CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761223Orig1s000

MULTI-DISCIPLINE REVIEW

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

BLA Multi-Disciplinary Review and Evaluation
Assessment Aid

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	Biologic Licensing Application (BLA)
Application Number(s)	761223
Priority or Standard	Priority
Submit Date(s)	12/18/20
Received Date(s)	12/18/20
PDUFA Goal Date	8/18/21
Division/Office	Division of Oncology-1/ Office of Oncologic Diseases
Review Completion Date	*Electronic Stamp Date*
Established Name	Dostarlimab-gxly
(Proposed) Trade Name	JEMPERLI
Pharmacologic Class	Programmed death-1 (PD-1) Blocking Antibody
Code name	TSR-042
Applicant	GlaxoSmithKline LLC
Formulation(s)	500 mg/10 mL, single-dose vial
Dosing Regimen	Dose 1 through 4: 500 mg every 3 weeks; Subsequent dosing beginning 3 weeks after dose 4 (Dose 5 onwards): 1,000 mg every 6 weeks
Applicant Proposed Indication(s)/Population(s)	JEMPERLI is indicated for the treatment of adult patients with mismatch repair deficient (dMMR) recurrent or advanced solid tumors, as determined by an FDA-approved test, that have progressed on or following prior treatment and who have no satisfactory alternative treatment options. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).
Recommendation on Regulatory Action	Accelerated Approval
Recommended Indication(s)/Population(s) (if applicable)	JEMPERLI is indicated for the treatment of adult patients with mismatch repair deficient (dMMR) recurrent or advanced solid tumors, as determined by an FDA-approved test, that have progressed on or following prior treatment and who have no satisfactory alternative treatment options. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued

	approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

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LIST OF ABBREVIATIONS

ADA	anti-drug antibody
ADR	adverse drug reaction
AE	adverse event
ALB	albumin
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{ss}	area under the concentration versus time curve at steady state
$AUC_{0\text{-}tau}$	area under the concentration versus time curve for a dosing interval
BICR	blinded independent central review
BLA	biologics license application
BMI	body mass index
BOR	best overall response
BTD	breakthrough therapy designation
CBER	Center for Biologics Evaluation and Research
CBC	complete blood count
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CI	confidence interval
CL	clearance
CL_{ss}	steady-state clearance
C_{max}	maximum concentration
$C_{max, ss}$	maximum concentration at steady-state
CMC	chemistry, manufacturing, and controls
C_{min}	minimum concentration
COA	clinical outcome assessment
CR	complete response
CRC	colorectal cancer
CRF	case report form
CRT	clinical review template
CSR	clinical study report
CT	computerized tomography
CV	coefficient of variation
CYP	cytochrome P450
DCR	disease control rate
DDI	drug-drug interaction
dMMR	mismatch repair-deficient
DOR	duration of response
EC	endometrial cancer
ECG	electrocardiogram

ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
eCTD	electronic common technical document
EMA	European Medicines Agency
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer quality of life questionnaire
EOT	end-of-treatment
EQ-5D-5L	European quality of life scale, 5 dimensions, 5 levels
E-R	exposure-response
FDA	Food and Drug Administration
FIGO	International Federation of Gynecology and Obstetrics
GCP	good clinical practice
GLP	good laboratory practice
GSK	GlaxoSmithKline
hERG	human ether-a-go-go-related gene
HIV	human immunodeficiency virus
ICH	International Conference on Harmonization
IDMC	independent data monitoring committee
IgG	Immunoglobulin G
IHC	immunohistochemistry
I_{max}	maximal decrease in clearance relative to baseline
IMM	immune modulatory medications
IND	Investigational New Drug
irAE	immune-related adverse event
irBOR	immune-related best overall response
irCR	immune-related complete response
irDCR	immune-related disease control rate
irDOR	immune-related duration of response
irORR	immune-related objective response rate
irPD	immune-related progressive disease
irPFS	immune-related progression-free survival
irPR	immune-related partial response
irRECIST	immune-related response evaluation criteria in solid tumors
ISS	Integrated Summary of Safety
IV	intravenous
KM	Kaplan-Meier
mAb	monoclonal antibody
MedDRA	medical dictionary for regulatory activities
mITT	modified intent to treat
MMRp	mismatch repair-proficient
MRI	magnetic resonance imaging
MSI	microsatellite instability
MSI-H	microsatellite instability-high
MSS	microsatellite stable
NAb	neutralizing antibody

NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NDA	New Drug Application
OR	overall response
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PD-L2	programmed cell death-ligand 2
PDy	pharmacodynamic
PFS	progression-free survival
PI	prescribing information
PK	pharmacokinetics
POLE	polymerase ε
POLE-mut	polymerase ε mutated
PR	partial response
PREA	Pediatric Research Equity Act
PRO	patient-reported outcome
PROC	platinum resistant ovarian cancer
PT	preferred term
PTT	partial thromboplastin time
Q1	first quartile
Q3	third quartile
QTc	corrected QT interval
RECIST	response evaluation criteria in solid tumors
RO	receptor occupancy
RTD	recommended therapeutic dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SI	International Standard (of Units)
SOC	system organ class
TEAE	treatment emergent adverse event
ULN	upper limit of normal
US	United States
V1	central volume of distribution
V_c	volume of distribution of central compartment
WHO	World Health Organization

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1. EXECUTIVE SUMMARY

1.1. Product Introduction

Dostarlimab-gxly (referred to as dostarlimab) is a humanized monoclonal antibody (mAb) of the immunoglobulin G4 (IgG4) isotype. Dostarlimab binds to programmed cell death protein 1 (PD-1), a cell surface receptor expressed on activated T cells. Dostarlimab inhibits the binding of PD-1 to both of its known ligands, programmed cell death ligand-1 and 2 (PD-L1 and PD-L2). Blocking of the interaction between PD-1 and its ligands, PD-L1 and PD-L2 can release PD-1 mediated T-cell inhibitory regulation and therefore reduce inhibition of an anti tumor response.

At the time of submission of the current BLA 761223 on 12/18/20, dostarlimab was not yet approved in the United States for any indication. However, dostarlimab for the treatment of mismatch repair deficient (dMMR) endometrial cancer was under review by FDA under BLA 761174 at that time. Since the submission of the current application, dostarlimab was granted accelerated approval for the treatment of dMMR endometrial cancer under BLA 761174 on 4/22/21.

The Applicant's proposed indication at the time of BLA 761223 submission on 12/18/20 was as follows:

Dostarlimab is indicated for the treatment of adult patients with mismatch repair deficient (dMMR) recurrent or advanced solid tumors, as determined by an FDA approved test, that have progressed on or following prior treatment and who have no satisfactory alternative treatment options.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The review team recommends accelerated approval for dostarlimab in accordance with Title 21 of the Code of Federal Regulations (21CFR601.41, subpart E). This was supported by evidence of safety and effectiveness provided by submitted data from Cohorts A1 and F from Part 2B of Study 4010-01-001 (GARNET study).

Currently, there is one FDA-approved agent, pembrolizumab, for the treatment of patients with metastatic/ unresectable mismatch repair deficient (dMMR) solid tumors that has progressed following prior treatment. This product is approved under accelerated approval, pending confirmation of clinical benefit from additional studies. There are currently no agents with regular FDA approval for patients with dMMR advanced solid tumors.

Study 4010-001 was a Phase 1 dose escalation and cohort expansion study of dostarlimab (TSR-042) in patients with advanced solid tumors, was submitted and reviewed in consideration of the indication. Expansion cohort A1 enrolled patients with dMMR or microsatellite instability-high (MSI-H) endometrial cancer that had progressed on or after platinum-based chemotherapy and expansion cohort F enrolled patients with dMMR/MSI-H and/or POLE-mutant non-endometrial cancers who had experienced disease progression following up to 2 prior lines of systemic therapy for recurrent or advanced disease, had no alternative treatment options, and had documented progression and measurable disease according to RECIST 1.1, per central radiology

review. Additional criteria were included for specific tumors, including colorectal cancer patients.

Tumor testing for MMR and /or MSI status was required prior to enrollment. Acceptable testing methods to determine study eligibility according to MMR or MSI status included immunohistochemistry (IHC), polymerase chain reaction (PCR), or next generation sequencing (NGS). The protocol was amended once the study was ongoing to allow for use of either central or local MMR IHC testing to select patients for treatment with dostarlimab. Despite that the study allowed for patient enrollment based upon either MMR or MSI status, the Applicant only developed and submitted a Premarket Approval (PMA) application (P210001) to the Center for Devices and Radiological Health (CDRH) to seek approval for the VENTANA MMR RxDx Panel as a companion diagnostic device (CDx). As a result, the Applicant's proposed indication statement for dostarlimab under the current BLA761223 is for the treatment of patients with dMMR recurrent or advanced solid tumors, as determined by an FDA-approved test.

The efficacy results from a total of 209 patients with endometrial cancer and various solid tumors demonstrated a RECIST v1.1 confirmed ORR of 41.6% (95% CI: 34.9%, 48.6%) based upon 87 responders out of 209 patients included in the efficacy population. This included 19 patients with complete response and 68 patients with partial response. The median duration of response, using a data cutoff date of 11/1/20, was 34.7 months (range 2.6-35.8 months). Ninety-five percent (95%) of responders had a DOR ≥ 6 months and 75% had DOR ≥ 12 months. These efficacy results are considered to be better than available therapies for patients with advanced dMMR solid tumors and are supportive of an accelerated approval action.

The safety of dostarlimab was assessed in 267 patients with dMMR recurrent or advanced solid tumors from cohorts A1 and F in Part 2B of the GARNET trial who had received dostarlimab monotherapy. This included 126 patients with dMMR endometrial cancer and 141 patients with other dMMR solid tumors. The review was supplemented by an assessment of safety in 515 patients with various advanced solid tumor enrolled in Part 2B of Study 4010-01-001. Common toxicities for in ≥ 20% of patients with dMMR solid tumors treated with dostarlimab included fatigue/ asthenia, anemia, diarrhea, and nausea. Immune related adverse events (irAEs), which are an adverse event of special interest associated with anti-PD-1/PD-L1 therapies, including dostarlimab, occurred in 33% of patients with dMMR solid tumors enrolled on Cohorts A1 and F. The incidence of organ-specific irAEs seems similar to the incidence reported with other checkpoint inhibitors. Based upon review of the data submitted, the safety profile of dostarlimab is considered to be acceptable, in the context of the proposed indication.

With regard to the CMC and Product Quality aspects of the application, all CMC information is cross referenced to BLA 761174 for dostarlimab-gxly which was approved on April, 22, 2021. During review of BLA 761223, an inspection of the drug product manufacturing facility, (b) (4) was conducted (b) (4) and the outcome of that inspection was VAI.

The recommendation from the Office of Pharmaceutical Quality (OPQ), CDER, is to approve this product for human use under conditions specified in the package insert.

In conclusion, the review team recommends Accelerated Approval for the indication of dostarlimab in dMMR recurrent or advanced solid tumors based upon a favorable overall risk benefit assessment of the current application.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Dostarlimab is a programmed death receptor-1 (PD-1) blocking IgG_4 humanized monoclonal antibody.

