonsil; and cytoplasmic elements of human glial cells in the brain (cerebellum and cerebrum), eye (retina), pituitary, and spinal cord. Staining of the retina was unique to humans. Tissues stained in cynomolgus monkeys but not humans included the plasma membrane of mononuclear leucocytes in the thyroid and cytoplasmic elements in the following tissues: bladder, colon, small intestine, stomach, lung, salivary gland, thyroid, glial cells in the eye (optic disc), and pituitary. Except for these differences, REGN2810-Bio staining was generally similar between human and cynomolgus monkey tissues. The pattern of observed REGN2810-Bio staining was generally consistent with the expected pattern of PD-1 expression except for glial cell staining; however, PD-1 expression has been reported in neurons of the retina in mice (Chen et al. 2009) and can be induced in microglia of the murine central nervous system (Jin et al. 2013).

Literature Based Assessment of Potential for Effects on Infection
(Reviewed by Dr. Shawna Weis)

While loss of PD-1 function enhances clearance of some tumors and viral infections, it increases susceptibility to certain other pathogens such as tuberculosis in some animal models. PD-1-deficient mice (C57BL/6) infected with *M. tuberculosis* exhibited a dramatic decrease in survival (Figure 8, upper left panel), which correlated with uncontrolled bacterial proliferation (Figure 8, upper right panel; dark bars = wild-type) and a larger inflammatory response in the lungs of PD-1-deficient mice compared with wild-type controls (Figure 8, lower panel; dark bars = wild-type). Thus, PD-1 appears to be required to control infection and the inflammatory responses in the lungs of mice infected with M. tuberculosis (Lazar-Molnar, et al., 2010); however, the pathogenesis of this observation has not been clearly-defined. In particular, it is unclear whether the decreased survival reflects rampant bacterial growth resulting from an inability to mount appropriate antibacterial responses and/or whether it is a failure to downregulate the immune reaction that leads to massive tissue destruction and organ failure.

Figure 8: Decreased Survival, Increased Bacterial Proliferation and Increased Inflammation in PD-1-deficient Mice Infected with M. tuberculosis



(Figures derived from: Lazar-Molnar, et al. 2010)

These data suggest that there is concern that treatment with cemiplimab may increase susceptibility to tuberculosis infection and/or that infected patients may develop more severe disease.

The potential for increased toxicity in the presence of cemiplimab may also be a concern following viral infection. In mouse models of LCMV infection, the absence of PD-1 pathway signaling resulted in fatal CD8+ T cell-mediated pathology due to killing of virally infected endothelial cells, systemic vascular leakage, and ultimately cardiovascular collapse (Frebel et al. 2012; Mueller et al. 2010). Similarly, PD-L1 deficient mice died early after chronic systemic LCMV infection (Barber et al. 2006).

6 Clinical Pharmacology

6.1. Executive Summary

The Clinical Pharmacology Section of the BLA submission includes pharmacokinetics (PK) studies of cemiplimab after repeat doses in cancer patients and the population PK (pop-PK) and exposure-response (E-R) relationship analyses to support the proposed cemiplimab dosing regimen of 350 mg every 3 weeks (Q3W) administered as an intravenous (IV) infusion over 30 minutes for the proposed indication. The covariates identified by the pop-PK anaysis include body weight, albumin, body mass index (BMI), race (White, Black, Asian and other), immunoglobulin G (IGG) and alanine aminotransferase (ALT). The E-R analyses on efficacy suggest the relationship is flat between PK exposure and overall response rate (ORR) at a cemiplimab concentration range of 10 to 30 mcg/mL. The E-R analyses on safety do not suggest Grade 3+ adverse event (AE) and severe AE (SAE) incresing at higher PK exposure. However, conclusions of the E-R relationships for the safety and efficacy of cemiplimab cannot be made as the data available for the E-R analyses exclusively (89 – 99%) came from cemiplimab 3 mg/kg Q2W dosing regimen.

Recommendations

The proposed dosing regimen of cemiplimab 350 mg Q3W administered by intravenous infusion over 30 minutes is supported by the efficacy data of cemiplimab in patients with mCSCC or laCCSC at 3 mg/kg Q2W (N = 107), safety data of cemiplimab in patients with advanced solid tumor at cemiplimab doses up to 10 mg/kg Q2W (total N = 493, n=6 at 10 mg/kg Q2W) and preliminary safety (N = 49) and efficacy data (N = 32) in patients with mCSCC receiving 350 mg Q3W treatment. From a Clinical Pharmacology standpoint, the BLA is approvable provided that the Applicant and the FDA reach an agreement regarding the labeling language.

6.2. Summary of Clinical Pharmacology Assessment

The adequacy of the clinical pharmacology program in the overall cemiplimab development plan is summarized in the table below.

Review Issue	Sufficiently Supported?	Recommendations and Comments
Proposed dosing regimen of 350 mg Q3W for general patient population	☒ Yes ☐ No	Refer to **Section 6.3.2**
Effect of immunogenicity on PK, efficacy, and safety	☒ Yes ☐ No	**Labeling Recommendation:** In the patients who developed anti-cemiplimab antibodies, there was no evidence of an altered pharmacokinetic profile of cemiplimab. (b) (4) [redacted]

6.2.1. Pharmacology and Clinical Pharmacokinetics

Disposition

In a population PK analysis, the PK of cemiplimab at the dose range of 1 mg/kg to 10 mg/kg Q2W was best described by a 2-compartment model with linear elimination. The estimated elimination half-life of cemiplimab at steady state was approximately 19.2 days with steady-state volume of distribution of 5.2 L. The individual clearance estimates over the course of treatment in the overall patients suggest time-varying changes in clearance (CL) in the population PK model by a sigmoid-E_{max} function. The results showed that on average, clearance decreased by more than 30% over time compared to the baseline clearance, i.e., from 0.33 L/day to 0.21 L/day within 16 weeks of treatment. However, this decrease in CL with time is not considered clinically important.

Exposure-Response (E-R) Relationships

E-R for overall response rate (ORR): Cemiplimab exposures (i.e., C_{trough} and first cycle AUC_{0-2W}) have been evaluated in E-R analyses for overall response rate (ORR), which showed no correlation between PK exposure and ORR at a cemiplimab concentration range of 10 to 30 mcg/mL.

E-R for safety: Cemiplimab exposure (i.e., C_{max}) and safety have been evaluated in an E-R analysis, which showed no correlation between PK exposure and Grade 3+ AEs and SAEs at a cemiplimab concentration range of 15 to 350 mcg/mL.

Immunogenicity

Of 398 patients who received cemiplimab treatment and had evaluable immunogenicity testing results, 5 patients (1.3%) tested positive for treatment-emergent (TE) anti-drug antibodies (ADAs). No patients tested positive for neutralizing antibodies. The effect of ADAs on efficacy, safety, and exposure of cemiplimab could not be definitively assessed due to low incidence of treatment-emergent anti-cemiplimab antibody formation and limited number of patients

studied. However, there was no evidence of decreased cemiplimab exposures in these five patients who tested positive for ADAs compared to those in patients with negative ADAs, and no clear association was found between ADA formation and infusion-related reactions.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The proposed dosing regimen of cemiplimab for the treatment of mCSCC or laCSCC is 350 mg Q3W until symptomatic disease progression or unacceptable toxicity. This dosing regimen was proposed based on results from population PK analyses, with the majority of the PK data derived from patients who received the 3 mg/kg Q2W dosing regimen. The cemiplimab concentration data from 16 patients who received the 350 mg Q3W regimen were compared to the simulated profiles for the same regimen and confirmed the predicted exposure. The safety and efficacy data from the clinical trial with the 3 mg/kg Q2W regimen and preliminary safety and efficacy data with the 350 mg Q3W regimen from the ongoing trial submitted in the 90-day safety update are used to support the proposed dosing regimen of cemiplimab 350 mg Q3W.

Therapeutic Individualization

Factors including age (27-96 years), sex, race (white, black, Asian, others), renal function (creatinine clearance 25 - 420 mL/min) and hepatic function (total bilirubin 0.35-45 mcmol/L) were not found to have a clinically important effect on cemiplimab PK. Dose adjustment is not necessary for these factors.

Outstanding Issues

None.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

PHYSICOCHEMICAL PROPERTIES	
Chemical structure and molecular weight	Cemiplimab is an IgG4 mAb (143,567.1 Da relative molecular mass)
Aqueous solubility	Cemiplimab aqueous solubility at room temperature is at least 216.5 mg/mL.
PHARMACOLOGY	
Mechanism of action	Cemiplimab is an inhibitor of programmed cell death 1 (PD-1), (KD = 0.5 to 7.6 nM), which blocks the interaction between PD-1 and programmed death-ligand 1 (PD-L1) and programmed death-ligand 2 (PD-L2), countering PD-1-mediated inhibition of the immune response, including the anti-tumor immune response.
Active moiety	As a mAb, major circulating metabolite is not expected for cemiplimab.

QT/QTc prolongation	As a mAb, cemiplimab is not expected to cause QT prolongation. There were no clinically relevant changes from baseline in the QTc interval or ECG abnormalities and observed ECG findings were typical of the patient population.
GENERAL INFORMATION	
Bioanalytical assay	A validated sandwich ELISA assay was developed to measure the concentrations of cemiplimab in the serum samples collected from patients in the clinical studies included in this BLA (see Appendix 19.4.1).
Patient PK vs. healthy subject (HS) PK	Cemiplimab PK was only studied in patients.
Steady-state exposure at the proposed dosing regimen	Steady-state is achieved after 16 weeks dosing of cemiplimab 3 mg/kg Q2W. With 3 mg/kg Q2W at steady-state (prediction by population PK analyses): ▪ $AUC_{0\text{-}6W}$ ≈ 3710 mcg·day/mL (35.9% CV) ▪ C_{MAX} ≈ 135 mcg/mL (28.4% CV) ▪ C_{TROUGH} ≈ 65.7 mcg/mL (42.8% CV) With 350 mg Q3W at steady-state (prediction by population PK analyses): ▪ $AUC_{0\text{-}6W}$ ≈ 3800 mcg·day/mL (37.2% CV) ▪ C_{MAX} ≈ 166 mcg/mL (27.8% CV) ▪ C_{TROUGH} ≈ 58.7 mcg/mL (47.7% CV)
Minimal effective dose or exposure	In the FIH Study **1423**, 18 patients received cemiplimab 1 mg/kg Q2W treatment, including 1 patient with mCSCC, who had a partial response to the treatment.
Maximum tolerated dose or exposure	MTD was not reached in the FIH Study **1423** in patients with advanced solid tumors (maximum dose tested = 10 mg/kg Q2W).
Dose proportionality	Following both single dose and multiple-dosing, cemiplimab, exposures generally increased dose proportionally.
Accumulation	With 350 mg/kg Q3W at steady-state (prediction by population PK analyses): ▪ AUC ≈ 1.84-fold accumulation ▪ C_{MAX} ≈ 1.55-fold accumulation
Variability	Based on FIH Study **1423** at 3 mg/kg Q2W, inter-subject variability (%CV) following the first dose was 38% for $AUC_{0\text{-}2W}$, 43% for C_{MAX} and 45% for C_{TROUGH}.
ABSORPTION	
Bioavailability	Not applicable as cemiplimab is administered IV as a 30-minute infusion
T_{MAX}	Median T_{MAX} = 0.5 h (End of infusion)
Food effect	Not applicable, as cemiplimab is administered IV
DISTRIBUTION	
Volume of distribution (Vd)	Vss at steady-state ≈ 5.2 L (24% CV), as is typical for mAbs.
Substrate of transporter systems	N/A
ELIMINATION	
Terminal elimination half-life and clearance	Based on a population PK analysis, the mean elimination half-life of cemiplimab at steady-state in patients with solid tumors is 19.2 days. The total clearance of cemiplimab was estimated to be ~0.33 L/day (40% CV). In the overall patient population after repeated dosing, the total clearance of cemiplimab appears to decrease over time to ~0.21 L/day within 16 weeks of treatment.
Metabolism	As a monoclonal antibody, the metabolism of cemiplimab is limited to proteolytic catabolism into small peptides and individual amino acids, predominantly by the endoplasmic reticular system.

Excretion	N/A
Drug interaction liability	N/A

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes.

Study **1423** is a phase 1 first in human (FIH), open-label, multicenter, repeat-dose study with cemiplimab as monotherapy and as combination therapy. It comprised a dose escalation phase evaluating cemiplimab Q2W dose regimens in patients with various advanced solid tumors and an expansion phase evaluating various cemiplimab dose regimens in a broader population of patients with advanced solid tumor types (N = 397), including CSCC. Both studies evaluated cemiplimab as monotherapy and as combination therapy (cemiplimab with other anti-cancer treatments). Patients with mCSCC and laCSCC were evaluated in a dose escalation cohort at the 1 mg/kg Q2W dose regimen (N = 1), and expansion cohorts 7 and 8 at the 3 mg/kg Q2W dose regimen (N = 25). Cemiplimab PK after the first dose and concentrations of cemiplimab over time during the treatment period were evaluated.

Study **1540** evaluated the cemiplimab 3 mg/kg Q2W monotherapy dose regimen in patients with CSCC, grouped as mCSCC (Group 1, N = 59) or laCSCC (Group 2, N = 23), and the 350 mg Q3W monotherapy dose regimen in patients with mCSCC (Group 3, N = 49). The concentrations of cemiplimab over time during the treatment period were measured.

The integrated efficacy analyses have been conducted using pooled efficacy data (**Table 5**) from both Study **1423** and Study **1540**, where all patients except one received cemiplimab 3 mg/kg Q2W dose regimen:

- For the indication of mCSCC, efficacy data are integrated for all mCSCC patients (N = 75) from Study **1423** (N = 16) and all mCSCC patients from Group 1 of Study **1540** (N = 59)
- For the indication of laCSCC, efficacy data are integrated for all laCSCC patients (N = 33) from Study **1423** (N = 10) and only those laCSCC patients in Group 2 of Study **1540** who have potential for 9 months of follow-up at the time of the data cut (N = 23)

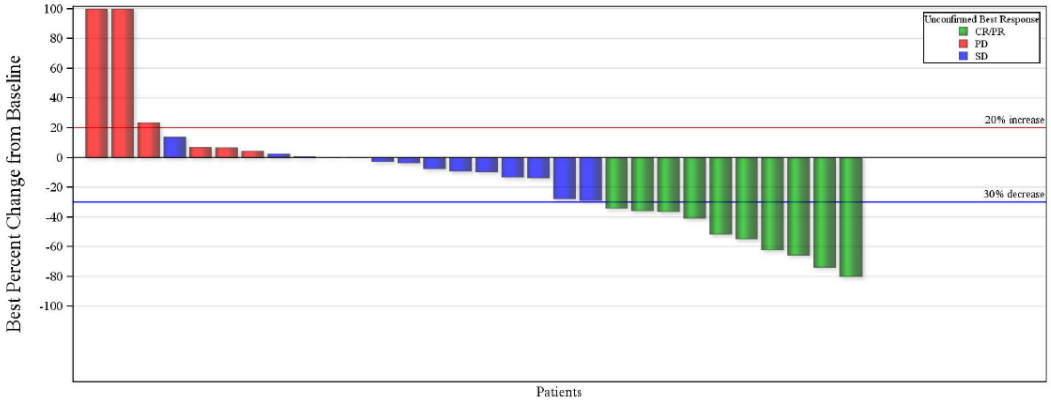
Table 5. Summary of integrated efficacy analyses for mCSCC, laCSCC and CSCC combined

	mCSCC (N = 75)	laCSCC (N = 33)	CSCC Combined (N = 108)
ORR (%)	46.7	48.5%	47.2%
PR (%)	41.3	48.5%	43.5%
CR (%)	5.3	-	3.7%
Range of DOR (Months)	2.8 to 15.2+	1.0 to 12.9+	1.0 to 15.2+

Source: Summary of Clinical Efficacy Table 43 and 44.

The efficacy and safety data for Study 1540 Group 3 (350 mg Q3W) was not available at time of the BLA submission. The preliminary efficacy and safety data from the 350 mg Q3W regimen were submitted in the 90-day safety update. Among 30 of 32 patients with response assessment data at week 9 (
Figure 9), BOR was CR = 1 patient, PR = 9 patients, SD = 13 patients, and PD = 7 patients, respectively.

Figure 9. Preliminary efficacy data for Study 1540 Group 3 at 350 mg Q3W: Waterfall Plot per RECIST 1.1 by Investigator Assessment (Patients who had at Least One Post Baseline Scan Available within the Data Cutoff)



Source: Preliminary Efficacy Results (per Investigator Assessment) of Cemiplimab 350 mg IV Q3W for Metastatic CSCC Patients Enrolled in Group 3 of Study R2810-ONC-1540 Figure 1.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. The Applicant's **proposed dosing regimen of 350 mg Q3W is appropriate** for the intended patient population of adult patients with mCSCC or laCSCC. The proposed dosing regimen is supported by the observed PK, safety, and efficacy data from the phase 1 FIH Study 1423 and the pivotal phase 2 Study 1540, as described below.

Dose selection rationale
Dose selection was based on results of the phase 1 Study **1423** and the pivotal phase 2 Study **1540**, which evaluated cemiplimab dosing regimens of 1 to 10 mg/kg in adult patients (N = 505) with advanced solid tumors, including mCSCC and laCSCC. Across the evaluated dose range,

Table 6), cemiplimab PK generally increase dose proportionally after the first dose and at steady state.

Table 6.Single Dose (Cycle 1) and Steady State (observed on Cycle 3, Day 1) PK Parameters of Cemiplimab as a monotherapy, in combination with Radiation and/or Cyclophosphamide, or in all patients with solid tumors

Dose Group	N	After the First Dose					At Steady State	
		C_{trough} (mg/L)	C_{eoi} (mg/L)	AUC_{2w} (day*mg/L)	AUC_{3w} (day*mg/L)	$t_{1/2}$ (day)	C_{trough} (mg/L)	C_{eoi} (mg/L)
		Mean (SD)						
Monotherapy								
1mg/kg Q2W	6	5.3 (1.32)	22.7 (4.62)	144.4 (28.04)		8.3 (1.53)	13.9 (5.98)	37.0 (6.73)
3mg/kg Q2W	97	19.8 (7.65)	71.3 (42.07)	447.0 (125.74)		11.3 (3.89)	60.3 (21.69)	124.8 (33.60)
10mg/kg Q2W	6	86.6 (14.87)	263.6 (84.19)	1811.1 (234.39)		12.9 (4.10)	228.2 (113.47)	434.3 (121.73)
200mg Q2W	20	17.1 (5.45)	61.3 (26.96)	415.3 (119.82)		10.6 (3.27)	52.1 (19.30)	105.5 (26.66)
Combination Therapy								
1mg/kg Q2W	21	6.6 (2.89)	23.1 (7.26)	175.9 (74.45)		9.5 (3.23)	20.8 (9.07)	55.2 (14.18)
3mg/kg Q2W	235	19.7 (9.32)	69.5 (23.85)	441.7 (183.24)		11.2 (5.66)	61.7 (27.52)	135.0 (40.42)
3mg/kg Q3W	12	15.5 (4.67)	72.1 (21.63)		630.7 (139.42)	13.3 (4.72)	29.7 (8.59)	83.4 (16.94)
Total								
1mg/kg Q2W	27	6.3 (2.66)	23.0 (6.68)	168.9 (67.77)		9.2 (2.95)	19.8 (8.91)	52.2 (14.83)
3mg/kg Q2W	332	19.7 (8.83)	70.0 (30.29)	443.3 (168.04)		11.2 (5.19)	61.2 (25.34)	131.0 (38.07)
3mg/kg Q3W	12	15.5 (4.67)	72.1 (21.63)		630.7 (139.42)	13.3 (4.72)	29.7 (8.59)	83.4 (16.94)
10mg/kg Q2W	6	86.6 (14.87)	263.6 (84.19)	1811.1 (234.39)		12.9 (4.10)	228.2 (113.47)	434.3 (121.73)
200mg Q2W	20	17.1 (5.45)	61.3 (26.96)	415.3 (119.82)		10.6 (3.27)	52.1 (19.30)	105.5 (26.66)

N = Number of patients; D = Dose

Source: Study R2810-ONC-1423 Clinical Pharmacology Report, Table 11, Page 33.

PK parameters of cemiplimab in mCSCC, laCSCC and overall CSCC patients are presented in Table 7. The results suggested that the PK of cemiplimab in CSCC patients and that in the overall patients, (Table 6), are similar.

Table 7. Single Dose (Cycle 1) and Steady State (observed on Cycle 3, Day 1) PK Parameters of Cemiplimab monotherapy in CSCC patients

Cemiplimab Dose Group	N	After the First Dose				At Steady State	
		C_{trough} (mg/L)	C_{eoi} (mg/L)	AUC_{2w} (day*mg/L)	$t_{1/2}$ (day)	C_{trough} (mg/L)	C_{eoi} (mg/L)
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
mCSCC (1 mg/kg Q2W)	1	6.0 (.)	20.3 (.)	151.0 (.)	10.6 (.)	19.2 (.)	40.8 (.)
mCSCC (3 mg/kg Q2W)	15	18.0 (6.47)	69.4 (21.48)	419.1 (100.76)	9.8 (2.41)	62.6 (30.62)	125.7 (34.22)
laCSCC (3 mg/kg Q2W)	10	23.5 (12.79)	62.5 (16.54)	489.3 (154.62)	12.5 (3.51)	64.2 (11.25)	120.7 (16.44)
CSCC (3 mg/kg Q2W)	25	20.2 (9.77)	66.6 (19.58)	448.4 (127.84)	10.8 (3.11)	63.2 (24.12)	123.7 (27.79)

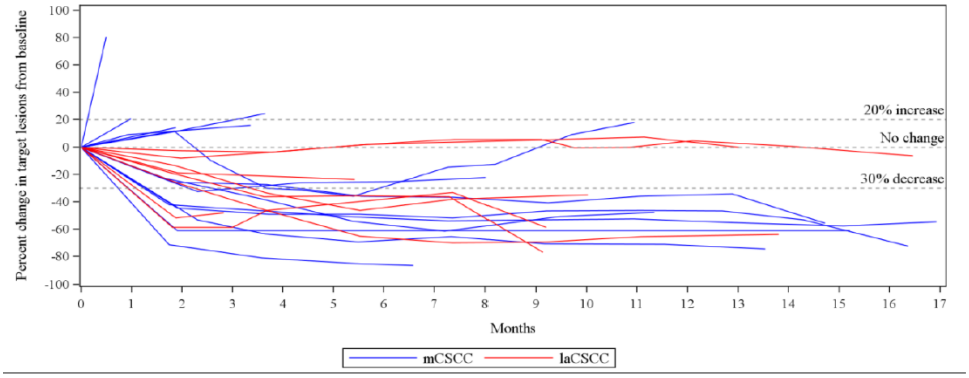
N = Number of patients; mCSCC = Metastatic CSCC; laCSCC = Locally advanced CSCC

Source: Study R2810-ONC-1423 Clinical Pharmacology Report, Table 12, Page 38.

Change in tumor size provides a pharmacodynamic perspective of the biological response to cemiplimab treatment effect. The reduction in target lesion size achieved in patients with mCSCC or patients with laCSCC after administration of cemiplimab 3 mg/kg Q2W was consistent between Study 1423 (

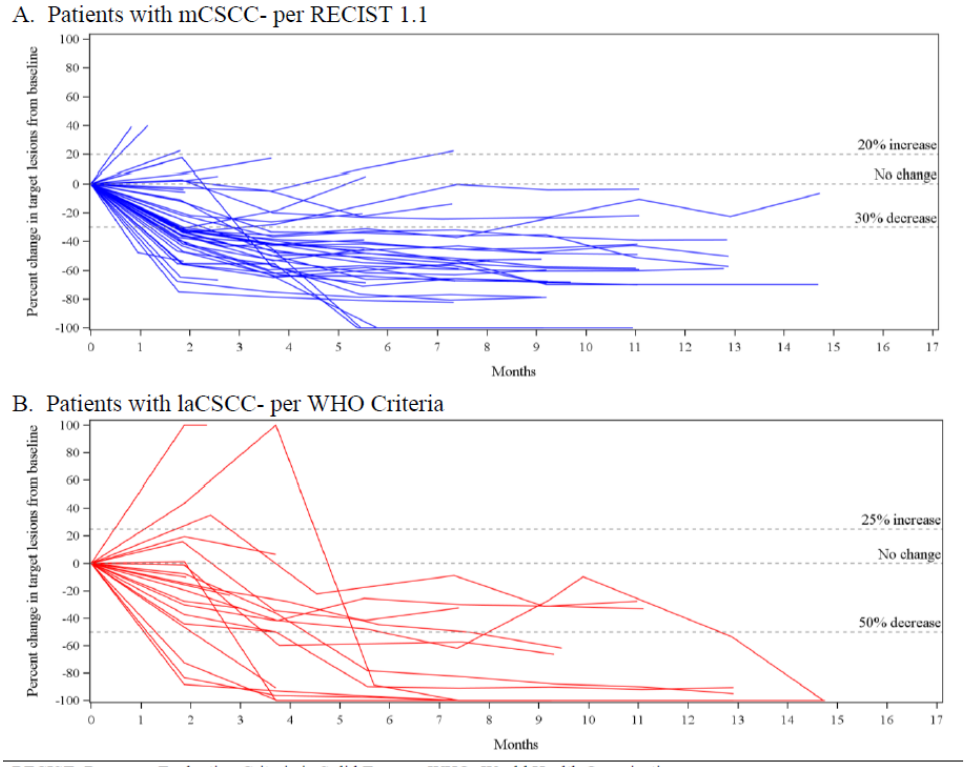
Figure 10) and Study 1540 (Figure 11).

Figure 10. Best Percentage Change From Baseline in Target Lesions by Patient Over Time by Independent Central Reviewer - mCSCC (blue) and laCSCC (red) – FAS (Study 1423)



Source: Summary of Clinical Pharmacology Figure 16.

Figure 11. Percent Change From Baseline in Target Lesions by Patient Over Time by Independent Central Review - mCSCC (blue) and laCSCC (red) – FAS (Study 1540)



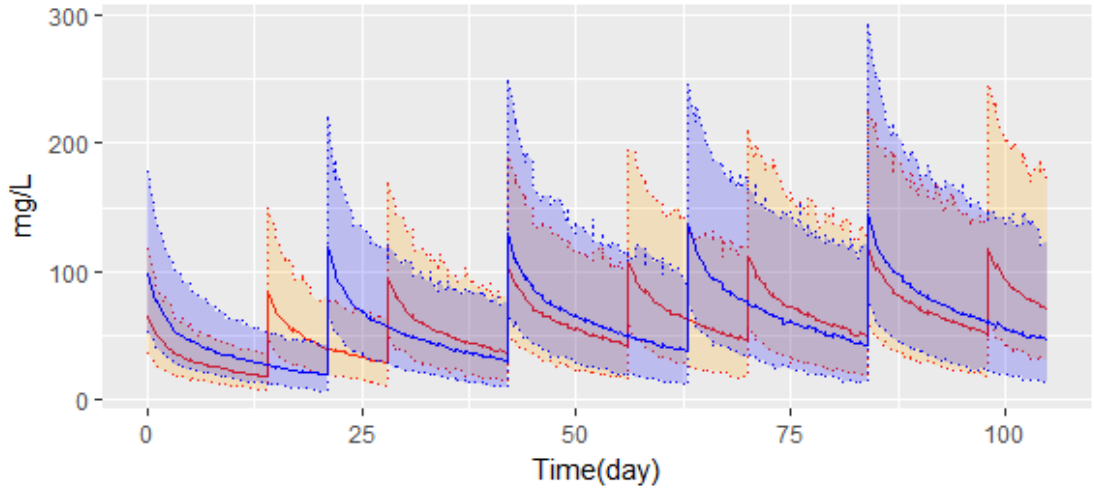
Source: Summary of Clinical Pharmacology Figure 17.

The MTD was not reached. No meaningful exposure-response relationships for any explored safety variables (irAEs of all grades and irAEs of grade ≥3) were identified.

The pop-PK analysis used the combined data sets from Study **1423** and Study **1540**. The final analysis set contained cemiplimab concentration data from 505 patients with solid tumors,

including 135 patients with CSCC (26 from study **1423** and 109 from study **1540** [groups 1 and 2]) following 1 to 10 mg/kg Q2W treatments. A comparison between the pop-PK model predicted-PK outcomes for the 3 mg/kg Q2W dosing regimen and the proposed 350 mg Q3W dosing regimen was conducted (Figure 12). Table 8 showed mean values of C_{trough} and C_{max} after first cycle and at steady state. The mean C_{max} was 51% higher and the mean C_{trough} was 6.5% higher at the first cycle of 350 mg Q3W dosing, and the mean steady state C_{trough} 13% lower and the mean steady state C_{max} 22.3% higher than those after 3 mg/kg Q2W dosing. See Pharmacometric Review in Appendix 19.4.2 for details of the analyses.

Figure 12. Comparison of Model Simulated 350 mg Q3W (Blue) vs. 3mg/kg Q2W (Red)



Model simulated 350 mg Q3W dosing regimen was conducted. Blue line indicated the median of 350 mg Q3W and blue shade is 95% quantile of 350 mg Q3W. Red line and orange shade indicated the median and 95% quantile of 3 mg/kg dosing regimen.
Source: Appendix 19.4.2 FDA Pharmacometric review: Reviewer's independent analysis
Figure 25.

Table 8. Comparison of Model Simulated 350 mg Q3W Exposure vs. 3 mg/kg Q2W at Population Level and Body Weight Stratified Subgroups

	First Ctrough			First cycle Cmax			Steady state Ctrough			Steady state Cmax		
	3mg/kg	350mg	% change	3mg/kg	350mg	% change	3mg/kg	350mg	% change	3mg/kg	350mg	% change
Median	18.6	19.8	↑6.5%	65.2	98.2	↑50.6%	49.8	43.3	↓13.1%	118.8	145.3	↑22.3%
(95% quantiles)	(9.4, 33.5)	(8.9,38.5)		(40.2, 107.6)	(60.2, 161.8)		(22.5, 107.3)	(16.1, 107.7)		(68.5, 200)	(85.2, 263.81)	
BW Subgroups (Mean)												
[31kg,52kg)	17	26.5	56%	54.9	124.9	128%	40.46	67.88	68%	95.6	215.2	125%
[52,65)	16.6	23.3	40%	62	118.9	92%	45.75	57.56	26%	105.4	175.9	67%
[65,76)	18.4	21.2	15%	63	109.4	74%	52.54	49.13	-6%	120	158	32%
[76,89)	21.5	20.8	-3%	72.4	99.5	37%	64.03	50.38	-21%	136	147.5	8%
[89,110)	21	17.6	-16%	73.8	85.8	16%	57.77	40.71	-30%	136	131.2	-4%
[110,156)	25.7	14.8	-42%	**89**	82.9	-7%	71.15	34.87	-51%	**153.5**	121	-21%

Model and simulation was conducted, and model predicted median and 95% quantile of 350 mg Q3W and 3 mg/kg Q2W dosing regimens are listed in above table. Body weight stratified subgroup analysis were also listed.
Source: Appendix 19.4.2 FDA Pharmacometric review: Reviewer's independent analysis Table 44.

The preliminary efficacy and safety data from the 350 mg Q3W regimen provided in 90-day safety update suggested that the safety of cemiplimab 350 mg Q3W (N = 49) is comparable to that of cemiplimab 3 mg/kg Q2W. The preliminary efficacy results demonstrate that 350 mg Q3W is an active dose (ORR: 31%). Among 30 of 32 patients with response assessment data at week 9, BOR was CR = 1 patient, PR = 9 patients, SD = 13 patients, and PD = 7 patients, respectively (

Figure 9). The preliminary safety results reported that the cumulative rates of TEAEs observed at the 90-day SUR cutoff date are lower in Group 3 (350 mg cemiplimab IV Q3W) compared to Groups 1 and 2 (3 mg/kg cemiplimab IV Q2W), most likely due to the lower duration of treatment exposure (**Table 9**).