DNA mismatch repair (MMR) deficiency/Microsatellite instability (MSI) can be identified in many solid tumor types and is attributable to defects in DNA MMR, a DNA repair system that repairs DNA replication errors. dMMR allows persistence of mismatch mutations throughout the genome and increases the tumor mutational burden (TMB). Repetitive regions such as microsatellites are specifically sensitive to dMMR, as demonstrated by the MSI-H phenotype of dMMR tumors. Tumors with increased TMB, dMMR, and MSI-H have been shown to upregulate immune checkpoints, including PD-1, to avoid detection by the immune system. As a result, tumors with these phenotypes have been found to be amenable and responsive to anti-PD-1 immunotherapy. This hypothesis, that dMMR/MSI-H tumors are amenable to anti-PD-1 therapy, was tested and resulted in the accelerated approval of pembrolizumab for the treatment of patients with unresectable, or metastatic MSI-H tumors, regardless of tumor histology. The approval was based upon overall response rate data including 149 patients, spanning 15 tumor types. However, confirmation of benefit to warrant regular approval is pending at this time. Additionally, pembrolizumab has accelerated approval for the first line treatment of unresectable or metastatic MSI-H or dMMR colorectal cancer. Nivolumab with or without ipilimumab have accelerated approval for MSI-H or dMMR metastatic colorectal cancer (CRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. There are no therapies with regular approval for a dMMR tumor agnostic indication.

The Applicant for the current dostarlimab BLA conducted a multi-cohort study 4010-01-001 (GARNET) to evaluate the efficacy of dostarlimab in the treatment of patients with dMMR/MSI-H tumors. Data from cohort A1 of the GARNET study enrolled patients with dMMR/ MSI-H relapsed endometrial cancer and resulted in accelerated approval of dostarlimab under BLA 761174 for the treatment of adult patients with dMMR recurrent or advanced endometrial cancer that has progressed on or following prior treatment with a platinum-containing regimen in April 2021.

Study 4010-001 (GARNET, NCT02715284) is an ongoing Phase 1 dose escalation and cohort expansion study of dostarlimab (TSR-042) in patients with advanced solid tumors. In this study, expansion cohort A1 enrolled patients with dMMR/MSI-H endometrial cancer that had progressed on or after platinum-based chemotherapy. Patients could have received no more than 2 prior lines of therapy for advanced, recurrent disease and had to have measurable disease according to BICR assessed RECIST v.1.1 to be eligible. The eligibility criteria for cohort F required subjects to have dMMR/MSI-H and/or POLE-mutant non-endometrial cancer. Subjects must have experienced disease progression following up to 2 prior lines of systemic therapy for recurrent or advanced

disease, have no alternative treatment options, and have documented progression and measurable disease according to RECIST 1.1, per central radiology review. Additionally, patients with dMMR/MSI-H colorectal cancer must have progressed after or been intolerant to treatment with fluoropyrimidine, oxaliplatin, and irinotecan and may have received a total of up to 3 prior lines. Patients with ovarian cancer were required to have platinum-resistant disease and could have received one additional line of therapy after becoming platinum resistant. Patients were screened based upon local testing results of MMR/MSI status using immunohistochemistry (IHC), polymerase chain reaction (PCR), or next generation sequencing (NGS) performed in a certified local laboratory, but eligibility required MMR IHC results to be submitted to a central laboratory prior to initiating treatment.

The Applicant partnered with Ventana Medical Systems and submitted PMA P210001 on 1/22/21, to seek approval for the VENTANA MMR RxDx Panel of antibodies as a companion diagnostic (CDx) to select patients in support of a tumor agnostic indication for dostarlimab. The VENTANA MMR RxDx Panel is a qualitative immunohistochemistry (IHC) test which assesses MMR proteins MSH6, PMS2, MSH2, and MLH1. CDRH review of the PMA has determined that the application is approvable.

The efficacy population for the current application included Cohorts A1 and F from study 4010-01-001, including a total of 103 patients with endometrial cancer in Cohort A1 and 106 patients with various solid tumors on Cohort F. Cohort F included 15 different solid tumor types including colorectal cancer, various other gastrointestinal tract tumors, ovarian, breast, renal cell, pleural, and adrenocortical tumors. Forty-three percent (43%) of patients had received one prior line of therapy, 36% had received 2 prior lines, and the remaining had received ≥ 3 prior lines. The study demonstrated a RECIST v1.1 confirmed ORR of 41.6% (95% CI: 34.9%, 48.6%) based upon 87 responders out of 209 patients included in the efficacy population. This included 19 patients with complete response and 68 patients with partial response. The median DOR, using a data cutoff date of 11/1/20, was 34.7 months (range 2.6-35.8 months). Ninety-five percent (95%) of responders had a DOR ≥ 6 months and 75% had DOR ≥ 12 months. These efficacy results are considered, by the review team, to be better than available therapies for advanced dMMR solid tumors that have recurred after prior lines of systemic therapy, and therefore support an accelerated approval action

The safety profile of dostarlimab was assessed based upon the safety data from Study 4010-01-001. The safety review focused on safety from 267 patients with dMMR recurrent or advanced solid tumors from cohorts A1 and F in Part 2B of the GARNET trial who had received at least one dose of dostarlimab at the recommended dose by the data cut off date. This included 126 patients with dMMR endometrial cancer and 141 patients with other dMMR solid tumors who received dostarlimab. Additionally, the safety analysis included assessment of immune-related adverse events (irAEs) and infusion related reactions in 515 patients with advanced solid tumor enrolled in Part 2B of Study 4010-01-001.

On study 4010-01-001 (Cohorts A1 and F), there were seven patients with fatal adverse reactions for an incidence of 2.6% in the safety population. The events included respiratory failure (n=1), cerebrovascular accident (n=1), aspiration (n=1), sepsis (n=1),

pneumonia/ respiratory failure (n=1), pleural effusion (n=1), rectovaginal fistula/ shock (n=1). After in-depth review of the narratives and case report forms, it was determined that only one of the deaths (respiratory failure) was possibly attributable to dostarlimab therapy, and this was the only fatal adverse reaction described in product labeling. Serious adverse reactions occurred in 34% of patients with dMMR solid tumors. The most common SAEs with an incidence of >2% included abdominal pain (3.7%), sepsis (2.6%), and acute kidney injury (2.2%). Discontinuations due to adverse event occurred in 9% of patients and increased alanine transaminase was the most common adverse event leading to discontinuation (1.1%). Dose reductions were not allowed, but dose interruptions due to adverse reaction occurred in 23% of patients treated with dostarlimab. Adverse reactions requiring interruption in ≥ 1% of patients included anemia, pneumonitis, diarrhea, adrenal insufficiency, and increased transaminases. Adverse events of special interest, namely immune-related adverse events (irAEs) occurred in 33% of patients with dMMR solid tumors enrolled on Cohorts A1 and F. The most common irAEs included transaminase elevation, diarrhea, and hypothyroid. The profile was similar in the larger safety database including 515 patients, in which the incidence of irAEs was 34%. Most irAEs were Grade 1-2 in severity and were managed with dose interruptions, systemic steroids, and hormone supplementation, as needed. The incidence rate of irAEs for dostarlimab has been found to be generally consistent with that of other anti-PD-1 agents. The overall safety profile of dostarlimab from Cohorts A1 and F of study 4010-01-001 was also unchanged from the previous review of the dostarlimab safety data.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Mismatch repair (MMR) proteins including MLH1, MLH2, MSH6, and PMS2 are responsible for recognizing and correcting errors in mismatched nucleotides and insertions/deletions that result from DNA polymerase slippage when microsatellites are being replicated. The MSI-H phenotype is associated with defective MMR proteins and can occur as a result of germline mutation in the MMR	Advanced, recurrent dMMR/ MSI-H solid tumors are serious and life-threatening.

	genes (eg, Lynch syndrome) or through methylation of an MMR gene promoter. • MSI-H cancers considered to be a set of cancers that share common immunobiology, characterized by high mutational burden, tumor-specific neo-antigen load mediated by MSI, and common defects in MMR. • Solid tumors, including those with underlying MSI-H /dMMR that have recurred following standard therapies, are incurable.	
Current Treatment Options	• Patients typically treated with available therapies for their specific tumor type, regardless of dMMR/MSI-H status. • No therapies have regular approval for patients with recurrent, advanced dMMR/ MSI-H solid tumors. • Pembrolizumab has accelerated approval for patients with unresectable or metastatic dMMR/MSI-H solid tumors. • Nivolumab alone or in combination with ipilimumab has an accelerated approval for patients with unresectable or metastatic dMMR/MSI-H colorectal cancer.	There is an unmet medical need for treatment options for patients with advanced dMMR or MSI-H solid tumors.
Benefit	• The efficacy population included 209 patients enrolled in two cohorts from Study 4010-01-001, Part 2B (the GARNET study). Cohort A1 enrolled 103 subjects with dMMR/MSI-H endometrial cancer and Cohort F enrolled 106 patients with dMMR/MSI-H and/or POLE-mut	Evidence of effectiveness of dostarlimab for patients with dMMR solid tumors was supported by an objective response rate and DOR that is substantially better than what is seen with other available standard therapy options.

	non-endometrial cancers. The non-endometrial cancer types included 69 subjects with colorectal cancer and 37 with various other (non-colorectal) cancers. • The confirmed ORR by BICR was 41.6% (95% CI: 34.9, 48.6), which included 87 responders out of 209 patients. An updated DOR analysis was conducted on 3/17/21, using a data cutoff date of 11/1/20 . The median DOR using this cutoff date was 34.7 months (range 2.6-35.8 months). Ninety-five percent (95%) of responders had a DOR ≥ 6 months and 75% had DOR ≥ 12 months.	
Risk and Risk Management	• The safety population included 267 patients with advanced dMMR solid tumors, including 126 patients with dMMR endometrial cancer and 141 patients with other dMMR solid tumors. • The most common adverse reactions in ≥ 20% of patients with dMMR solid tumors treated with dostarlimab were fatigue/ asthenia, anemia, diarrhea, and nausea. • Immune-related adverse reactions occurred in 33% patients with dMMR solid tumors and 34% of patients in the overall safety population. • No new safety signals were noted when compared to previous safety analysis of dostarlimab.	The safety profile of dostarlimab is similar to and consistent with other available agents in the same class of therapies (anti-PD-1/PD-L1 agents). No new safety signals arose as compared to those previously identified. The safe use of dostarlimab can be managed through accurate labeling and routine oncology care. Oncologists are knowledgeable in the identification and management of toxicities associated with anti-PD-1/ PD-L1 therapies.

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		
X			**Patient-reported outcome (PRO) was collected using the EORTC-QLQ-C30 and the EQL5D tools during Study 4010-01-001.**	**Discussed in Section 8.2.6 of the review.**
			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		
		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)		

X

Gwynn Ison, MD
Cross-Disciplinary Team Leader

2. THERAPEUTIC CONTEXT

2.1. Analysis of Condition

The Applicant's Position

Cancer is the second most common cause of death in the United States (US), with an estimated approximately 600,000 deaths in 2020 (Siegel et al. 2020). The greatest number of cancer deaths in men are caused by cancer within the lung, prostate, or colorectum, and in women by cancer within the lung, breast, or colorectum.

A wide variety of tumor types have DNA mismatch repair (MMR) deficiencies. A report from Le et al. evaluated 12,019 cancers representing 32 distinct tumor types for MMR deficiency using a next-generation sequencing (NGS) approach and found that >5% of adenocarcinoma of the endometrium, stomach, small intestine, colon and rectum, cervix, prostate bile duct, and liver as well as neuroendocrine tumors, nonepithelial ovarian cancers, and uterine sarcomas were mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) (Le et al. 2017). Cancers with a disproportionately high rate of dMMR/MSI-H are endometrial cancer (EC, up to 33%), gastrointestinal cancers, including gastric cancer (22%), hepatocellular carcinoma (16%), colorectal cancer (CRC; 13%), and esophageal adenocarcinoma (7%) (Mittica et al. 2017; Dudley et al. 2016; Hampel et al. 2005).

The FDA's Assessment:

FDA generally agrees with the Applicant's description of dMMR/MSI-H solid tumors. DNA mismatch repair (MMR) is a process that restores DNA integrity after mismatch errors occur during DNA replication. Four genes play a role in the MMR process, and these include MLH1, MSH2, MSH6, and PMS2. Inactivation of these genes, which can occur via germline or somatic mutations or epigenetic silencing, results in a dMMR mechanism. The deficiency results in accumulation of base mismatches that interfere with DNA replication and produce genomic instability. Various tumor types have DNA MMR deficiencies, which can be identified using NGS testing. Tumors with the highest rates of dMMR include endometrial, colorectal, stomach, small intestine, cervix, prostate, bile duct, liver, nonepithelial ovarian, and uterine sarcomas. Patients with recurrent/ metastatic dMMR/ MSI-H tumors were historically treated similarly to solid proficient MMR (pMMR) tumors.

2.2. Analysis of Current Treatment Options

The Applicant's Position:

2.2.1. dMMR/MSI-H Solid Tumors

Prior to the accelerated approval of programmed cell death protein 1 (PD-1) inhibitors in the US and other countries, treatment of patients with recurrent or advanced dMMR/MSI-H tumors was limited to agents that typically were associated with a very poor response rate and limited overall survival (OS) (eg, regorafenib and trifluridine/tipiracil for patients with recurrent or advanced CRC; objective response rate (ORR) 1% to 2% and median OS of 6 to 7 months) (Lonsurf® USPI 2019 and Stivarga® USPI 2020, respectively).

Recently, the PD-1 inhibitors nivolumab and pembrolizumab have demonstrated favorable outcomes for patients with recurrent or advanced dMMR/MSI-H solid tumors. Pembrolizumab currently has accelerated approval in the US for the treatment of patients with unresectable or metastatic MSI-H or dMMR solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options (Keytruda® USPI 2020). Pembrolizumab demonstrated an ORR of 39.6% in the overall pooled population, which included 149 patients with dMMR/MSI-H solid tumors (90 CRC and 59 non-CRC) across 15 different tumor types, with 6 of the tumor type groups including more than 2 patients.

At this time, there are no anti-PD-1 treatments with regular approval for patients with recurrent or advanced dMMR/MSI-H tumors in the US, indicating that an unmet medical need remains for this patient population.

2.2.2. dMMR/MSI-H Endometrial Cancer

The observed rate of dMMR/MSI-H can be as high as 33% in patients with EC, although the incidence varies depending on histology and tumor grade, being lower in low-grade endometrioid EC (28.6%) relative to high-grade endometrioid EC (54.3%) (Mittica et al. 2017). Although data on MMR/microsatellite instability (MSI) status in the metastatic setting are limited, the rate of dMMR/MSIH in EC classified as Stage III or IV according to the International Federation of Gynecology and Obstetrics (FIGO) was shown to range from 6% to 17% (Basil et al. 2000).

At this time, there are no anti-PD-1 treatments with regular approval for patients with recurrent or advanced dMMR/MSI-H EC in the US or the European Union (EU). Pembrolizumab received accelerated approval for patients with unresectable or metastatic dMMR/MSI-H cancers, including those with EC, in the US and other markets. An ORR of 36% was observed in 14 patients with dMMR/MSI-H EC (Keytruda® USPI 2020).

2.2.3. dMMR/MSI-H Colorectal Cancer

Although the overall rate of dMMR/MSI-H in CRC is up to 13%, the distribution of dMMR/MSI-H rates can differ by tumor stage. dMMR/MSI-H is more often observed in early stage tumors than in late-stage tumors, with a rate of only 5% in Stage IV CRC (Zhao et al. 2019). dMMR/MSI-H appears to be a positive prognostic marker for patients with Stage II/III CRC, as demonstrated by improved survival of patients with dMMR/MSI-H tumors compared to patients with MMR-proficient/microsatellite stable tumors (Oliveira et al. 2019).

Prior to 2017, treatment options for patients with recurrent or advanced CRC (independent of MMR and MSI status) who experienced progressive disease (PD) after or were intolerant to treatment with fluoropyrimidine, oxaliplatin, and irinotecan were limited to regorafenib and trifluridine/tipiracil. Both of these treatments demonstrate a very poor response rate and limited OS, with a 1% response rate and median OS of 6.4 months with regorafenib treatment and a 1.6% response rate and median OS of 7.1 months with trifluridine/tipiracil treatment (Grothey et al. 2013; Mayer et al. 2015).

For dMMR/MSI-H CRC pembrolizumab has regular approval for the first line treatment of patients with unresectable or metastatic MSI-H or dMMR CRC, with an ORR of 44%, and accelerated approval for unresectable or metastatic dMMR/MSIH CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, with an ORR of 36%

(Keytruda®USPI 2020). In addition, nivolumab currently has accelerated approval in the US, as a single agent or in combination with ipilimumab, for the treatment of patients with MSI-H or dMMR metastatic CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. In a clinical study, the ORR was 28% in the monotherapy cohort and 46% in the combination therapy cohort (Opdivo® USPI 2020; Yervoy® USPI 2020).

2.2.4. dMMR/MSI-H Small Intestinal Cancer

The National Comprehensive Cancer Network (NCCN) guidelines for small bowel adenocarcinoma recommend pembrolizumab or nivolumab with or without ipilimumab for the treatment of patients with advanced or metastatic dMMR/MSI-H tumors who have progressed on or after first-line chemotherapy. Pembrolizumab has accelerated approval in unresectable or metastatic dMMR/MSI-H solid tumors, including small intestinal cancer. In 8 participants with dMMR/MSI-H small intestinal cancer, pembrolizumab administered at 10 mg/kg every 2 weeks (Q2W) or 200 mg every 3 weeks (Q3W) demonstrated an ORR of 38%, with a duration of response (DOR) ranging from 1.9 to 9.1 months (Benson et al. 2017). Nivolumab and ipilimumab are not approved for the treatment of small intestinal cancer, and the NCCN's recommendation of use of these drugs with nivolumab is based on results in CRC.

2.2.5. dMMR/MSI-H Gastric Cancer

Ramucirumab is indicated for use in previously treated patients with metastatic gastric cancer (independent of MMR or MSI status); in clinical studies, median OS was 5.2 months for monotherapy and 9.6 months for combination therapy with paclitaxel (Cyramza® USPI 2014; Casak et al. 2015). The ORR was 3%. In the dataset supporting its approval in dMMR/MSI-H solid tumors, an ORR of 56%, with a DOR ranging from 5.8 to 22.1 months, was observed in 9 participants treated with pembrolizumab, 7 of whom received the 10 mg/kg every 2 weeks dose (Benson et al. 2017).

The FDA's Assessment:

FDA agrees with the Applicants' assessment of the available treatment options for patients with dMMR/MSI-H solid tumors. Prior to the approval of PD-1 inhibitors, treatments in the recurrent, metastatic setting were limited to agents with low response rates and limited survival (eg, regorafenib and trifluridine/ tipiracil for patients with recurrent/ metastatic colorectal cancer is ORR 1-2% and median OS 6-7 months). However, PD-1 inhibitors were shown to demonstrate improved response rate over available therapies, as evidenced by the 2017 approval of pembrolizumab (under accelerated approval) for the treatment of patients with unresectable or metastatic, MSI-H or dMMR solid tumors that have progressed following prior treatment and who have no satisfactory alternatives. This approval was based upon a pooled population of 149 patients with MSI-H/dMMR solid tumors, including 90 CRC and 59 non-CRC across 15 tumor types. The overall response rate (ORR) in the pooled population was 39.6%, and this was determined to be an approvement over available chemotherapies at that time. There are currently no therapies with regular approval specifically for the treatment of previously treated dMMR/MSI-H solid tumors

3. REGULATORY BACKGROUND

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Dostarlimab (also known as TSR-042 and GSK4057190A) is not currently registered (or approved) in the US or in any other part of the world. A BLA was submitted to the FDA for dMMR EC on 19 December 2019 (BLA 761174) and for dMMR solid tumors on 18 December 2020 (BLA 761223), both of which are currently under review. Marketing applications have been submitted for dMMR EC to the EMA, Brazil, and Australia and are also under review.

The FDA's Assessment:

FDA granted accelerated approval to dostarlimab on April 22, 2021 for the treatment of adult patients with mismatch repair deficient (dMMR) recurrent or advanced endometrial cancer, that has progressed on or following prior treatment with a platinum-containing regimen. Dostarlimab also received conditional marketing authorization by the EMA for the same indication on April 23, 2021.

3.2. Summary of Pre-Submission/Submission Regulatory Activity

The Applicant's Position:

The clinical trials included in this application were conducted under Investigational New Drug (IND) 126472.

Key regulatory activities relevant to the proposed indication in this Biologic License Application (BLA) are summarized in Table 1.

Table 1: Key FDA Interactions

Date	Regulatory Activity	Topics
December 2015	Submitted IND Application to CDER	Initiation of clinical development with dostarlimab in US
July 2017	Type B Meeting	Discussed the proposed development plan for dostarlimab including clinical, non-clinical, and clinical pharmacology
October 2017	CMC Type C Meeting	CMC development
May 2018	CMC Type C Meeting	CMC development
September 2018	Type B Meeting	Discussed the pivotal Phase 3 study design of dostarlimab in combination with chemotherapy in 1L EC
February 2019	Type C Meeting	Discussed a potential data package for an accelerated approval of dostarlimab in recurrent or advanced and organization of proposed BLA to support accelerated approval

Date	Regulatory Activity	Topics
May 2019	Breakthrough Therapy Designation (BTD) granted	BTD for dMMR EC granted
June 2019	CMC Type C Meeting	CMC development

Table 1: Key FDA Interactions (Continued)

Date	Regulatory Activity	Topics
October 2019	Pre-BLA Meeting for BLA 761174	Discussed the plan for BLA submission for dostarlimab as a 2L agent in recurrent or advanced dMMR EC. There was agreement on the data to support a filing for a dMMR EC indication
December 2019	Original BLA 761174 Submission	Original BLA submitted for dostarlimab for patients with recurrent or advanced dMMR EC that has progressed on or following prior treatment with a platinum-containing regimen
September 2020	Type C Meeting	Discussed a potential data package for a filing of dostarlimab in recurrent or advanced dMMR solid tumors
November 2020	Pre-BLA Meeting for BLA 761223	Discussed the plan (b) (4) Agreement was obtained on the data package to support a BLA for accelerated approval in a dMMR solid tumor indication
December 2020	BLA 761223 Submission	BLA submitted for dostarlimab for adult patients with dMMR recurrent or advanced solid tumors, as determined by an FDA-approved test, that have progressed on or following prior treatment and who have no satisfactory alternative treatment options

Abbreviations: 1L=first-line; 2L=second line; BLA=biologics license application; BTD=breakthrough therapy designation; CDER=Center for Drug Evaluation and Research; CMC=chemistry, manufacturing, and control; dMMR=mismatch repair-deficient; EC=endometrial cancer; FDA=US Food and Drug Administration; IND=Investigational New Drug; US=United States

The FDA's Assessment:

FDA agrees with the Applicant's assessment of pre-submission regulatory activities in regard to this BLA application.