Table 9. Summary of Treatment-Emergent Adverse Events in Study 1540 at 90-Day Safety Update

	mCSCC Cemiplimab: 3 mg/kg Q2W (N=59)	laCSCC Cemiplimab: 3 mg/kg Q2W (N=64)	mCSCC Cemiplimab: 350 mg Q3W (N=49)	Total (N=172)
Number of TEAEs	490	486	169	1145
Number of NCI grade 3/4/5 TEAEs	54	51	25	130
Number of Serious TEAEs	35	36	19	90
Number of Patients with any TEAE, n (%)	59 (100%)	60 (93.8%)	39 (79.6%)	158 (91.9%)
Number of Patients with any NCI grade 3/4/5 TEAE, n (%)	26 (44.1%)	22 (34.4%)	14 (28.6%)	62 (36.0%)
Number of Patients with any Serious TEAE, n (%)	23 (39.0%)	17 (26.6%)	12 (24.5%)	52 (30.2%)
Number of Patients who discontinued study treatment due to TEAE, n (%)	5 (8.5%)	6 (9.4%)	1 (2.0%)	12 (7.0%)
Number of Patients with any TEAE leading to a drug interruption/delay, n (%)	20 (33.9%)	21 (32.8%)	6 (12.2%)	47 (27.3%)
Number of Patients with any TEAE leading to a dose reduction, n (%)	1 (1.7%)	0	1 (2.0%)	2 (1.2%)
Number of Patients with any TEAE leading to both a drug interruption/delay and a dose reduction, n (%)	0	0	1 (2.0%)	1 (0.6%)
Number of Patients with any TEAE resulting in death, n (%)	2 (3.4%)	2 (3.1%)	1 (2.0%)	5 (2.9%)

Source: 90-Day Safety Update Report Post-text Table 14.3.1.2.1.

In summary, the following supported the 350 mg Q3W dosing regimen:

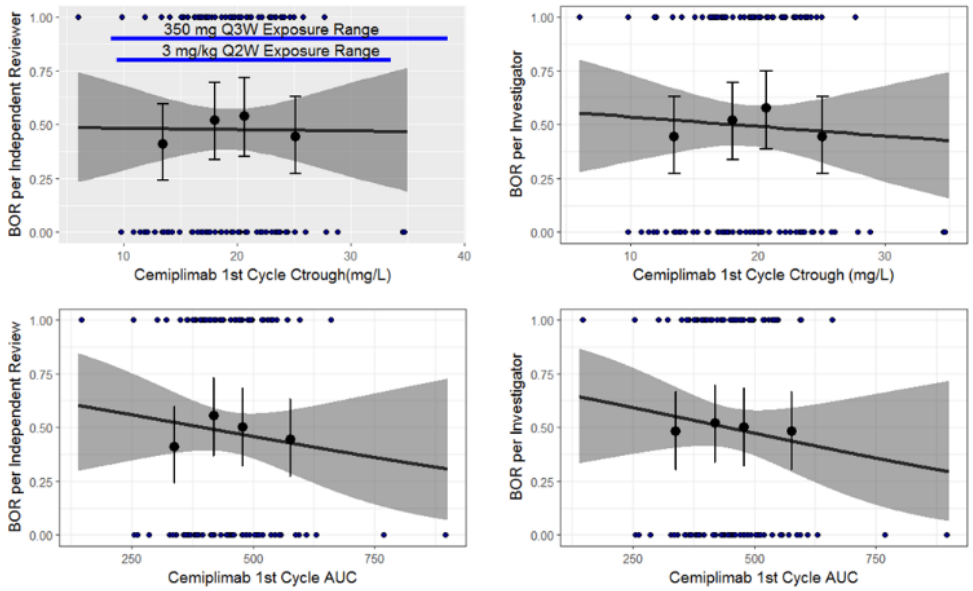
- **PK:** linear PK from 1 to 10 mg/kg Q2W. The 350 mg Q3W regimen resulted in similar steady-state exposure compared to the 3 mg/kg Q2W regimen (C_{trough})
- **PD:** The preliminary efficacy results demonstrate that 350 mg Q3W is an active dose.
- **Safety:** no meaningful exposure-response relationships identified for any explored safety variables (irAEs of all grades and irAEs of Grade ≥3). The safety data of cemiplimab 350 mg IV Q3W is comparable to that of cemiplimab 3 mg/kg IV Q2W.

Exposure-Response (E-R) Analyses

The applicant performed E-R analyses for efficacy and safety with data collected from the phase 1 Study **1423** and the pivotal phase 2 Study **1540.** See Pharmacometric Review in Appendix for details of the analyses (Appendix 19.4.2).

For efficacy, logistic regression was conducted on overall response rate (ORR) with PK exposure, including C_{trough} and $AUC_{0\text{-}2W}$ at first cycle. There appears to be no clear trend of correlation with efficacy at the evaluated exposures (Figure 13).

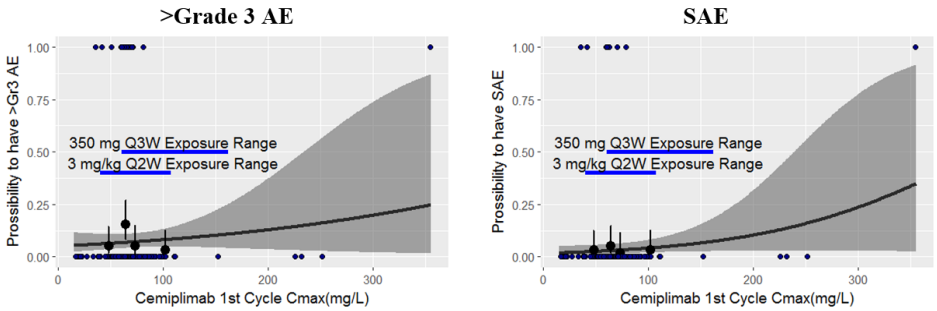
Figure 13. Exposure response for efficacy by logistic regression



Solid line is the logistic regression of the predicted ORR per investigator (right panel) or independent reviewer (left panel). The grey area is the 95% CI. For each exposure quartile, the observed response rate and its 95% CI is plotted as circle and error bar vs the mean concentration. The blue bar is the exposure range of each dosing regimen. Exposure-response analyses showed no correlation between PK exposure (first cycle C_{trough} or AUC) and overall response rate (ORR).
Source: Appendix 19.4.2 FDA Pharmacometric review: Reviewer's independent analysis Figure 27.

Exposure-safety analyses were conducted for safety endpoints including Grade 3+ AEs and SAEs. Logistic regression analysis indicated that no evident relationship between PK exposure, i.e. C_{max}, and Grade 3+ AEs and SAEs was identified (
Figure 14).

Figure 14. Exposure Response Relationship for First Cycle Cmax versus Incident Rate of >Gr3 AE and SAE

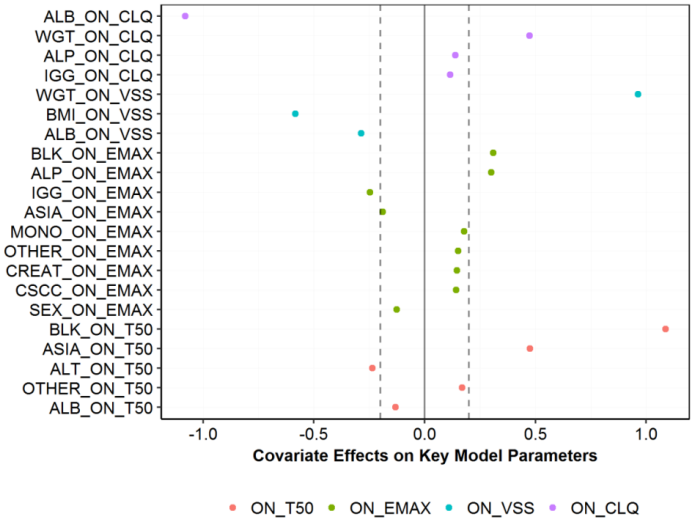


Source: Appendix 19.4.2 FDA Pharmacometric review: Reviewer's independent analysis Figure 28.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Multiple covariates were assessed for their effect on cemiplimab PK in patients with advanced solid tumors in a popPK analysis. Body weight (BW) was found to be one of the most influential covariates on cemiplimab clearance parameters (CL and Q) and on volume of distribution (Vss), supporting incorporation of BW into the base structural model. Results also indicated that baseline albumin, baseline immunoglobulin G (IGG) and baseline alanine aminotransferase (ALT) were important covariates on clearance parameters (CL/Q); baseline BMI was an important covariate on Vss; and race (Black) was an important covariate on T50 (the time for CL to decline by 50% of maximum value). Notably, disease status (ECOG or LDH) was not statistically significant in this assessment (Figure 15).

Figure 15. Forest Plot of Covariates and Their Effect on Model Parameters, Estimated by the Full Model, Relative to the Parameter Values of a Reference Patients



Source: R2810-MX-18022-SR-01V1 Quantitative Pharmacology Population Pharmacokinetics Report Figure 7.

Immunogenicity

Serum samples were collected from Study **1423** and Study **1540** for the analysis of anti-drug antibodies (ADAs) to cemiplimab at scheduled time points (Table 10). Of 398 evaluable patients, 5 patients (1.26%) tested positive for treatment-emergent ADAs. Samples were identified as treatment-emergent (TE) positive if the post-baseline sample had an increase of ≥ 9-fold in titer from baseline values or in the case of a baseline value that was not detected or was not present, a 1:30 titer after treatment. Neutralizing antibodies were assessed but were not detected in these 5 patients who tested positive for treatment-emergent anti-cemiplimab antibodies (TE-ADAs). Of note, none of the patients with CSCC tested positive for the binding ADAs. Therefore, NAbs were not tested in CSCC patients.

Table 10. Summary of the ADA Status, Category, Maximum Titer, and NAb Status in All Patients with Solid Tumors by Dose (Study 1423 and Study 1540)

		3 mg/kg				
ADA Category NAb Status	1 mg/kg Q2W	**Q2W**	Q3W	10 mg/kg Q2W	200 mg Q2W	Overall
Total ADA N (%)	23 (100%)	**341 (100%)**	10 (100%)	5 (100%)	19 (100%)	398 (100%)
Negative & Pre-Existing	22 (95.7%)	**337 (98.8%)**	10 (100%)	5 (100%)	19 (100%)	393 (98.7%)
Treatment Boosted Response[a]	0 (0%)	**0 (0%)**	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Treatment Emergent Response[b]	1 (4.35%)[c]	**4 (1.17%)[d]**	0 (0%)	0 (0%)	0 (0%)	5 (1.26%)
Persistent[e]	0 (0%)	**1 (0.293%)[f]**	0 (0%)	0 (0%)	0 (0%)	1 (0.251%)
Transient	0 (0%)	**2 (0.587%)**	0 (0%)	0 (0%)	0 (0%)	2 (0.503%)
Indeterminate	1 (4.35%)[g]	**1 (0.293%)**	0 (0%)	0 (0%)	0 (0%)	2 (0.503%)
Maximum Titer						
Low	1 (4.35%)[g]	**3 (0.880%)**	0 (0%)	0 (0%)	0 (0%)	4 (1.01%)
Moderate	0 (0%)	**1 (0.293%)[f]**	0 (0%)	0 (0%)	0 (0%)	1 (0.251%)
High	0 (0%)	**0 (0%)**	0 (0%)	0 (0%)	0 (0%)	0 0
NAb Negative[h]	23 (100%)	**341 (100%)**	10 (100%)	5 (100%)	19 (100%)	398 (100%)
NAb Positive[i]	0 (0%)	**0 (0%)**	0 (0%)	0 (0%)	0 (0%)	0 (0%)

ADA=anti-drug antibody; ESC=Escalation cohort; EXP=Expansion cohort; N = Number of patients; NAb=neutralizing antibody; Q2W=every 2 weeks

Source: Study 1423 and Study 1540 datasets

a. Patients with positive ADA response at baseline with <4-fold increase in titer in the post-baseline period.
b. Patients with no positive ADA response at baseline but with any positive response in the post-baseline period.
c. 1 patient on combination therapy (Patient (b) (6) in the ESC5 cohort) in Study 1423
d. 1 patient on monotherapy (patient (b) (6) in EXP12 cohort), and 3 patients on combination therapy (patient (b) (6) in EXP6 cohort, patient (b) (6) in EXP5 cohort, and patient (b) (6) in EXP14 cohort) in Study 1423
e. Persistent response was defined as a treatment-emergent ADA positive response with 2 or more consecutive ADA positive samples separated by greater than a 12-week period with no ADA negative or missing samples in between.
f. Patient (b) (6) in EXP14 in Study 1423
g. Patient (b) (6) in ESC5 cohort in Study 1423
h. NAb negative totals include samples that were negative in the ADA assay, and samples positive in the ADA assay that were negative in the NAb assay.
i. A patient is considered to be NAb-positive when tested positive in the NAb assay at any time.

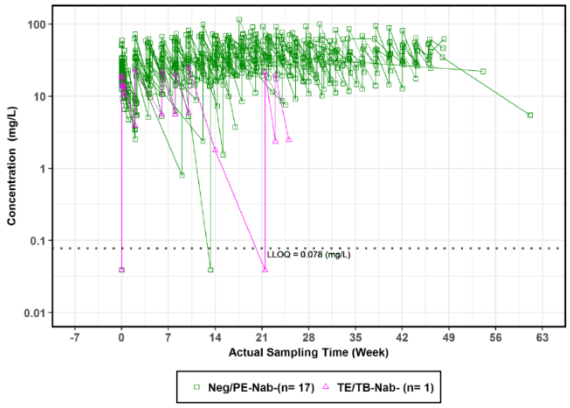
Source: Summary of Clinical Pharmacology Table 12.

A definitive conclusion on the effect of anti-cemiplimab antibodies on efficacy, safety, and exposure could not be made due to the limited number of patients tested positive for treatment-emergent anti-cemiplimab antibodies. Analyses of immunogenicity using data from Study 1423 and Study 1540 are shown below:

Effect of Immunogenicity on PK

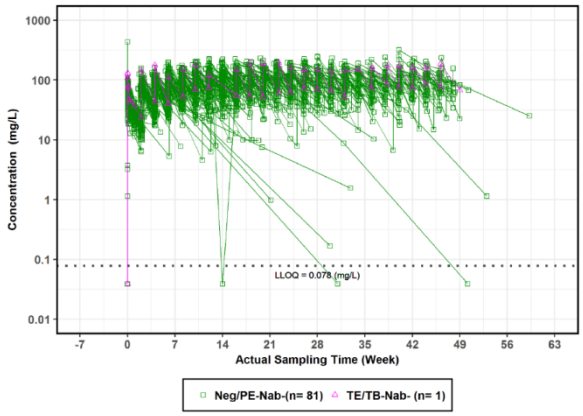
Concentration-time profiles using intensive PK data of patients with positive TE-ADAs were within the range of those with no TE-ADAs in **Study 1423** at 1 mg/kg Q2W combination therapy Figure 16), at 3 mg/kg Q2W monotherapy (Figure 17), and at 3 mg/kg combination therapy (Figure 18). Among the 5 patients who tested positive for TE-ADAs, the ADA titers were generally low. Only one patient (ID (b) (6)) who received 3 mg/kg cemiplimab Q2W exhibited ADA titer level of 2430, who also had persistent antibody responses defined as having at least 2 consecutive positive post-baseline samples separated by at least 16 weeks. Comparing PK profiles of cemiplimab in the patients who developed ADAs and those who are ADA negative, it appears that pharmacokinetic profile of cemiplimab was not affected by ADA status.

Figure 16. Individual Cemiplimab Concentrations (Log Scale) vs. Actual Time by ADA Category and NAb Status in Patients with Solid Tumors at 1 mg/kg Q2W in Combination Therapy (Study R2810-ONC-1423)



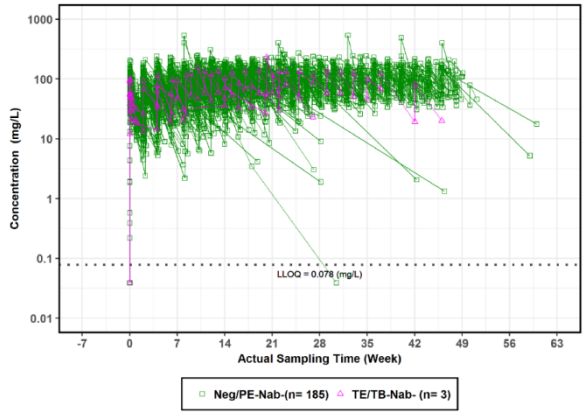
Source: R2810-ONC-1423-CP-01V1 Clinical Pharmacology Report, Figure 7.

Figure 17. Individual Cemiplimab Concentrations (Log Scale) vs. Actual Time by ADA Category and NAb Status for all Patients at 3 mg/kg Q2W in Monotherapy (Study R2810-ONC-1423)



Source: R2810-ONC-1423-CP-01V1 Clinical Pharmacology Report, Figure 8.

Figure 18. Individual Cemiplimab Concentrations (Log Scale) vs. Actual Time by ADA Category and NAb Status for Patients at 3 mg/kg Q2W in (Study R2810-ONC-1423)



Source: R2810-ONC-1423-CP-01V1 Clinical Pharmacology Report, Figure 9.

Effect of Immunogenicity on Safety

The effect of immunogenicity on safety was not assessed due to the low incidence of treatment-emergent ADA (1.26% [5/398]) in all patients with solid tumors in Study **1423** and Study **1540**. Infusion-related reactions (IRRs) occurred in 9.0% (48/534) of all cemiplimab treated patients. Among five patients tested positive for ADAs, one patient (ID# (b) (6)) experienced IRRs, the impact of ADAs on IRRs is inclusive, as the 20% rate is based on this small size.

Effect of Immunogenicity on Efficacy

In Study **1423** and Study **1540**, none of the patients with CSCC tested positive for binding ADAs; therefore, the effect of immunogenicity on efficacy could not be assessed.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

N/A

Question on clinically relevant specifications (TBD)?

N/A

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 11 below lists the clinical trials included in the original BLA submission.

- The primary evidence to support the clinical efficacy of cemiplimab in patients with CSCC is from a total of 109 patients with adequate follow-up pooled from Study 1423 (Expansion cohorts 7 and 8) and Study 1540 Groups 1 and 2.
- The primary evidence to support the safety of cemiplimab is derived from 534 patients with various advanced solid tumors across both studies who received at least one dose of cemiplimab, including 163 patients with advanced CSCC.

Table 11. Listing of Clinical Trials Relevant to this BLA

Trial Identity	Trial Design	Regimen/ schedule/ route	Key Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers/ Countries
R2810 ONC-1540	Multicenter, nonrandomized, multicohort study in patients with advanced CSCC	Groups 1 and 2: 3 mg/kg Q2W Group 3 (flat dose): 350 mg Q3W	BOR by central review per RECIST 1.1 -DOR -PFS -OS -CR rate -TTR -DCR -Quality of life	Treatment until completion of 96 weeks (Grp 1, 2) or 54 weeks (Grp 3), or until unacceptable toxicity, withdrawal of consent, death Post-treatment follow-up: approximately 6.4 months	137 Group 1: 59 Group 2: 55 Group 3: 23	Advanced CSCC -Groups 1 & 3: mCSCC -Group 2: laCSCC	45 sites in U.S., Australia, Germany
R2810-ONC-1423	Multicenter, first-in-human, dose-escalation with expansion phase consisting of several disease-specific cohorts	Doses evaluated: -1 mg/kg Q2W -3 mg/kg Q2W -10 mg/kg Q2W -3 mg/kg Q3W -200 mg Q2W Single agent or in combination with cyclophosphamide or radiation	-Safety -PK BOR per RECIST 1.1 -DOR -PFS -OS -TTR DCR	Treatment until completion of 48 weeks or until unacceptable toxicity, withdrawal of consent, death Post-treatment follow-up: approximately 5.5 months	397 [includes mCSCC =16 laCSCC =10]	Metastatic or locally advanced solid tumors with no available curative therapy. Multiple disease-specific expansion cohorts including mCSCC (cohort 7) and aCSCC (cohort 8)	50 sites in North America, the EU, and Asia-Pacific

7.2. **Review Strategy**

The FDA statistical and clinical BLA review team consisted of one primary statistical reviewer of efficacy and one primary clinical reviewer of safety and efficacy.

The BLA submission contained data from two multicenter, nonrandomized, multicohort trials summarized in Table 11. The safety review focused on all patients exposed to any dose of cemiplimab. The efficacy review focused on the pooled results of patients enrolled in Study 1423 (Expansion cohorts 7 and 8) and patients enrolled in Study 1540 Groups 1 and 2. The efficacy results from Group 3 of Study 1540 were not mature at the time of data cutoff and were not reviewed to support the indication. Limited results were submitted to support the safety and PK for the intended fixed-dose regimen.

The statistical and clinical review of safety and efficacy included the following:

- Review of the current literature on CSCC epidemiology and treatment and the Applicant's orientation materials
- Review of Trial 1540, including the clinical study report (CSR), protocol, protocol amendments, SAP and SAP amendments
- Review of Trial 1423, including the CSR, protocol, and protocol amendments
- Review of datasets submitted as SAS transport files
- Review of photographic data submitted for patients who experienced objective response in cutaneous target CSCC lesions
- Review of patient narratives of SAEs, deaths, and adverse events of special interest (AESI)
- Review of minutes of key meetings conducted with FDA during the cemiplimab development program for CSCC
- Review and assessment of the Module 2 summaries including the Summary of Clinical Efficacy (SCE) and the Summary of Clinical Safety (SCS)
- Review of the 90-Day safety update report (SUR)
- Review of consultation reports from the Office of Scientific Investigation (OSI), Office of Prescription Drug Promotion (OPDP) and Patient Labeling Team (PLT)
- Review of Applicant responses to multiple FDA requests for additional analyses and clarifications throughout the review
- Formulation of the benefit: risk analysis and recommendations
- Review and evaluation of proposed labeling

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Studies R2810-ONC-1423 and R2810-ONC-1540

Trial Design

Study R2810-ONC-1423
Study R2810-ONC-1423 (Study 1423) was an open-label, multi-center, non-randomized, dose-finding, expansion trial in patients with advanced solid tumors, including metastatic CSCC (Cohort 7) and locally regionally advanced CSCC (Cohort 8). Eligible patients were treated with cemiplimab 3 mg/kg administered intravenously every 2 weeks of each 8-week treatment cycle up to 48 weeks of treatment. Treatment continued until disease progression, unacceptable treatment-related toxicity, or patient or physician decision to discontinue. Disease status was assessed by central review per RECIST v1.1 criteria every 8 weeks.

The primary efficacy objective of Study 1423 was to evaluate overall response rate (ORR) by central review. Secondary objectives included duration of response (DOR). The study data cut-off (DCO) date for the primary analysis of ORR was October 16, 2017.

Study R2810-ONC-1540
Study R2810-ONC-1540 (Study 1540) was an open-label, multi-center, non-randomized, multicohort trial in patients with metastatic CSCC and locally advanced unresectable CSCC.

Groups 1 and 3 included patients with metastatic (nodal or distant) CSCC. Group 2 included patients with locally advanced CSCC. For Group 2, the patients could not be candidates for local treatment options. Specifically, surgery had to have been deemed contraindicated in the opinion of a Mohs surgeon, a head and neck surgeon, or plastic surgeon. A copy of the surgeon's consultation notes from a clinical visit within 60 days of enrollment had to be submitted. Acceptable contraindications in the surgeon's note included: CSCC that has recurred in the same location after 2 or more surgical procedures and curative resection was deemed unlikely; CSCCs with significant local invasion that precludes complete resection; CSCCs in anatomically challenging locations for which surgery may result in severe disfigurement or dysfunction (e.g., removal of all or part of a facial structure, such as nose, ear, or eye; or requirement for limb amputation). Additionally, patients could not be candidates for radiation based on further radiation therapy exceeding the acceptable cumulative dose, judgement by a radiation oncologist that the tumor would be unlikely to respond to radiation, or, based on a benefit-risk assessment performed by a multidisciplinary medical team including a radiation oncologist that radiation was contraindicated (e.g., due to location).

Eligible patients were treated with cemiplimab 3 mg/kg administered intravenously every 2 weeks of each 8-week treatment cycle up to 96 weeks of treatment. Treatment continued until

disease progression, unacceptable treatment-related toxicity, or patient or physician decision to discontinue. Disease status was assessed by central review per RECIST v1.1 criteria every 8 weeks. Disease status was evaluated based on RECIST v1.1 criteria for patients with metastatic CSCC; and per composite response assessment (RECIST v1.1 plus clinical response criteria for externally visible tumor[s] requiring bi-dimensional measurements according to the World Health Organization [WHO] criteria) for locally advanced CSCC. See Additional Efficacy Considerations for details of composite response assessment.

The primary objective of Study 1540 was to evaluate ORR by central review. Secondary objectives included DOR. The study was initiated on April 7, 2016 and the DCO date for the analysis of ORR was October 27, 2017.

Study Endpoints

The primary efficacy endpoint of both Study 1423 and Study 1540 was ORR as assessed by central review. ORR was defined as the proportion of patients with best overall response of complete response (CR) or partial response (PR) in the intent-to-treat (ITT) population. Patients who were not evaluable (NE) were not considered to have achieved PR or CR for ORR.

Major secondary endpoints included DOR, defined as the time of initial assessment of response (CR/PR) until date of recurrent or progressive disease or death due to any cause.

Other secondary endpoints for Study 1540 included quality of life (QoL) as assessed by European Organization for Research and Treatment of Cancer 30-item core quality of life questionnaire (EORTC QLQ-C30). Patient-reported outcome (PRO) assessments were collected repeatedly on Day 1 of each treatment cycle and at the end of study. The Applicant did not specify PRO's of interest in the SAP. Global health status/QoL and pain were described in this review. Higher scores indicated higher QoL/pain.

Statistical Analysis Plan

<u>ORR</u>
The sample size for each expansion cohort in Study 1423 was determined separately. A total of 10 and 20 patients were planned to be enrolled in the metastatic CSCC and locally advanced CSCC cohorts, respectively. In Amendment 3, 45 metastatic CSCC and 70 locally advanced CSCC patients were planned to be enrolled, but expansion of the cohorts was halted early for the enrollment of Study 1540 (see Protocol Amendments section for further details). The primary analysis of ORR was analyzed using the exact binomial confidence interval (CI) using the Clopper-Pearson method.

The sample size calculation in Study 1540 was based on the primary endpoint of ORR. For the metastatic CSCC group, a total of 53 patients were needed for an ORR of 15% to be excluded using the lower limit of a two-sided 95% CI. For the locally advanced CSCC group, a total of 76 patients were needed for an ORR of 25% to be excluded using the lower limit of a two-sided

95% CI. The primary analysis of ORR was analyzed using the exact binomial CI using the Clopper-Pearson method.

The primary analysis was summarized together and by group using pooled data from Study 1423 and Study 1540.

PRO
For Study 1540, descriptive statistics for each post-baseline time point were computed for QOL. No additional PRO analyses were pre-specified.

Protocol Amendments

Substantial protocol and SAP amendments are summarized below:

Study R2810-ONC-1423

- Amendment 1 (February 4, 2015):
  - Clarified patients were to have confirmed histological or cytological evidence of malignancies at study entry.
  - Clarified other minor details regarding inclusion and exclusion criteria.
- Amendment 2 (May 15, 2015):
  - Added Expansion Cohorts 1-6 in NSCLC, head and neck cancer, breast cancer, advanced solid tumors in patients previously treated with another anti-PD-1/PD-L1 antibody, and other advanced solid tumors.
- Amendment 3 (August 7, 2015):
  - Added Expansion Cohorts 7-20 in CSCC, colorectal with microsatellite instability (MSI), endometrial with MSI, prostate with MSI, other advanced solid tumors with MSI, hepatocellular carcinoma, advanced solid tumors refractory to first-line therapy in which treatment with carboplatin and/or docetaxel is clinically inappropriate, previously untreated NSCLC, GBM, and solid tumors in patients infected with HIV.
  - A total of 45 metastatic CSCC and 70 locally advanced CSCC patients were planned to be enrolled, but it was decided to halt expansion of cohorts for the enrollment of Study 1540. Amendment 3 was not opened. The protocol was further revised, and Amendment 4 was activated instead.
- Amendment 4 (September 30, 2015):
  - Implemented addition of Expansion Cohorts 7-20.
  - Reduced the number of patients enrolled in the metastatic and locally advanced CSCC expansion cohorts due to enrollment of Study 1540.
- Amendment 5 (June 28, 2016):
  - Added Expansion Cohorts 21-26.
- Amendment 6 (July 17, 2017):
  - Added exclusion criterion to exclude patients previously treated with idelalisib from treatment.

Study R2810-ONC-1540

- Amendment 1 (January 26, 2016):
  - Added further justification for including patients with regional metastases in the metastatic CSCC group (Group 1) rather than the locally advanced CSCC group (Group 2).
  - Provided additional language to clarify the approach to response assessments of externally visible tumors.
- Amendment 2DE (August 17, 2016): Incorporate changes requested by (b) (4)
  - Clarified exclusion criteria for active infection that required therapy and for known allergy to doxycycline or tetracycline.
  - Extension of post-treatment follow-up of 5 half-lives (105 days) after last dose of cemiplimab.
- Amendment 2 Global (December 12, 2016):
  - Revised text for toxicity management.
- Amendment 3 Global (May 18, 2017):
  - Added enrollment of additional 53 metastatic CSCC patients to receive 350 mg flat dose Q3W (Group 3) to be opened after completion of enrollment of metastatic CSCC group (Group 1) to support Q3W dosing.
- Amendment 4 Global (September 22, 2017):
  - Added exclusion criterion to exclude patients previously treated with idelalisib from treatment.
- Amendment 5 Global (September 22, 2017):
  - Added interim analysis for locally advanced CSCC group (Group 2) at the time of the primary analysis of the metastatic CSCC group in response to health authority guidance.

- SAP v2.0 (May 10, 2016):
  - Renamed per protocol set as Efficacy Analysis Set and removed requirement of receiving at least 1 dose of cemiplimab to adhere to the ITT principle.
- SAP v3.0 (August 25, 2017):
  - Added Group 3 cohort. Group 3 was not included in the primary efficacy analysis.
  - Planned interim analysis for locally advanced CSCC group.

8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant stated the following: “The clinical studies presented in this submission were conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the International Council for Harmonization guidelines for Good Clinical Practice and applicable regulatory requirements.” (Module 2.5, *Clinical Overview*).

DOP2 consulted OSI on March 8, 2018 to perform an audit of select clinical sites. The studies supporting the application were not randomized and, given the small sample sizes at each center and the independent review procedures, it is unlikely that one center was driving the efficacy data. Therefore, the selected sites were chosen based on protocol violations and safety events. Four domestic sites were chosen for inspection: Sites 840008, 840001, 840015, and 850013. Additionally, Regeneron Pharmaceuticals was inspected.

There were no significant issues identified at three of the four clinical sites and no issues identified upon inspection of Regeneron. The inspections conducted by OSI identified the following items:

- One serious violation involving incorrect medication preparation and administration for two patients. The doses prepared using two specific vials and diluents were infused into the wrong patients (i.e., each patient received the other's prescribed dosage). Both patients were in the same cohort and receiving the same cemiplimab regimen; however, because of the weight-based dosing, the patients received an incorrect dose. Neither patient experienced a safety issue due to the error. This site received an inspection classification of VAI. Although there was a serious violation, the data from this site were considered acceptable for review of safety and efficacy.
- No serious violations at any other inspection site.

Reviewer: *These events do not substantially affect the quality or ability to interpret the data submitted in the application. See the FDA Clinical Inspection review for details.*

Financial Disclosure

In accordance with 21 CFR 54, the Applicant submitted a financial disclosure certification document in module 1.3.4. The document includes three tables listing all investigators who participated in the two covered studies supporting BLA 761097 and grouped per those with disclosable financial interests, no disclosable interests, and those whose financial disclosure information is missing or incomplete.

Four sub-investigators who participated in Study 1423 received varying amounts of compensation from Sanofi for activities such as consulting services, speaker programs, and advisory board meetings. Copies of the Disclosure Statement (FORM 3455) for each of the four sub-investigators are included in the BLA. Sanofi and Regeneron state that no bias was introduced by these arrangements and that the study was protected from potential bias by the fact that the primary and key secondary efficacy endpoints were determined by an independent central review. The independent central reviewers were blinded to the investigator assessments. Additionally, a limited number of patients with CSCC were potentially enrolled by these investigators (less than three). None of the investigators participating in Study 1540 had disclosable interests.

The Applicant provided a list of all investigators and sub-investigators from Studies 1423 and 1540 who had no disclosable interests, and a copy of the Certification (FORM 3454) for these participants. For the investigators and sub-investigators with missing financial disclosure information, the Applicant submitted certification that Regeneron acted with due diligence but was unable to obtain the missing information (option 3 on FORM FDA 3454).

Patient Disposition

Study 1423 enrolled 26 patients with advanced CSCC including one patient from the dose-escalation portion of the trial and 25 patients from expansion cohorts 7 (metastatic CSCC) and 8 (locally advanced CSCC). There were 16 patients with metastatic CSCC and 10 patients with locally advanced CSCC. Among the 26 patients, 42% completed the planned 48 weeks of treatment. Of the 14 patients who discontinued cemiplimab, the most common reasons for discontinuation were progressive disease (n=7), adverse events (n=2), and death (n=2).

Study 1540 screened 194 and enrolled 137 patients as of the data cutoff for the original BLA submission. The most common reasons for screen failure were not meeting eligibility criteria (72%) and withdrawal of consent (14%). As of the data cutoff, no patient had the opportunity to complete the planned 98 weeks (Group 1, 2) or 54 weeks (Group 3) of cemiplimab, and treatment was ongoing for 70% of patients. The most common reason for cemiplimab discontinuation was disease progression (15%). Other reasons for premature discontinuation included adverse events (4%), death (4%), and “other” (2%).

Table 12 summarizes disposition for all patients with metastatic or locally advanced CSCC treated across Studies 1423 and 1540 who received at least one dose of cemiplimab (n=163) as of the data cutoff date for the original BLA submission (October 27, 2017).

Table 12. Patient disposition, Advanced CSCC Population

Disposition	Cemiplimab N=163 n (%)
Number receiving at least one dose of cemiplimab	163 (100)
Treatment ongoing at data cutoff	97 (60)
Off treatment	66 (40)
Completed Discontinued	11 (7) 55 (34)
Reasons for treatment discontinuation Progressive disease Death Adverse event	 28 (17) 7 (4) 7 (4)

Disposition	Cemiplimab N=163 n (%)
Patient decision	4 (3)
Physician decision	3 (2)
Other	3 (2)
Withdrawal of consent	2 (1)
Non-compliance	1 (1)
Lost to follow-up	0
Patients in post-treatment follow-up at cutoff	38 (23)

Source: ADSL.xpt, ISS

Protocol Violations/Deviations

Major protocol deviations were pre-specified in the SAPs for Studies 1540 and 1423.

Study 1540

- Patients enrolled on the study despite not meeting inclusion criteria, or despite meeting exclusion criteria
- Patients met criteria for hold or discontinuation of study drug due to an AE, but study drug was not held or discontinued
- Patients received incorrect dose (>20% dose error for cemiplimab)
- Failure to obtain adequate informed consent for study drug during the screening period

There were 17 major deviations in 12 patients in Study 1540. The most common deviation was not having archival tissue submitted prior to day 1 and central pathology confirmation after enrollment (six patients). Table 13 summarizes the other deviations during Study 1540.

Table 13: Major Protocol Deviations during Study 1540

PATIENT ID	PROTOCOL DEVIATION
Eligibility Criteria	
(b) (6)	Patient had an active infection and was not excluded.
	Patient received systemic anticancer treatment within 30 days of cemiplimab initiation.
	Pathologic confirmation of CSCC following radiation of target lesion was not obtained prior to enrollment.
	Did not meet organ function requirement (Hb < 9) at enrollment
Study Procedures	
(b) (6)	Baseline radiologic imaging of target lesions not obtained. (Photographic assessments were obtained at baseline)
Enrollment	

PATIENT ID	PROTOCOL DEVIATION
(b) (6)	Patient enrolled into Group 2 instead of Group 3 (flat dose). This patient is not part of the efficacy analysis.
Safety	
(b) (6)	SAE reported late.
	SAE of infusion reaction reported late on two separate occasions.
	SAE of arthritis reported late.
	Cemiplimab was not interrupted during pneumonitis AE.

Source: CSRs and post-text table listings for Studies 1423 and 1540

Study 1423

The following events were considered major protocol deviations during Study 1423.

- Patients that were enrolled on study despite not meeting inclusion criteria or despite meeting exclusion criteria
- Patients who met the criteria for hold or discontinuation of study drug due to an AE, but study drug was not held or discontinued
- Patients that received the wrong treatment
- Patients that received incorrect dose (>20% error in dose for cemiplimab or high-dose chemotherapy)
- Failure to obtain adequate informed consent for study treatment during the screening period
- Failure to perform procedure at screening if required for eligibility
- Serious adverse event reported late or not reported
- Release of patient confidential information from site personnel

There was one major deviation among the 26 patients with CSCC enrolled in Study 1423. This event involved a breach of confidentiality in which a study site staff member disclosed a patient's name to the Applicant.

***Reviewer**: The protocol deviations were clearly described in the study reports and do not substantially impact the integrity of the study or the reliability of the study results for conducting the safety and efficacy reviews.*

Table of Demographic Characteristics

Study 1423 and Study 1540 were conducted in 33 centers internationally. A total of 26 patients were enrolled in Study 1423 and 82 patients were enrolled in Study 1540. There were 75 patients (16 from Study 1423, 59 from Study 1540) in the metastatic CSCC pooled analysis and 33 patients (10 from Study 1423, 23 from Study 1540) in the locally advanced CSCC pooled analysis. Table 14 shows baseline patient demographics. The majority of patients were male (85%), white (97%), from the U.S. (64%), and had a median age of 71 years.

Table 14. Demographic characteristics at baseline

Demographic Parameters	Metastatic CSCC (N = 75)	Locally Advanced CSCC (N = 33)	Combined CSCC (N = 108)
Sex			
Female	9 (12.0)	7 (21.2)	16 (14.8)
Male	66 (88.0)	26 (78.8)	92 (85.2)
Age			
Mean years (SD)	71 (11)	70 (13)	71 (12)
Median (years)	72	70	71
Min, max (years)	38, 93	47, 96	38, 96
Age Group			
< 65 years	20 (26.7)	12 (36.4)	32 (29.6)
≥ 65 years	55 (73.3)	21 (63.6)	76 (70.4)
Race			
White	74 (98.7)	31 (93.9)	105 (97.2)
Black or African American	1 (1.3)	0 (0)	1 (0.9)
Unknown	0 (0)	2 (6.1)	2 (1.9)
Ethnicity			
Hispanic or Latino	2 (2.7)	1 (3.0)	3 (2.8)
Not Hispanic or Latino	72 (96.0)	31 (93.9)	103 (95.4)
Unknown	1 (1.3)	1 (3.0)	2 (1.9)
Region			
United States	41 (54.7)	28 (84.8)	69 (63.9)
Rest of the World	34 (45.3)	5 (15.2)	39 (36.1)
Europe	10 (13.3)	5 (15.2)	15 (13.9)
Australia	24 (32.0)	0 (0)	24 (22.2)

Other Baseline Characteristics

Table 15 shows the patient clinical characteristics at baseline. Fifty percent received prior systematic anti-cancer therapy, 78% received prior cancer radiotherapy, and 57% had ECOG performance status of 1.

Table 15. Patient clinical and disease characteristics at baseline

Demographic Parameters	Metastatic CSCC (N = 75)	Locally Advanced CSCC (N = 33)	Combined CSCC (N = 108)
Prior systemic anti-cancer therapy			
Yes	44 (58.7)	10 (30.3)	54 (50.0)
No	31 (41.3)	20 (60.6)	51 (47.2)
Missing	0 (0)	3 (9.1)	3 (2.8)
Prior cancer radiotherapy			
Yes	61 (81.3)	24 (72.7)	85 (78.7)
No	14 (18.7)	9 (27.3)	23 (21.3)
ECOG performance status			
0	29 (38.7)	17 (51.5)	46 (42.6)
1	46 (61.3)	16 (48.5)	62 (57.4)

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Noncompliance, concomitant and rescue medication use are variables unlikely to affect the study results or the overall assessment of efficacy of cemiplimab for patients with CSCC.

Efficacy Results – Primary Endpoint

Table 16 shows the results of the primary endpoint of ORR by central review. ORR was 46.7% (95% CI 35.1%, 58.6%) in the metastatic CSCC group, 48.5% (95% CI 30.8%, 66.5%) in the locally advanced CSCC, and 47.2% (95% CI 37.5%, 57.1%) in the combined CSCC group.

Table 16. Results of objective response rate by central review

		Metastatic CSCC (N = 75)	Locally Advanced CSCC (N = 33)	Combined CSCC (N = 108)
ORR	Number of Responses	35	16	51
	Response Rate (95% CI)	46.7% (35.1%, 58.6%)	48.5% (30.8%, 66.5%)	47.2% (37.5%, 57.1%)
	Complete Responses	5.3%	0%	3.7%
	Partial Responses	41.3%	48.5%	43.5%

		Metastatic CSCC (N = 75)	Locally Advanced CSCC (N = 33)	Combined CSCC (N = 108)
DOR	Range in months	2.8 – 15.2+	1 – 12.9+	1 – 15.2+
	Patients with DOR ≥ 6 months, n %	21 (60%)	10 (63%)	31 (61%)

Abbreviations: CSCC, cutaneous squamous cell carcinoma; ORR, overall response rate; CI, confidence interval; DOR, duration of response
+ denotes ongoing at last assessment

Additional Analyses Conducted on the Individual Trial

Table 17 shows the results of ORR by study. A total of 26 patients were enrolled in Study 1423 (16 in metastatic CSCC, 10 in locally advanced CSCC). ORR was 43.8% (95% CI 19.8%, 70.1%) in the metastatic CSCC group, 60.0% (95% CI 26.2%, 87.8%) in the locally advanced CSCC, and 50.0% (95% CI 29.9%, 70.1%) in the combined CSCC group.

A total of 82 patients were enrolled in Study 1540 (59 in metastatic CSCC, 23 in locally advanced CSCC). ORR was 47.5% (95% CI 34.3%, 60.9%) in the metastatic CSCC group, 43.5% (95% CI 23.2%, 65.5%) in the locally advanced CSCC, and 46.3% (95% CI 35.3%, 57.7%) in the combined CSCC group.

Table 17. Results of objective response rate by central review by study

		Metastatic CSCC	Locally Advanced CSCC	Combined CSCC
ORR[1]	**Study 1423**	**N = 16**	**N = 10**	**N = 26**
	No. responses	7	6	13
	Objective response rate	43.8%	60.0%	50.0%
	(95% CI)	(19.8%, 70.1%)	(26.2%, 87.8%)	(29.9%, 70.1%)
	Complete Response	0 (0%)	0 (0%)	0 (0%)
	Partial Response	7 (43.8%)	6 (60.0%)	13 (50.0%)
	Study 1540	**N = 59**	**N = 23**	**N = 82**
	No. responses	28	10	38
	Objective response rate (95% CI)	47.5%	43.5%	46.3%
		(34.3%, 60.9%)	(23.2%, 65.5%)	(35.3%, 57.7%)
	Complete Response	4 (6.8%)	0 (0%)	4 (4.9%)
	Partial Response	24 (40.7%)	10 (43.5%)	34 (41.5%)

Reviewer's Comments: *The ORRs were consistent across studies for metastatic, locally advanced, and combined CSCC.*

Data Quality and Integrity

The submission contained all the required components of the electronic Common Technical Document (eCTD) and was of adequate quality and integrity to allow for review of the clinical trial data supporting the proposed indication. The primary safety and efficacy datasets and the updated safety databases submitted with the 90-Day SUR were reproducible. FDA could confirm the Applicant's analyses of the primary and secondary endpoints.

Multiple information requests were sent to the Applicant during the review cycle. Examples of these were requests to clarify the location of specific components in the application, to obtain additional case report forms, to conduct additional specified safety analyses, and to provide alternative presentations of efficacy results. The Applicant provided timely responses to satisfy all FDA information requests.

The Applicant submitted documentation of data quality assurance procedures under Section 4.9 of the clinical study reports for Studies 1423 and 1540. These procedures included regular site monitoring in addition to conducting investigator meetings and training sessions for clinical research associates, and site initiation visits to review the clinical protocol, CRF, and study procedures. Additionally, sites were subject to independent Quality Assurance audits which could be conducted by the sponsor or regulatory authorities at any time during or after the study.

Efficacy Results – Secondary and other relevant endpoints

Table 16 shows the range in DOR for metastatic CSCC was 2.8-15.2+ months, locally advanced CSCC was 1-12.9+ months, and combined CSCC was 1-15.2+ months. DOR ≥ 6 months was 60%, 63%, and 61% for patients with metastatic, locally advanced, and combined CSCC, respectively. The median duration of follow-up was 8.1 months for metastatic CSCC, 10.2 months for locally advanced CSCC, and 8.9 months for combined CSCC.

Dose/Dose Response

All patients with CSCC in the efficacy analysis set except for one patient who was treated with cemiplimab 1 mg/kg every two weeks in the dose-escalation phase of Study 1423, received 3 mg/kg every two weeks. Efficacy results from Group 3 of Study 1540 (350 mg flat dose every three weeks) were immature at the data cutoff date for the BLA submission. Therefore, dose response relationships for efficacy could not be evaluated.

Persistence of Effect

Results of subgroup analyses of ORR are presented in Table 18, Table 19, and Table 20. Table 18 includes comparisons of treatment arms in subgroups based on gender, age, region, prior systematic anti-cancer therapy, prior cancer radiotherapy, type of metastatic disease, and ECOG performance status among patients with metastatic CSCC.

Table 18. Subgroup analysis of objective response rate in metastatic CSCC

		#Responses/N	ORR[1] (95% CI)
Gender	Female	2/9	22.2 (2.8, 60.0)
	Male	33/66	50.0 (37.4, 62.6)
Age (years)	<65	11/20	55.0 (31.5, 76.9)
	≥65	24/55	43.6 (30.3, 57.7)
Region	U.S.	16/41	39.0 (24.2, 55.5)
	Rest of World	19/34	55.9 (37.9, 72.8)
Prior systemic anti-cancer therapy	No	16/31	51.6 (33.1, 69.8)
	Yes	19/44	43.2 (28.3, 59.0)
Prior cancer radiotherapy	Yes	28/61	45.9 (33.1, 59.2)
	No	7/14	50.0 (23.0, 77.0)
Type of metastatic disease	Distant	25/52	48.1 (34.0, 62.4)
	Nodal	10/23	43.5 (23.2, 65.5)
ECOG Performance Status	0	17/29	58.6 (38.9, 76.5)
	1	18/46	39.1 (25.1, 54.6)

Abbreviations: CSCC, cutaneous squamous cell carcinoma; ORR, objective response rate; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group
[1] Independent central review

Table 19 includes comparisons of treatment arms in subgroups based on gender, age, region, prior systematic anti-cancer therapy, prior cancer radiotherapy, and ECOG performance status among patients with locally advanced CSCC.

Table 19. Subgroup analysis of objective response rate in locally advanced CSCC

		# Responses/N	ORR[1] (95% CI)
Gender	Female	3/7	42.9 (9.9, 81.6)
	Male	13/26	50.0 (29.9, 70.1)
Age (years)	<65	5/12	41.7 (15.2, 72.3)
	≥65	11/21	52.4 (29.8, 74.3)
Region	U.S.	14/28	50.0 (30.6, 69.4)
	Rest of World	2/5	40.0 (5.3, 85.3)
Prior systemic anti-cancer therapy	No	12/20	60.0 (36.1, 80.9)
	Yes	3/10	30.0 (6.7, 65.2)
Prior cancer radiotherapy	Yes	11/24	45.8 (25.6, 67.2)

	No	5/9	55.6 (21.2, 86.3)
ECOG Performance Status	0	6/17	58.6 (38.9, 76.5)
	1	10/16	39.1 (25.1, 54.6)

Abbreviations: CSCC, cutaneous squamous cell carcinoma; ORR, objective response rate; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group
[1] Independent central review

Table 20 includes comparisons of treatment arms in subgroups based on gender, age, region, prior systematic anti-cancer therapy, prior cancer radiotherapy, and ECOG performance status among patients with combined CSCC.

Table 20. Subgroup analysis of objective response rate in combined CSCC

		# Responses/N	ORR[1] (95% CI)
Gender	Female	5/16	31.2 (11.0 , 58.7)
	Male	46/92	50.0 (39.4 , 60.6)
Age (years)	<65	16/32	50.0 (31.9 , 68.1)
	≥65	35/76	46.1 (34.5 , 57.9)
Region	U.S.	30/69	43.5 (31.6 , 56.0)
	Rest of World	21/39	53.8 (37.2 , 69.9)
Prior systemic anti-cancer therapy	No	28/51	54.9 (40.3 , 68.9)
	Yes	22/54	40.7 (27.6 , 55.0)
Prior cancer radiotherapy	Yes	39/85	45.9 (35.0, 57.0)
	No	12/23	52.2 (30.6, 73.2)
ECOG Performance Status	0	23/46	50.0 (34.9 , 65.1)
	1	28/62	45.2 (32.5 , 58.3)

Abbreviations: CSCC, cutaneous squamous cell carcinoma; ORR, objective response rate; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group
[1] Independent central review

Reviewer's Comments: *These subgroup analyses are exploratory only. The subgroup analyses showed no outliers in subpopulations of adequate size compared to the primary analyses of ORRs for metastatic, locally advanced, and combined CSCC.*

PD-L1 Expression and Response

The Applicant provided an additional exploratory analysis of response rate and duration of response based on PD-L1 expression status. The sampling of patients with CSCC enrolled in Studies 1423 or 1540 with evaluable specimens for assessment of PD-L1 (n=28) was relatively small. In Study 1423, tumor biopsies were required at enrollment for all patients (unless considered unsafe in the opinion of the investigator for an individual patient). In Study 1540,

tumor biopsies during the screening period were required for patients with locally advanced CSCC (Group 2), but not for patients with metastatic CSCC (Groups 1 and 3). In both groups of patients who had available tumor specimens, some samples had an insufficient number of cells for evaluating PD-L1 and could not be included in the subgroup analysis.

Responses were observed in both PD-L1 positive and PD-L1 negative patients. In summary, 10 of 18 (56%) patients with tumors positive for PD-L1 (≥ 1%), had an objective response. Three of 10 (30%) patients with tumors negative for PD-L1 (<1%), had an objective response. Durable responses were observed in both groups.

Reviewer's Comments: *Durable responses occurred in patients who were positive or negative for PD-L1 expression; however, the number of patients with PD-L1 expression status results available was very small and no formal comparisons of response rate based on this variable can be performed.*

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Results of mean global health status/QOL and pain over time for patients with available data in the metastatic and locally advanced CSCC study arms in Study 1540 are given in Figure 19 and Figure 20. The Applicant concluded no consistent changes in QOL and a downward trend in mean pain score.

Figure 19. Mean global health status/QOL over time, by study arm

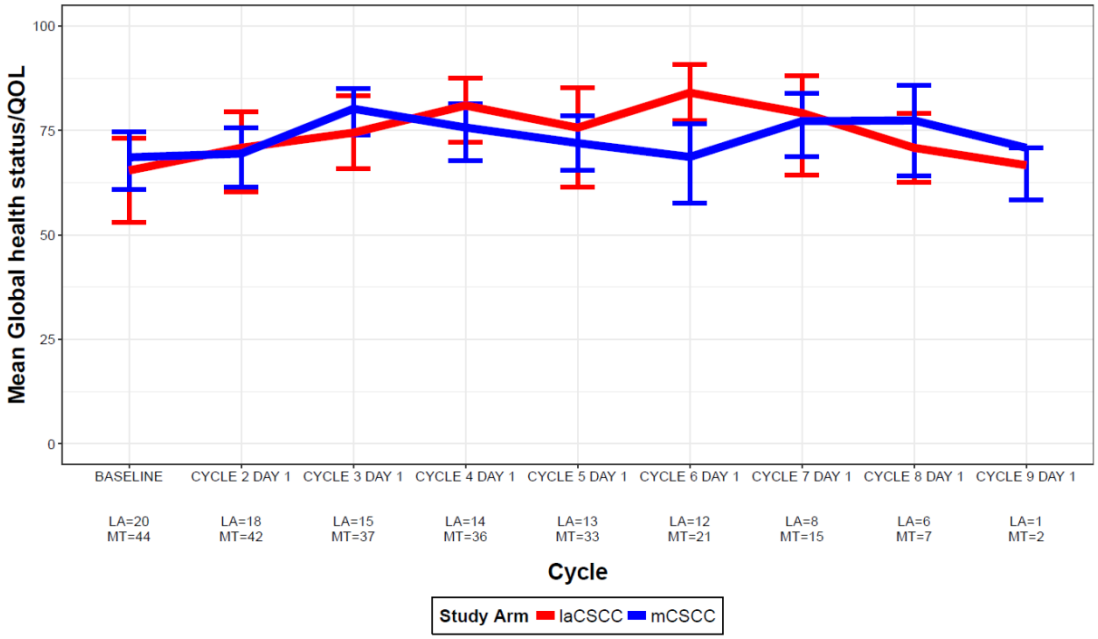
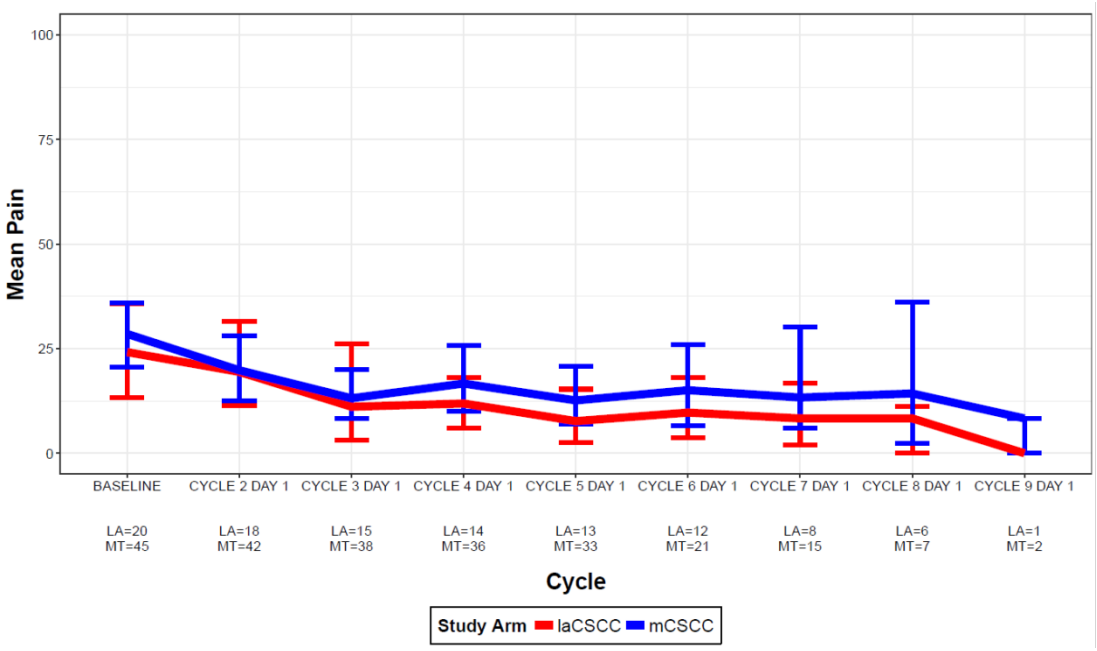


Figure 20. Mean pain (subscale) over time, by study arm



Reviewer's Comments: *The analyses of PRO's were based on a single-arm trial, and are considered descriptive and exploratory.*

Additional Efficacy Considerations for Patients with Locally Advanced CSCC

At the time of data cutoff for the BLA submission, Study 1540 Group 2 was partially enrolled. FDA had agreed to review efficacy data for the subgroup of patients with locally advanced CSCC who had been treated or followed for at least nine months from study enrollment (n=23) to allow for at least six months of follow-up after the first response assessment for each patient. The Applicant also submitted photographic data for all responding patients to support the radiographic response and DOR results.

Study 1540 required baseline and on-study digital medical photographic assessments of externally visible target lesions for patients with locally advanced CSCC (Group 2) as part of the overall assessment of response. Annotated and non-annotated photographs were collected with annotated photos including areas of subdermal palpable tumor within the marked perimeter. Specific instructions were provided to investigators regarding the types of views that were to be obtained for each lesion. Patients also underwent required baseline radiologic assessments (CT or MRI) of all known target lesions. However, if the investigator considered that no significant added information was provided by baseline radiology of the lesion (beyond the information that was provided by baseline digital medical photography), digital medical photography only (without radiologic imaging) at subsequent response assessments of that lesion was permitted. Similarly, if a patient had a deeply invasive (e.g., a subdermal recurrence),

lesion not amenable to photographic assessments, the target lesion could be followed with radiographic assessments only.

A composite response assessment was made by an independent review committee (IRC) based on clinical response criteria and RECIST 1.1. The clinical response criteria required bi-dimensional measurements according to World Health Organization (WHO) criteria of externally visible lesions that had baseline and on-treatment photographic evaluations. Responses were defined as follows (adapted from Appendix 3 of Study 1540 protocol):

- **Complete response of externally visible disease (vCR)**: all target lesion(s) and nontarget lesion(s) no longer visible, maintained for at least 4 weeks. *Documentation of vCR requires confirmation by biopsies of site(s) of externally visible target lesion(s) with histologic confirmation of no residual malignancy, per central pathology review. In the absence of such histologic confirmation, a patient cannot be deemed to have experienced vCR and the best response would be partial response.*
- **Partial response of externally visible disease (vPR)**: decrease of 50% (WHO criteria) or greater in the sum of the products of perpendicular longest dimensions of target lesion(s), maintained for at least 4 weeks.
- **Stable externally visible disease (vSD)**: not meeting criteria for vCR, vPR, or progressive disease.
- **Progression of visible disease (vPD)**: increase of ≥ 25% (WHO criteria) in the sum of the products of perpendicular longest dimensions of target lesion(s). *In rare cases, unequivocal progression of a non-target lesion may be accepted as vPD.*

For lesions with scar tissue or fibrosis, biopsies were required to establish benign status. For baseline ulcerated lesions, complete response was defined as re-epithelialization of the entire area of ulceration of target lesion(s), maintained over at least 4 weeks.

New lesions were also considered in the clinical response criteria. If a new lesion was $\geq$ 10 mm in both maximal perpendicular diameters, unless it was confirmed on biopsy to not be CSCC, it was deemed progressive disease. If a biopsy was not obtained or inconclusive, it was considered progressive disease.

Table 21 summarizes the overall clinical response criteria.

Table 21. Clinical Response Criteria, Locally Advanced CSCC

Overall Clinical Responses For Locally Advanced CSCC Lesions that are Measured by Digital Medical Photography

Externally Visible Tumor Dimension[a]	New Lesions[a]	Clinical Response
vCR	No	cCR[b,c]
vPR	No	cPR[d]
vSD	No	cSD[e]
vPD	Yes or No	cPD[f]
Any	Yes	cPD[f]

[a] See above for definitions
[b] Clinical Complete Response
[c] Negative biopsy showing no residual malignant cells is required for any lesion be deemed cCR
[d] Clinical Partial Response
[e] Clinical Stable Disease
[f] Clinical Progression of Disease

Source: Appendix 2, Study 1540 Protocol

Independent central review of all radiographic and photographic response results was performed by two separate committees. In addition to the independent radiologic and photographic review committees, there was an independent composite response committee (ICRC) responsible for the overall composite response and DOR determinations for each patient. The ICRC also evaluated results of any biopsies that the investigators chose to perform during the study to confirm the presence or absence of CSCC in tumor lesions. Biopsies were reviewed by independent central pathologists prior to ICRC meetings. The following table summarizes the composite response criteria used for Group 2 patients and any patient with metastatic CSCC who had both photographic and radiographic response assessments of target lesions.

Table 22. Composite Response Criteria: Locally Advanced CSCC

Clinical Response (Digital Medical Photography)	RECIST 1.1 Response (Radiology)	Composite (Overall): Clinical + RECIST Response
cCR	CR or NA[a]	CR
NA	CR	CR
cCR	PR or SD	PR
cPR	CR, PR, or SD, or NA	PR
NA	PR	PR
cSD	CR or PR	PR
cSD	SD or NA	SD
NA	SD	SD
cPD	Any	PD
Any	PD	PD

[a] NA indicates "Not applicable" (eg, because the assessment was not done)

Source: Appendix 2, Study 1540 Protocol

The Applicant submitted photographic data for nine of the 10 Group 2 patients with tumors that experienced an objective response during treatment with cemiplimab. The photographs were considered important supportive data supplementing the radiographic overall response rate and DOR results for the relatively small sample size of patients with available results at the time of the data cutoff for the BLA submission. The photographs were not intended to verify or substitute for the results obtained from the independent reviewers, but they served as a verification of the treatment effect and clinical benefit to patients. The clinical reviewer evaluated the baseline and on-treatment annotated and unannotated photography for each of the nine Group 2 responders in Study 1540 in addition to select photographs included in the CSR for Study 1423. Comments are provided below in Table 23 which summarizes relevant patient variables and the cemiplimab treatment effects in patients with locally advanced CSCC who experienced an objective response during Studies 1423 and 1540.

Table 23.Characteristics of Response in Patients with Locally Advanced CSCC

Patient ID	Target Lesion(s)	Prior Therapy	BOR (IRC)	TTR (mo)	DOR (mo)	Response Ongoing	Reviewer comments - prior therapy and photographic data
Study 1423							
(b) (6)	Right eye	Surgery and RT	PR	1.9	1	N	Four prior surgical procedures and prior RT. Select screening and Day 56 photos from interim CSR show large tumor protruding from right eye with normal eye not visible at study entry.

Patient ID	Target Lesion(s)	Prior Therapy	BOR (IRC)	TTR (mo)	DOR (mo)	Response Ongoing	Reviewer comments - prior therapy and photographic data
							Day 56 photo shows marked shrinkage and eye area visible. Censored – Patient withdrew consent.
(b) (6)	Head and neck	Surgery, RT, and Systemic	PR	3.6	5.6	N	Two prior surgical procedures and prior RT. No photography available. Censored - last response assessment prior to data cutoff was considered nonevaluable by IRC.
	Head and neck	Surgery and RT	PR	3.7	10.2 +	Y	Three prior surgical procedures and prior RT. No photography available.
	Head and neck	Surgery and RT	PR	3.7	6.4+	Y	Five prior surgical procedures and prior RT. No photography available.
	Head and neck	Surgery and RT	PR	1.8	7.4+	Y	Four prior surgical procedures and prior RT. No photography available.
	Scalp	Surgery, RT and Systemic	PR	7.3	5.7+	Y	Two prior surgical procedures and prior RT. Select screening and Day 221 photos demonstrate obvious shrinkage and overall improvement of lesion.
Study 1540							
(b) (6)	Trunk	Surgery	PR	1.9	5.6+	Y	A total of 28 prior surgical procedures. Four truncal target lesions; largest nodular lesion in left shoulder region; all lesions demonstrated marked improvement at Cycle 4 Day 56.
	Face, cheek	Surgery	PR	1.9	7.4+	Y	Two prior surgical resections. Large nodular preauricular lesion appears invasive of outer ear canal. Lesion appears completely resolved in Cycle 4Day56 photography. Normal ear anatomy visible after response.
	Neck	Surgery	PR	1.9	1.9	N	Eight prior surgical procedures. Right neck large nodular lesion with tumor extending upward around lower ear and covering mandible. Lesion is much smaller at Cycle 2 Day 56 photography with normal-appearing skin over

Patient ID	Target Lesion(s)	Prior Therapy	BOR (IRC)	TTR (mo)	DOR (mo)	Response Ongoing	Reviewer comments - prior therapy and photographic data
							primary tumor and mandibular contour relative to ear and neck more evident. Censored – Patient placed on hospice for comorbid medical problems.
(b) (6)	Scalp and right ear	Surgery and RT	PR	3.7	9.2+	Y	Five prior surgical procedures and prior RT. Multiple scalp lesions and right preauricular lesion invading ear. Cycle 6 Day 56 photos show all target lesions smaller in size, normal skin replacing prior necrotic areas in at least two lesions including the right ear lesion.
	Right ear	Surgery, RT and Systemic	PR	5.6	7.4+	Y	Three prior surgical procedures and prior RT and carboplatin/paclitaxel. Large tumor invading entire right ear with ulceration. Disfiguring large tumor evident over pre and postauricular skin and in the ear canal. Cycle 7 Day 56 photography shows much smaller lesion with new normal-appearing skin over former ulcerated ear canal and preauricular area; postauricular necrotic area still visible but much smaller.
	Scalp	Surgery and RT	PR	1.9	7.5+	Y	Six prior surgical procedures and prior RT. Two target lesions large and nodular. Cycle 5 Day 56 photos show resolution of nodules and new normal-appearing skin present.
	Distal lower extremity	Surgery	PR	1.9	12.9+	Y	Seven prior surgical procedures. Two target lesions with overlying necrosis and inflammation. Cycle 2Day 56 photos show smaller target lesions with evidence of new normal skin in some areas.
	Left face and ear	Surgery and RT	PR	3.7	9.2+	Y	Three prior surgical procedures and prior RT. Large tumor surrounding and invading left ear and filling former ear canal. Cycle 2 Day 56 photography shows smaller lesion, normal skin over the entire tumor area and a patent canal.