4. SIGNIFICANT ISSUES FROM OTHER REVIEW DISCIPLINES PERTINENT TO CLINICAL CONCLUSIONS ON EFFICACY AND SAFETY

4.1. Office of Scientific Investigations

Inspections by the CDER Office of Scientific Investigations (OSI) were requested by the Division of Oncology 1 (DO1). Three investigators, Dr. Charles Leath, III (Site 840047), Dr. Susan Ellard (Site 124019), and Dr. Thierry Andre (Site 250016), were selected for clinical inspections.

The inspection of Dr. Leath found no regulatory violations. The Applicant's submitted data were verifiable with source records at the investigator site. There was no evidence of underreporting of adverse events or protocol deviations. For Dr. Ellard in Canada, a Remote Regulatory Assessments (RRA) was performed since an onsite Good Clinical Practice (GCP) inspection was not possible due to the COVID-19 pandemic-related travel restrictions. The RRA revealed no GCP violations and the reviewed subject source records supported the Applicant's submitted data for the investigator site, with no discrepancies noted in subject cohort assignments and related efficacy and safety assessments. For Dr. Andre in France, the inspection was planned but later was canceled due to the COVID-19 pandemic related travel restrictions to the investigator site. RRA is unable to be performed due to the European Union General Data Protection Regulation (GDPR) which limits international transfers of personal data. This cancellation and the inability to conduct an RRA for Dr. Andre were communicated to the DO1 review team in March 2021 and a decision was made by the review division to forgo the intended inspection for the current submission.

Based on the results of the clinical site inspections and the RRA, Cohorts A1 and F of Study 4010-01-001-P2B appear to have been adequately conducted and the clinical data generated from Drs. Leath and Ellard appear to be acceptable in support of this BLA.

Site 840047: Dr. Charles Leath, III

Dr. Leath III was inspected on April 19-22, 2021, as a data audit for Study 4010-01-001- P2B. For the investigator, this was the first FDA inspection. The site enrolled four subjects into Cohort A1 of the study and had no subjects in Cohort F. As of the data cutoff date, two subjects remained on study treatment and two subjects were discontinued from study treatment due to adverse event (AE) or confirmed disease progression. Of note, one subject died from pneumonia following AE-related discontinuation of study treatment. All subjects' source records were reviewed during the inspection and were compared with the Applicant's submitted data for the site. The reviewed source records included the informed consent forms, medical history, subject eligibility criteria, protocol-required assessments, submissions of scans to the central review vendor, AEs and serious AEs (SAE), laboratory reports, concomitant medications, and subject data in electronic case report forms (eCRF). Regulatory files and study procedures were also examined, including the documented site training for the study, Institutional Review Board (IRB) approvals of all the protocol/amendments and related informed consent versions and dates, signed FDA 1572s, Delegation of Authority, financial disclosures, data entry into the designated eCRF system [Medidata RAVE] and access management, study monitoring, reporting of SAEs

to the Applicant, study drug control and accountability logs. The inspection found that source records were complete and accurate, with no regulatory violations identified. All the treated subjects were found to have met the eligibility criteria, including documented evidence of their dMMR status and prior platinum therapy. The Applicant's submitted data were verifiable with source records. All the scans were performed according to the study protocol and were subsequently transmitted to the Applicant's designated central review laboratory (b) (4) There was no evidence of unreported AEs, SAEs, or protocol deviations. Of note, an additional subject in Cohort A1 was discontinued from study treatment due to an SAE of pneumonitis, which occurred after the data cutoff date of 3/1/2020. This SAE was also reported in a timely manner. No Form FDA 483, Inspectional Observations, was issued to Dr. Leath III at the conclusion of this inspection.

Site 124019: Dr. Susan Ellard

For Dr. Ellard, a Remote Regulatory Assessment (RRA) was performed from March 9 through March 30, 2021, to review the investigator's conduct of Study 4010-01-001-P2B. The RRA served as an alternative to the intended onsite inspection because the COVID-19 pandemic made travel to the investigator site impossible. For the investigator, there was no prior FDA inspection. The investigator site screened 20 subjects and enrolled 14 into the study, with 3 allocated to Cohort A1, 6 to Cohort F, and 5 to other cohorts. As of the data cutoff date of 3/1/2020, four subjects in Cohort F continued receiving study treatment. The three subjects in Cohort A1 and the other two subjects in Cohort F were discontinued from study treatment due to confirmed disease progression or adverse event(s). The RRA involved WebEx conference calls with the investigator and study staff, reviews of source documents uploaded by the site to an FDA-designated online account, and comparisons of source records with the Applicant's submitted data for the site. The reviewed subject records consisted of redacted electronic copies of the informed consent, eligibility criteria and related case medical history, histopathology reports for the dMMR status, CT scans performed and related central submission confirmations, adverse events and serious adverse event reporting forms. In addition, the RRA reviewed the administration of this study at the investigator site, including the signed Statement of Investigator, study protocol/amendments at the site and related approvals from the Research Ethics Board (REB) as well as the REB's approved informed consents and continuing oversight of this ongoing study. This RRA identified no GCP compliance issues. All the subjects in Cohorts A1 and F were examined for their dMMR status and eligibility, with no issues noted. The Applicant's submitted data were verifiable with the source data reviewed. All scans were found to have been submitted to the independent central review vendor (b) (4) per the Image Acquisition Guideline and the site had no results from the central review. All serious adverse events were reported to the study Applicant in a timely manner.

Reviewer's Comments: *The RRA was associated with some logistical constraints of information exchange, which limited in-depth reviews of some compliance components (i.e., site training, monitoring activities, etc.) and/or prevented direct access to site's case report system and a detailed examination of site's control of investigational product (i.e., total amounts received and the storage condition upon receipt). However, the information obtained was considered to be acceptable to serve as a metric for the reliability of the data and study results in this case, and to allow for a regulatory action to be determined.*

4.2. Product Quality

The Office of Pharmaceutical Quality (OPQ), CDER, reviewed the product quality of Jemperli (dostarlimab-gxly) manufactured by GSK under BLA 761174 submission that received accelerated approval action on April 22, 2021. GSK indicated that information on product quality in Module 3 in the current BLA 761223 is incorporated by cross-reference to BLA 761174 for Jemperli (dostarlimab-gxly).

The assessment of information provided in the cross-referenced application BLA 761174 concluded that the methodologies and processes used for dostarlimab-gxly DS and DP manufacturing, release and stability testing are robust and sufficiently controlled to lead to a product that is safe, pure and potent.

The drug substance manufacturing site (b) (4) was evaluated by multiple tools including 704 (a)(4) record review, remote assessment, and on-site inspection to support approval of BLA 761174. The on-site pre-license inspection resulted in a VAI recommendation (b) (4) The drug product manufacturing site (b) (4) was inspected by CDER/OPQ/OPMA and ORA during the review cycle of BLA 761174 (b) (4) (b) (4) and it was concluded as VAI to support approval of BLA 761174. (b) (4) (b) (4) was also inspected by ORA (b) (4) and the outcome of that inspection was VAI. The immunogenicity assays are sufficiently specific and sensitive to detect anti-dostarlimab antibodies in presence of the expected level of dostarlimab-gxly in serum.

OPQ, CDER, recommended that this product under BLA 761223 be approved for human use under conditions specified in the package insert.

4.3. Clinical Microbiology

Refer to the OPQ Executive Summary and full review by Madushini Dharmasena, Reyes Candau-Chacon, and Michael Shanks. The team recommends dostarlimab-gxly for approval from the microbial control, sterility assurance, and microbiology product quality perspective.

4.4. Devices and Companion Diagnostic Issues

The Applicant submitted a Premarket Approval (PMA) application (P210001) to the Center for Devices and Radiological Health (CDRH) on January 22, 2021, to seek approval for the VENTANA MMR RxDx Panel of antibodies as a companion diagnostic (CDx) to select patients with dMMR solid tumors eligible for treatment with JEMPERLI.

The VENTANA MMR RxDx Panel (MMR RxDx panel) is a qualitative immunohistochemistry (IHC) test intended for use in the assessment of MMR proteins MSH6, PMS2, MSH2 and MLH1 in formalin-fixed, paraffin-embedded (FFPE) tumor tissue specimens by light microscopy. The OptiView DAB IHC Detection Kit is used for MLH1, MSH2, and MSH6. The OptiView DAB IHC Detection Kit with the Overview Amplification Kit is used for PMS2 on a VENTANA

BenchMark ULTRA instrument. This Class III device is fully automated, and the MMR antibodies in the panel are:

VENTANA anti-MSH6 (SP93) Rabbit Monoclonal Primary Antibody (MSH6)

VENTANA anti-PMS2 (A16-4) Mouse Monoclonal Primary Antibody (PMS2)
VENTANA anti-MSH2 (G219-1129) Mouse Monoclonal Primary Antibody (MSH2)
VENTANA anti- MLH1 (M1) Mouse Monoclonal Primary Antibody (MLH1)

The PMA approval will occur contemporaneously with approval of this BLA 761223.

5. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

5.1. Executive Summary

Pharmacology and toxicology data were reviewed previously under BLA 761174. The Applicant did not submit changes to nonclinical sections of the prescribing information. From the nonclinical perspective, Jemperli is recommended for approval for the proposed indication.

5.2. Referenced NDAs, BLAs, Drug Master Files

The Applicant's Position:

No nonclinical pharmacology/toxicology data were submitted in this BLA. Cross-reference was made to BLA 761174.

The FDA's Assessment:

FDA agrees.

6. CLINICAL PHARMACOLOGY

6.1. Executive Summary

The FDA's Assessment:

Dostarlimab is an anti-programmed cell death protein 1 (PD-1) humanized immuno-globulin G4 (IgG4) monoclonal antibody (mAb) produced by recombinant DNA technology using a stable Chinese hamster ovary (CHO) cell line. The Applicant seeks an accelerated approved of dostarlimab for the treatment of adult patients with mismatch repair deficient (dMMR) recurrent or advanced solid tumors, as determined by an FDA-approved test, that have progressed on or following prior treatment and who have no satisfactory alternative treatment options. The proposed clinical dose is 500 mg given every 3 weeks (Q3W) for 4 cycles followed by 1000 mg every 6 weeks (Q6W) for subsequent cycles.

The Clinical Pharmacology Review evaluated the immunogenicity, population pharmacokinetic (PPK) and exposure-response (E-R) data obtained from **Study 4010-01-001** (**GARNET**). The incidence of treatment-emergent positive anti-dostarlimab antibodies (ADAs) was generally low at the proposed clinical dose (2.1%, n=8/384) with 1.0% being neutralizing antibody (NAb) positive at the proposed clinical dose. The impact of immuno-genicity on each of efficacy and safety of dostarlimab is inconclusive because of the limited number of ADAs observed in the study. In a population PK analysis, the incidence of ADAs did not have a significant effect on dostarlimab CL. Dostarlimab has an elimination half-life of 23.5 days. There were no clinically significant effects of various covariates (such as Age, sex, race, body weight, tumor size, tumor type, RI or HI) on dostarlimab PK.

The proposed clinical dose of 500 mg Q3W for 4 cycles followed by 1000 mg Q6W for subsequent cycles appears acceptable based on the clinically significant improvement in ORR (41.6% N=209) and an acceptable and safety profile observed in **GARNET** study.

Recommendations

The Office of Clinical Pharmacology has reviewed the information and data submitted in BLA 761223. This BLA is approvable from a clinical pharmacology perspective with no major review issues as seen in the table below.