Patient ID	Target Lesion(s)	Prior Therapy	BOR (IRC)	TTR (mo)	DOR (mo)	Response Ongoing	Reviewer comments - prior therapy and photographic data
(b) (6)	Distal lower extremity	Surgery	PR	7.6	1.9+	Y	Six prior surgical procedures. Large nodular tumor with surrounding erythema and inflammation and areas of necrosis throughout tumor. Cycle 5 Day 56 photography shows smaller target lesion with central tumor still nodular and open but much of the prior tumor area has been replaced by normal appearing skin. No surrounding erythema.
	Scalp	Surgery and RT	PR	3.7	9.3+	Y	Three prior surgical procedures and prior RT. CRF states that patient had deep lesion not amenable to photography.

Source: Applicant response to FDA Information Request (June 13, 2018) and serial photographic images for Study 1540 responders submitted as part of the BLA; For Study 1423 patients, limited, select photos provided by Applicant in the interim CSR as photographic response results were not routinely collected for all patients. BOR: Best overall response; CR: complete response; DOR: duration of response (calculated from onset of confirmed response); IRC: Independent review committee PR: partial response; TTR: time to response

***Reviewer comments**: The following general conclusions were drawn after the evaluation of patient level prognostic variables at study entry, response and DOR results, and serial digital photography of target lesions in patients with locally advanced CSCC who experienced an objective response to cemiplimab:*

- *An objective response was evident within the first two response evaluations for most patients.*
- *For two of 16 patients who experienced an objective response, the response occurred more than 6 months following treatment initiation and was ongoing at data cutoff.*
- *Ten of 16 patients (63%) had durable responses for at least six months from onset of response.*
- *Thirteen of 16 patients had ongoing responses at data cutoff, and three patients were censored.*
- *All patients who had been designated responders by the ICRC and who had available photographic data to review, had, in the opinion of the reviewer, significant improvement in what appeared as baseline disfiguring lesions (several were in highly visible locations such as the face, scalp, and ear regions).*

The reviewer additionally notes that available photographic data were presented to the multidisciplinary review team and the Associate Division Director at the FDA midcycle meeting for the cemiplimab BLA.

8.1.3. Integrated Assessment of Effectiveness

Advanced CSCC generally refers to metastatic (nodal or distant) disease or locally advanced disease that is deemed inoperable or not appropriate for radiation therapy. Studies 1423 and 1540 enrolled and treated patients with advanced CSCC with single agent cemiplimab. The similarities in the study populations and the treatment protocols allows for pooling the efficacy results across the trials. The pooled results for ORR and DOR are presented in Table 16.

For patients with metastatic CSCC who had at least six months of follow-up after initiation of cemiplimab (N = 75), the centrally-reviewed ORR was 44% (95% CI: 35.1% to 58.6%). Five percent of patients with metastatic CSCC experienced a CR. Among the 35 responding patients with metastatic CSCC, the median DOR was not reached (range: 2.8 to 15.2+ months) and 21 (60%) patients experienced responses of at least six months.

For patients with locally advanced CSCC who had at least nine months of follow-up after initiation of cemiplimab (N = 33) the centrally-reviewed ORR was 49% (16/33; 95% CI: 30.8% to 66.5%). All responses were PRs. Among the 16 responding patients with locally advanced CSCC, the median DOR was not reached (range: 1.0 to 12.9+ months) and 10 (63%) patients experienced responses of at least six months. While the sample size of patients with locally advanced disease was relatively small, the effect size on ORR and DOR was substantial.

Although patients with metastatic disease are expected to have poorer outcomes than patients with locally advanced, node-negative disease, the consistencies observed in the metastatic and locally advanced subgroup analyses in terms of effect size on response rate and DOR and the relatively high-risk nature of both conditions allows for pooling the results of the two subtypes of advanced CSCC as a supportive efficacy analysis. For the larger pooled population (N = 108), centrally reviewed ORR was 47% (51/108; 95% CI: 37.5% to 57.1%). Among the 51 responding patients, the median DOR was not reached (range: 1.0 to 15.2+ months). At the time of data cutoff, 61% (31/51) of responding patients had sustained responses for at least 6 months. Eight percent of the patients who experienced an objective response had subsequent disease progression.

8.2. Review of Safety

8.2.1. Safety Review Approach

The safety of cemiplimab was primarily evaluated in 163 patients with advanced CSCC (Pool 1) who received at least one dose of single-agent cemiplimab during Studies 1423 or 1540. A pooled population of 534 patients (Pool 3) with various advanced solid tumors who received cemiplimab as a single agent or in combination with chemotherapy and/or radiation was also

analyzed to support the safety review. The Applicant additionally pooled patients from the two trials who received single-agent cemiplimab (Pool 2). This pool excluded patients with hepatocellular carcinoma and any patient receiving concomitant radiation or chemotherapy in Study 1423 and was analyzed to further assess the safety of single agent cemiplimab in a larger group of patients (N=240). For most analyses, the focus of the safety review was on the results from Pool 1 supported by Pool 3. Since the primary safety concern for the class of monoclonal antibodies to PD-1 is immune-mediated adverse reactions (imARs), and because concomitant chemotherapy or radiation should not substantially impact immune-based events, the larger safety population (Pool 3) was considered the main safety database for assessing common and rare types of imARs across a larger sampling of patients with cancer.

The on-treatment safety monitoring periods were from the time the patient initiated cemiplimab through the End of Treatment visit scheduled 30 days following the last dose of study drug. In Study 1423, any treatment-related AE occurring more than 30 days from the last dose of study drug was also reported, and all SAEs were followed until resolution or stabilization. In Study 1540, AEs were reported from the signing of informed consent until 105 days (5 half-lives) after the last dose of cemiplimab. Any AE assessed as related to study treatment and persisting after 105 days (5 half-lives) post-last dose was followed until resolution to baseline or Grade ≤1.

The primary efficacy and safety analyses were conducted when all Group 1 patients in Study 1540 had been followed for at least six months from initiating cemiplimab treatment. The data cut-off dates for the safety results are as follows: Study 1423: Oct 2, 2017 for patients with CSCC and September 1, 2017, for all other patients; Study 1540: Oct 27, 2017.

The Applicant submitted an updated safety analysis with corresponding datasets (data cut-off date of January 20, 2018), to supplement the SCS as part of the 90-day safety update report (SUR). During the 90-day interval, an additional 36 patients were exposed to cemiplimab, 35 of which were patients with advanced CSCC who were added to Pool 1. Key safety analyses from the updated dataset were verified by the reviewer for assessing safety with longer exposures to cemiplimab and detecting new signals. Narratives of deaths and SAEs were reviewed for events that occurred up until the data cutoff date of January 20, 2018.

8.2.2. Review of the Safety Database

Overall Exposure

Patients with advanced CSCC (Pool 1) received cemiplimab for a median of 20 weeks (range: 0.4 to 71 weeks) with 46% of patients with CSCC and 38% of patients from Pool 3 receiving study drug for at least six months. Most patients with CSCC received cemiplimab 3 mg/kg every three weeks. As of the data cutoff date, 23 patients with CSCC received at least one flat dose of 350 mg administered every three weeks in the Group 3 cohort of Study 1540. The median duration of exposure to the 350 mg flat dose cemiplimab was 6.6 weeks (range: 1.6 to 14.7 weeks).

Table 24. Exposure Summary

	Pool 1 CSCC Patients N=163	Pool 2 Single Agent N=240	Pool 3 All Patients N= 534
Duration of exposure in weeks			
Median	20	20	16
Mean	26	26	23
Range	0.4-71	0.4-71	0.4-71
Number of infusions			
Median	10	10	8
Mean	13	13	11
Range	1-36	1-36	1-36
Cumulative dose (mg/kg)			
Median	2104	2081	1628
Mean	3026	3079	2525
Range	160-12062	160-19008	144-19008
Dose intensity (mg/kg/week)			
Median	1.5	1.5	1.5
Mean	1.5	1.6	1.5
Range	0.5-7	0.5-7	0.3-7
Relative dose intensity (%)			
Median	1	1	1
Mean	1	1	1
Range	0.6-4.7	0.6-4.7	0.3-4.7

Source: ADEX.xpt, ISS dataset

Relevant characteristics of the safety population:

FDA agreed to the presentation of the safety data using three pooled populations from Studies 1423 and 1540 prior to the BLA submission.

- **Pool 1: All patients with CSCC (N=163)**
  This pool represents the primary data used for the analysis of safety in the intended population (N=163). This dataset includes 98 patients with metastatic CSCC and 65 patients with laCSCC. There was one patient in the group treated with cemiplimab 1 mg/kg every two weeks. Most patients received cemiplimab 3 mg/kg every two weeks

(n=139) and the rest of the patients (n=23) received the flat dose of 350 mg every three weeks. The flat dose is proposed for product labeling.

- **Pool 2: All patients who received single agent cemiplimab excluding patients with hepatocellular carcinoma (HCC) (N=240)**
  This pool is intended for further evaluation of the safety of single agent cemiplimab in a larger sample size of patients (N=240). Patients with HCC are excluded because patients enrolled in the HCC cohort had different entry criteria for liver function.

- **Pool 3: All patients who received any dose of cemiplimab (N=534)**
  This pool provides safety results for all patients who received at least 1 dose of cemiplimab either as a single agent or in combination with chemotherapy and or radiation.

Adequacy of the safety database:

Overall, the safety database submitted by the Applicant was adequate. No major deficiencies were identified. The size of the safety database was sufficient to identify adverse events that occur at an incidence of less than 1%.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The data submitted was well-organized and the quality was adequate to perform a complete review of the safety of cemiplimab. Multiple information requests were sent to the Applicant during the review of safety to confirm data, request additional data, narratives and case report forms, request alternative presentations of per patient safety data or clarify minor discrepancies in the pooled database. The Applicant provided timely and sufficient responses including additional analyses and clarifications as required.

Categorization of Adverse Events

The Applicant coded verbatim AE terms for the integrated database using MedDRA version 20.0 for the primary analyses and the 90-day safety update. Treatment-emergent adverse events (TEAEs) were defined as all AEs occurring from initiation of study drug through 30 days after the last dose of cemiplimab for Study 1423 and 105 days for Study 1540. NCI CTCAE Version 4.03 was used for toxicity grading.

The reviewer assessed the adequacy of the Applicant's mapping of AE verbatim terms to MedDRA preferred terms (PTs) for 100% of the AE.xpt dataset for Pool 1. Of the 1105 line listings in this dataset, the reviewer used matching of identical verbatim and MedDRA PTs (n=384 line listings) as well as manual evaluation of the remaining verbatim terms (n=721 line listings). Most nonidentical terms were due to spelling differences (diarrhoea versus diarrhea), similar conditions (e.g., anorexia versus decreased appetite), laboratory abnormality descriptions, and verbatim terms that included

descriptors (e.g., cellulitis of leg versus cellulitis). Overall, the MedDRA PTs listed in the dataset adequately represented the verbatim terms from the CRFs.

An audit for data integrity was conducted using 10% (17) CRFs and comparing AE terms in the SDTM, ADaM and ISS datasets. The review identified apparent discrepancies regarding the AE severity grade including instances where the values in the dataset appeared to represent initial rather than maximum severity grades per event. The Applicant was able to provide clarification regarding how the events of maximum severity were mapped and included in the ADaM dataset. FDA was able to confirm that the maximum severity grades in the CRFs were included in the ADaM dataset used for the safety review.

Routine Clinical Tests

Routine hematology and core chemistry laboratory assessments were performed within 28 days of enrollment and every two weeks prior to cemiplimab administrations, and when medically necessary. Vital signs, physical examination and performance score assessments were performed prior to each infusion. Antinuclear antibody (ANA), rheumatoid factor (RF), CRP and thyroid stimulating hormone (TSH) were collected at screening and every 8 weeks thereafter and as medically indicated. Immunogenicity labs were collected on Day 1 of Cycles 1, 3, 5, 7, and 11 during Study 1540. A 12-lead ECG was assessed at screening, and 30 minutes after infusion on Day 1 of Cycle 1 and 3.

8.2.4. Safety Results

Deaths

Twelve percent (n=20) of patients in Pool 1 died. Seven percent (n=12) died due to progressive disease. Four percent (n=7) died due to an adverse event or for "other" reasons; including one fatal AE that was deemed related to cemiplimab treatment. The following table summarizes the deaths in patients with CSCC (Pool 1) treated with cemiplimab that were not caused by disease progression (i.e., cause was AE or "other"). In some of the cases described below, there is uncertainty as to the cause of death given underlying clinical history (of cancer and other co-morbidities) of the patients.

Table 25. Deaths Due to Causes other than Disease Progression: Pool 1

(b) (6)	82-year-old man with laCSCC of the right parotid who received a total of two doses of cemiplimab who died in his sleep at home. The patient's past medical history was notable for aspiration and stroke. A chest x-ray obtained for cough on Day 15 showed bilateral lower lobe infiltrates and the patient was started on antibiotics for **pneumonia**. The patient, per family, was not behaving differently on the day before he died in his sleep. No autopsy was performed. **The investigator considered the death to be possibly related to cemiplimab but not immune-mediated** as there was no other obvious cause and an autopsy had not been performed. ***Reviewer:*** *Despite baseline risk factors and clinical findings of recent pneumonia,*

	cemiplimab cannot be completely ruled out as a causal factor in this event as described.
(b) (6)	93-year-old man with CSCC of head and neck with metastasis to thoracic lymph nodes who received three doses of cemiplimab 3 mg/kg. On Day 35, he presented with a fever and productive cough. The patient was prescribed oral antibiotics in the outpatient setting. He worsened after one day of antibiotics and was admitted to the hospital. Chest X-ray consistent with pneumonia, including a right upper lobe infiltrate. Intravenous antibiotics were added. The patient clinically declined, developed **acute respiratory distress syndrome (ARDS)** and was transitioned to comfort care. The patient died 38 days after the start of study drug. The investigator considered the death to be due to a community acquired pneumonia and unrelated to study drug. ***Reviewer:*** *Given the fever, productive cough and focal infiltrate in the chest x-ray, agree with the investigator that the fatal event is unlikely related to cemiplimab and more likely an infectious etiology.*
	86-year-old man with multiple scalp CSCC experienced a SAE of **pneumonia** after approximately four months of cemiplimab treatment. The event was complicated by **sepsis and congestive heart failure** requiring intubation. Ventilator support withdrawn by family and the patient died within two days of being admitted. The chest x-ray showed a bilateral pneumonia with consolidation of the left lower lobe. The patient did not receive steroids according to the narrative. The investigator considered the event to be unrelated to cemiplimab. ***Reviewer:*** *Requested CRF for review. The investigator attributed the death to the AE of pneumonia. It does not appear that steroids were administered at the time the patient presented with symptoms. The patient was transitioned off ventilator support fairly quickly and died soon after. Given the focal infiltrate, the event was possibly infectious, however, the contribution of cemiplimab cannot be ruled out.*
	66-year-old woman with right lower extremity CSCC metastatic to inguinal lymph nodes and lung. She received cemiplimab for two months. On Day 48, she required IV antibiotics and interruption of cemiplimab for cellulitis of the leg around the primary tumor site. The SAE narrative states that there was a small amount of bleeding noted during the admission but no vessels that could be cauterized. The cellulitis resolved, and the patient resumed treatment. The cellulitis was deemed a SAE unrelated to cemiplimab and due to the fungating tumor. On Day 62, she was started on rivaroxaban for pulmonary embolism and experienced arterial hemorrhage at the primary tumor site four days after starting anticoagulant therapy. The narrative states that part of the tumor fell off and there was arterial bleeding. On Day 69, the patient transitioned to hospice and died from **progressive hemorrhage from tumor site** on Day 71. The investigator considered the event unrelated to cemiplimab. ***Reviewer:*** *Agree with causality assessment for this patient's death.*

(b) (6)	72-year-old man with metastatic CSCC of the head and neck. Prior therapies included multiple surgeries and five prior courses of radiation. The patient died in his sleep 41 days after the start of cemiplimab. The **cause of death was unknown,** and there was no autopsy. Prior to his death, he had no AEs greater than Grade 1. The Applicant notes that the patient had baseline cardiovascular risks and risks for aspiration pneumonia. ***Reviewer:*** *Despite baseline risk factors, cemiplimab cannot be ruled out as a causal factor in this event as described. CRF requested and did not indicate details of the death event attributed to "other." When queried for details, the investigator stated the cause of death was unknown.*
	90-year-old man with left arm CSCC metastatic to the lungs who elected to stop treatment after four doses of cemiplimab because he "was getting weaker" according to the CRF. Two weeks later he had tumor imaging which demonstrated progressive disease. Three days afterward, the patient was hospitalized and treated for gastrointestinal bleeding, esophagitis and duodenal ulcer. These resolved, but four weeks later he developed Grade 3 hypercalcemia. The patient died three days later. On the Death page, the cause of death is "Other", and the patient was noted to have Failure to Thrive due to the underlying cancer. The Applicant notes that **disease progression and malignant hypercalcemia** are consistent with the natural history of end stage metastatic squamous cell carcinoma. ***Reviewer:*** *Agree with Applicant's causality assessment for this patient's death.*
	81-year-old man with locally advanced head and neck CSCC. Relevant medical history included type 2 diabetes mellitus, renal insufficiency, benign prostatic hyperplasia, hypertension, decreased baseline left ventricular ejection fraction of 25%, and supraventricular tachycardia. The patient received 2 doses of cemiplimab. On day 29, the patient experienced Grade 2 **acute kidney injury**. The patient was diagnosed with a urinary tract infection (UTI) which was treated with levofloxacin. The patient was admitted for IV fluids, IV antibiotics, and methylprednisolone was given empirically for a **possible auto-immune nephritis**. The patient became anuric and the patient and family opted for comfort care. On day 33, the patient died. The death was considered by the investigator to be unrelated to cemiplimab. ***Reviewer:*** *Unlikely related to cemiplimab, but cemiplimab cannot be ruled out as a causal factor in the death. Despite baseline risk factor of renal insufficiency, there was risk for development of an immune-mediated nephritis with cemiplimab. Lack of improvement with steroids favors alternative causes, but the patient had developed anuria within a day of starting steroids and was soon after transitioned to palliative care. The renal damage may have been irreversible at the time of starting corticosteroids.*

(b) (6)	67-year-old man with head and neck CSCC metastatic to the large intestine, peritoneum, bone, esophagus, and gluteal (subcutaneous). He received 18 infusions of cemiplimab. The patient developed brain metastases and received whole brain RT for new CNS metastasis on day 274 and discontinued treatment due to progression of disease. The end of treatment date was day 289 and the patient died on Day 415 from **"unknown"** cause. ***Reviewer:*** *Given the evidence of progressive disease and the timing of this death, it seems unlikely related to cemiplimab.*

Across the larger safety dataset (Pool 3), 34% of patients died including 29% of patients who died from disease progression, 1.5% of patients who died due to an AE, and 4% of patients had the primary cause of death listed as "other." Patients with CSCC who experienced a fatal AE or death due to "other" causes are summarized in Table25. The following patient summaries reflect the four additional TEAEs that ended in a fatality and three additional fatal events occurring within 90 days of the last dose of cemiplimab for which the cause was listed as "other" in patients with non-CSCC tumors.

(b) (6): 58-year-old man with metastatic HCC enrolled in Study 1423. The patient received 3 doses of cemiplimab and subsequently experienced a Grade 3 **pulmonary embolism** which led to his death nine days later. The TEAE was considered unrelated to cemiplimab treatment by the investigator.

Reviewer: *Narrative reviewed. Agree with assessment.*

(b) (6): 51-year-old man with NSCLC enrolled in Study 1423 who received five doses of cemiplimab. On Day 68, he was diagnosed with a Grade 3 lung Infection treated with antibiotics, methylprednisolone, morphine, and ipratropium bromide. The patient resumed treatment with cemiplimab on day 85 and experienced Grade 3 **pneumonitis** five days later. Despite high dose corticosteroids, the patient had worsening of the pneumonitis and died one week later. This fatal event was considered related to cemiplimab treatment by the investigator.

Reviewer: *Narrative reviewed. Agree with assessment of* ***cemiplimab-related fatal pneumonitis.***

(b) (6): 46-year-old man with refractory, well differentiated extraskeletal myxoid chondrosarcoma enrolled in Study 1423. He received 5 doses of cemiplimab prior to experiencing **fatal encephalomyelitis**. On day 59, the patient was reported to experience Grade 3 **paraneoplastic encephalomyelitis**, worsening to 4 and leading to permanent discontinuation of study drug. Per the autopsy results, the anatomic cause of death was reported as bilateral bronchopneumonia which was related to the primary diagnosis of limbic encephalitis. The report notes that samples obtained on study day 1 and day 57 both showed an anti-HuD Antibody positive titer. The AE was considered related to the study drug by the investigator. The Applicant notes that while a causal

relationship between the administration of cemiplimab and the paraneoplastic encephalomyelitis cannot be ruled out, given the temporal relationship and the known risk for encephalitis with checkpoint blockade treatments, the presence of a preexisting elevated titer of anti-HuD antibody at baseline that did not increase eight weeks following the initiation of treatment with cemiplimab suggests possible confounding from a paraneoplastic encephalitis stemming from the underlying chondrosarcoma.

Reviewer: *Full narrative reviewed. Agree with assessment of causality. Cemiplimab cannot be excluded as a causal factor in this fatal event; however, patient may have had a paraneoplastic encephalitis due to the underlying chondrosarcoma and baseline presence of the anti-HuD antibodies rather than an immune-mediated adverse drug reaction causing the encephalitis. Alternatively, cemiplimab treatment may have lowered the threshold for this patient to develop an anti-HuD encephalitis.*

(b) (6): 69-year-old man with HCC who was enrolled in Study 1423. Past medical history included cirrhosis. The patient received 8 doses of cemiplimab. Response assessment on day 113 demonstrated disease progression due to 2 new hepatic lesions. The patient experienced progressive hepatic insufficiency on day 148 that led to permanent discontinuation of study drug. The patient was treated with steroids, but the event worsened and was fatal on day 156. The patient had been transitioned to hospice care three days prior to dying. The investigator and consulting gastroenterologist considered the **hepatic failure** mainly due to the underlying cirrhosis and HCC with a possible component of immune-mediated toxicity from cemiplimab.

Reviewer: *Full narrative reviewed. Agree with assessment of causality. Cemiplimab cannot be excluded as a causal factor; however, patient had baseline risk factors including progressive HCC and cirrhosis.*

(b) (6): 67-year-old man enrolled in Study 1423 with metastatic NSCLC with bilateral lung involvement. The patient's last dose of cemiplimab was on day 71. Study treatment was discontinued on day 87 due to **disease progression**. The patient died on day 117. The cause of death was entered as Other; the following information was provided on the Death CRF page: "Unknown—patient had known radiologic progression." The interval between last dose of cemiplimab and death was 46 days.

Reviewer*: Death likely secondary to disease progression.*

(b) (6) 70-year-old woman with metastatic breast cancer who was enrolled in Study 1423 who experienced bilateral leg fractures after four months on study. She had bony metastases. Cemiplimab was discontinued after the diagnosis of fractures. She subsequently died, and the cause of death was entered as "Other." The Death CRF page states "Unconfirmed **progression of disease.**" The Applicant notes that the interval between the last dose of cemiplimab and death was 70 days.

Reviewer: *Requested CRF during the review. It appears the patient had progressive metastatic disease and cemiplimab did not cause fractures or the fatal event. The patient seems to have died from progressive disease.*

(b) (6): 56-year-old woman with metastatic ovarian cancer enrolled in Study 1423. She had 3 doses of cemiplimab and died with **progressive disease and a bowel obstruction** approximately 10 days later. The cause of death was listed as "other."

Reviewer*: Requested CRF. Upon query for additional information, the investigator changed the cause of death to "unknown." However, in the End of Treatment visit section, in the free text area for documenting why the patient discontinued treatment, it states: "Per PI subject was taken off for clinical progression in the form of a small bowel obstruction." Disease progression seems the more likely the reason for this patient's fatal AE.*

In the 90-day SUR, four additional patients in Pool 1 died; the reported primary cause of death was progression or recurrence of disease for three of the patients and was "Other" for one patient; however, after the data cut-off for the SUR, the site clarified that this patient (ID: (b) (6)) also died from disease progression. Across the larger safety dataset (Pool 3), one additional patient died from possible fatal pneumonitis.

(b) (6) 57-year-old woman with cervical cancer enrolled in Study 1423 who received 17 doses of cemiplimab and experienced **pneumonitis**. The patient did not improve with steroid or antibiotic treatment and eventually died. The investigator assed the **fatal event as related to cemiplimab**. The Applicant agreed but also posed alternative etiologies including infection, lung tumors and presence of pericardial tumors impacting filling pressure in the heart.

Reviewer*: Agree that cemiplimab treatment is at least possibly related to the development of* ***pneumonitis and subsequent fatality*** *in this patient.*

Serious Adverse Events

SAEs, including Grade 5 events, occurred in 46 patients (28%) in Pool 1. Nonfatal SAEs occurred in 40 patients (25%). SAEs (related or unrelated) that occurred in two or more of the 163 patients receiving cemiplimab included cellulitis (6), sepsis (5), pneumonia (3), pneumonitis (3), urinary tract infection (3), acute kidney injury (2), death (2), fatigue (2), hypercalcemia (2), myocardial infarction (2), pyrexia (2), and skin infection (2).

Thirteen patients (8%) experienced an SAE that was considered related to avelumab. Most cemiplimab-related SAEs were immune-mediated adverse events. The most common related SAEs were pneumonitis which occurred in three patients and hepatitis which occurred in two

patients. All other cemiplimab-related SAEs occurred in one patient each. Table 26 summarizes all cemiplimab-related SAEs (determination made by the investigators) that occurred in patients with advanced CSCC treated with cemiplimab.

Table 26. Treatment-Related SAEs, Pool 1

Preferred Term	N=163	
	All Grades (%)	Grade ≥ 3 (%)
Pneumonitis	3 (2)	2 (1)
Autoimmune hepatitis	2 (1)	2 (1)
Anemia	1 (1)	1 (1)
Autoimmune myocarditis	1 (1)	1 (1)
Death	1 (1)	1 (1)
Duodenal ulcer/SI bleed /Esophagitis	1 (1)	1 (1)
Fatigue	1 (1)	0
Hypophysitis	1 (1)	1 (1)
Meningitis aseptic	1 (1)	1 (1)
Myalgia	1 (1)	1 (1)
Pyrexia	1 (1)	0
Rash maculo-papular	1 (1)	1 (1)

Source: ADAE.xpt

Narratives for the 12 patients who experienced nonfatal treatment-related SAEs in Pool 1 were reviewed. Serious reactions that were immune-mediated are listed here and described in more detail under Section 8.2.5, Immune-mediated Adverse Reactions. In cases where serious nonimmune adverse reactions and imARs occurred in the same patient, all AEs are included in one summary.

(b) (6): 62-year-old man with metastatic CSCC experienced **Grade 3 anemia resulting in study drug interruption.** The patient had received two doses of cemiplimab. The patient had medical history of Klippel-Trenaunay syndrome (a congenital disorder characterized by abnormal vessel development and soft tissue growth), thrombocytosis, and hypertension. The baseline hemoglobin two days prior to initiation of cemiplimab was 10.5 (Grade 1 anemia). On Day 42, the patient had a hemoglobin of 7.0 g/dL. He was hospitalized and received a transfusion. There were no signs of bleeding and no other laboratory assessments aside from the blood counts reported. The patient was discharged on Day 45. The anemia resolved. The investigator assessed the event as related to cemiplimab and that it was immune mediated because the tumor responded to cemiplimab leading to necrosis and bleeding. There was no

obvious bleeding observed at the tumor site. The Applicant agreed that cemiplimab administration could not be ruled out in the causality analysis but considered tumor bleeding because of response (necrosis) to be the cause and not that it was an imAR. Additionally, it did not appear that there was a work up for, or a disease course consistent with, an immune-related hemolytic anemia.

***Reviewer**: Agree with Applicant's causality assessment.*

(b) (6): 90-year-old man with metastatic CSCC who experienced **Grade 3 duodenal ulcer, duodenal hemorrhage, and esophagitis**. The patient had electively discontinued cemiplimab three days prior to the event because he was getting weaker. The patient was admitted with symptoms consistent with a gastrointestinal bleed and received pantoprazole and transfusion. The location of the bleeding was identified as a duodenal ulcer. The patient had been taking aspirin prior to the event. While admitted, the patient also developed a left upper extremity deep vein thrombosis, but anticoagulants were deferred due to the concurrent GI bleeding. The patient was discharged 5 days after being admitted for the GI bleed. He died approximately three weeks later due to "failure to thrive" and the CRF stated that the "underlying cancer was a contributing factor."

***Reviewer**: While cemiplimab cannot be ruled out as a causal factor in the GI bleeding event, there are multiple confounders including concomitant aspirin use. The description of this event is not consistent with a colitis or an immune-mediated adverse reaction.*

(b) (6): 88-year-old man experienced **immune-mediated Grade 3 increased alanine transaminase (ALT) and aspartate transaminase (AST).**

(b) (6): 80-year-old man experienced the following AEs: **myalgia, UTI, fatigue, and serious failure to thrive (FTT) resulting in drug interruption. The patient also experienced immune-mediated hypothyroidism and Sjogren's Syndrome.**

(b) (6) 69-year-old man with metastatic CSCC with lung metastases experienced **immune-mediated Grade 3 pneumonitis resulting in permanent discontinuation.**

(b) (6): 70-year-old man experienced an **immune-mediated Grade 3 maculopapular rash resulting in drug interruption**.

(b) (6): 77-year-old man experienced **immune-mediated Grade 3 hypophysitis, Grade 4 myocardial infarction and Grade 1 acute kidney injury.**

(b) (6) 67-year-old man with me**tastatic CSCC with lung metastases experienced immune-mediated Grade 3 pneumonitis resulting in permanent discontinuation of cemiplimab and Grade 4 cerebral infarction.**

(b) (6): 83-year-old man experienced **immune-mediated Grade 2 pneumonitis resulting in study drug interruption and hospitalization**.

(b) (6): 84-year-old woman experienced **Grade 3 autoimmune myocarditis leading to study drug discontinuation.**

(b) (6): 79-year-old man with metastatic CSCC experienced **Grade 3 aseptic meningitis leading to permanent discontinuation of cemiplimab.**

(b) (6): 80-year-old woman experienced **fever and Grade 3 autoimmune hepatitis leading to study drug interruption.**

Narratives submitted with the 90-Day safety update included three additional patients in Pool 1 who experienced SAEs of pneumonitis and one patient who experienced a colitis that were considered related to cemiplimab treatment. One event was a Grade 5 pneumonitis described above under Deaths (ID: (b) (6). The other narratives were reviewed and there were no new safety signals detected.

Discontinuations Due to Adverse Effects

Eight patients (5%) in Pool 1 discontinued treatment due to adverse events. All events were deemed related to cemiplimab treatment. Most events were imARs including pneumonitis (n=2), myocarditis, hepatitis, aseptic meningitis, and muscle weakness. Two other patients discontinued cemiplimab due to a nonserious Grade 2 cough and a nonserious Grade 2 complex regional pain syndrome. SAEs leading to discontinuation in patients with CSCC are described above under Serious Adverse Events.

Table 27. AEs Leading to Discontinuation of Cemiplimab, Pool 1

Preferred Term	Toxicity Grade	SAE
Pneumonitis	3	Y
Pneumonitis	3	Y
Autoimmune myocarditis	3	Y
Aseptic meningitis/confusion/neck pain	3	Y
Hepatitis with liver enzyme elevations	3	N
Muscular weakness	2	N
Cough	2	N
Complex regional pain syndrome	2	N

Source: ADAE.xpt

Across the larger Pool 3 population, the discontinuation rate was similar at 6% (n=31); most events requiring discontinuation of cemiplimab were imARs.

The 90-Day SUR described three additional patients from Pool 1 who permanently discontinued cemiplimab treatment for the following AEs: non-serious Grade 3 psoriasis, serious Grade 2 pneumonitis, both related to cemiplimab, and one event of a Grade 3 psoas abscess that was serious but unrelated to study drug.

Significant Adverse Events

Dose Interruptions

Forty-five patients (28%) in Pool 1 experienced AEs that resulted in interruption of cemiplimab dosing. The most common AEs leading to withholding drug were infusion reactions (4%) and pneumonia, cellulitis, diarrhea, and fatigue (2.5% each). The rate of cemiplimab interruption in Pool 3 was similar (30%) and the most common AEs leading to withholding were similar (IRRs, pneumonia, AST elevation, and fatigue).

The 90-Day SUR identified an additional 11 patients in Pool 1 who had treatment interruptions due to AEs. The only AE that resulted in cemiplimab interruption in more than one patient during the additional three-month interval was pneumonitis (n=2).

Grade 3-4 AEs

Thirty-seven percent (n=60) of patients in Pool 1 experienced at least one Grade 3 or 4 AE at the data cutoff for the original BLA submission. Twelve percent (n=19) had Grade 3 AEs that were related to cemiplimab treatment. These included liver enzyme elevations, hepatitis, pneumonitis, rash, adrenal insufficiency, anemia, diarrhea/colitis, constipation, myocarditis, bleeding duodenal ulcer, meningitis, polyarthritis, myalgia, hypophysitis, and asthenia. There were no Grade 4 AEs related to cemiplimab. Table28 lists treatment emergent Grade 3 and 4 AEs that occurred in more than one patient with advanced CSCC during treatment with cemiplimab.

Table 28. Grade 3-4 Adverse Events, Pool 1

Preferred Term	N=163 n (%)
Cellulitis	6 (4)
Hypertension	5 (3)
Sepsis	5 (3)
Urinary tract infection	4 (2)
Hypercalcemia	4 (2)
Musculoskeletal pain	4 (2)
Fatigue	3 (2)
Pneumonia	3 (2)
Hyponatremia	3 (2)

Preferred Term	N=163 n (%)
Cellulitis	6 (4)
Hypertension	5 (3)
Sepsis	5 (3)
Urinary tract infection	4 (2)
Hypercalcemia	4 (2)
Musculoskeletal pain	4 (2)
Skin infection	3 (2)
Anemia	2 (1)
Aspartate aminotransferase increased	2 (1)
Atrial fibrillation	2 (1)
Autoimmune hepatitis	2 (1)
Dehydration	2 (1)
Delirium	2 (1)
Dysphagia	2 (1)
Failure to thrive	2 (1)
Hypokalemia	2 (1)
Myocardial infarction	2 (1)
Pleural effusion	2 (1)
Pneumonitis	2 (1)
Rash	2 (1)
Syncope	2 (1)

Source: ADAE.xpt,
Musculoskeletal pain includes terms back pain, myalgia, neck pain, pain in extremity.
Fatigue includes terms fatigue and asthenia.
Rash includes terms rash maculopapular, rash, dermatitis, rash generalized, dermatitis bullous, drug eruption, erythema, rash erythematous, rash macular, rash pruritic, and skin reaction

The 90-day SUR did not reveal any new or amplified safety signals regarding severity of AEs with longer term dosing of cemiplimab.

Treatment Emergent Adverse Events and Adverse Reactions

The primary safety database for Pools 1, 2, and 3 were analyzed at each level of the MedDRA hierarchy for common AEs. The tables in this section summarize the incidence of TEAEs, defined as AEs that occurred from the time of the first dose of cemiplimab up to 30 days (study 1423) or 105 days (study 1540) after the last dose of cemiplimab or data cutoff date if that date was earlier. Almost all patients (98%) exposed to cemiplimab (Pool 3) had at least one AE during treatment.

At the system organ class (SOC) level, the most frequently affected systems (> 20% incidence) were gastrointestinal disorders, general disorders and administration site conditions, skin and subcutaneous tissue disorders, infections and infestations, respiratory, thoracic and mediastinal disorders, metabolism and nutrition disorders, musculoskeletal and connective tissue disorders, nervous system disorders, and investigations. The incidences of AEs at the SOC level were mostly similar across Pools 1, 2 and 3. Table 29 summarizes all AEs by SOC for patients with advanced CSCC exposed to cemiplimab.

Table 29: Adverse Events by SOC, Pool 1

System Organ Class	N=163 N (%)
Gastrointestinal disorders	76 (47)
General disorders and administration site conditions	69 (42)
Skin and subcutaneous tissue disorders	69 (42)
Infections and infestations	67 (41)
Respiratory, thoracic and mediastinal disorders	54 (33)
Metabolism and nutrition disorders	53 (33)
Musculoskeletal and connective tissue disorders	46 (28)
Nervous system disorders	46 (28)
Investigations	38 (23)
Injury, poisoning and procedural complications	31 (19)
Eye disorders	25 (15)
Vascular disorders	25 (15)
Blood and lymphatic system disorders	21 (13)
Psychiatric disorders	19 (12)
Endocrine disorders	18 (11)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	15 (9)
Renal and urinary disorders	15 (9)

System Organ Class	N=163 N (%)
Ear and labyrinth disorders	13 (8)
Cardiac disorders	10 (6)
Reproductive system and breast disorders	4 (2)
Hepatobiliary disorders	3 (2)

Source: ADAE.xpt

The Applicant also provided subgroup analyses of the AE data for all patients receiving single agent cemiplimab (Pool 2) according to diagnosis: CSCC patients (n=163) and non-CSCC patients (n=77). SOC Categories in which there was at least a 5% increase in the frequency of AEs in patients with CSCC compared to patients with other types of cancer included skin and subcutaneous disorders (42% vs 29%), cardiac disorders (6% vs. 0), infections and infestations (41% vs. 36%), and investigations (23% vs. 18%). The differences in the safety profiles for certain AE categories are likely related to specific risk factors in patients with CSCC as compared to other cancers. Patients with CSCC had higher frequencies of skin infections, cellulitis, rash, dry skin and pruritus at the PT level. This is likely related to the underlying skin cancer and prior treatments to the skin (radiation, surgery) and is less likely the result of a difference in drug effect in patients with CSCC. Regarding the increased cardiac disorders in patients with CSCC, the Applicant notes that patients with CSCC were more likely to have baseline risk factors for cardiovascular disease at enrollment. At the PT level, three of the 10 patients with CSCC who experienced cardiac TEAEs had atrial fibrillation, two had myocardial infarction and the other cardiac AEs occurred in one patient each. One patient experienced autoimmune myocarditis likely related to cemiplimab treatment.

At the PT level, AEs that occurred in 10% or more of patients with CSCC treated with cemiplimab included fatigue, rash, diarrhea, nausea, pruritus, cough, constipation, and decreased appetite. Grade 3 and 4 AEs were infrequent. Grade 3-4 AEs that occurred in at least 2% of patients included cellulitis, hypertension, sepsis, urinary tract infection, hypercalcemia, pneumonia, hyponatremia, and skin infection. Table 30 summarizes common TEAEs in Pool 1 by preferred term.

Table 30. TEAEs in at least 5% of patients, Pool 1

Preferred Term	Any Grade N=163 n (%)	Grade ≥ 3 N= 163 N (%)
Fatigue	48 (29)	3 (2)
Rash	40 (25)	2(1)
Diarrhea	36 (22)	1 (1)

Preferred Term	Any Grade N=163 n (%)	Grade ≥ 3 N= 163 N (%)
Nausea	31 (19)	0
Pruritus	25 (15)	0
Cough	21 (13)	0
Musculoskeletal pain	23 (14)	4 (2)
Constipation	20 (12)	1 (1)
Decreased appetite	17 (10)	0
Headache	14 (9)	0
Hypothyroidism	14 (9)	0
Vomiting	14 (9)	1 (1)
Anemia	13 (8)	2 (1)
Arthralgia	13 (8)	2 (1)
Dry skin	13 (8)	0
Urinary tract infection	11 (7)	4 (2)
Alanine aminotransferase increased	10 (6)	1 (1)
Dizziness	10 (6)	1 (1)
Dry mouth	10 (6)	0
Hypertension	10 (6)	5 (3)
Hypokalemia	10 (6)	2 (1)
Pyrexia	10 (6)	0
Peripheral edema	10 (6)	0
Fall	9 (6)	0
Abdominal pain	9 (5)	1 (1)
Cellulitis	8 (5)	6 (4)
Dyspnea	8 (5)	1 (1)
Infusion related reaction	8 (5)	0
Skin infection	8 (5)	3 (2)

Source: ADAE.xpt
Disease progression events are not included in the table.
Fatigue includes terms fatigue and asthenia.
Rash includes terms rash maculopapular, rash, dermatitis, rash generalized, dermatitis bullous, drug eruption, erythema, rash erythematous, rash macular, rash pruritic, and skin reaction
Diarrhea includes terms diarrhea and colitis
Pruritus includes terms pruritus and pruritus allergic
Musculoskeletal pain includes terms back pain, myalgia, neck pain, pain in extremity
Peripheral edema includes: peripheral edema and peripheral swelling.

Abdominal pain includes terms abdominal pain and abdominal pain upper.

The Applicant's analysis of longer term safety data submitted with the 90-Day safety update did not provide evidence of new safety signals, and the frequency and severity of common AEs were similar in the cumulative analysis when compared to the results submitted with the original BLA.

Laboratory Findings

In Studies 1423 and 1540, laboratory tests to assess hematology parameters, liver function (alkaline phosphatase, ALT, AST, bilirubin), chemistries (sodium, potassium, chloride, BUN, creatinine, glucose), and minerals (magnesium, phosphorus, calcium) were measured at least every two weeks for all patients receiving cemiplimab every two weeks. For expansion cohorts of Study 1423 evaluating various Q3W dosing regimens and for Group 3 in Study 1540 receiving the intended 350 mg flat dose Q3W regimen, the same laboratory evaluations were performed every three weeks. Coagulation assessments were generally performed once per cycle in both studies. Table 31 summarizes the common laboratory abnormalities for patients with CSCC treated with cemiplimab in either study and at any dose. Grade 3 or 4 chemistry abnormalities were uncommon and those that occurred in 2% or more of patients included elevations in AST, hyponatremia, hypophosphatemia, lymphopenia, anemia, and prolonged INR.

Forty-two percent of patients in Pool 1 experienced anemia. However, anemia was considered an AE by investigators in 13 (8%) patients and was deemed related to cemiplimab in only two patients (1%), one of which was reported as a SAE requiring interruption of treatment. All anemia AEs were Grade 1-2 except for two patients who experienced Grade 3 anemia. Additionally, the inclusion criteria for both studies allowed patients with preexisting anemia to participate in the trial (hemoglobin level > 9 g/dl), and 58% of Pool 3 patients had Grade 1 or 2 anemia at study entry. Baseline low-grade anemia and lymphopenia could be manifestations of prior cytotoxic chemotherapy administered for advanced CSCC and the relatively older study population.

Treatment emergent elevations in creatinine were also common. Seventy-five percent of patients experienced creatinine levels higher than baseline during treatment with cemiplimab. The Applicant therefore re-derived CTCAE grades for creatinine in a separate database using CTCAE version 5.0 which defines Grade 1 elevation as a creatinine > 1.5 times the upper limit of normal (ULN). The prior CTCAE version 4.03 defined Grade 1 creatinine elevation as any elevation above baseline or the ULN for the laboratory. Using CTCAE version 5, 24% of patients in Pool 1 experienced increased creatinine including one patient with Grade 3 elevation. Investigators reported increased creatinine as an AE in 4% of patients in Pool 1, and there were no Grade 3-4 increased creatinine AEs. Table 31 summarizes common treatment emergent laboratory abnormalities during cemiplimab treatment for patients with CSCC.

Table 31. Laboratory Abnormalities Occurring in ≥10% of Patients, Pool 1

Lab Abnormality	Any Grade N=163 n/N (%)	Grade 3-4 N=163 n/N (%)
Chemistry		
Creatinine increased*	37/157 (24)	1/157 (<1)
Hypoalbuminemia	52/157 (33)	2/157 (1)
Hyponatremia	38/157 (24)	5/157 (3)
Hypophosphatemia	32/156 (21)	6/156 (4)
Hypocalcemia (Uncorrected Calcium)	31/157 (20)	0/157
Aspartate Aminotransferase increased	25/156 (16)	5/156 (3)
Hypokalemia	24/157 (15)	1/157 (<1)
Hyperkalemia	23/157 (15)	1/157 (<1)
Alkaline Phosphatase increased	22/157 (14)	1/157 (<1)
Hypomagnesemia	21/157 (13)	0/157
Alanine aminotransferase increased	20/157 (13)	1/157 (<1)
Hypercalcemia	15/157 (10)	2/157 (1)
Hematology		
Anemia	66/157 (42)	3/157 (2)
Lymphocyte count decreased	65/157 (41)	11/157 (7)
Leukocyte count decreased	22/157 (14)	0/157
Coagulation		
Activated Partial Thromboplastin Time prolonged	16/116 (14)	0/116

Lab Abnormality	Any Grade N=163 n/N (%)	Grade 3-4 N=163 n/N (%)
Prothrombin Intl. Normalized Ratio increased	13/106 (12)	2/106 (2)

Source dataset: adlb.xpt
Treatment-emergent consists of new onset abnormality or worsening of baseline abnormality.
Percentages based on number of patients with at least one post-baseline value available for the parameter.
Creatinine increased is graded per CTCAE version 5.0. Other abnormalities are graded per CTCAE version 4.0.

Laboratory abnormalities were similar between patients in Pools 1 and 2. There were some differences noted in lab alterations between patients treated with single agent cemiplimab (Pools 1 and 2) and patients in Pool 3 which also included patients treated with cemiplimab in combination with cytotoxic chemotherapy and/or radiation. In general, there were no clinically relevant trends that would impact the safety profile of cemiplimab in patients with CSCC and most lab abnormality incidence rates were greater in Pool 3 as compared to Pools 1 and 2. Table 32 summarizes lab abnormalities that occurred in at least 5% of patients in Pool 1, sorted by highest incidence in Pool 1, and provides a side by side comparison with the frequencies observed in Pools 2 and 3.

Table 32. Laboratory Abnormalities, Pools 1, 2 and 3

Laboratory Abnormality	Pool 1 N=163 n/N (%)		Pool 2 N=240 n/N (%)		Pool 3 N=534 n/N (%)	
	All Grades	Grade 3-4	All Grades	Grade 3-4	All Grades	Grade 3-4
Increased creatinine	117/157 (75)	1/157 (1)	177/233 (76)	5/233 (2)	403/526 (77)	6/526 (1)
Anemia	66/157 (42)	3/157 (2)	113/234 (48)	8/234 (3)	285/527 (54)	30/527 (6)
Lymphopenia	65/157 (41)	11/157 (7)	110/233 (47)	29/233 (12)	295/524 (56)	98/524 (19)
Hypoalbuminemia	52/157 (33)	2/157 (1)	88/233 (38)	3/233 (1)	233/526 (44)	8/526 (2)
Hyponatremia	38/157 (24)	5/157 (3)	61/233 (26)	9/233 (4)	169/526 (32)	39/526 (7)
Hypophosphatemia	32/156 (21)	6/156 (4)	44/231 (19)	8/231 (4)	122/523 (23)	30/523 (6)
Hypocalcemia	31/157 (20)	0/157	54/233 (23)	0/233	177/526 (34)	2/526 (< 1)
Increased AST	25/156 (16)	5/156 (3)	42/232 (18)	7/232 (3)	144/525 (27)	26/525 (5)

Laboratory Abnormality	Pool 1 N=163 n/N (%)		Pool 2 N=240 n/N (%)		Pool 3 N=534 n/N (%)	
	All Grades	Grade 3-4	All Grades	Grade 3-4	All Grades	Grade 3-4
Hypokalemia	24/157 (15)	1/157 (1)	44/233 (19)	2/233 (1)	108/526 (21)	8/526 (2)
Hyperkalemia	23/157 (15)	1/157 (1)	29/233 (12)	2/233 (1)	57/526 (11)	4/526 (1)
Increased alkaline phosphatase	22/157 (14)	1/157 (1)	38/233 (16)	1/233 (<1)	139/526 (26)	15/526 (3)
Leukopenia	22/157 (14)	0/157	46/234 (20)	1/234 (< 1)	136/527 (26)	15/527 (3)
Prolonged aPTT	16/116 (14)	0/116	33/173 (19)	2/173 (1)	81/372 (22)	5/372 (1)
Increased ALT	20/157 (13)	1/157 (1)	35/233 (15)	1/233 (<1)	114/526 (22)	16/526 (3)
Hypomagnesemia	21/157 (13)	0/157	35/233 (15)	0/233	93/526 (18)	2/526 (< 1)
Increased INR	13/106 (12)	2/106 (2)	22/166 (13)	3/166 (2)	52/375 (14)	6/375 (2)
Hypercalcemia	15/157 (10)	2/157 (1)	18/233 (8)	2/233 (1)	42/526 (8)	6/526 (1)
Thrombocytopenia	14/157 (9)	0/157	26/234 (11)	0/234	99/527 (19)	2/527 (< 1)
Hypoglycemia	13/156 (8)	0/156	25/232 (11)	0/232	56/525 (11)	0/525
Neutropenia	9/157 (6)	0/157	23/233 (10)	0/233	77/523 (15)	14/523 (3)
Increased bilirubin	8/157 (5)	0/157	17/233 (7)	4/233 (2)	60/526 (11)	15/526 (3)

Source dataset: adlb.xpt
Table created from analysis performed by Jinzhong Liu, FDA statistician

Vital Signs

Vital signs were assessed and recorded at baseline and regularly pre- and post-cemiplimab infusions every two or three weeks depending on the dose regimen. There were no clinically significant changes in vital signs in patients in Pool 1 during cemiplimab infusions. Observations made from evaluating the vital sign tables for Study 1540:

- Fever was not common during cemiplimab infusions. One patient experienced a temperature of 38.0^{o} C. Most patients had less than 1^{0}C change from baseline.
- Most patients remained within 10 beats per minute when evaluating the median change from baseline heart rate per infusion visit.

- The median change from baseline for diastolic and systolic blood pressures per infusion visit was usually less than 10.
- The highest respiratory rate reported on the day of an infusion was 28 breaths per minute. The median change from baseline in respiratory rate was usually less than 2 breaths per minute.

Electrocardiograms (ECGs)

A 12-lead ECG was performed at screening and 30 minutes after the end of the cemiplimab infusion at day 1 visits during cycles 1 and 3 in Studies 1423 and 1540. According to the CSR for 1423, no clinically relevant changes from baseline were noted for ECG parameters in patients treated with cemiplimab, including mean ventricular rate, PR duration, QRS duration, QT duration, and RR duration during treatment with cemiplimab. In Study 1540, there was one ECG abnormality AE reported (First degree AV Block) based on ECG changes that developed during treatment. These included: ECG ventricular rate (52 beats/minute), PR duration (224 msec), QRS duration (106 msec), QT duration (466 msec; baseline value was 464 msec), and RR duration (1153 msec). The repeat ECG taken in the next minute did not continue to show this level of abnormality and the patient was reported to go on to receive another 10+ months of cemiplimab without additional cardiac events.

QT

A thorough QT study was not requested or submitted with the BLA as there is low potential for QT prolongation for this monoclonal antibody product. Exposure-QTc analyses were not conducted. From the ECG database submitted in the integrated safety analysis with pooled data from 519 patients exposed to cemiplimab and who had a baseline and at least one post baseline QTc assessment 9% of patients experienced a >450 msec, 4% had at least one > 480 msec, and 2% experienced at least one QTc of > 500 msec. Three percent of patients had a QTc increase from baseline of more than 60 msec. The ISS AE database for Pool 3 included one preferred term “electrocardiogram abnormal.” This was a Grade 1 AE and did not lead to any changes in cemiplimab dosing. There were no AEs with the preferred term of “ECG QT prolonged” or “torsades de pointes.”

Reviewer: *Most QT changes from baseline identified in the dataset were not reported as AEs and did not impact treatment. Without an internal control, it is difficult to assess attribution, and QT prolongation would generally not be expected based on the mechanism of action of cemiplimab.*

Immunogenicity

The blood samples for screening for anti-drug antibodies (ADA) were collected pre-infusion on day 1 of cycles 1, 2, and 4 in Study 1423 and day 1 of cycles 1, 3, 5, 7, and 11 in Study 1540.

ADA data was available for 398 of 534 patients who received cemiplimab. The incidence of cemiplimab treatment-emergent ADA was 1.3% using an electrochemiluminescent (ECL) bridging immunoassay. No patient developed neutralizing antibodies.

Reviewer*: The development of treatment-emergent ADA against cemiplimab did not appear to alter the pharmacokinetic profile or risk of imARs or IRRs with cemiplimab. See Clinical Pharmacology Review for details.*

8.2.5. Analysis of Submission-Specific Safety Issues

Adverse events of special interest (AESI) for cemiplimab are imARs and IRRs.

Immune-mediated adverse reactions (imARs)

The Applicant used the following case definition for the analysis of imARs that occurred in patients treated with cemiplimab (adapted from Summary of Clinical Safety, page 48).

- Level 1: A MedDRA PT list was established based on known irAEs in the class of PD-1/ PD-L1 inhibitors.

- Level 2: Investigators in Studies 1423 and 1540 were provided with lists of PTs commonly associated with immune reactions and were informed that the lists were not exhaustive. They were instructed to evaluate all AEs of unknown etiology associated with cemiplimab exposure to determine possible immune etiology and to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes prior to labeling an AE as an irAE. Guidelines were provided on the use of immunosuppressant drugs for the treatment of suspected irAEs. Apart from ruling out other possible etiologies, response to corticosteroid was used to support the evaluation that an event was a possible irAE and to support ruling out other etiologies. Temporal relationship was also considered before making a final decision on assessing an AE as irAE. If an investigator assessed an AE PT within the list of possible irAEs as not related to cemiplimab, the reason for this assessment was documented (confirmed alternative etiology).

- Level 3: Additional PTs that were deemed immune-related by an investigator but were not on the Level 1 PT list were reviewed by a team of four physicians to assess whether based on the case review, the PT should be added to a master list of immune-related PTs. Additionally, some of the PTs were expanded by including relevant PTs within the same MedDRA high-level term or Standardized MedDRA Queries. Some PTs for similar pathogenic events were combined into composite PTs to ensure that the true frequencies of such AEs were reported by combining the similar event terms.

TEAEs identified using the above 3-level approach were considered *potential* irAEs. From the

potential irAEs, the Applicant created a subsequent case definition for *identified* irAEs, defined as potential irAEs requiring treatment with corticosteroid or events that were immune-related endocrinopathies.

***Reviewer**: The case definition for imARs and the MedDRA PT list and composite PT list for immune-related AEs was reviewed by FDA and agreed upon prior to submission of the BLA. The Applicant's methods for evaluating risk for imARs with cemiplimab treatment appear thorough and relevant. For pneumonitis and endocrinopathies, almost all "potential" irAEs were also "identified" irAEs as would be expected given the unlikeliness of alternative etiologies for these events during treatment with a PD-1 antibody. For categories such as immune-mediated colitis and hepatitis, the incidence of "potential" irAEs was higher because of the inclusion of general AEs such as diarrhea, hepatitis, and elevations in liver enzymes that could have alternative nonimmune etiologies and may or may not have been treated with corticosteroids. Therefore, the reviewer focused on analysis of the "identified" irAEs in each imAR category. Additionally, the incidences and severities of identified imARs were used to inform product labelling.*

The review of imARs associated with cemiplimab focused on Pool 3 to best characterize relatively common and rare imARs across the larger safety population. These results were used to describe imARs in the product label. Although a subgroup of patients in Pool 3 were receiving concomitant chemotherapy and/or radiation, it is unlikely that these treatments would have substantial impact on the occurrence of cemiplimab-related immune-mediated reactions based on mechanism of action. Further, the overall frequency of imARs and incidences of relevant categories of imARs are similar in Pools 1, 2 and 3 as shown in Table 33.

Table 33. Overview of imARs, Pools 1, 2 and 3

Treatment-Emergent "Identified" imARs	Pool 1 N=163 n (%)	Pool 2 N=240 n (%)	Pool 3 N= 534 n (%)
Any grade imAR	35 (22)	49 (20)	92 (17)
Grade ≥ 3	13 (8)	18 (8)	42 (8)
Serious imAR	8 (5)	12 (5)	29 (5)
imARs resulting in interruption/delay	13 (8)	21 (9)	36 (7)
imARs resulting in discontinuation	6 (4)	8 (3)	20 (4)
imARs resulting in death	0	1 (0.4)	3 (0.6)

Source: ADIRAE.xpt

The most common imARs occurring in at least 2% of patients in Pool 3 were hypothyroidism pneumonitis, hepatitis, and rash. The most common ≥ Grade 3 imARs were hepatitis, rash and pneumonitis. Serious imARs that occurred in more than two patients were pneumonitis and

hepatitis. The median time to onset of any imAR was 2.4 months (range: 1 day to 13.7 months) and the median duration was 2.6 months (range: 1 day to 15.4 months). Of the 92 patients who experienced any imAR, 65% received corticosteroids for the reaction, and 52% received high dose corticosteroids (i.e., $\geq$ 40 mg prednisone equivalent).

Table 34, copied from the SCS submitted with the original BLA, summarizes the types, incidences and severity of imARs during cemiplimab treatment in the three safety pools. FDA verified the results in this table.

Table 34. Identified ImARs by Composite/Preferred Term and Grade, Pools 1, 2 and 3

	Pool 1 - All CSCC Patients (N=163)		Pool 2 - All Monotherapy Patients (Excluding HCC) (N=240)		Pool 3 - All Patients (N=534)	
Composite*/Preferred Term, n (%)	**All Grades**	**Grades 3/4/5**	**All Grades**	**Grades 3/4/5**	**All Grades**	**Grades 3/4/5**
Total number of treatment-emergent identified irAEs	49	16	66	21	126	49
Number of patients with any treatment-emergent sponsor-identified irAE, n (%)	35 (21.5%)	13 (8.0%)	49 (20.4%)	18 (7.5%)	92 (17.2%)	42 (7.9%)
Hypothyroidism*	12 (7.4%)	0	17 (7.1%)	0	32 (6.0%)	1 (0.2%)
Immune-related Pneumonitis*	5 (3.1%)	2 (1.2%)	9 (3.8%)	3 (1.3%)	13 (2.4%)	5 (0.9%)
Immune-related hepatitis*	3 (1.8%)	3 (1.8%)	3 (1.3%)	3 (1.3%)	11 (2.1%)	11 (2.1%)
Immune-related skin adverse reaction*	1 (0.6%)	1 (0.6%)	1 (0.4%)	1 (0.4%)	9 (1.7%)	6 (1.1%)
Hyperthyroidism*	3 (1.8%)	0	3 (1.3%)	0	8 (1.5%)	1 (0.2%)
Arthralgia	2 (1.2%)	0	4 (1.7%)	0	6 (1.1%)	0
Immune-related colitis*	4 (2.5%)	1 (0.6%)	4 (1.7%)	1 (0.4%)	5 (0.9%)	2 (0.4%)
Type 1 diabetes mellitus*	0	0	1 (0.4%)	1 (0.4%)	4 (0.7%)	4 (0.7%)
Immune-related nephritis*	1 (0.6%)	0	2 (0.8%)	1 (0.4%)	3 (0.6%)	2 (0.4%)
Adrenal insufficiency*	1 (0.6%)	1 (0.6%)	1 (0.4%)	1 (0.4%)	2 (0.4%)	1 (0.2%)
Meningitis*	1 (0.6%)	1 (0.6%)	1 (0.4%)	1 (0.4%)	2 (0.4%)	2 (0.4%)
Myalgia*	1 (0.6%)	1 (0.6%)	2 (0.8%)	2 (0.8%)	2 (0.4%)	2 (0.4%)
Stomatitis	0	0	0	0	2 (0.4%)	0
Arthritis*	1 (0.6%)	1 (0.6%)	1 (0.4%)	1 (0.4%)	1 (0.2%)	1 (0.2%)
Autoimmune myocarditis*	1 (0.6%)	1 (0.6%)	1 (0.4%)	1 (0.4%)	1 (0.2%)	1 (0.2%)
Chronic inflammatory demyelinating polyradiculoneuropathy	1 (0.6%)	0	1 (0.4%)	0	1 (0.2%)	0
Encephalitis*	0	0	0	0	1 (0.2%)	1 (0.2%)
Hypophysitis	1 (0.6%)	1 (0.6%)	1 (0.4%)	1 (0.4%)	1 (0.2%)	1 (0.2%)
Immune thrombocytopenic purpura	0	0	1 (0.4%)	0	1 (0.2%)	0
Muscular weakness	1 (0.6%)	0	1 (0.4%)	0	1 (0.2%)	0
Neuropathy peripheral*	1 (0.6%)	0	1 (0.4%)	0	1 (0.2%)	0
Paraneoplastic encephalomyelitis	0	0	1 (0.4%)	1 (0.4%)	1 (0.2%)	1 (0.2%)
Pruritus*	0	0	0	0	1 (0.2%)	1 (0.2%)
Sjogren's syndrome	1 (0.6%)	0	1 (0.4%)	0	1 (0.2%)	0
Vasculitis	0	0	0	0	1 (0.2%)	0

Source: SCS, pg. 56. AEs coded using MedDRA Version 20.0. NCI grades coded using CTCAE Version 4.03. * Each composite term includes multiple MedDRA PTs based on predefined list. A patient is counted only once for multiple occurrences within a composite term/PT.

Table 35 summarizes the imARs by PT and severity that occurred in patients in Pool 3.

Table 35. Identified ImARs by Composite/Preferred Term and Grade, Pool 3

Preferred Term	Any Grade N=534 n (%)	Grade ≥ 3 N= 534 n (%)
Hypothyroidism	32 (6)	1 (0.2)
Pneumonitis	13 (2)	5 (1)
Hepatitis	11 (2)	11 (2)
Dermatologic adverse reaction	9 (2)	6 (1)
Hyperthyroidism	8 (1)	1 (0.2)
Arthralgia	6 (1)	0
Colitis	5 (1)	2 (0.4)
Diabetes mellitus	4 (1)	4 (1)
Nephritis	3 (1)	2 (0.4)
Adrenal insufficiency	2 (0.4)	1 (0.2)
Meningitis	2 (0.4)	2 (0.4)
Myalgia	2 (0.4)	2 (0.4)
Stomatitis	2 (0.4)	0
Arthritis	1 (0.2)	1 (0.2)
Autoimmune myocarditis	1 (0.2)	1 (0.2)
Paraneoplastic encephalomyelitis	1 (0.2)	1 (0.2)
Encephalitis	1 (0.2)	1 (0.2)
Hypophysitis	1 (0.2)	1 (0.2)
Pemphigoid	1 (0.2)	1 (0.2)
Pruritus	1 (0.2)	1 (0.2)
Immune thrombocytopenic purpura	1 (0.2)	0
Muscular weakness	1 (0.2)	0
Neuritis	1 (0.2)	0
Chronic inflammatory demyelinating polyradiculoneuropathy	1 (0.2)	0
Sjogren's syndrome	1 (0.2)	0
Vasculitis	1 (0.2)	0

Source: ADIRAE.xpt

Table 36 summarizes the types and frequencies of serious imARs occurring in patients treated with cemiplimab.