Review Issues	Recommendations and Comments
Supportive evidence of effectiveness	The primary evidence of effectiveness comes from the FIH phase 1 Study 4010-01-001 (GARNET) in 209 adult patients with dMMR recurrent or advanced solid tumors, as determined by an FDA-approved test, that have progressed on or following prior treatment and who have no satisfactory alternative treatment options. An ORR of 41.6%% was observed at the proposed clinical dose. Refer to Section 7 of this review for further details.
General dosing instructions	The proposed dose is 500 mg every 3 weeks (Q3W) for 4 cycles, followed by 1000 mg every 6 weeks (Q6W) for subsequent cycles, starting from Cycle 5 until disease progression or unacceptable

	toxicity. This dosing regimen is supported by the clinically significant improvement in ORR (44.7%, N=103) and an acceptable safety profile observed in GARNET study. Refer to Section 7 of this review for further details.
Dosing in patient subgroups (intrinsic and extrinsic factors)	The population PK (PPK) analysis of data from 512 patients treated at the proposed clinical dose in the GARNET study indicates that the various covariates such as age (24-86 years), sex (male = 117, females = 395), race/ethnicity (74% Whites), body weight (range = 34-182 kg), ADAs, alkaline phosphatase (ALP), tumor type, tumor size, normal renal function (RF) to moderate renal impairment (RI) (normal RF = 196, mild RI = 223, moderate RI = 91, severe RI = 2) or normal hepatic function (HF) to moderate hepatic impairment (HI) (normal HF = 456, mild HI = 51, moderate HI = 5) have no clinically significant effect on dostarlimab PK. No dosage adjustments are needed for any intrinsic or extrinsic factors.
Labeling	Overall, the proposed labeling recommendations are acceptable upon the Applicant's agreement to the FDA revisions to the labeling. Clinical pharmacology labeling recommendations are detailed in Section 10 of this review.
Bridge between the to-be marketed and clinical trial formulations	No *in vivo* comparability studies have been conducted. There were no changes to the formulation during clinical development. The only changes during clinical development were to (b) (4) and to change the manufacturing facility. (b) (4) (b) (4)

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The Applicant's Position:

The clinical pharmacology portion of the submission characterizes the pharmacokinetics (PK) and pharmacodynamics (PDy) of dostarlimab, based on data following single and repeated intravenous (IV) administration from 546 patients with various cancers enrolled in the first-in-human Study 4010-001-01 (GARNET).

Dostarlimab peak concentrations are observed shortly after the end of a 30 minute IV infusion, followed by a bi-exponential decline. Dostarlimab PK was approximately dose-proportional over the dose range and dosing regimens studied, with an approximate two-fold accumulation.

The overall dostarlimab PK profile was well described by a two-compartment population PK model, with time-dependent linear elimination and body weight as an allometric covariate on clearance (CL), volume of distribution of central compartment (V_c), and volume of distribution

of peripheral compartment (V_p). Dostarlimab CL at steady-state (full effect of time-dependent CL) and volume of distribution at steady state (V_{ss}) were estimated to be 0.00682 L/h and 5.26 L, respectively, with a $t_{1/2}$ of 23.5 days. The maximum change in CL over time was estimated as 14.9%. Baseline age, gender, time-varying albumin (ALB), and time-varying alanine aminotransferase (ALT) were statistically significant covariates on CL. Time-varying ALB and gender were statistically significant covariates on Vc, but were not considered clinically relevant. No adjustment in dose or dosing regimen is deemed warranted based on covariates, including age, body weight, race, gender, or ethnicity in patients receiving dostarlimab. No statistically significant effects of mild to moderate renal impairment and mild hepatic impairment were found on dostarlimab PK. Therefore, no dose adjustment is needed for patients with mild or moderate renal impairment or for patients with mild hepatic impairment. There are limited data in patients with severe renal impairment, end -stage renal disease undergoing dialysis and moderate hepatic impairment and no data in patients with severe hepatic impairment.

Dostarlimab produces a sustained, consistent engagement of the receptor and functional effects at all dose levels studied. The recommended therapeutic dose (RTD) regimen of 500 mg Q3W followed by 1,000 mg Q6W results in full target engagement for the duration of treatment.

The overall immunogenicity risk for dostarlimab is low. The current clinical data are consistent with this assessment; the incidence of treatment-emergent positive anti-drug antibody (ADA) samples was low (2.1%) and there was no evidence of a clinically-meaningful impact of pre-existing ADA or ADA formation on pharmacokinetics, safety or efficacy of dostarlimab.

Dostarlimab does not have a clinically meaningful effect on electrocardiogram (ECG) changes or QT prolongation at the recommended therapeutic dosing regimen.

The exposure-response (E-R) analyses did not demonstrate a meaningful relationship between exposure and response and support the RTD regimen. Univariate logistic regression of ORR in patients from Part 2B of GARNET showed no exposure response relationship for the full dataset nor for the subgroup analysis with only EC patients. The subgroup analysis of patients with tumor subtype dMMR showed statistically significant relationships with Cycle 1 area under the plasma concentration-time curve (AUC) and minimum concentration (C_{min}). However, the relationships were nonsignificant when other covariates, which adjusted the E-R relationship, were included in the analysis. DOR analysis showed no statistically significant relationships with any of the exposure metrics, although the smaller number of patients with DOR reported (compared with ORR) and the truncation of DOR at the time of the data cut will reduce the likelihood of detecting a relationship. None of the tested exposure metrics had a statistically significant relationship with any of the five most prevalent drug-related adverse events (AEs) (asthenia, diarrhea, fatigue, hypothyroidism, and nausea).

The clinical efficacy, safety, E-R analyses for efficacy and safety, and the PK/PDy modeling supports the use of dostarlimab as a single agent at the RTD of 500 mg Q3W for 4 cycles followed by 1,000 mg Q6W for subsequent cycles.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

The Applicant's Position:

The recommended dose of dostarlimab is 500 mg Q3W for the first four cycles followed by 1,000 mg Q6W for all subsequent cycles administered as an IV infusion over approximately 30 minutes.

Based on findings in Study 4010-001-01 (GARNET), the RTD is expected to result in full receptor occupancy (RO) for the duration of treatment based on the PDy analysis. Although only one dose regimen was evaluated in the intended target population, the lack of an E-R relationship between dostarlimab exposure and the efficacy and safety do not suggest any necessary changes of the RTD and regimen in the intended treatment population at the RTD to improve safety or efficacy. This, combined with meaningful efficacy responses in dMMR patients (Section 8.1.1.16) and overall satisfactory safety profile (Section 8.2) of dostarlimab at the RTD supports the choice of recommended therapeutic dose and regimen.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

6.2.2.2. Therapeutic Individualization

The Applicant's Position:

Therapeutic individualization of dose is not required for subpopulations based on intrinsic patient factors according to the results of population PK and E-R analyses. Please see Section 6.3.2.3 for more details.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

6.2.2.3. Outstanding Issues

The Applicant's Position:

None

The FDA's Assessment:

None

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Data:

Absorption: Bioavailability of dostarlimab is complete since it is administered by IV infusion. Maximum dostarlimab serum concentrations were generally observed at, or shortly after, the end of the infusion.

Distribution: Based on the population PK analysis, dostarlimab had a small volume of distribution (geometric mean [percentage coefficient of variation {CV%}] 5.26 L [14.2%]), consistent with distribution largely in the systemic circulation and interstitial spaces.

Metabolism: Dostarlimab is a therapeutic monoclonal antibody (mAb) immunoglobulin G4 (IgG4), which is expected to be catabolized into small peptides, amino acids, and small carbohydrates by lysosome through fluid-phase or receptor-mediated endocytosis. Therefore, the metabolic pathways are well understood, and conventional metabolism and elimination studies are not required for dostarlimab.

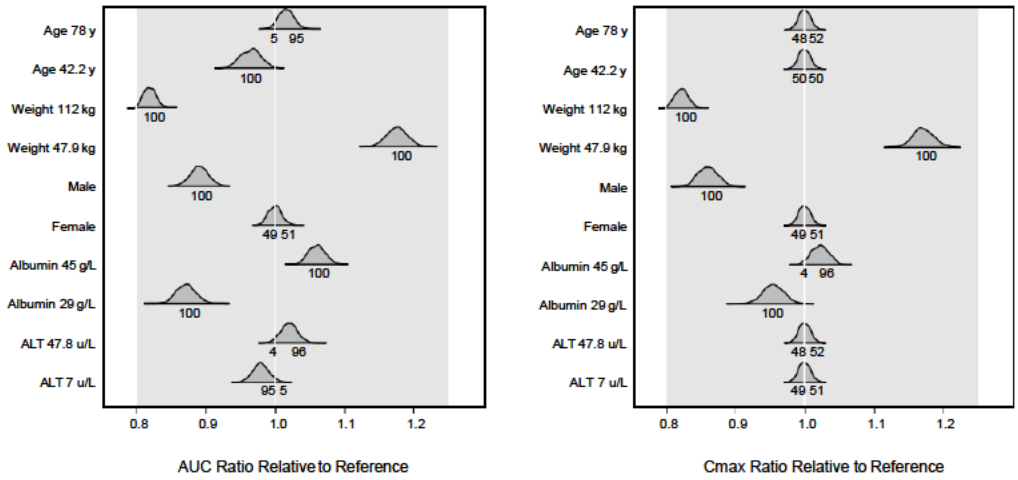
Elimination: Molecules of the size of dostarlimab are essentially excluded from glomerular filtration, (Norden et al. 2001)and there is no evidence for renal tubular secretion of an IgG antibody(Bohle et al. 1988) Based on the population PK analysis, dostarlimab had a baseline systemic clearance of 0.00745 L/hour for a typical patient. Over time, the clearance was reduced to 0.00682 L/hour with a terminal elimination half-life ($t_{1/2}$) of 23.5 days.

Clinical Pharmacokinetics: A population PK model was developed using concentration-time data through the cutoff date of 01 March 2020, with a total of 4,804 PK observations from 546 patients included in the model development.

The dostarlimab PK profile was well described by a 2-compartment model with a time-dependent linear elimination. Time dependency in CL was described by a sigmoid maximal change in clearance relative to baseline (sigmoid I_{max} function), with a maximum change in CL over time of 14.9%. The model incorporated inter-individual variability on CL, Vc, and I_{max}. The effect of body weight was modeled based on the principles of allometry and included as a covariate for CL, Vc, and Vp prior to the stepwise covariate modeling (SCM) search. The exponents were estimated to 0.47 CL and 0.419 for Vc and Vp. Although body weight was statistically significant covariate, the impact on exposure (area under the concentration versus time curve at steady state [AUC_{ss}] and maximum concentration at steady-state [$C_{max,ss}$]) was minimal, suggesting limited clinical relevance and supporting fixed-dosing of dostarlimab.

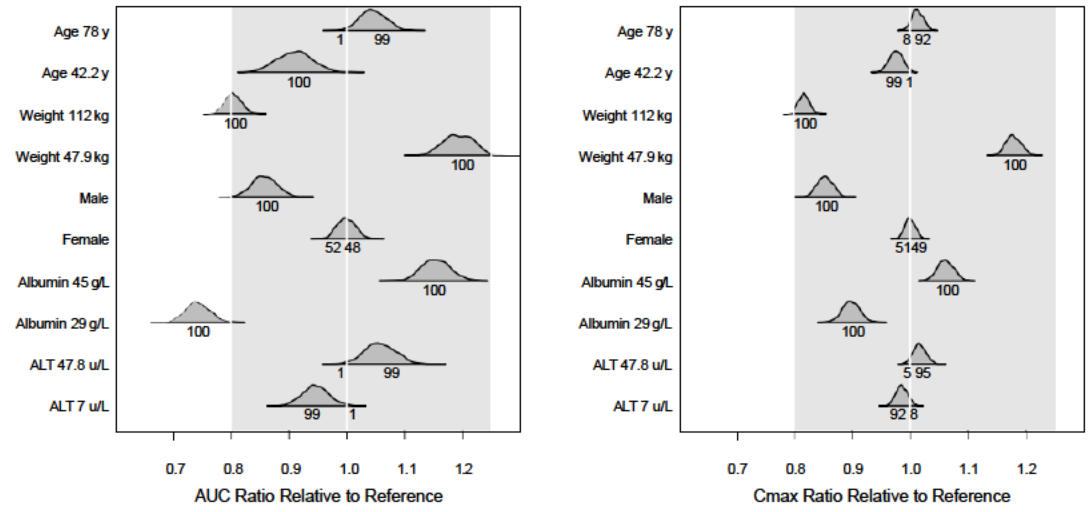
Results from the SCM procedure suggested that baseline age, gender, time-varying ALB, and time-varying ALT were statistically significant predictors of CL. Both time-varying ALB and gender were found to be statistically significant predictors of Vc. The impact of the identified covariates on the relevant PK parameters is illustrated in Figure 1 for Cycle 1 following the first dose and in Figure 2 at steady-state. ALB demonstrated the largest impact on exposure with 25.9% lower and 15.5% higher AUC in a typical patient with the 5th and 95th percentiles of the covariate value, respectively. All other identified covariates (gender, age and time-varying ALT) had limited impact on dostarlimab exposure.

Figure 1: Forest Plots Illustrating the Covariate Effects on Exposure at Cycle 1



Source: Population PK Report, Figure 16
Abbreviations: ALB=albumin; ALT=alanine aminotransferase; AUC=area under the plasma concentration-time curve; AUC_{ss}=area under the concentration versus time curve at steady state; $C_{max,ss}$: maximum concentration at steady-state
Note: Forest plot of AUC_{ss} and $C_{max,ss}$ ratios as compared to median reference patient (female, 70 kg, age 64, ALB 39 g/dl and ALT 18 U/L). The distributions represent the ratios based on 1,000 set of parameter estimates re-sampled from the variance covariance matrix. Plotted numbers indicate actual percent of each distribution in a bounded region (here the central reference line). The grey area represents the 0.8 and 1.25 boundaries.

Figure 2: Forest Plots Illustrating the Covariate Effects on Exposure at Steady-State



Source: Population PK Report, Figure 17
Abbreviations: ALB=albumin; ALT=alanine aminotransferase; AUC=area under the plasma concentration-time curve; AUC_{ss}=area under the concentration versus time curve at steady state; $C_{max,ss}$: maximum concentration at steady-state
Note: Forest plot of AUC_{ss} and $C_{max,ss}$ ratios as compared to median reference patient (female, 70 kg, age 64, ALB 39 g/dl and ALT 18 U/L). The distributions represent the ratios based on 1,000 set of parameter estimates re-sampled from the variance covariance matrix. Plotted numbers indicate actual percent of each distribution in a bounded region (here the central reference line). The grey area represents the 0.8 and 1.25 boundaries.

Dostarlimab PK was similar between patients with normal renal function and those with mild or moderate renal impairment. Similarly, mild hepatic impairment did not appear to cause a significant change in the PK of dostarlimab when compared to patients with normal hepatic function.

Area under the concentration versus time curve for a dosing interval ($AUC_{0\text{-}tau}$) values from the population PK model simulations indicated an approximately dose proportional increase in exposure at steady-state for the clinically relevant 500 mg and 1,000 mg fixed doses (Table 2). Additionally, dostarlimab showed approximately 2-fold accumulation when comparing exposure ($AUC_{0\text{-}tau}$ and maximum concentration [C_{max}]) after the first 500 mg dose Q3W with steady-state exposure following both 500 mg Q3W and 1,000 mg Q6W doses. Dostarlimab $AUC_{0\text{-}tau}$ was similar across the two treatments within the respective dosing intervals suggesting similar overall dostarlimab exposure following either the 500 mg Q3W or 1,000 mg Q6W dosing regimens.

Table 2: Summary of Exposure at First Dose and Steady-State (Simulated Dostarlimab Exposures)

Dose	$AUC_{0\text{-}tau}$ (mg*h/L) (CV%)	C_{max} (mg/L) (CV%)
First dose (500 mg)	33550 (18.2)	172 (19.4)
Steady-state (500 mg)	73270 (30.1)	286.4 (22.8)

Table 2: Summary of Exposure at First Dose and Steady-State (Simulated Dostarlimab Exposures) (Continued)

Dose	$AUC_{0\text{-}tau}$ (mg*h/L) (CV%)	C_{max} (mg/L) (CV%)
Steady-state (1,000 mg)	146600 (30.1)	433.6 (21.1)

Source: Population PK Report, Table 16
Abbreviations: $AUC_{0\text{-}tau}$=area under the concentration versus time curve for a dosing interval; C_{max}: maximum concentration; CV%=percentage coefficient of variation.

Table 3 presents a summary of PK parameters for the proposed dostarlimab dosing regimen based on the population pharmacokinetic analysis (500 mg Q3W for the first 4 cycles followed by 1,000 mg Q6W for all subsequent cycles).

Table 3: Dostarlimab PK Parameters in Patients with Solid Tumors

Parameter	Estimate (CV%)
Clearance at Steady-State (CL_{ss})	0.00682 (30.2%) L/hour
Volume of Distribution at Steady-State (V_{ss})[a]	5.26 (14.2%) L
Terminal elimination half-life ($t_{1/2}$)	23.5 (22.4%) days

Abbreviations: CV%=percentage coefficient of variation; PK=pharmacokinetics
[a] V_{ss} calculated as central volume of distribution (V_c) + peripheral volume of distribution (V_p).

Immunogenicity: Samples collected predose and at/after 96 hours postdose were analyzed for ADA in Parts 1 and 2 of Study 4010-01-001. Overall, 547 of 549 patients (99.6%) had at least one immunogenicity sample result and were included in the analysis of prevalence. A total 418 out of 549 enrolled patients (76.1%) were evaluable for treatment-emergent antibodies to dostarlimab, with 384 patients from Part 2B included in this analysis. The incidence of treatment-emergent positive ADA samples was low and comparable to that of other anti-PD-1

antibodies. Thirteen patients (3.1%) developed ADA during the entire study, and for patients receiving the recommended therapeutic dose, the overall incidence of treatment-emergent ADA was only 2.1%, with 1.0% being neutralizing antibody (NAb) positive. The presence of ADA did not appear to impact dostarlimab PK when the noncompartmental data were analyzed. In addition, ADA was evaluated during population PK model development, and did not have a statistically significant effect on CL and therefore had no impact on dostarlimab exposure. Importantly, there was no evidence of a clinically meaningful impact of ADA formation on any safety or efficacy measures.

E-R for Safety and Efficacy Endpoints: An E-R analysis explored the relationship of model-predicted dostarlimab exposure with both safety and efficacy variables. PK data from Parts 1, 2A, and 2B were included through the data cutoff date of 01 March 2020 as appropriate for each analysis.

Efficacy: The dichotomous response (response/non-response) for ORR was assessed using logistic regression and exposure as the independent predictor. For the E-R of efficacy, Cycle 1 (day 21) predictions of AUC, C_{max}, and C_{min} were generated based on planned dose and individual post-hoc PK parameters. As a first step, a univariate analysis with exposure as the independent predictor was performed. Subsequently, covariates were explored via a full model approach. The following covariates were included: total line of prior therapy (TOTPLA), baseline Eastern Cooperative Oncology Group (ECOG) Performance Status , baseline tumor mutational burden status and presence of NAb. Covariate effects were considered significant if the 95% confidence interval (CI) for the odds ratio or hazard ratio did not include a value of 1. The E-R analysis was performed for all patients on cohort A1, A2, and F from Part 2B (N=362) and for 2 overlapping patient subgroups:

- EC patients, with dMMR or MMRp as covariate (N=249)
- dMMR solid tumor patients, with EC or non-EC as covariate (N=217)

Univariate logistic regression of ORR showed no E-R relationship for the full dataset that included EC and non-EC patients further supporting the recommended therapeutic dose of 500 mg Q3W for four cycles followed by 1,000 mg Q6W for subsequent cycles in the intended treatment population. Similarly, univariate logistic regression of ORR showed no E-R relationship for the subgroup of EC patients. The subgroup analysis of patients with tumor subtype dMMR showed statistically significant E-R relationships between ORR and AUC and C_{min}. After inclusion of additional covariates the E-R relationship found in the univariate analysis for dMMR patients was no longer significant. Subgroup analysis showed no statistically significant difference between dMMR and MMRp nor between EC and non-EC for the EC patients and tumor subtype dMMR on the probability of ORR, respectively. ECOG was the only covariate that was significant in all three of the analysis (full, EC, and dMMR) with an odds ratio CI well separated from 1 for the dMMR subgroup analysis, suggesting that it may be a clinically relevant covariate. This indicates that patients with better performance status at baseline may have a higher probability of response.

DOR showed no statistically significant relationships with any of the exposure metrics and no consistent trends could be seen in the Kaplan-Meier (KM) plots. The power to detect a relationship between exposure and DOR was limited due to the overall low number of patients

with available DOR data (n=116) and the current data cutoff date truncating DOR to the time of the data cut.

Safety: Binary data for the five most prevalent drug-related adverse events (AEs: asthenia, diarrhea, fatigue, hypothyroidism, and nausea) from 546 patients in the study were analyzed using univariate logistic regression. The explanatory variables were AUC, C_{max}, and C_{min} during the first 6 weeks after the first dose (ie, 42 days). None of the tested exposure metrics had a statistically significant relationship ($\alpha = 0.05$) with any of the five AEs.

Concentration-QTc analysis: The results of a concentration-QT interval using Fridericia's formula (QTcF) and central tendency analysis demonstrated that dostarlimab does not have a clinically meaningful effect on ECG changes or QT prolongation at the RTD.

The Applicant's Position:

The clinical pharmacology of dostarlimab has been well characterized following IV single and repeat dose administration in Study 4010-001-01 (GARNET) and available data support the proposed dose and regimen.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

6.3.2. Clinical Pharmacology Questions

6.3.2.1. Does the clinical pharmacology program provide supportive evidence of effectiveness?

Data:

Based on findings in Study 4010-001-01 (GARNET), the RTD is expected to result in full RO for the duration of treatment based on the PDy analysis. At the data cutoff, for participants with dMMR solid tumors, the ORR was 41.6%, and included 9.1% CRs and 32.5% PRs. Clinical activity was consistent across EC (N=103), CRC (N=69), and other tumor types (non-CRC; N=37): 44.7%, 36.2%, and 43.2%, respectively (Module 2.7.3 Table 28). A total of 18.7% of participants with dMMR solid tumors had a best overall response (BOR) of stable disease (SD) and 34.0% had a BOR of PD. Despite being a heavily pretreated patient population, the safety profile of dostarlimab in participants with dMMR solid tumors and participants treated with dostarlimab as a single agent at the RTD in Study 4010-01-001 was consistent with AEs observed in patients with cancer and cancer-related comorbidities and the known safety profile of other anti-PD-1 agents.

Although only one dose regimen was administered in the intended target population, the results of the E-R analysis did not suggest any necessary changes of the RTD and regimen at the RTD to improve safety or efficacy. Specifically, no relationship was seen between exposure following the first 500 mg Q3W dose (Cycle 1) and overall response (OR) in any of the populations studied, especially after inclusion of covariates. There was also no significant relationship between dostarlimab exposure and OR among dMMR patients (Section 6.3.1), the relevant population.