Table 36. Serious imARs by PT and Grade, Pool 3

Preferred Term	Any Grade N=534 n (%)	Grade ≥ 3 N= 534 n (%)
Pneumonitis	8 (1)	5 (1)
Autoimmune hepatitis	3 (1)	3 (1)
Diabetes mellitus	2 (<1)	2 (<1)
Diabetic ketoacidosis	2 (<1)	2 (<1)
Acute kidney injury	1 (<1)	1 (<1)
Alanine aminotransferase increased	1 (<1)	1 (<1)
Aspartate aminotransferase increased	1 (<1)	1 (<1)
Autoimmune myocarditis	1 (<1)	1 (<1)
Colitis	1 (<1)	1 (<1)
Hepatic failure	1 (<1)	1 (<1)
Hyperthyroidism	1 (<1)	1 (<1)
Hypophysitis	1 (<1)	1 (<1)
Hypothyroidism	1 (<1)	1 (<1)
Meningitis	1 (<1)	1 (<1)
Meningitis aseptic	1 (<1)	1 (<1)
Myalgia	1 (<1)	1 (<1)
Noninfective encephalitis	1 (<1)	1 (<1)
Paraneoplastic encephalomyelitis	1 (<1)	1 (<1)
Pemphigoid	1 (<1)	1 (<1)
Transaminases increased	1 (<1)	1 (<1)

Source: ADIRAE.xpt

Summary narratives describing serious imARs occurring in patients with CSCC (n=8) receiving cemiplimab are included under the relevant imAR categories below.

Review of imARs by Subtypes

ImARs are generally categorized into subtypes based on the safety profile of cemiplimab and other antibodies targeting the PD-L1 protein and PD-1 receptor protein. The results described under each category of immune-mediated events are based on analyses of Pool 3 (n=534) to best characterize relatively common and rare imARs by disease category across the larger safety population. Information that was considered clinically relevant when analyzing imARs included the frequency and severity of events, events that led to discontinuation of cemiplimab, the requirement for treatment with high dose corticosteroids or other immunosuppressants, the rate of resolution for specific events and whether events recurred

after resuming cemiplimab treatment. Time to onset and duration of imARs was considered relevant; however, due to insufficient numbers of patients to have reliable medians, and because the data-cutoff date affected reliability of ranges (e.g., many of the events were ongoing), (b) (4)

Immune-mediated pneumonitis

Immune-related pneumonitis occurred in 2.4% (13/534) of patients receiving cemiplimab, including one Grade 5 (0.2%), and four Grade 3 (0.7%) events. Pneumonitis led to permanent discontinuation of cemiplimab in 1.3% (7/534) of patients. Systemic corticosteroids were required in all patients who experienced pneumonitis, and 85% of the patients received high dose corticosteroids (prednisone ≥ 40 mg per day or equivalent). Pneumonitis resolved in 62% (8/13) of patients. The fatal pneumonitis event is discussed under Deaths. The following summary narratives describe serious nonfatal pneumonitis events that occurred in patients with CSCC during cemiplimab treatment.

(b) (6): 69-year-old man with metastatic CSCC with lung metastases experienced **Grade 3 pneumonitis resulting in permanent discontinuation.** The patient had shortness of breath prior to starting cemiplimab treatment. The patient required oxygen soon after the first cemiplimab infusion and was treated with dexamethasone orally, inhaled steroids and albuterol. Imaging revelated diffuse nodules and left upper lobe collapse and a possible infectious process. Patient received antibiotics. He was discharged home and returned with respiratory distress. The investigator considered this may have been due to an early steroid wean. The patient was retreated with corticosteroids and antibiotics. The patient died on Day 35 after transitioning to palliative care and after presenting two days earlier to the ED with shortness of breath.

Reviewer: *The pneumonitis was possibly related to cemiplimab as there was initial improvement with corticosteroids. The patient had extensive lung disease at enrollment, and progression of disease is mostly likely the direct cause of death. Cemiplimab cannot be ruled out as a contributing factor as an immune-mediated pneumonitis may have facilitated disease-related pulmonary failure.*

(b) (6): 67-year-old man with metastatic CSCC with lung metastases experienced **Grade 3 pneumonitis resulting in permanent discontinuation of cemiplimab and a Grade 4 cerebral infarction.** Four days after his second dose of cemiplimab, the patient experienced acute onset pulmonary edema. The patient presented to the ED with acute shortness of breath and was hypoxic Two days later, the patient experienced the SAE of cerebral infarction and was hospitalized. A chest X-ray showed diffuse bilateral infiltrates consistent with pulmonary edema per the narrative. An echocardiogram was normal. The patient experienced Grade 4 dyspnea in the hospital and the working diagnosis was infection with the differential including pneumonitis and lung metastases. The patient was treated with high dose corticosteroids, furosemide, broad antibiotics, and enoxaparin. The next day, the chest X-ray showed near complete resolution and the investigator considered

the possibility of flash pulmonary edema due to cardiac dysfunction given an elevated troponin. A cardiology consult concluded that the troponin rise was due to cardiac stress from a noncardiac cause. The rapid resolution was not consistent with an infectious cause. Blood cultures were negative. The patient improved and restarted cemiplimab. The patient experienced a SAE of Grade 3 pneumonitis and cemiplimab was permanently discontinued.

Reviewer: *The Grade 3 pneumonitis was most likely related to cemiplimab. The prior events of dyspnea and chest x-ray findings seemed acute and resolved very quickly making cemiplimab less likely a causal factor; however, the patient had received high-dose corticosteroids for this event. The patient also experienced a stroke. It is unclear if the patient had baseline stroke risk factors. Cemiplimab seems less likely related to the stroke occurrence based on safety profile of the drug class. Additionally, it is possible that the stroke could have been caused from the unclear acute event that caused the short-lived pulmonary edema, dyspnea and rise in cardiac enzymes.*

(b) (6): 83-year-old man with metastatic CSCC who experienced a **Grade 2 pneumonitis resulting in study drug interruption and hospitalization**. This event occurred after the patient had received 16 doses. The patient improved with high dose steroids and resumed treatment on study.

Reviewer*: Agree the event was related to cemiplimab treatment.*

The 90 Day-SUR reports four additional patients experienced pneumonitis. One patient from Pool 3 experienced fatal pneumonitis (described in Deaths). Three other patients from Pool 1 had clinical and radiologic findings consistent with pneumonitis and were treated with steroids and improved. One patient experienced recurrent pneumonitis after resolution of the initial event and after resuming study treatment. This patient required permanent discontinuation.

Immune-mediated Colitis

Immune-mediated colitis occurred in 0.9% (5/534) of patients receiving cemiplimab There were no fatal events. Two patients (0.4%) experienced Grade 3 colitis. Colitis led to permanent discontinuation of cemiplimab in one patient. Systemic corticosteroids were required in all patients who experienced colitis, and 60% of the patients received high dose corticosteroids (prednisone ≥ 40 mg per day or equivalent). Colitis resolved in 80% (4/5) of patients.

The 90-Day SUR included no additional immune-mediated diarrhea or colitis events.

Immune-mediated Hepatitis

Immune-mediated hepatitis occurred in 2.1% (11/534) of patients receiving cemiplimab, including one Grade 5 (0.2%), one Grade 4 (0.2%) and nine Grade 3 (1.7%) events. Hepatitis led to permanent discontinuation of cemiplimab in 0.9% (5/534) of patients. Systemic corticosteroids were required in all patients who experienced hepatitis, and 91% (10/11) of the patients received high dose corticosteroids (prednisone ≥ 40 mg per day or equivalent). Hepatitis resolved in 64% (7/11) of patients. The fatal hepatitis event is discussed under Deaths.

The following summary narratives describe serious nonfatal hepatitis events that occurred in patients with CSCC during cemiplimab treatment.

(b) (6): 88-year-old man who experienced **Grade 3 increased alanine transaminase (ALT) and aspartate transaminase (AST).** The patient had received six doses of cemiplimab. He presented to the ED after falling twice at home. Lab workup revealed the elevated transaminases, normal total bilirubin and elevated creatine kinase (CK), CPK-MB, LDH and C-reactive protein. The patient was diagnosed with Grade 2 muscle weakness possibly related to immune-mediated liver toxicity and myopathy. He received corticosteroids. The SAEs of Grade 3 increases in ALT and AST were considered by the investigator to be immune-mediated and related to cemiplimab.

Reviewer: *Agree with investigator assessment.*

(b) (6): 80-year-old woman with locally advanced CSCC experienced **fever and Grade 3 autoimmune hepatitis leading to study drug interruption.** Three days after the first cemiplimab infusion, the patient was admitted with fevers and a urinary tract infection. She also had elevated liver enzymes. She was not treated with steroids because of the possible concurrent infection. The liver enzymes trended down over a week. The Applicant noted in the causality analysis that the patient went on to receive nine more doses of cemiplimab with no recurrence of liver enzyme elevation.

Reviewer*: Cemiplimab cannot be excluded given the relative frequency of liver enzyme elevation and autoimmune hepatitis events with other drugs in class; however, there are other variables that point to alternative causes including relatively rapid onset after one dose, concomitant medication use (warfarin, a statin, ceftriaxone), and the condition started to improve without steroid treatment. Further, the patient did not have any recurrence of liver enzyme elevation during the rest of the study.*

The 90-Day SUR included no additional immune-mediated hepatitis events.

Immune-mediated Endocrinopathies

Adrenal Insufficiency

Adrenal insufficiency occurred in 0.4% (2/534) patients receiving cemiplimab, including one Grade 3 and one Grade 2 event. Both patients received corticosteroids, one receiving high dose corticosteroids for one day, and neither patient had resolution of adrenal insufficiency.

Hypophysitis

Hypophysitis occurred in one patient (0.2%) receiving cemiplimab. The patient had a serious Grade 3 hypophysitis and was treated with high dose corticosteroids initially and transitioned to daily cortisone replacement. The patient had temporary interruption of cemiplimab for the event. The patient continues to require hormone replacement therapy.

(b) (6) (Study 1540): 77-year-old man with metastatic CSCC experienced serious **Grade 3 hypophysitis and Grade 4 myocardial infarction**. On Day 225, after 16 doses of cemiplimab, the patient developed hypophysitis. The patient had been admitted with nausea and general deterioration per the narrative and diagnostic workup revealed increased thyroid stimulating hormone (TSH), low cortisol and elevated prolactin. The patient received high dose corticosteroids followed by daily cortisone replacement. Cemiplimab was temporarily interrupted. On Day 247, the patient experienced a myocardial infarction and required placement of two coronary stents. Cemiplimab was interrupted for both AEs. The patient resumed cemiplimab after resolution of the cardiac event.

Reviewer: *Agree with causality assessment that cemiplimab was directly related to the hypophysitis event and not likely related to the myocardial infarction.*

Hypothyroidism

Hypothyroidism occurred in 6% (32/534) of patients receiving cemiplimab, including one Grade 3 (0.2%) event. Patients were managed with hormone replacement therapy. No patients required permanent discontinuation of cemiplimab for hypothyroidism. One patient required temporary interruption. No patients could discontinue hormone replacement therapy.

Hyperthyroidism

Hyperthyroidism occurred in 1.5% (8/534) of patients receiving cemiplimab, including one Grade 3 event. No patients required permanent discontinuation of cemiplimab for hyperthyroidism. Two patients required temporary interruption of cemiplimab. Hyperthyroidism resolved in 38% (3/8) of patients.

Type 1 Diabetes Mellitus

Type 1 diabetes mellitus occurred in 0.7% (4/534) of patients, including two patients with Grade 4 and two patients with Grade 3 events. Two patients presented with diabetic ketoacidosis (DKA), one experienced Grade 4 and one experienced Grade 3 DKA. Type 1 diabetes mellitus events led to permanent discontinuation of cemiplimab in one patient and temporary interruption in two patients. All patients required insulin treatment and no patients had resolution of type 1 diabetes mellitus.

The 90-Day SUR included one additional event of non-serious hypothyroidism and no other new endocrinopathy events.

Nephritis

Immune-mediated nephritis occurred in 0.6% (3/534) patients receiving cemiplimab, including two Grade 3 events. Nephritis led to permanent discontinuation of cemiplimab in one patient and temporary interruption in the other two patients. Systemic corticosteroids were required in all three patients, and two of the three patients required high dose corticosteroids. Nephritis resolved in all patients.

The 90-Day SUR included no additional immune-mediated nephritis events.

Dermatologic Reactions

Immune-mediated dermatologic reactions, including erythema multiforme and pemphigoid, occurred in 1.7% (9/534) patients receiving cemiplimab, including six Grade 3 (1.1%) events. Temporary interruption of cemiplimab was required in five patients (0.9%) for adverse skin reactions. Systemic corticosteroids were required in all patients with dermatologic reactions, including 89% (8/9) who received high dose corticosteroids. Dermatologic reactions resolved in 33% (3/9) of patients. Two patients had recurrence of dermatologic reactions after re-initiation of cemiplimab.

(b) (6): 70-year-old man with metastatic CSCC experienced a **Grade 3 maculopapular rash resulting in drug interruption**. The patient had developed a Grade 1 back rash on Day 19 and a Grade 1 facial rash on Day 23. The patient was treated with cetirizine, fexofenadine hydrochloride and topical steroids for several weeks, but cemiplimab treatment continued. The rash worsened to Grade 3 by Day 72 and the study drug was held. At data cutoff, the patient reportedly had improved but had not resumed cemiplimab treatment.

> ***Reviewer:*** *Agree with causality assessment that the rash was immune mediated and related to cemiplimab.*

The 90-Day SUR included one additional Grade 3 rash event that was ongoing at data cutoff. Narratives describing additional serious dermatologic adverse reactions that occurred in patients treated in Study R1979-ONC-1504 are summarized under "ImARs in Patients Previously Treated with Idelalisib" in the next section of the review.

Other imARs

The following additional clinically significant imARs occurred at an incidence of ≤1% in patients receiving cemiplimab: paraneoplastic encephalomyelitis (0.2%, n=1, Grade 5), encephalitis (0.2%, n=1, Grade 3), meningitis (0.4%, n=2, one Grade 4 and one Grade 3), autoimmune myocarditis (0.2%, n=1, Grade 3), myasthenia gravis (0.4%, n=2, one Grade 4 and one Grade 2), myalgia (0.4%, n=2, Grade 3), arthritis (0.2%, n=1, Grade 3), Guillain-Barre syndrome (0.2%, n=1, Grade 3), chronic inflammatory demyelinating polyradiculoneuropathy (0.2%, n=1, Grade 2), CNS Inflammation (0.2%, n=1, Grade 2), immune thrombocytopenic purpura (0.2%, n=1, Grade 2), Sjogren's syndrome (0.2%, n=1, Grade 2), and vasculitis (0.2%, n=1, Grade 2).

The fatal paraneoplastic encephalomyelitis event is described under Deaths. The Grade 4 myasthenia gravis event is described under "ImARs in Patients Previously Treated With Idelalisib." The following three summary narratives describe "other" imARs that were serious and that occurred in patients with CSCC.

(b) (6): 84-year-old woman with recurrent, locally-advanced CSCC who experienced Grade 3 autoimmune myocarditis leading to permanent discontinuation of cemiplimab. After the patient completed her fifth cemiplimab infusion (Day 58), the ECG showed sinus arrhythmia and suspected anteroseptal infarct. Laboratory results revealed: elevated troponin T 0.508 ng/mL and 607 ng/L, creatinine-kinase (CK) 330 U/L (Grade 1), and creatinine-kinase MB 42 U/L, not significant (Grade 1). She was asymptomatic but was admitted and underwent diagnostic workup with imaging, echocardiogram and cardiac MRI. She was treated with prednisolone. The coronary artery angiography excluded any significant coronary artery disease. A cardiac MRI reported that myocarditis could not be excluded, but there was no enlargement of heart, minimal hypertrophy of the myocardium of the left ventricle, normal motion, and an ejection fraction of 66%. The echocardiogram showed aortic insufficiency. A transthoracic echo noted no wall motion abnormalities or high grade valvular defects. Follow-up cardiology consultant suggested that myocarditis was not supported by the workup. The patient discontinued study drug. The investigator assessed the event as myocarditis related to cemiplimab. The Applicant agreed that the event could have been related to cemiplimab and could have been immune-mediated but noted that the workup did not support the diagnosis of myocarditis.

***Reviewer**: Agree with Applicant's assessment. Although the patient was asymptomatic, there were nonspecific cardiac abnormalities noted on her ECG, angiography, and cardiac MRI. The patient had received corticosteroids promptly, so perhaps some damage was reversed by the time the patient was seen by the outpatient cardiologist. Cemiplimab cannot be excluded as a causal factor for this AE, however the echo and cardiac MRI findings and sequence of events do not clearly fit with a typical autoimmune myocarditis.*

(b) (6) (Study 1540): 79-year-old man with metastatic CSCC experienced **Grade 3 aseptic meningitis leading to permanent discontinuation of cemiplimab.** The patient had received one dose of cemiplimab and developed a fever and hypertension. The patient developed neck stiffness and pain on Day 11. He was diagnosed with confusional state and cemiplimab was discontinued. The LP showed no signs of infection. Empiric antibiotics were stopped. High dose dexamethasone was administered on Day 14 and tapered two days later. On Day 17, the patient had no neck stiffness and he was discharged home on a steroid taper. The investigator assessed the event as an acute inflammatory reaction associated with cemiplimab.

***Reviewer**: Agree with investigator and Applicant assessments. Cannot rule out an immune-mediated drug reaction underlying this patient's aseptic meningitis. It appears that the patient improved following treatment with steroids or with time.*

(b) (6): 80-year-old man who experienced **myalgia, hypothyroidism and Sjögren's syndrome** which were considered immune-related, rash and flu-like symptoms, and Grade 1 FTT Grade. He also experienced persistent myalgia which increased to Grade 3. He returned

to clinic on Day 165 and was admitted for dehydration, generalized weakness and acute kidney injury. FTT was considered Grade 4 in severity as he had lost 15 pounds and was not tolerating oral intake. He received hydration, antibiotics, and prednisone. The patient improved and restarted cemiplimab on Day 193. He completed the study on Day 322.

Reviewer: *The adverse reactions of hypothyroidism, myalgia and Sjogren's syndrome are likely immune-mediated and related to cemiplimab. The fatigue, FTT and UTI are less likely directly related to cemiplimab treatment but could be secondary events to the treatment-related AEs (e.g., hypothyroidism and myalgia).*

ImARs in Patients Previously Treated with Idelalisib

The Applicant included additional safety information regarding patients treated with cemiplimab who had prior therapy with idelalisib, a PI3K inhibitor, and who experienced severe and fatal imARs during cemiplimab treatment. These patients were not included in the primary safety dataset supporting the BLA. The patients were enrolled in Study R1979-ONC-1504 (1504), a study of single-agent cemiplimab or cemiplimab in combination with REGN1979 (CD20xCD3 bispecific antibody) in patients with B-cell malignancies. During Study 1504, two patients experienced a fatal skin adverse reaction after receiving a single dose of cemiplimab, and a third patient developed life-threatening myositis and myasthenia gravis following two doses of cemiplimab. A safety review identified that all patients had received prior idelalisib. This prompted Protocol Amendment 6 (July 17, 2017) to Study 1423 and Amendment 4 to Study 1540 (September 22, 2017), each adding an exclusion criterion to exclude patients previously treated with idelalisib from enrollment. The following summary narratives describe imARs that occurred in patients treated with cemiplimab who received prior idelalisib (in one patient the idelalisib was initiated after cemiplimab stopped). A total of eight patients received both drugs, and five patients had SAEs or other AESIs.

(b) (6): 75-year-old patient with follicular lymphoma experienced **Grade 5 Toxic Epidermal Necrolysis (TEN**) **and stomatitis** after receiving the first dose of cemiplimab. The patient's most recent treatment for lymphoma was idelalisib and the last dose given was 20 weeks prior to the start of cemiplimab. Cemiplimab treatment was discontinued after a single dose. The patient presented with a Grade 2 rash and stomatitis on Day 4. The patient had had prior stomatitis, but this case was reportedly worse. The patient worsened to Grade 3 TEN And stomatitis and was admitted to the hospital and treated with high dose steroids. Dermatology consulted and diagnosed the patient with overlapping **Stevens Johnson Syndrome (SJS)** and TEN. The patient became septic and was treated with antibiotics and antifungals. On Day 20, a punch biopsy of the left upper leg (medial area) showed completely necrotic epithelial cells separated from the dermis below consistent with the diagnosis of TEN/SJS syndrome. On study day 21, a blood culture was positive for *Enterobacter cloacae.* The patient developed acute renal failure acute renal failure. Human immunoglobulin was infused. The patient died on study day 29 due to septic shock. Grade 5 TEN and stomatitis were considered by the investigator to be related to cemiplimab treatment.

(b) (6): A 73-year-old patient with follicular lymphoma experienced **Grade 4 mucositis and Grade 3 erythema multiforme and Grade 5 pneumonia** after receiving a single dose of cemiplimab. The patient was receiving idelalisib prior and the last dose was 11 weeks before initiating cemiplimab. The patient presented on Day 10 with fever, and oral mucositis causing dysphagia. He developed a rash that was progressive, and a biopsy showed erythema multiforme. Steroids and mycophenolate were administered; however, the cutaneous rash and mucosal involvement became extensive such that the patient experienced blistering skin lesions and hematochezia. The patient continued to worsen and developed pneumonia which resulted in death on Day 41. Both the mucositis and pneumonia were considered by the investigator to be related to cemiplimab treatment.

(b) (6): A 69-year-old patient with follicular lymphoma and prior idelasib use eight months prior to starting cemiplimab. The patient received two doses of cemiplimab. On Day 20 the patient experienced an SAE of **myositis with Grade 4 CPK elevation and Grade 3 hepatitis**. The patient received high dose corticosteroids. On Day 30, the patient was diagnosed with Grade 3 **myasthenia gravis, myocardial infarction and dyspnea**. The patient was treated with plasmapheresis. There was eventual improvement. Cemiplimab was discontinued. The events myositis, myasthenia gravis, myocarditis, rash and dyspnea were considered related to cemiplimab.

> ***Reviewer****: Agree with the causality assessment in the three cases above. While all imAR events have been described with cemiplimab or other drugs in class, it is possible that prior treatment with a PI3K inhibitor may have altered the host immune profile and amplified these fatal skin events and the serious myositis/myasthenia gravis event.*

(b) (6): 66-year-old patient with diffuse large B-cell lymphoma who received idelalisib for fifth line therapy 2 years prior to the start of study treatment. On Day 1 the patient received cemiplimab and 0.5 mg REGN1979, and the patient received a second infusion of 0.5 mg REGN1979 on Day 2. The patient experienced an **SAE of Grade 1 Cytokine Release Syndrome (CRS) three times**, each time it occurred the days following the administration of the two study drugs. The investigator assessed two of the events as related to both drugs and one event as related to REGN1979 but not cemiplimab. The Applicant assessed the events as related to REGN1979 given the mechanism of action of the bispecific antibody.

> ***Reviewer****: Agree that cemiplimab is less likely related to the CRS experienced by this patient.*

(b) (6) A 62-year-old male with follicular lymphoma who received cemiplimab prior to ever receiving idelalisib or any other PI3K inhibitor. The patient was discontinued from cemiplimab because of worsening **eosinophilia**. He received a total of three doses. The patient began taking rituximab and idelalisib three weeks later. The patient experienced further eosinophilia and on Day 121, he experienced an **SAE of pneumonitis** with suspected attribution to idelalisib and cemiplimab. The event was ongoing at the time of the data cut-off. The Applicant did not rule out cemiplimab as a causal factor but stated that idelalisib could have

been the primary causal factor as pneumonitis is a known risk for this drug and the temporal association.

***Reviewer**: Agree with Applicant's causality assessment.*

***Reviewer**: No patients with CSCC enrolled in Studies 1423 or 1540 had prior treatment with idelalisib. It is unlikely that a patient with advanced CCSC would have had prior idelalisib or a PI3K inhibitor as this drug class is not generally used for treatment of CSCC. If there is potentiation of immune-mediated toxicity with cemiplimab based on prior idelalisib exposure, theoretically, there would be potentiation of immune-mediated AEs in patients receiving any checkpoint inhibitor following exposure to any PI3K inhibitor. Additionally, some of the data for these reactions are confounded and are by no means definitive.* (b) (4)

Infusion-related reactions (IRRs)

The Applicant initially used the following case definition for identifying possible IRRs: any AE that occurred during the infusion or within 2 hours after the infusion was completed. The Applicant later proposed, and FDA agreed to an updated case definition to reliably identify events that were true IRRs. Two lists of PTs were created. The first included PTs commonly used to describe IRR diagnoses. The second was a list of PTs representative of commonly observed symptoms of IRRs. Treatment-related AEs mapping to 1 of the 2 lists were identified as IRRs only if the onset date was the day of or day after cemiplimab infusion and if a symptom, resolved within two days of onset. Table 37 lists the MedDRA PTs used in the case definition.

Table 37. MedDRA Query for IRR Diagnoses and Symptoms

Customized MedDRA Query	MedDRA PTs
IRR Diagnoses	Infusion-Related Reaction, Drug Hypersensitivity, Hypersensitivity, Type I Hypersensitivity, Anaphylactic Reaction, Anaphylactic Shock, Anaphylactoid Reaction, Anaphylactoid Shock, Anaphylaxis, Shock, Respiratory Failure, Respiratory Arrest
IRR Symptoms	Abdominal Pain, Allergic Oedema/Edema, Angioedema, Back Pain, Blood Pressure Decreased, Bronchial Oedema, Bronchospasm, Cardiac Arrest, Cardio-Respiratory Arrest, Chest Pain, Chills, Choking, Choking Sensation, Circulatory Collapse, Cough, Cutaneous Reactions, Diaphoresis, Dyspnoea, Erythema, Flushing, Generalised Erythema, Hypotension, Laryngeal Oedema, Laryngospasm, Lip Oedema, Lip Swelling, Mouth Swelling, Nausea, Oedema, Oedema Mouth, Oropharyngeal Oedema, Oropharyngeal Spasm, Oropharyngeal Swelling, Pruritus, Pruritus Allergic, Pruritus Generalised, Pyrexia, Rash, Rash Erythematous, Rash Generalised, Rash Pruritic, Respiratory Distress, Respiratory Dyskinesia, Rigors, Shock Symptom, Skin Swelling, Sneezing, Stridor, Swelling, Swelling Face, Swollen Tongue, Tachycardia, Tachypnoea, Tongue Oedema, Tracheal Obstruction, Tracheal Oedema, Upper Airway Obstruction, Urticaria, Urticaria Papular, Vomiting, Wheezing

Source: SCS, pg. 44

IRRs were mostly low grade and occurred in 9% of patients with CSCC and 9% of patients across the development program. IRRs led to permanent discontinuation of cemiplimab in two (0.4%) patients and treatment delays in 16 (3%) patients. Among the 48 patients who experienced an IRR in Pool 3, eight (17%) were treated with systemic corticosteroids. There was one Grade 3 IRR in a patient who developed chills, rigors, fever, hypertension, and tachycardia two hours after the first cemiplimab infusion. The AE resolved the next day, and cemiplimab was permanently discontinued. Table 38 summarizes the types of IRRs occurring in Pools 1 and 3.

Table 38. Summary of IRRs, Pools 1 and 3

	Pool 1 N=163 n (%)		Pool 3 N=534 n (%)	
Preferred Term	**Any Event**	**Grade ≥ 3**	**Any Event**	**Grade ≥ 3**
Any IRR	20	0	57	1
Number of patients with at least one IRR	15 (9)	0	48 (9)	1 (0.2)
PTs categorized as infusion related reactions				
Infusion reaction	7 (4)	0	22 (4)	1
Nausea	3 (2)	0	6 (1)	0
Abdominal pain	1 (1)	0	9 (1)	0
Pyrexia	1 (1)	0	7 (1)	0
Flushing	1 (1)	0	3 (1)	0

	Pool 1 N=163 n (%)		Pool 3 N=534 n (%)	
Rash	1 (1)	0	2 (<1)	0
Wheezing	1 (1)	0	1	0
Vomiting	0	0	3 (1)	0
Pruritis	0	0	3 (1)	0
Chills	0	0	2 (<1)	0

Source: ADAE.xpt,

Reviewer*: The frequencies, types, and severities of infusion reactions occurring with cemiplimab are like those occurring with other approved PD-1 and PD-L1 antibodies. Management guidelines including drug interruption, decreasing the infusion rate and discontinuation based on clinical severity of the reaction will be described in product labelling.*

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

COA analyses to inform long-term tolerability were not conducted by the Applicant. The ongoing Study 1540 is a single arm trial and such analyses are not interpretable without an internal control. EORTC QLQ-C30 was administered to patients to describe global health status during treatment. Descriptive statistics for each post-baseline time point were computed for QOL. See Figures 19 and 20 in Section 7.

8.2.7. Safety Analyses by Demographic Subgroup

Age: The median age in Pool 1 was 71 years (range: 38-96 years). Twenty-eight percent of patients in Pool 1 were less than 65 years old, 36% were between 65 and 75 years of age, 37% were between 75 and 85, and 9% (n=15) were 85 or older. Almost all specific TEAEs were similar across age groups. Gastrointestinal toxicity AEs were most frequent in all age groups. Grade 3-4 AEs increased in number in the older age groups. SAEs were also more frequent.

Table 39. AEs by age subgroups, Pool 1

Age Subgroups	Any grade event n (%)	Grade 3-5 events n (%)	SAEs n (%)
< 65 (N=45)	43 (96)	19 (22)	4 (9)
≥ 65 - < 75 (N=58)	54 (93)	21 (36)	17 (29)
≥ 75 (N=60)	58 (96)	31 (52)	25 (42)

Source: ADAE.xpt

Gender: There were 138 male and 25 female patients in Pool 1. There were no obvious differences in AE incidence between male and female patients. Almost all patients had at least one any grade AE and 38% of males and 36% of females had at least one ≥ Grade 3 AE.

Reviewer: Age and gender comparisons should be considered exploratory and limited by the small number of patients.

Race: No conclusions can be drawn regarding the effect of race on safety as there were a limited number of non-White patients (n=3) of the 160 patients with ethnicity data in Pool 1.

8.2.8. Specific Safety Studies/Clinical Trials

None.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant did not conduct carcinogenicity studies.

Human Reproduction and Pregnancy

Cemiplimab has not been studied in pregnant or lactating women.

Pediatrics and Assessment of Effects on Growth

Cemiplimab has not been studied in the pediatric population to date. A waiver for the PREA requirement for pediatric evaluation was requested for the proposed indication in CSCC based on pediatric studies being "impossible or highly impractical" given the extreme rarity of the condition in the pediatric population.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No studies have been conducted to evaluate the abuse potential with cemiplimab. There is no evidence that suggests a risk for dependence on cemiplimab. No cases of withdrawal symptoms were reported during human clinical trials.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Not applicable. Cemiplimab is a new molecular entity with no prior approval history in the United states or in any other country.

Expectations on Safety in the Postmarket Setting

As a clinical post marketing commitment (PMC), the Applicant will complete and submit the results of Study 1540. (b) (4)

8.2.11. **Integrated Assessment of Safety**

The evaluation of the safety of cemiplimab in patients with advanced CSCC was primarily based on a pooled database including 163 patients with CSCC enrolled and treated with single agent cemiplimab in Study 1423 or in Study 1540 (Pool 1). A larger pool of patients with various malignancies, enrolled in the same studies and treated with cemiplimab as a single agent or in combination with chemotherapy and/or radiation (Pool 3), was reviewed as supportive safety data. Pool 3 was also the focus for the review of imARs and IRRs, adverse reactions that are expected with monoclonal antibodies to the PD-1 receptor protein. The risks for these reactions should not be amplified or reduced by use of concomitant chemotherapy or radiation; therefore, the larger safety population allowed for better identification of relatively common and rare immune-mediated reactions. The size of the safety databases submitted in the BLA were considered adequate to characterize the safety profile of cemiplimab.

Among the 534 patients treated with cemiplimab across the two trials, there was at least one cemiplimab-related fatal AE in Pool 1 and at least three other cemiplimab-related fatal AEs in Pool 3 leading to a treatment-related death rate of 0.7%. Cemiplimab may have also played an indirect role in other fatal AEs (see summary narratives under Deaths). Among the 163 patients with CSCC treated with cemiplimab, 28% experienced at least one treatment-emergent SAE including 8% who experienced a cemiplimab-related SAE. The majority of treatment-related SAEs were immune-mediated. AEs leading to permanent discontinuation occurred in 5% of patients with CSCC. The most common adverse reactions reported in at least 20% of patients with CSCC were fatigue, rash and diarrhea. The most common Grade 3-4 adverse reactions ($\geq$2%) were cellulitis, sepsis, hypertension, pneumonia, musculoskeletal pain, skin infection, urinary tract infection and fatigue. Similar incidences of nonfatal AE categories were observed in the larger Pool 3.