No statistically significant E-R relationship was found for any of the investigated top 5 occurring drug related AEs (asthenia, diarrhea, fatigue, hypothyroidism, and nausea). Based on all of the

above collective evidence, the clinical efficacy, safety, E-R analyses of efficacy and safety, and the PK/PDy modeling provides supportive evidence of the use of dostarlimab as a single agent at the RTD of 500 mg Q3W for 4 cycles followed by 1,000 mg Q6W for subsequent cycles.

The Applicant's Position:

The clinical pharmacology program provides supportive evidence of effectiveness and dosing regimen.

The FDA's Assessment:

In general, the E-R analysis is considered acceptable for the purpose of characterizing the E-R relationships of dostarlimab for efficacy and adverse events (AEs) on efficacy and safety for the adult subjects with recurrent or advanced solid tumor including EC (MSS or MMRp and MSI-H or dMMR tumors), NSCLC, and non-endometrial dMMR/MSI-H and polymerase Ɛ-mutated cancer. However, Dostarlimab-gxly exposure-response relationships have not been fully characterized due to only one dose level studied ER analysis (Refer to **APPENDIX 19.4** for more details).

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

Data:

The proposed dosing regimen for dostarlimab as a single agent in the treatment of patients with solid tumors which are dMMR is 500 mg Q3W for four cycles and 1,000 mg Q6W thereafter as an IV infusion over approximately 30 minutes. This dosing regimen was selected based on population PK modeling and RO data, and confirmed based on the clinical results of dMMR patients in Study 4010-001-01 as well as PK/PDy and E-R analyses for efficacy and safety endpoints (Module 2.7.2 Section 3.5).

Study 4010-001-01 was not designed to assess efficacy or safety at different dose levels, however, the findings from the population PK, PDy and E-R analyses (Section 6.3.1) do not suggest that the dose regimen should be adjusted in the relevant patient population. This combined with meaningful efficacy responses in dMMR patients (Section 8.1.1.16) and overall satisfactory safety profile (Section 8.2) of dostarlimab at the RTD supports the choice of recommended therapeutic dose and regimen.

The Applicant's Position:

The proposed dosing regimen of 500 mg Q3W for the first four cycles and 1,000 mg Q6W thereafter administered as an IV infusion over approximately 30 minutes is appropriate as monotherapy in the dMMR population.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

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

Data:

In population PK analyses, potential covariates influencing the PK of dostarlimab have been evaluated (Section 6.3.1). Statistically significant covariates included: body weight, time-varying albumin, time-varying ALT, gender and age on CL and time-varying ALB, body weight, and gender as covariates on central volume of distribution. The impact of covariates on dostarlimab exposure was minimal. Therefore, no adjustment in dose or dosing regimen is required based on these covariates in patients receiving dostarlimab.

No statistically significant effects of mild to moderate renal impairment and mild hepatic impairment were found. There are limited data in patients with severe renal impairment, end-stage renal disease undergoing dialysis and moderate hepatic impairment and no data in patients with severe hepatic impairment. Further, there was no effect of tumor type, lactate dehydrogenase, lymphocyte count, ECOG status, race, ethnicity, geographic location and use of systemic glucocorticoids found on dostarlimab PK.

The Applicant's Position:

Dose adjustment is not required for subpopulations based on intrinsic and extrinsic patient factors based on the results of population PK analyses.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

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

Data:

As dostarlimab is administered intravenously, no clinical assessment of potential food-drug interactions has been performed. No specific clinical studies to assess potential drug-drug interactions (DDIs) have been performed. Dostarlimab is a mAb isotype IgG4. Nonspecific CL of mAbs through lysosome degradation disqualifies dostarlimab as a victim drug or a perpetrator in combination with small molecule drugs (Silva et al., 2015; Wang et al., 2014; Varga et al., 2015). In addition, there is no evidence of DDIs mediated by nonspecific CL of lysosome degradation for antibodies and comedicated biologic(s) (Silva et al., 2015). Dostarlimab is not a substrate for cytochrome P450 (CYP) or drug transporters and is not a cytokine. The potential for dostarlimab to induce cytokine release and proliferation was directly assessed by exposing peripheral blood mononuclear cells (PBMCs) from healthy human donors to a dose titration of dostarlimab. The results indicated that dostarlimab did not stimulate cytokine release from PBMCs (Dostarlimab IB Study XLB-069), suggesting that dostarlimab is unlikely to independently induce cytokine release during in vivo exposure and to change the expression of either CYP or drug transporters. Thus, dostarlimab is not deemed a perpetrator in DDIs with standard treatments, in this specific case, carboplatin (metabolized mainly through renal clearance as parent) in combination with paclitaxel (metabolized by CYP 2C8 and 3A4).

During the population PK analysis, immune suppressors, stimulators, and the systemic use of corticosteroids were planned to be evaluated as covariates. While there were not enough patients in each category of immune suppressors or stimulators for evaluation as covariates, the systemic use of corticosteroids as a separate covariate was evaluated. No impact of systemic use of corticosteroids on dostarlimab PK was found. Total prior lines of therapy was evaluated as one possible covariate in the E-R analysis and was found not to be significant. Prior standard of care

anticancer treatment was evaluated for its impact on efficacy. Analyses of ORR were performed in subgroups defined by prior anticancer treatments (previously summarized: Number of prior anticancer therapy regimens, prior radiation therapy, and prior bevacizumab use), BOR from last platinum-containing prior anticancer therapy, and progression-free interval from last platinum containing prior anticancer therapy. A comparison of ORR between these different subgroups is hampered by the small sample size of some of the subgroups.

The Applicant's Position:

As dostarlimab is administered intravenously, no food-drug interactions are anticipated. As summarized above, the current assessment is that the risk for clinically relevant DDIs is low.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

X	X
Safaa Burns, PhD	Nam Atiqur Rahman, PhD
Primary Reviewer	Team Leader

X	X
Primary Reviewer	Team Leader

7. SOURCES OF CLINICAL DATA AND REVIEW STRATEGY

7.1. Table of Clinical Studies

The Applicant's Position:

The clinical studies to support efficacy and safety that are relevant to this BLA are summarized in Table 4.

Table 4: Listing of Clinical Studies Relevant to This BLA

Phase of Study	Study ID, NCT Number, Title	Location of Study Report	Study Objective	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route Of Administration	Number of Subjects	Patient Population	Treatment Duration	Study Status: Report Type
1	4010-01-001 (GARNET), NCT 02715284, A Phase 1 Dose Escalation and Cohort Expansion Study of TSR-042, an anti-PD-1 Monoclonal Antibody, in Patients with Advanced Solid Tumors	Module 5.3.5.2: Part 2B Cohorts A1 + A2 Module 5.3.5.4: Part 2B Cohort E and Part 2B Cohort F	Part 1/2A: To establish an RP2D for dostarlimab based on safety and tolerability, PK, and PDy in patients with advanced solid tumors Part 2B: To confirm the RP2D and establish the safety and clinical activity of dostarlimab in patients with advanced solid tumors	Multicenter open-label, first-in-human, 2-part, dose escalating and expansion study	Part 1 (dose escalation): dostarlimab 1, 3, or 10 mg/kg Q2W IV Part 2A (fixed-dose): Q6W Cohort - dostarlimab 1,000 mg Q6W IV; Q3W Cohort - dostarlimab 500 mg Q3W IV Part 2B (expansion): dostarlimab 500 mg Q3W IV for first 4 cycles, dostarlimab 1,000 mg Q6W IV for all subsequent cycles (all cohorts)	Part 1: 21 Part 2A: 13 Part 2B: Cohort A1 – 129 Cohort A2 – 161 Cohort E – 67 Cohort F - 158	Parts 1/2A: Patients with advanced solid tumors Part 2B: Cohort A1 - Patients with dMMR/MSI-H EC Cohort A2 - Patients with MMRp/MSS EC Cohort E - Patients with non small cell lung cancer Cohort F - Patients with dMMR/MSI-H or POLE-mut solid tumors	Up to 2 years, or until the patient meets protocol specific discontinuation criteria	Full CSR Part 2B Cohorts A1 + A2 Full CSR Part 2B Cohort F

Table 4: Listing of Clinical Trials Relevant to This BLA (Continued)

Abbreviations: CSR=clinical study report; dMMR=mismatch repair-deficient; EC=endometrial cancer; ID=identity; IV=intravenous; MMRp=mismatch repair proficient; MSI-H=microsatellite instability-high; MSS=microsatellite stable; NCT=national clinical trial; NSCLC=non-small cell lung cancer; PK=pharmacokinetic; PO=by mouth; POLE-mut=DNA polymerase epsilon mutation; QD=daily; QxW=every x weeks; RP2D=recommended phase II dose; TSR-042=anti-PD-1 (dostarlimab).
Note: Parts 1A and 1B are not included as no patients in these parts were treated with dostarlimab.
Note: Parts E through I are not included as no patients in these parts were treated with dostarlimab.

The FDA's Assessment:

FDA agrees with the Applicant's assessment of sources of clinical data. The clinical data supporting this BLA was derived from GARNET trial (Study 4010-01-001), a phase 1, dose escalation/cohort-expansion, non-randomized, open-label, multicenter clinical trial that enrolled patients with recurrent or advanced solid tumors who have limited available treatment options. FDA's analysis of efficacy was based on two of the expansion cohorts (total 209 patients) in Part 2B of GARNET: Cohort A1 that include patients with dMMR endometrial cancer (N=103), and Cohort F that include patients with non-endometrial dMMR solid tumors (N=106). For FDA's analysis of safety, data from 515 patients with a variety of advanced solid tumors in the expansion cohorts of GARNET were submitted to support this BLA; the expansion cohorts included: Cohort A1, Cohort A2, Cohort E, and Cohort F.