Serious risks of cemiplimab are similar to those of other monoclonal antibodies acting in the PD -1/PD-L1 pathway including serious and fatal imARs and IRRs. Among 534 patients treated with cemiplimab, 17% (92/534) experienced at least one imAR during treatment. Four percent of patients required permanent discontinuation and 7% required temporary interruption of cemiplimab for imARs. ImARs were rarely fatal and generally manageable with corticosteroid administration. IRRs occurred in 9% of patients in Pool 3, and all were Grade 1-2 except for one patient who experienced one Grade 3 IRR. Two patients required permanent discontinuation of cemiplimab due to an IRR. IRRs were manageable with temporary interruptions, infusion rate reductions and administration of symptomatic treatments including antihistamines and corticosteroids.

Overall, the safety of cemiplimab is consistent with the expected toxicity profile of immunologically-mediated anticancer therapies. The safety data submitted in the BLA do not change the favorable benefit-risk assessment for cemiplimab for the treatment of patients with advanced CSCC.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

There are no outstanding statistical issues with the study design, statistical analysis plan, or efficacy results of Study 1423 and Study 1540. The proposed indication of cemiplimab for treatment of patients with metastatic CSCC or locally advanced CSCC who are not candidates for surgery is mainly supported by non-randomized studies in 108 patients. No statistical comparison was conducted in Study 1423 and Study 1540 and therefore no statistical inference can be drawn from the studies. Additionally, patient-reported outcomes were assessed in Study 1540. However, since this study was non-randomized, PRO endpoints were not interpretable for making efficacy claims.

8.4. Conclusions and Recommendations

Patients with advanced CSCC represent a rare disease population with a serious and life-threatening condition for which there is no FDA-approved therapy and no known curative treatment. Off-label use of cytotoxic chemotherapy and small molecule kinase inhibitors have not been shown to provide durable responses and have not demonstrated improvement in overall survival.

The clinical benefit of cemiplimab for patients with advanced CSCC, including patients with metastatic CSCC and patients with locally advanced CSCC who are not candidates for surgical resection or radiation, is based on the pooled results of patients with metastatic and locally advanced CSCC treated with single agent cemiplimab in Studies 1423 and 1540. Efficacy analyses conducted when all patients with metastatic CSCC (N=75) had been treated or followed for at least six months after accrual demonstrate a confirmed, centrally reviewed ORR per RECIST v 1.1 of 47% (95% CI: 35, 59); four patients (5%) experienced CR and 31 patients (41%) had PR. Among the 35 responding patients, the median DOR was not reached (range 2.8 to > 15.2 months) and 80% (28/35) had ongoing responses at data cutoff. Sixty percent (21/35) of responding patients maintained responses for $\geq$ 6 months. Most responding patients experienced objective responses at the first disease assessment (Week 8) and the median time to response was 1.9 months.

Efficacy analyses conducted when patients with locally advanced CSCC (N=33) had been treated or followed for at least nine months after accrual demonstrate a confirmed, centrally reviewed ORR of 49% (95% CI: 31, 67). Among the 16 responding patients, the median DOR was not reached (range 1 to > 12.9 months) and 81% (13/16) had ongoing responses at data cutoff. Sixty-three percent (10/16) of responding patients maintained responses of $\geq$ 6 months. The median time to response was 3.7 months with more than 80% of responders experiencing objective response at the first or second evaluation (Week 8 or 16).

Exploratory subgroup analyses showed efficacy was consistent across relevant subgroups: those who had or did not have prior systemic or radiotherapy, and those with nodal or distant metastases. For the small subset of patients who had PD-L1 expression results for their tumors, patients experienced durable responses whether the tumors tested positive or negative for PD-L1 expression.

The primary safety risks of cemiplimab are imARs and IRRs. In the pooled safety population supporting the BLA (Pool 3, N=534), 17% of patients experienced at least one imAR. The most common imARs occurring in more than 2% of patients were hypothyroidism, pneumonitis and hepatitis. Eight percent of all immune-mediated events were Grade 3 or 4 in the pooled analysis. Serious imARs observed at a lower frequency across the cemiplimab development program included autoimmune myocarditis, encephalomyelitis, hypophysitis, pemphigoid and paraneoplastic encephalomyelitis. The frequency and types of imARs in patients treated with cemiplimab are consistent with the safety profiles of other approved PD-1 and PD-L1 antibodies. ImARs were usually manageable with corticosteroids and hormone replacement therapy. Dose-modification and management guidelines for imARs are included in product labeling. IRRs during cemiplimab treatment were mostly low-grade in severity and led to permanent discontinuation in two (0.4%) patients. IRRs were manageable with temporary interruptions, infusion rate reductions and administration of symptomatic treatments including antihistamines and corticosteroids. Management guidelines in case of IRRs are included in the product labeling.

In summary, review of the efficacy and safety data in the BLA determined that cemiplimab should receive regular approval for both types of advanced CSCC: patients with metastatic CSCC and patients with locally advanced CSCC who are not candidates for surgery or curative radiation. Durable objective response rate of sufficient magnitude is an acceptable surrogate endpoint considered reasonably likely to predict clinical benefit (i.e., improved survival) in patients with advanced cancers. There is also regulatory precedent for durable tumor shrinkage as a primary endpoint to support regular approval for drugs treating malignancies with primary skin involvement. In the cemiplimab development program, radiographic response rate correlated with visible improvement of baseline disfiguring lesions during treatment, as demonstrated in the photographic data submitted in the application for the group of responding patients in Study 1540. In some cases, there was near complete resolution of cosmetically deforming lesions that had been refractory to multiple prior local and systemic treatments. Clinically meaningful shrinkage of disfiguring lesions located in highly visible areas such as the face, scalp, neck or extremities, is considered a direct clinical benefit for patients.

The proposed recommended dose of cemiplimab is 350 mg Q3W IV. The Applicant reasonably selected this dose based on similar exposures between the weight-based 3 mg/kg Q2W and flat dose 350 mg Q3W dosing regimens that were evaluated in the cemiplimab development program. Although there is less clinical experience with the flat dose regimen in the proposed indication (n=35), the Applicant provided population PK modeling and simulation results and additional safety and efficacy data for the flat dose in the 90 Day safety update. FDA confirmed

that the 350 mg Q3W regimen resulted in similar steady-state exposure compared to the 3mg/kg Q2W regimen to allow for bridging the safety and efficacy data between the two regimens. See Clinical Pharmacology Review (Section 6) for further details.

In conclusion, the benefit: risk assessment is favorable for the use of cemiplimab for the treatment of patients with metastatic CSCC or patients with locally advanced CSCC who are not candidates for curative surgery or radiation, at a dose of 350 mg IV every three weeks. Cemiplimab has demonstrated clinically meaningful efficacy, including confirmed ORR and durable responses per independent central review and correlative substantial shrinkage of disfiguring cutaneous tumors. These results represent clinical benefit in patients with metastatic or locally advanced CSCC. The safety profile of cemiplimab is consistent with other anti-PD-1/PD-L1 monoclonal antibodies, favorable compared to available cytotoxic chemotherapy regimens that have been used for this disease, and acceptable in view of the serious and life-threatening nature of metastatic or locally advanced CSCC.

Both the primary clinical and statistical reviewers recommend approval for cemiplimab for patients with metastatic CSCC and patients with locally advanced CSCC who are not candidates for curative surgery or curative radiation.

The reviewers do not recommend a REMS be implemented for cemiplimab given the current safety profile and the experience of the medical community in managing imARs with other FDA-approved immune-modulating agents. Risk management based on labeling and routine pharmacovigilance will be employed to ensure the safe and effective use of cemiplimab.

9 Advisory Committee Meeting and Other External Consultations

The Division did not obtain the advice of the Oncologic Drug Advisory Committee (ODAC) or Special Government Employees (SGEs) for this application as there were no public health issues raised that would benefit from a public discussion or that required the expert opinions of the Committee. In addition, the safety profile of the drug is deemed acceptable for the indicated population of patients.

10 Pediatrics

Trials with safety or efficacy data pertaining to pediatric patients were not submitted with the BLA. Included in the BLA was a request for a full waiver for the requirement to assess the safety and effectiveness of the product for the claimed indication under PREA based on necessary studies being impossible or highly impracticable due to the rarity of this indication in the pediatric population.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Labeling negotiations were ongoing at the time of completing the primary clinical review. The table below summarizes significant changes to the proposed label made by FDA during the review. The package insert for LIBTAYO will include the finalized prescribing information.

Table 40. Summary of Significant Labeling Changes

Section	Proposed Labeling	Approved Labeling
1 Indications and Usage	For the treatment of patients with metastatic cutaneous squamous cell carcinoma or patients with locally advanced cutaneous squamous cell carcinoma who are not candidates for (b) (4)	For the treatment of patients with metastatic cutaneous squamous cell carcinoma or patients with locally advanced cutaneous squamous cell carcinoma who are not candidates for curative surgery or curative radiation *Reviewer:* (b) (4)
2 Dosage and Administration	Table 1 summarizing dosage modifications for adverse events (b) (4)	Table 1 was adapted for brevity (b) (4)

Section	Proposed Labeling	Approved Labeling
		(b) (4) .
3 Dosage Forms and Strengths	(b) (4)	
5 Warnings and Precautions	(b) (4	(b) (4)
6 Adverse Reactions		(b) (4)

Section	Proposed Labeling	Approved Labeling
		(b) (4)
12 Pharmacokinetics	(b) (4)	Ranges added for patient variables evaluated for an effect on exposure.
14 Clinical Studies	(b) (4)	
17 Patient Counseling Information		Revised for brevity and to be consistent with Section 5.

12 Risk Evaluation and Mitigation Strategies (REMS)

Serious risks of cemiplimab are immune-mediated adverse reactions, including fatalities, and infusion-related reactions.
The label includes listings of immune-related reactions that have been observed across the class as well as dose modifications and treatment for these events. As this class of drugs is admitting newly approved members regularly over the past few years, prescribers have become more experienced with monitoring and treating these types of events, and generally, oncologists are experienced in the monitoring and management of these serious risks.

In summary, the reviewer does not recommend a risk evaluation and mitigation strategy (REMS) be implemented for cemiplimab. Recommendations for safe and effective use of cemiplimab, including adequate safety monitoring for immune-mediated adverse reactions and infusion reactions, will be addressed in product labeling.

APPEARS THIS WAY ON ORIGINAL

13 Postmarketing Requirements and Commitment

After previous discussion with Regeneron, FDA sent the following PMC description to the Applicant on August 8, 2018. The Applicant agreed to and proposed a reasonable timeline for completion of the PMC study.

"To submit the (b) (4) trial report for trial R2810-ONC-1540 that includes the final analysis of objective response rate and duration of response in patients with advanced cutaneous squamous cell carcinoma (CSCC) including patients with metastatic disease and patients with locally advanced CSCC who are not candidates for surgery or radiation. Trial R2810-ONC-1540 will enroll at least 150 patients including at least 75 patients with locally advanced CSCC. All patients will have at least 1.5 years of follow-up following completion of cemiplimab treatment to further characterize the durability of responses in both subgroups."

The proposed PMC will provide additional data to inform labeling with respect to response duration and efficacy in patients with CSCC.

14 Division Director (DHOT)

X _____

15 Division Director (OCP)

X

16 Division Director (OB)

X

17 Division Director (Clinical)

The risk-benefit profile of cemiplimab 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 was assessed by Dr. Denise Casey and Suzanne Demko who recommend approval of the application. All other review disciplines also recommend approval of the BLA from their perspective. I concur and recommend approval of this application which is indicated by my signature below.

X _____

18 Office Director (or designated signatory authority)

This application was reviewed under the auspices of the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. The risk-benefit of cemiplimab was also assessed by Drs. Lemery, Casey and Ms. Demko and I concur with their recommendation to approve this drug. My signature below represents an approval recommendation for the clinical portion of this application under the OCE. My signature below also represents the approval decision of this application under CDER.

X Richard Pazdur, MD

19 Appendices

19.1. References

Nonclinical References

Barber, DL, EJ Wherry, D Masopust, B Zhu, JP Allison, AH Sharpe, GJ Freeman, R Ahmed, 2006, Restoring function in exhausted CD8 T cells during chronic viral infection, Nature, 439:682-687.

Chen, L, V Pai, R Levinson, AH Sharpe, GJ Freeman, J Braun, and LK Gordon, 2009, Constitutive neuronal expression of the immune regulatory, programmed death 1 (PD-1), identified during experimental autoimmune uveitis, Ocul Immunol Inflamm, 17(1):47-55.

Frebel, H, V Nindi, RA Schuepbach, T Braunschweiler, K Richter, J Vogel, CA Wagner, D Loffing-Cueni, M Kurrer, B Ludewig, A Oxenius, 2012, Programmed death 1 protects from fatal circulatory failure during systemic virus infection of mice, J Exp Med, 209(13):2485-2499.

Guleria, I, A Khosroshahi, MJ Ansari, A Habicht, M Azuma, H Yagita, RJ Noelle, A Coyle, AL Mellor, SJ Khoury, and MH Sayegh, 2005, A critical role for the programmed death ligand 1 in fetomaternal tolerance, J Exp Med, 202(2):231-237.

Habicht, A, S Dada, M Jurewicz, BT Fife, H Yagita, M Azuma, MH Sayegh, and I Guleria, 2007, A Link between PDL1 and T Regulatory Cells in Fetomaternal Tolerance, J Immunol, 179(8):5211-5219.

Jin, YH, W Hou, HS Kang, CS Koh, and BS Kim, 2013, The role of interleukin-6 in the expression of PD-1 and PDL-1 on central nervous system cells following infection with Theiler's murine encephalomyelitis virus, J Virol, 87(21):11538-11551.

Lazar-Molnar E, B Chen, KA Sweeney, EJ Wang, W Liu, J Lin, SA Porcelli, SC Almo, SG Nathenson, WR Jacobs, 2010, Programmed death-1 (PD-1)-deficient mice are extraordinarily sensitive to tuberculosis, Proc Natl Acad Sci, 107(30):13402-13407.

Mueller, SN, VK Vanguri, SJ Ha, EE West, ME Keir, JN Glickman, AH Sharpe, R Ahmen, 2010, PD-L1 has distinct functions in hematopoietic and nonhematopoietic cells in regulating T cell responses during chronic infection in mice, J Clin Invest, 120(7):2508-2515.

Okazaki, T and T Honjo, 2007, PD-1 and PD-1 ligands: from discovery to clinical application, Int Immunol, 19:813-824.

Petroff, MG, L Chen, TA Phillips, D Azzola, P Sedlmayr, and JS Hunt, 2003, B7 Family Molecules are Favorably Positioned at the Human Maternal-Fetal Interface, Biol Reprod, 68(5):1496-14504.

Wafula, PO, A Teles, A Schumacher, K Pohl, H Yagita, HD Volk, and AC Zenclussen, 2009, PD-1 but not CTLA-4 Blockade Abrogates the Protective Effect of Regulatory T Cells in a Pregnancy Murine Model, Am J Reprod Immunol, 62(5):283-292.

Clinical References

Foote, M, McGrath, M, Guminski A, et al., 2014, Phase II study of single-agent panitumumab in patients with incurable cutaneous squamous cell carcinoma, Annals of Oncology, 25(10):2047-2052.

Jarkowski A, Hare R, Loud P et al., 2016, Systemic Therapy in Advanced Cutaneous Squamous Cell Carcinoma (CSCC): The Roswell Park Experience and a Review of the Literature Am J Clin Oncol, 39(6):545-548.

Karia S, Han J, and Schmults D, 2013, Cutaneous squamous cell carcinoma: Estimated incidence of disease, nodal metastasis, and deaths from disease in the United States, J Am Acad Dermatol, 68 (6):957-966.

Kudchadkar R, Yushak M, Lawson D, et al., 2018 Phase II trial of pembrolizumab (MK-3475) in metastatic cutaneous squamous cell carcinoma (cSCC), J Clin Oncol 36, (suppl; abstr 9543).

Lampson, BL, Kasar, SN, Matos, TR, et. al., 2016, Idelalisib given front-line for treatment of chronic lymphocytic leukemia causes frequent immune-mediated hepatotoxicity, Blood, 128 (2):195-203.

Lewis C, Glisson B, Feng L, et al., 2012, A Phase II Study of Gefitinib for Aggressive Cutaneous Squamous Cell Carcinoma of the Head and Neck, 18 (5):1435-1446.

Maubec E, Petrow P, Scheer-Senyarich I, et al., 2011, Phase II Study of Cetuximab As First-Line Single-Drug Therapy in Patients With Unresectable Squamous Cell Carcinoma of the Skin, J Clin Oncol, 29 (25): 3419-3426.

NCCN Clinical Practice Guidelines in Oncology, Squamous Cell Skin Cancer, Version I.2017-October, 2016. NCCN.org.

Samstein R, Ho A, Lee N et al., 2014, Locally advanced and unresectable cutaneous squamous cell carcinoma: outcomes of concurrent cetuximab and radiotherapy, J Skin Cancer, epub 284582.

Stratigos A, Garbe C, Lebbe C, et al., 2015, Diagnosis and treatment of invasive squamous cell carcinoma of the skin: European consensus-based interdisciplinary guideline, 51 (14): 1989-2007.

Thompson A, Kelley B, Prokop L et al., 2016, Risk Factors for Cutaneous Squamous Cell Carcinoma Recurrence, Metastasis, and Disease-Specific Death: A Systematic Review and Meta-analysis, JAMA Dermatol, 152 (4):419-428.

Veness M, 2008, The important role of radiotherapy in patients with non-melanoma skin cancer and other cutaneous entities, Journal of Medical Imaging and Radiation Oncology, 52: 278–286.

19.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): R2810-ONC-1423

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 673		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 4		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: 4 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 78		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

For Study 1423 investigators, all of the initial financial disclosure forms that noted Regeneron as the sole study sponsor were obtained. During the conduct of the study, Sanofi became a collaborator and financial disclosure forms listing Sanofi as a collaborator were provided to all study investigators to complete. Despite due diligence procedures, Regeneron was unable to obtain the additional financial disclosure forms.		

Covered Clinical Study (Name and/or Number): R2810-ONC-1540

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 368		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 10		

Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

19.3. OCP Appendices (Technical documents supporting OCP recommendations)

19.3.1. Summary of Bioanalytical Method Validation and Performance

For studies R2810-ONC-1423 and R2810-ONC-1540, serum cemiplimab (REGN2810) concentrations were determined using the following method.

Bioanalytical review summary	No major issue. Method was sufficiently validated to support PK studies with adequate dynamic range.		
Method description	Serum cemiplimab (REGN2810) was measured using a validated sandwich ELISA in which REGN1480, a recombinant protein containing the extracellular domain of human PD-1, was used as capture reagents and a biotinylated mouse anti-human IgG4 monoclonal antibody (Biotin-REGN1298), and horseradish-peroxidase-conjugated NeutrAvidin (NeutrAvidin-HRP), were used as detection reagents (Validation report REGN2810-AV-17008-VA-01V1). Calibration standard was prepared by spiking REGN2810 in 100% serum. Method validation and analysis for measurement of serum REGN2810 for the study were performed at Regeneron Pharmaceuticals, Inc. (Tarrytown, NY 10591-6707).		
Material for calibration curve & Concentration	REGN2810 (Lot9017300001, 50.4 μg/mL)		
Validated assay range	0.078 (LLOQ) – 5 (ULOQ) μg/mL in 100% serum		
Source & reagents	REGN1480 (Lot REGN1480-L3, 2.0 μg/mL), Biotin-REGNI298 (Lot RSCHI2054, 4.5 μg/mL)		
Regression model & weighting	4 parameter logistic weight formula = $1/RLU^2$		
Validation parameters	**Method validation summary**		**Acceptability**
Standard curve performance during accuracy & precision	No of levels in standard calibrators from LLOQ to ULOQ	7	Yes
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-1 to 0%	Yes
	Cumulative precision (%CV) from LLOQ to ULOQ	0 to 2%	Yes
QCs performance during accuracy & precision LBA QCs: ±20% bias (±25% at LLOQ), ≤ 20%CV and ≤ 30% total error (≤ 40% at LLOQ)	**Cumulative accuracy (%bias) in 5 QCs**	4 to 9%	Yes
	Interbatch %CV	3 to 6%	Yes
	Total error (TE)	8 to 13%	Yes
Selectivity & matrix effect	Selectivity at LLOQ (0.078 μg/mL) in naïve individual samples: 10 serum samples tested. 100% of the samples within 20% bias (AR%: 95 – 103%)		Yes

	Matrix Interference in naïve individual samples: 10 serum samples tested. 100% of the samples BLQ	
Interference & specificity	NA	NA
Hemolysis effect	Selectivity at LLOQ (0.078 µg/mL) in naïve individual samples with hemoglobin (2 mg/mL): 10 serum samples tested. 100% of the samples within 20% bias (AR%: 96 – 103%)	Yes
Lipemic effect	Selectivity at LLOQ (0.078 µg/mL) in high triglycerides/LDL individual samples: 10 serum samples tested. 100% of the samples within 20% bias (AR%: 92 – 105%)	Yes
Dilution linearity & hook effect	Dilution Recovery tested at 500, 100 and 20 µg/mL: 100% of the samples within 20% bias (AR%: 98 – 113%) following 250 to 100000-fold dilutions.	Yes
Bench-top/process stability	Stable at room temperature (20-25°C) for 4 hrs in serum Stable at refrigerator (4°C) for 16 hrs in serum	Yes
Freeze-Thaw stability	Up to 8 cycles	Yes
Long-term storage	At nominal -20°C and -80°C for 24 months within	Yes
Parallelism	NA	NA
Carry over	NA	NA
Robustness	100% of the QC samples within 20 %bias (AR%: 101 – 113%)	Yes
Ruggedness	100% of the QC samples within 20 %bias (AR%: 103 – 111%)	Yes
Method performance in study R2810-ONC-1423		
Assay passing rate	• 300 out of 331 runs met the method acceptance criteria.	Yes
Standard curve performance	• Cumulative bias range: -1.0 to 1.0% • Cumulative precision: ≤ 2% CV	Yes
QC performance	• Cumulative bias range: -2.0 to 1.0% • Cumulative precision: ≤ 9% CV • TE: ≤ 11%	Yes
Method reproducibility	• Incurred sample reanalysis was performed in approximately 5% of study samples and 91 % of samples met the pre-specified criteria	Yes
Study sample stability	Analyzed within 596 days from collection (within established stability)	
Method performance in study R2810-ONC-1540		
Assay passing rate	• 46 out of 46 runs met the method acceptance criteria.	Yes
Standard curve performance	• Cumulative bias range: -1.0 to 1.0% • Cumulative precision: ≤ 2% CV	Yes
QC performance	• Cumulative bias range: 0 to 3.0% • Cumulative precision: ≤ 10% CV • TE: ≤ 13%	Yes

Method reproducibility	• Incurred sample reanalysis was performed in approximately 8% of study samples and 91 % of samples met the pre-specified criteria	Yes
Study sample stability	Analyzed within 437 days from collection (within established stability)	

19.3.2. Pharmacometric Review

Key Review Question

Is the dosing regimen conversion from 3 mg/kg Q2W to 350 mg Q3W acceptable from a clinical pharmacology perspective?

In this submission, the sponsor proposed a 350 mg Q3W intravenous infusion of cemiplimab in patients with cutaneous squamous cell carcinoma. The overall efficacy is proved by a 47.2% overall response rate (ORR) in 134 patients who received 3 mg/kg Q2W and 1 patient who received 1 mg/kg Q2W. A two-compartment model with zero-order IV infusion, first-order elimination and time varying clearance could best describe cemiplimab PK at a dosing range from 1mg/kg Q2W to 10mg/kg Q2W and it is utilized to simulate 350 mg Q3W.

Dosing regimen conversion from the body weight proportional dosing regimen to the flat dosing regimen is supported by the pop-PK model. The exponent index for body weight on clearance is 0.454.

Extending the dosing interval from 3 mg/kg Q2W to 350 mg Q3W is not expected to cause a clinically meaningful impact:

1. Pop-PK model suggested at population level, the mean of first cycle C_{max} increased by 51%. The mean level of steady state C_{max} increased by 22.3% and steady state C_{trough} decreased by 13%. These differences are not considered clinical significant based on exposure-response for efficacy and safety:
    a. Efficacy: Among all the 135 patients, 134 patients received the 3 mg/kg Q2W dosing regimen and 1 patient received the 1 mg/kg Q2W dosing regimen. This one patient who received 1 mg/kg experienced an anti-tumor responder based on both independent reviewer and investigator. ER analyses for efficacy showed no correlation between first cycle C_{trough} vs. overall response rate (ORR) at an exposure range from 10 to 30 mg/L. The median and 5%-95% percentile of first cycle C_{trough} for 350 mg Q3W and 3 mg/kg is 19.8 mg/L (8.9 mg/L, 38.5 mg/L) and 18.6 mg/L (9.4 mg/L, 33.5 mg/L) respectively.
    b. Safety: No evident of exposure response relationship for Grade 3+ AEs and SAEs was identified at an exposure range below 100 mg/L.

2. Additional preliminary efficacy and safety data from patients who received 350 mg Q3W was received at 90 days' safety update and further supported the dosing regimen conversion to 350 mg Q3W. The preliminary efficacy results demonstrate that 350 mg Q3W is an active dose (ORR: 31%). The 90-Day safety update for cemiplimab contains the updated safety information with at data cutoff date of 20 Jan 2018. The prevalence

of TEAE at all grades and Grade 3/4/5 of 350 Q3W regimen is comparable or slightly lower than 3 mg/kg Q2W regimen.

Sponsor's analysis

Population Pharmacokinetics

Data: The population PK analysis was based on the combined data sets from Study 1423 and Study 1540; the final analysis set contained cemiplimab concentration data from 505 patients with solid tumors, including 135 patients with CSCC (26 from study 1423 and 109 from study 1540 [groups 1 and 2]). The final population PK Analysis Set included concentration data from 75 patients with mCSCC and 60 patients with laCSCC. The dataset was shown in Table 41.

Table 41: Summary of Studies Included in Pop PK Analysis

Study Number	Dosing Regimens	Study Population	PK/ADA Samples
1423	Cemiplimab administrated via IV infusion 1, 3, 10 mg/kg, 200 mg Q2W, and 3 mg/kg Q3W 1 mg/kg Q2W (n=27) 3 mg/kg Q2W (n=331) 10 mg/kg Q2W (n=6) 200 mg/kg Q2W (n=20) 3 mg/kg Q3W (n=12) Total = 396	Patients with advanced malignancies (solid tumors) that are incurable and have failed to respond to or showed tumor progression despite standard therapy, or patients who are not candidates for standard therapy, or for whom no available therapy is expected to convey clinical benefit, or for whom PD-1 blockade has been shown to be at least equivalent to standard of care. The last sample was collected on September 6th 2017.	Serial sampling during the first cycle: prior to and at the end of 30 mins infusion, 1, 4, 8, 24, 48, 72 hours post the first infusion, day 8, 15, 29, and day 43; Sparse sampling at trough and/or the end of infusion at day 1, 15, 29, 43 in cycle 2-6. Anti-cemiplimab antibody samples collected pre-infusion on day 1 of cycles 1, 2, and 4.
1540	Cemiplimab administrated via IV infusion 3 mg/kg Q2W (Group 1 and Group 2) 3 mg/kg Q2W (n=109) Total = 109	Patients with metastatic CSCC (mCSCC) or with locally advanced CSCC (laCSCC) The last sample was collected on October 6th 2017.	Sparse sampling at trough and/or the end of infusion at days 1, 15, 29, and 43 of cycle 1, and on day 1 of cycles 2 through 6, 7, 9, and 11. The final PK samples collected either at the end of study visit or at the follow-up visit. ADA samples collected prior to treatment on day 1 of cycles 1, 3, 5, 7, and 11.

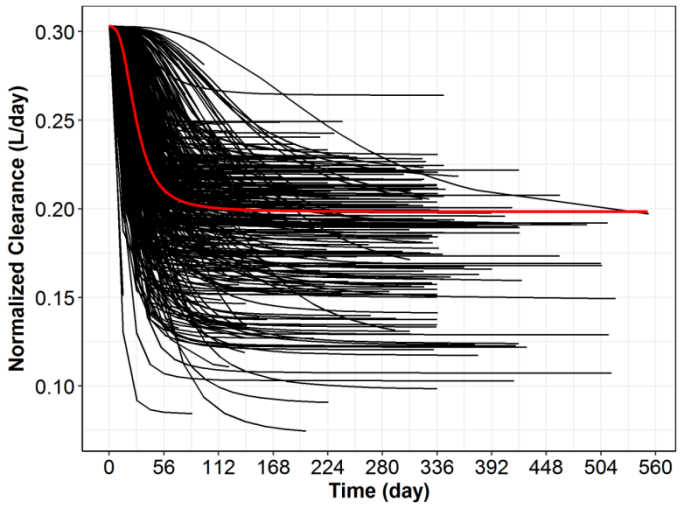
Source: Table 1 of population pharmacokinetics report

Methods: Data from two studies of 1423 and 1540 were used to build a population model for cemiplimab. Model selection was based on physiological and pharmacological rationale and the principle of parsimony – simpler models were chosen over more complex models when statistically justified. The Pop PK model was developed in three stages, consisting of the base model, full covariate, and final covariate models. First, a base model was developed to describe the PK of cemiplimab without consideration of covariate effects. Second, a full covariate model was developed by incorporating the effect of all pre-specified covariate parameter relationships. In the third stage, the final Pop PK model was developed by retaining covariates that improved a goodness-of-fit statistic (MOFV).

Result: The final Pop-PK model parameter estimation is shown in Table 42. For the final base-model, a 2-compartment model with zero-order IV infusion and first-order elimination was selected. In this model, between-subject variability is expressed as exponential terms on clearance (CL)/ Inter-compartmental clearance between the central and peripheral compartments (Q) and distribution volume of central compartment (V_2)/distribution volume of peripheral compartment (V_3), with an off-diagonal correlation between them, and residual error is modeled as additive and proportional residual error. This model was implemented with time varying CL, described using a sigmoid-E_{max} function.

Time-Varying CL vs. fixed CL: The inclusion of a time-varying change on clearance significantly improved the model fit and resulted in a reduction of the minimum objective function value (MOFV) greater than 300 points relative to the model with constant clearance. In particular, the MOFV value for the sigmoid-E_{max} based model was markedly lower than the one with constant CL (by 638 points) and hyperbolic (E_{max}) effect on CL (by 91 points). Therefore, time-varying CL with sigmoid-E_{max} functional form was selected for subsequent model development. Figure 21, a plot of normalized individual clearance over the course of treatment duration, illustrates the changes of clearance over time. The results show that on average clearance decreases by more than 30% over time compared to the baseline clearance, i.e. from ~0.30 L/day to ~0.20 L/day within 16 weeks of treatment. The half-life (T50) of time-varying clearance was estimated to be ~30 days in a typical patient.

Figure 21: Post-hoc Individual Clearance Decreased Over the Course of Treatment Duration Using the final Base Model (LN014)

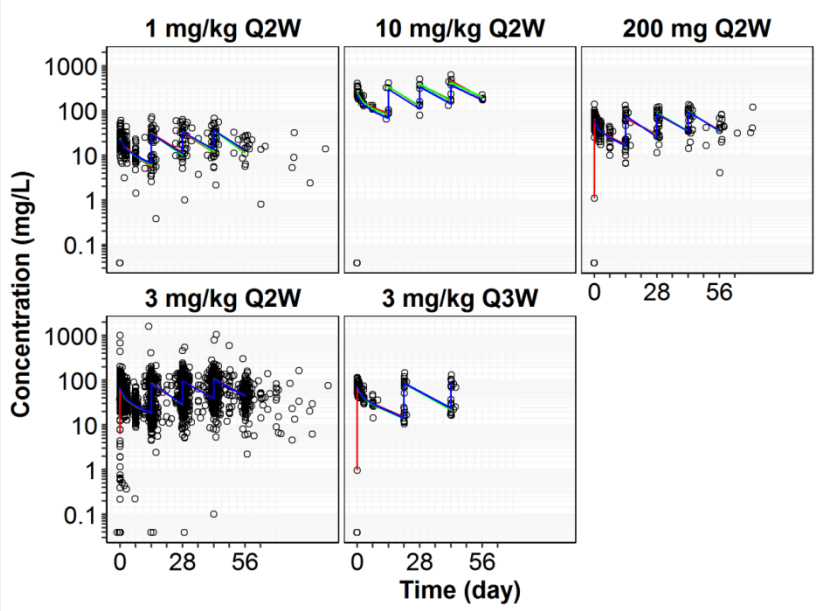


Source: Figure 3 of population pharmacokinetics report

Individual predicted (IPRED), population predicted (PRED) and observed cemiplimab concentrations versus time by dose group are presented in

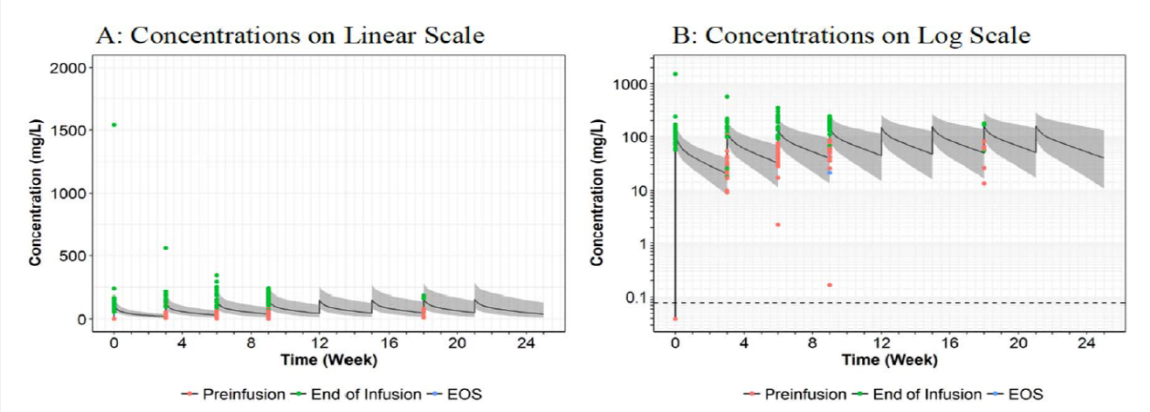
Figure 22. Inspection of the goodness-of-fit plots suggested good agreement between observed geometric mean data and model predictions for most conditions.

Figure 22: Goodness of fit Plot for the Final Model by Dose Groups During the First Treatment Cycle in Study 1423 and 1540



Source: Figure 10 of population pharmacokinetics report

Figure 23: 350 mg Q3W Dose Regimen – Observed Cemiplimab Concentrations in Patients with mCSCC and Simulated Cemiplimab Concentration-Time Profiles (95% CI) in Patients With Solid Tumor



The concentration data (C_{eoi} and C_{trough}) from 35 patients with mCSCC who received at least 1 dose of cemiplimab at 350 mg Q3W (Group 3 in Study 1540) were overlaid on the simulated concentration-time profiles created using the population PK model.

Note: The black solid line represents the median of 2000 simulated concentration-time profiles, and the gray area shows the 95% CI with 2.5 percentile and 97.5 percentile of the simulated profiles.

Source: Figure 15 of Summary of Clinical Pharmacology

Table 42: Sponsor's Parameter Estimates of the Final Model (LN900)

Name	Description	Unit	Estimate(RSE)	CI95
TVCL	Typical clearance	L/day	0.287(2.15%)	[0.274-0.309]
TVV2	Typical central volume of distribution	L	3.34(1.11%)	[3.28-3.40]
TVQ	Typical inter-compartmental clearance	L/day	0.647(4.50%)	[0.579-0.722]
TVV3	Typical peripheral volume of distribution	L	1.69(3.06%)	[1.53-1.85]
RUVCV	proportional error		0.180(0.360%)	[0.173-0.187]
RUVSD	additive error	mg/L	1.34(5.25%)	[0.0245-1.95]
EMAX	Typical maximum effect in sigmoid model		-0.382(5.53%)	[-0.476--0.324]
T50	Typical half-life to achieve half of the maximum effect	day	32.1(6.16%)	[24.0-38.6]
HILL	hill exponent in Sigmoid model		3.17(9.08%)	[2.33-4.13]
WGT_ON_CLQ	Weight on CL/Q		0.454(13.3%)	[0.300-0.609]
WGT_ON_VSS	Weight on Vss		0.935(8.36%)	[0.779-1.08]
ALT_ON_CLQ	ALT on CL/Q		-0.0818(25.0%)	[-0.137--0.0240]
ALB_ON_CLQ	Albumin on CL/Q		-1.00(8.72%)	[-1.23--0.722]
IGG_ON_CLQ	IgG on CL/Q		0.182(15.4%)	[0.110-0.270]
BMI_ON_VSS	BMI on Vss		-0.553(16.1%)	[-0.707--0.378]
BLK_ON_T50	Black on T50		0.946(30.0%)	[0.417-1.70]
IIV_CLQ	IIV on CL/Q		0.0893(5.52%)	[0.0655-0.120]
IIV_VSS	IIV of Vss		0.0412(6.38%)	[0.0345-0.0484]
IIV_EMAX	IIV of Emax		0.260(15.3%)	[0.159-0.357]
IIV_T50	IIV on T50		0.583(16.9%)	[0.394-0.970]
OMEGA.2.1.	IIV between CLQ and VSS		0.0403(8.57%)	[0.0323-0.0502]

Source: Table 13 of population pharmacokinetics report

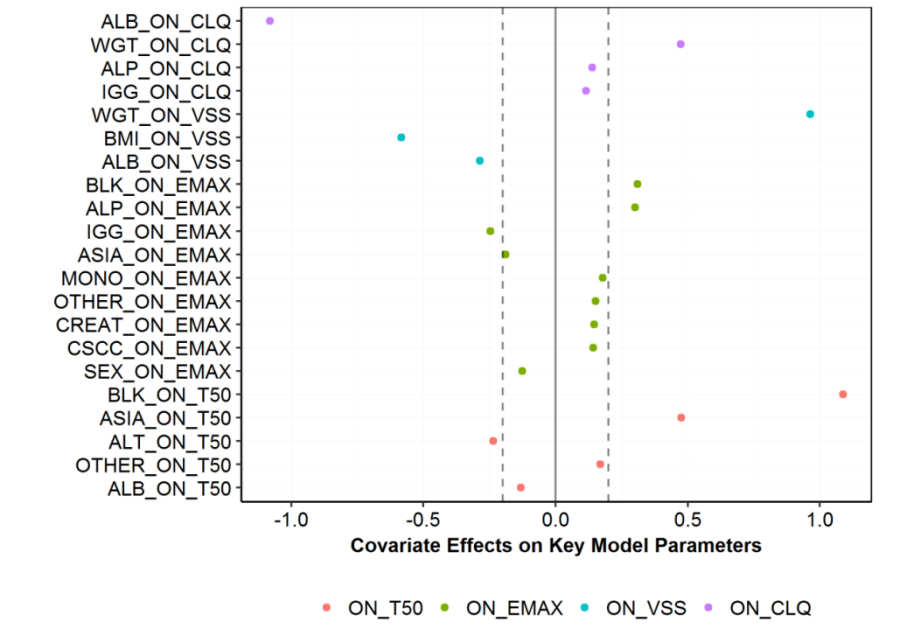
Covariate Effect:

Body weight and baseline albumin are the most influential covariates based on the magnitude of their effect sizes on cemiplimab clearance. Several covariates were found to be associated with E_{max} and T50 in the sigmoid E_{max} model for the time-varying clearance. A total of 35 pairs of covariate-parameter including WGT_ON_CLQ and WGT_ON_VSS, were selected to characterize the covariate-parameter relationship.

Using the listed pairs of covariate-parameter, a full covariate model, LN103, was constructed to further assess the covariate effects on the key model parameters (CL/Q, V_{ss}, E_{max} and T50) and the resulting covariate effects (greater than 0.1) are presented in Figure 24. The results confirmed that body weight was one of the most influential covariates on cemiplimab clearance parameters (CL and Q) and on volume of distribution (V_{ss}), and they supported the correctness of incorporating body weight into the base structural model. Results also indicated that albumin was an important

covariate on clearance parameters (CL and Q). BMI was identified as an important covariate on V_{ss}. For sigmoid Emax functional form of CL, race (black, Asia and other), immunoglobulin G (IGG), alkaline phosphatase (ALP), creatinine concentration (CREAT), alanine aminotransferase (ALT), and mono-therapy (MONO) were found to have impacts on E_{max} and T50. Notably, disease status (ECOG or LDH) was not (nominally) statistically significant in this assessment.

Figure 24: Forest Plot of Covariates and Their Effect on Model Parameters, Estimated by the Full Model, Relative to the Parameter Values of a Reference Patients



Source: Figure 7 of population pharmacokinetics report. Color represents the category of the covariate model parameters (either on CLQ, VSS, Emax or T50); each dot represents the covariate effects (exponent, α) relative to the reference value. ALB: albumin (g/L), ALB: albumin (g/L), ALP: alkaline phosphatase (IU/L), ALT: alanine aminotransferase (IU/L), AST: Aspartate Aminotransferase(IU/L), BMI: body mass index, BSA: body surface area, BILI: Total Bilirubin(μmol/L), CRCL: Creatinine Clearance (mL/min), CREAT: creatinine concentration (μmol/L), IgG: immunoglobulin G (g/L), LDH: lactate dehydrogenase (IU/L). The reference patient is a 60-year-old white male weighing 75 kg with a baseline BMI (BMI) of 26.5 kg/m2, albumin level (ALB) of 38 g/L, lactate dehydrogenase (LDH) of 250 IU/L, alkaline phosphatase (ALP) of 90 IU/L, alanine aminotransferase (ALT) of 21 IU/L, creatinine (CREAT) of 75 umol/L, immunoglobulin G (IGG) of 9.7 g/L and body surface area (BSA) of 1.88 m2.Parameter estimate in the reference patient is considered 0.0% (vertical solid line), and dashed vertical lines are at -20% and 20% of this value.

Reviewer's comments: Sponsor's pop-PK model is acceptable; however, there is a minor discrepancy between sponsor vs. FDA's executed result. FDA's pop-PK executed result is shown in Table 43. Briefly, there is no clinical significant covariate effect identified.

Table 43: Parameter comparison between sponsor's final Pop-PK model and FDA's final Pop-PK model

Theta	*Description*	*Estimate*	*FIX*	*SE*	*RSE*	*95%CI*
1	TVCL	0.295	-	0.0021	0.7%	0.291-0.299
2	TVV2	3.44	-	0.0255	0.7%	3.39-3.49
3	TVQ	0.652	-	0.0217	3.3%	0.609-0.695
4	TVV3	1.81	-	0.017	0.9%	1.777-1.843
5	TVF1	0.7	FIX	0	0%	0.7-0.7
6	TVKA	0.4	FIX	0	0%	0.4-0.4

7	RUVCV	0.179	-	0.0006	0.4%	0.178-0.18
8	RUVSD	1.48	-	0.0526	3.6%	1.377-1.583
9	EMAX	-0.374	-	0.0036	1%	-0.381--0.367
10	T50	30.2	-	0.245	0.8%	29.72-30.68
11	HILL	3.08	-	0.0094	0.3%	3.062-3.098
12	WGT_ON_CLQ	0.508	-	0.0275	5.4%	0.454-0.562
13	WGT_ON_VSS	1	-	0.0301	3%	0.941-1.059
14	ALT_ON_CLQ	-0.0808	-	0.009	11.2%	-0.098--0.063
15	ALB_ON_CLQ	-0.98	-	0.04	4.1%	-1.058--0.902
16	IGG_ON_CLQ	0.198	-	0.02	10.1%	0.159-0.237
17	BMI_ON_VSS	-0.564	-	0.0323	5.7%	-0.627--0.501
18	BLK_ON_T50	0.984	-	0.0905	9.2%	0.807-1.161

Source: Reviewer's analysis

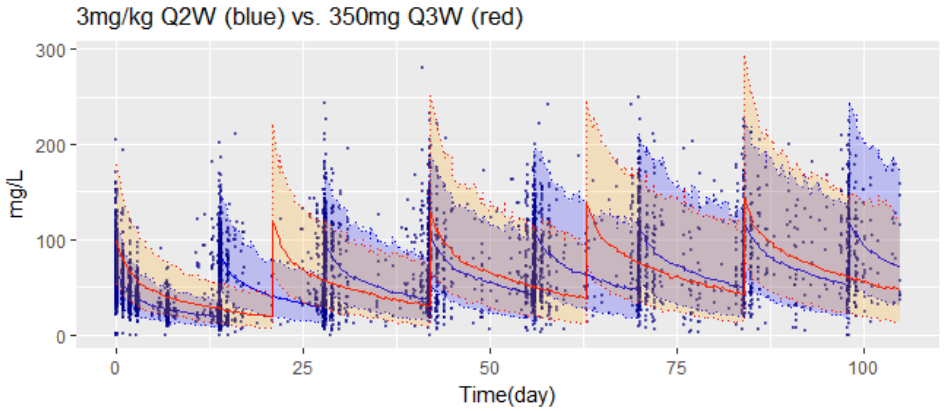
FDA analysis

Modeling and Simulation of 350mg Q3W flat Dose

Modeling and simulation of 350 mg Q3W dosing regimens was conducted in 505 patients shown in red in

Figure 25. The red solid line is the median of 350 mg Q3W and orange shade is the 95% quantile of the 350 mg Q3W dosage regimen. The blue solid line is the median of 3 mg/kg Q2W and the blue shade is the 95% quantile of 3 mg/kg Q2W. Table 44 showed mean value of C_{max} right after the first dose at first cycle as well as steady state. The mean of first cycle C_{max} increased by 51%. The mean level of steady state C_{trough} decreased by 13%. The mean level of steady state C_{max} increased by 22.3%.

Figure 25: Comparison of Model Simulated 350 mg Q3W (Red) vs. 3mg/kg Q2W (Blue)



Source: Reviewer's independent analysis. Model simulated 350 mg Q3W dosing regimen was conducted. Red line indicated the median of 350 mg Q3W and orange shade is 95% quantile of 350 mg Q3W. Blue line and blue shade indicated the median and 95% quantile of 3 mg/kg dosing regimen. Blue dots are PK observation from 3mg/kg dosing regimens.

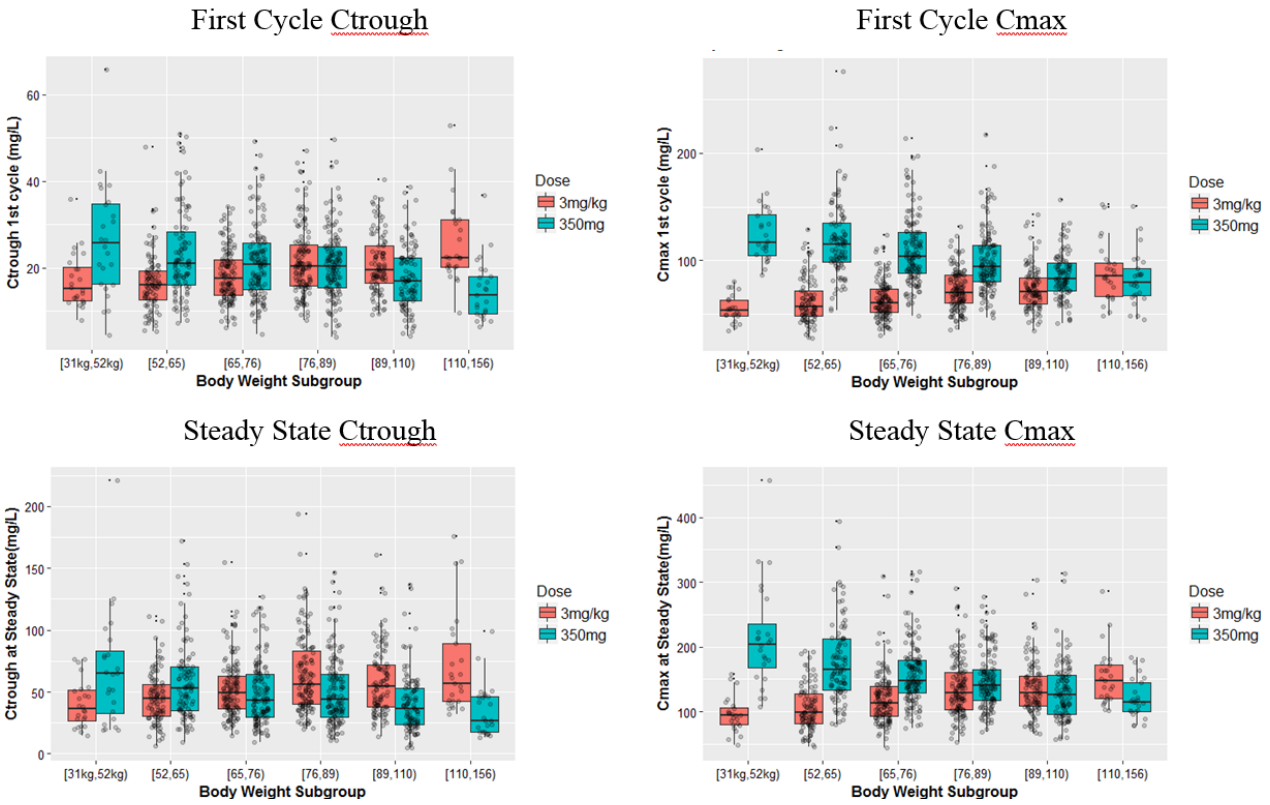
Table 44: Comparison of Model Simulated 350 mg Q3W Exposure vs. 3 mg/kg Q2W at Population Level and Body Weight Stratified Subgroups

	First Ctrough			First cycle Cmax			Steady state Ctrough			Steady state Cmax		
	3mg/kg	350mg	% change	3mg/kg	350mg	% change	3mg/kg	350mg	% change	3mg/kg	350mg	% change
Median	18.6	19.8	↑6.5%	65.2	98.2	↑50.6%	49.8	43.3	↓13.1%	118.8	145.3	↑22.3%
(95% quantiles)	(9.4, 33.5)	(8.9,38.5)		(40.2, 107.6)	(60.2, 161.8)		(22.5, 107.3)	(16.1, 107.7)		(68.5, 200)	(85.2, 263.81)	
BW Subgroups (Mean)												
[31kg,52kg)	17	26.5	56%	54.9	124.9	128%	40.46	67.88	68%	95.6	215.2	125%
[52,65)	16.6	23.3	40%	62	118.9	92%	45.75	57.56	26%	105.4	175.9	67%
[65,76)	18.4	21.2	15%	63	109.4	74%	52.54	49.13	-6%	120	158	32%
[76,89)	21.5	20.8	-3%	72.4	99.5	37%	64.03	50.38	-21%	136	147.5	8%
[89,110)	21	17.6	-16%	73.8	85.8	16%	57.77	40.71	-30%	136	131.2	-4%
[110,156)	25.7	14.8	-42%	89	82.9	-7%	71.15	34.87	-51%	153.5	121	-21%

Source: Reviewer's independent analysis. Model and simulation was conducted, and model predicted median and 95% quantile of 350 mg Q3W and 3 mg/kg Q2W dosing regimens are listed in above table. Body weight stratified subgroup analysis were also listed.

To compare the change within each body weight subgroup, a body weight-stratified subgroup analysis was conducted and is shown in Table 44. Body weight cut off was the 5%, 25%, 50%, 75% and 95% quantile of the 505 patients in population PK database. Percentage of change is also shown in Table 44 and a bar graph comparison stratified by body weight is shown in Figure 26. Compared with the 3 mg/kg Q2W dosing regimen, low body weight patients generally have increased C_{max} when switching to 350 mg Q3W. C_{max} in patients with body weight below 52 kg by switching to 350 mg Q3W flat dose is around 2.3-fold compared with 3 mg/kg Q2W. Moreover, C_{max} of 350 mg Q3W exceeded the exposure range of the 3 mg/kg dosing regimen. For the first cycle $C_{max,}$ patients below 76 kg have C_{max} higher than 109.4mg/L while the upper 95 quantiles of exposure range in 3 mg/kg Q2W is 107.6 mg/L (Table 44). Similarly, at steady state, patients below 52 kg had an average exposure of 215.2 mg/L and exceeded 200 mg/L which is the upper 95% quantile of exposure range in 3 mg/kg Q2W (Table 44).

Figure 26: Comparison of PK Stratified by Body Weight Subgroup

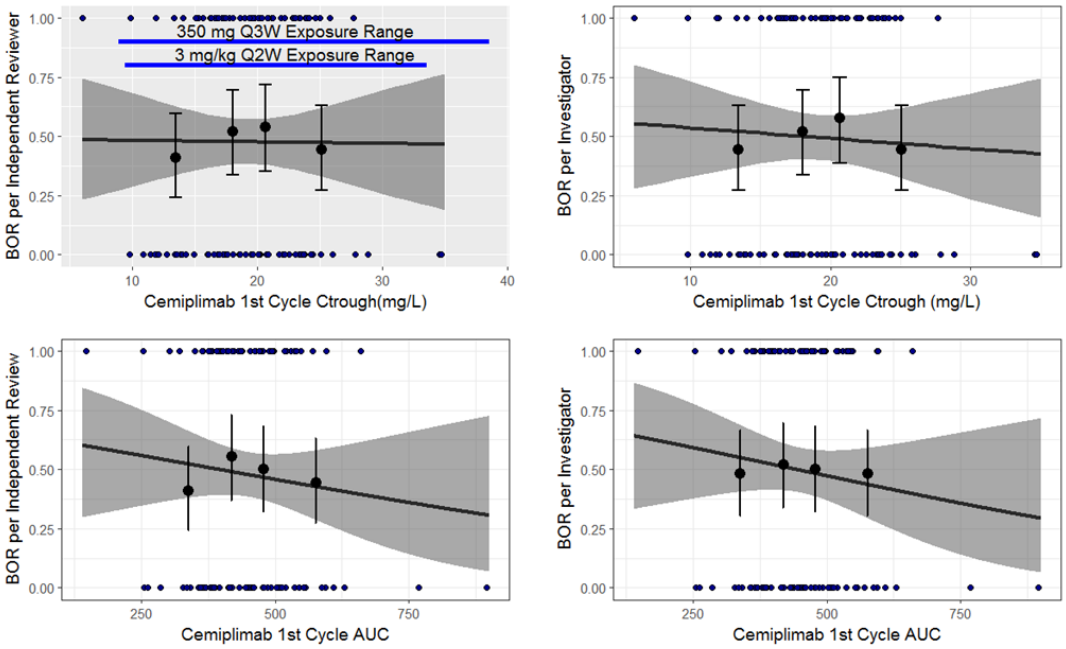


Source: Reviewer's independent analysis. Blue bar indicated simulated PK result of 350 mg Q3W stratified by body weight subgroup. Red bar indicated simulated PK result of 3 mg/kg Q2W stratified by body weight subgroup. Dots indicate individual result.

Exposure Response Relationship for Efficacy

We have conducted exposure response analysis for efficacy and safety for cemiplimab. For exposure efficacy: 107 patients with CSCC (metastatic CSCC: n=75, la CSCC: n=32) from both study 1423 (n=26) and study 1540 (n=81) were included in the exposure-response analysis of efficacy outcomes. Among these patients, 106 patients received the 3 mg/kg Q2W dosing regimen and 1 patient received the 1 mg/kg Q2W dosing regimen. The solid line in the figures below are the logistic regression of ORR per independent reviewer. Results of ER per the investigators is very similar. Exposure-response analyses showed no correlation between PK exposure and overall response rate (ORR) at a range of around 10 to 30 mg/L. The grey area is the 95% CI. For each exposure quartile, the observed response rate and its 95% CI is plotted as a black circle and error bar vs the mean concentration. The blue bar is the exposure range of cemiplimab at the dosing regimen of 3 mg/kg Q2W and simulated 350 mg Q3W. The dots in the upper part of the figures represent responders at their concentration and the blue dots in the lower part of the figures represent the non-responders at their concentration.

Figure 27: Exposure response for efficacy by logistic regression



Source: FDA reviewer's analysis. Solid line is the logistic regression of the predicted ORR per investigator (right panel) or independent reviewer (left panel). The grey area is the 95% CI. For each exposure quartile, the observed response rate and its 95% CI is plotted as circle and error bar vs the mean concentration. The blue bar is the exposure range of each dosing regimen. Exposure-response analyses showed no correlation between PK exposure (first cycle C_{trough} or AUC) and overall response rate (ORR).

Table 45: Estimated Parameters in logistic regression for ER relationship for efficacy

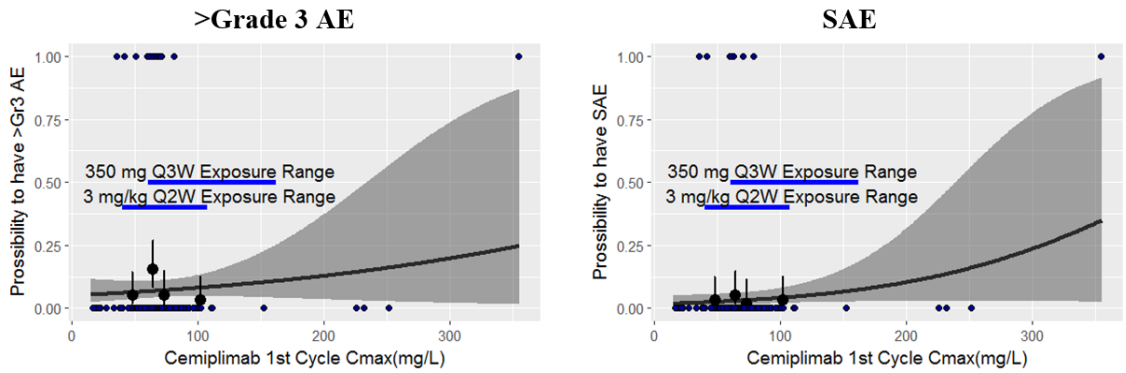
		Estimate	Std. Error	P value
Investigator ~ AUC	Intercept	0.63	0.8996	0.481
	Exposure Slope	-0.0014	0.0019	0.458
IRC ~ AUC	Intercept	0.508	0.899	0.572
	Exposure Slope	-0.0013	0.00194	0.494
Investigator ~ Ctrough	Intercept	0.1	0.813	0.901
	Exposure Slope	-0.006	0.04	0.88
IRC ~ Ctrough	Intercept	-0.04	0.81	0.957
	Exposure Slope	-0.0026	0.04	0.95

Source: FDA's analysis

Exposure Response Relationship for Safety

238 patients with cemiplimab monotherapy were included in exposure safety relationship analyses. No evident relationships for Grade 3+ AEs and SAEs were identified. The confidence intervals were wide beyond the dosing range above 100mg/L. The blue bar indicated the simulation of C_{max} of 3mg/kg Q2W and 350mg Q3W exposure range.

Figure 28: Exposure Response Relationship for First Cycle Cmax versus Incident Rate of >Gr3 AE and SAE



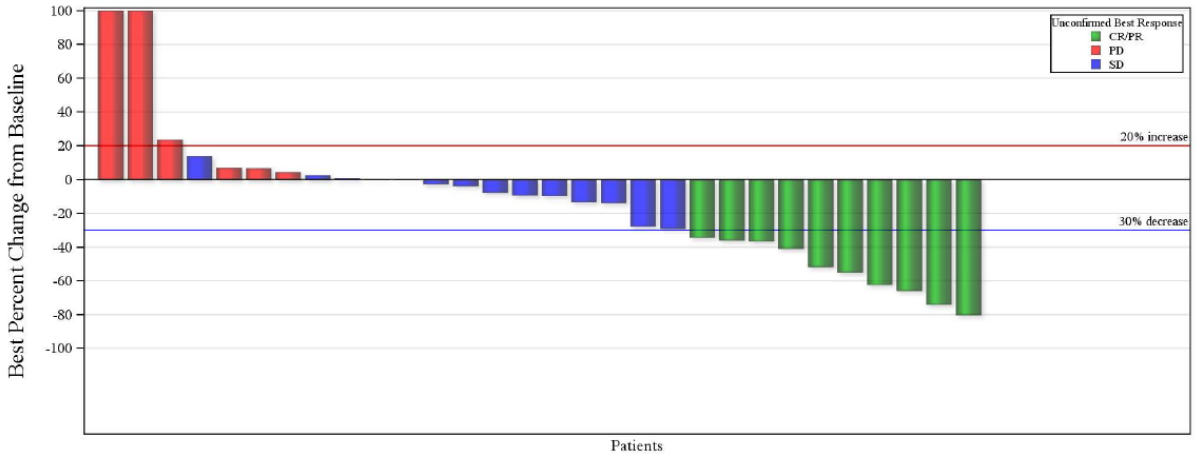
Source: FDA's Analysis. Solid line is the logistic regression of the predicted probability of Grade 3+ AEs and SAEs. The grey area is the 95% CI. For each exposure quartile, the observed AE incidence and its 95% CI is plotted as a circle and error bar vs the mean concentration. The blue bar is 5% to 95% quantile of exposure of cemiplimab at the dosing regimen of 350 mg Q3W exposure range (upper) and at dosing regimen of 3mg/kg Q2W exposure range. The black dots at y=0 or y=1 are observed individuals with x axis indicating the exposure and incidence of AEs or SAEs.

Preliminary Efficacy and Safety Data of 350 mg Q3W Flat Dose

Additional preliminary efficacy and safety data from patients received 350 mg Q3W flat dose was received at 90 days' safety update.

Among the 32 patients who enrolled on or before 22 Nov 2017, and had the opportunity to reach first response assessment at week 9 (±3 days) prior to the data cutoff date (20 Jan, 2018), BOR (including unconfirmed responses) at time of data cutoff was CR = 1 patient, PR = 9 patients, SD = 13 patients, and PD = 7 patients. Among the 10 patients with PR/CR, all remain on study treatment; among the 13 patients with SD, 10 remain on study treatment and most had initial reductions in target lesions (
Figure 29).

Figure 29: Waterfall Plot per RECIST 1.1 by Investigator Assessment (Group 3: Patients Who Had At Least One Post Baseline Scan Available Within the Data Cutoff)



The 90-Day safety update for cemiplimab contains the updated safety information with at data cutoff date of 20 Jan, 2018. It includes a total of 49 patients with mCSCC (including 26 new patients with mCSCC who enrolled during the 90-day interval) in Group 3 of Study 1540 who received at least 1 dose of 350 mg cemiplimab IV Q3W. The prevalence of TEAE at all grades and Grade 3/4/5 of 350 Q3W regimen is comparable or slightly lower than 3 mg/kg Q2W regimen (Table 46).

Table 46: 90-Day Safety Update of Cemiplimab at Dosing Level of 350 mg Q3W

	mCSCC Cemiplimab: 3 mg/kg Q2W (N=59)		laCSCC Cemiplimab: 3 mg/kg Q2W (N=64)		mCSCC Cemiplimab: 350 mg Q3W (N=49)		Total (N=172)	
System Organ Class, n (%) Preferred Term, n (%)	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5
Total number of TEAEs	490	54	486	51	169	25	1145	130
Number of Patients with any TEAE, n (%)	59 (100%)	26 (44.1%)	60 (93.8%)	22 (34.4%)	39 (79.6%)	14 (28.6%)	158 (91.9%)	62 (36.0%)

Source: Table 14.3.1.2.4 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and NCI Grade:

Listing of Analyses Codes and Output Files

File Name	Description	Location in \\cdsnas\pharmacometrics\
ln900.mod	Final Pop-PK model	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Cemiplimab_BLA761097_YX\Pop-PK
ln901.mod	Simulation of 350mg Q3W dosing regimen	
ln902.mod	Simulation of 3mg/kg Q2W dosing regimen	
ln903.mod	Simulation of 250mg Q2W dosing regimen	
cemiplimab ER.R	Exposure response analysis file	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Cemiplimab_BLA761097_YX\ER\ER
ADEXPAE.csv	AE file	
ADEXPEFF.csv	ORR file	

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MISSIRATCH BIABLE
09/21/2018

EMILY F WEARNE
09/21/2018

WHITNEY S HELMS
09/21/2018

JOHN K LEIGHTON
09/21/2018

XILING JIANG
09/21/2018

HONG ZHAO
09/21/2018
I concur.

YUAN XU
09/21/2018

JIANG LIU
09/21/2018

NAM ATIQUR RAHMAN
09/21/2018

MALLORIE FIERO
09/21/2018

PALLAVI S MISHRA-KALYANI
09/23/2018

RAJESHWARI SRIDHARA
09/23/2018

DENISE A CASEY
09/23/2018

DENISE A CASEY
09/23/2018

SUZANNE G DEMKO
09/24/2018

STEVEN J LEMERY
09/28/2018

RICHARD PAZDUR
09/28/2018