8. STATISTICAL AND CLINICAL EVALUATION

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study 4010-01-001 (GARNET)

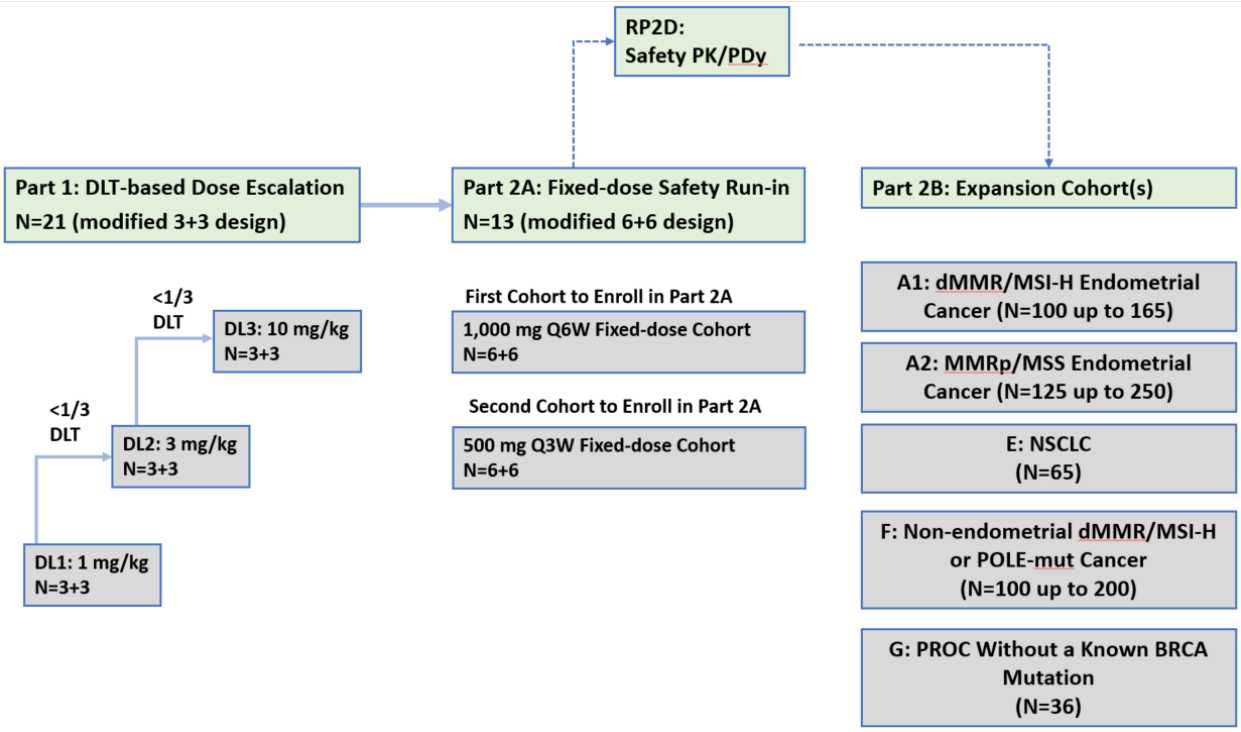
The Applicant's Description:

Efficacy data are derived from Study 4010-01-001 (GARNET), an ongoing, global, multicenter, open-label, FIH, Phase 1, dose escalation study with expansion cohorts in patients with recurrent or advanced solid tumors who have limited available treatment options.

The study is being conducted in 2 parts (Figure 3). In Part 1 of the study, ascending weight-based doses of dostarlimab were evaluated based on dose-limiting toxicities, overall safety, and the PK/PDy profile of dostarlimab. Part 2 of the study is further subdivided into Part 2A and Part 2B. Part 2A of the study evaluated the safety, tolerability and confirmation of PK of dostarlimab at 2 fixed doses, which were derived from safety and tolerability data and the PK/PDy profile of weight-based doses tested in Part 1. In Part 2B of the study, the clinical activity and safety of dostarlimab using the RTD schedule is being evaluated in several expansion cohorts based on the patients' tumor type.

The RTD was chosen as 500 mg of dostarlimab Q3W for 4 cycles followed by 1,000mg Q6W for all subsequent cycles.

Figure 3: Study 4010-01-001 (GARNET) Schema



Source: Module 2.5
Abbreviations: DL=dose level; DLT=dose-limiting toxicity; dMMR= mismatch repair-deficient; MSI-H=microsatellite instability-high; MMRp=mismatch repair proficient; MSS=microsatellite stable; NSCLC=non-small cell lung cancer; N=number (of patients); PDy=pharmacodynamic; PK=pharmacokinetic; POLE-mut=polymerase ε mutated; Q3W=every 3 weeks; Q6W=every 6 weeks; RP2D=recommended Phase 2 dose, also known as recommended therapeutic dose: 500 mg Q3W for 4 cycles followed by 1,000 mg Q6W thereafter.

Patient enrollment was based on local laboratory test results of MMR/MSI status, which were to be confirmed by central laboratory testing. Local testing included immunohistochemistry (IHC) to detect dMMR and polymerase chain reaction (PCR) and NGS to determine MSI status. Central laboratory testing was originally performed using NGS (FoundationOne). Preliminary efficacy analysis (data cutoff date 21 January 2019) demonstrated that local tests results obtained with IHC were more likely to identify participants responding to dostarlimab treatment than those obtained with NGS. Therefore, central IHC testing was initiated. Test results from IHC testing (local when available, otherwise central) are used for the final determination of MMR status for all efficacy and safety analyses.

Testing of MSI status using PCR or NGS is based on the detection of unstable microsatellites. For PCR-based methods, MSI is defined as the presence of instability at 2 or more of 5 microsatellite repeats tested. MSI status determination by NGS is routinely done using computational algorithms applied to the sequencing data (Salipante et al. 2014; Stadler et al. 2016; Nowak et al. 2017). In clinical practice, MMR status is nearly always detected using IHC. MMR IHC is a widely available laboratory test and utilizes antibodies against mutL homologue 1 , mutS homologue 2, mutS homologue 6, and postmeiotic segregation increased 2 to determine protein levels for individual MMR proteins based on the amount of antibody-positive stain

(Baretti et al. 2018). Loss of nuclear expression of at least 1 MMR protein in the tumor sample tested categorizes the sample as dMMR.

As MSI is a marker of dMMR, PCR, IHC, and NGS testing results are indicative of the same phenotype: dMMR/MSI-H. Thus, enrollment as of protocol amendment 5 (10 May 2019) is based on local MMR/MSI testing results (including PCR, IHC, and NGS tests) that are centrally confirmed by MMR IHC.

8.1.1.1. Trial location

Study 4010-01-001 was activated in 123 investigational sites in 9 countries.

8.1.1.2. Inclusion Criteria

For inclusion into Cohort A1 and Cohort F of Part 2B of this study, participants were required to fulfill all of the following criteria:

1. Participant was at least 18 years old.
2. Participant had proven recurrent or advanced solid tumor and disease progression after treatment with available anticancer therapies or was intolerant to treatment that met the requirements for the study they participated in, ie, histologically or cytologically proven recurrent or advanced solid tumor with measurable lesion(s) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and met one of the following disease types:
    a. Cohort A1 – Participants with dMMR/MSI-H EC
        - Participants had progressed on or after platinum doublet therapy.
        - Participants had received no more than 2 lines of anticancer therapy for recurrent or advanced (≥Stage IIIB) disease. Prior treatment with hormone therapies was acceptable and did not count toward the number of anticancer therapies noted in the criterion above for this cohort.
        - All EC histologies were allowed, except endometrial sarcoma (including carcinosarcoma).
        - Participants submitted 2 scans demonstrating an increase in tumor measurement that met criteria for PD on or after the latest systemic anticancer therapy based on RECIST v1.1 to Central Radiology prior to the first dose of dostarlimab.
        - Presence of at least 1 measurable lesion on baseline scan was confirmed by Central Radiology review.
        - Status of tumor MMR/MSI: Participants could be screened based on local MMR/MSI testing results using IHC, PCR, or NGS performed in a certified local laboratory, but participant eligibility was determined by MMR IHC results. For participants with available local MMR IHC results for the respective cohort(s), tumor samples were submitted to a central IHC laboratory, and the quality was checked and cleared prior to Cycle 1/Day 1. For participants without available local MMR IHC test results (ie, participants with local PCR or NGS test results), central IHC results confirmed eligibility

prior to proceeding with other screening procedures. After the central IHC test was completed, remaining tumor tissue may have been tested for exploratory biomarkers or sent to a central NGS laboratory for further testing.

b. Cohort F – Participants with recurrent or advanced dMMR/MSI-H or polymerase ε mutated (POLE)-mutated solid tumors, except ECs, that progressed following up to 2 prior lines of systemic therapy for recurrent or advanced (≥Stage IIIB) disease and who had no alternative treatment options. Prior treatment with hormone therapies alone given for recurrent or advanced disease was acceptable and did not count toward the number of anticancer therapies.

- Participants with dMMR/MSI-H CRC must have progressed after or been intolerant to treatment with fluoropyrimidine, oxaliplatin, and irinotecan. Disease progression following up to 3 prior lines of therapy was allowed.
- In participants with platinum resistant ovarian cancer (PROC) (ie, disease progression occurred <6 months on or after platinum doublet chemotherapy), receipt of up to 1 line of systemic therapy after becoming platinum resistant was allowed.
- Participants submitted 2 scans demonstrating an increase in tumor measurement that met criteria for PD based on RECIST v1.1 to Central Radiology prior to the first dose of dostarlimab.
- Tumor MMR/MSI or POLE status: Participants could be screened based on local MMR/MSI testing results using IHC, PCR, or NGS performed in a certified local laboratory, but participant eligibility was determined by MMR IHC results. For participants with available local MMR IHC results, tumor samples were submitted to a central IHC laboratory, and the quality was checked and cleared prior to Cycle 1/Day 1. For participants without available local MMR IHC test results (ie, participants with local PCR or NGS test results), central IHC results confirmed eligibility prior to proceeding with other screening procedures. After the central IHC test was completed, remaining tumor tissue may have been tested for exploratory biomarkers or sent to a central NGS laboratory for further testing.
- Participants who were considered for the study based on POLE mutation had local laboratory results available showing tumor mutation(s) in the exonuclease domain of the POLE gene (amino acid residues 268-471) to begin screening. The quality of submitted tumor samples was checked and cleared by a central IHC laboratory prior to a participant receiving study treatment.

3. Participants had archival tumor tissue available that was formalin fixed and paraffin embedded.

- For participants who did not have archival tissue, a new biopsy was performed to obtain a tissue sample prior to study treatment initiation. For participants without available archival tissue, the biopsy was taken from the tumor lesions (either primary

or metastatic) that had easy accessibility and low biopsy-associated risks and excluded biopsies of the liver, brain, lung/mediastinum, pancreas, or endoscopic procedures extending beyond the esophagus, stomach, or bowel.

4. Female participants must have had a negative serum pregnancy test within 72 hours prior to the date of the first dose of study medication, unless they were of nonchildbearing potential. Nonchildbearing potential was defined as follows:
    a. ≥45 years old and had not had menses for >1 year
    b. Amenorrheic for <2 years without a hysterectomy and oophorectomy and had a follicle-stimulating hormone value in the postmenopausal range upon prestudy (screening) evaluation
    c. Posthysterectomy, post-bilateral oophorectomy, or post-tubal ligation. Documented hysterectomy or oophorectomy must have been confirmed with medical records of the actual procedure or confirmed by an ultrasound, magnetic resonance imaging (MRI), or computerized tomography (CT) scan. Tubal ligation must have been confirmed with medical records of the actual procedure; otherwise, the participant must have fulfilled Inclusion Criterion 5. Information must have been captured appropriately within the site's source documents.
5. Female participants of childbearing potential (see above) must have agreed to use 1 highly effective form of contraception with their partners (Protocol 4010-01-001 Section 5.6.3 for a list of acceptable contraception methods) starting from the Screening Visit through 150 days after the last dose of study treatment.
6. Participant had an ECOG performance status of ≤1 for Part 2.
7. Participant had adequate organ function, defined as follows:
    a. absolute neutrophil count (ANC) ≥1,500/μL
    b. platelets ≥100,000/μL
    c. hemoglobin ≥9 g/dL or ≥5.6 mmol/L
    d. serum creatinine ≤1.5×upper limit of normal (ULN) or calculated creatinine clearance ≥50 mL/min using the Cockcroft-Gault equation for participants with creatinine levels >1.5×institutional ULN
    e. total bilirubin ≤1.5×ULN AND direct bilirubin ≤1×ULN
    f. aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5×ULN, unless liver metastases were present, in which case they must be ≤5×ULN
    g. international normalized ratio or prothrombin time ≤1.5×ULN, unless the participant was receiving anticoagulant therapy or as long as prothrombin time or partial thromboplastin time (PTT) was within the therapeutic range of intended use of anticoagulants. Activated partial thromboplastin time (aPTT) ≤1.5×ULN, unless the participant was receiving anticoagulant therapy or as long as prothrombin time or PTT was within the therapeutic range of intended use of anticoagulants.

8.1.1.3. Exclusion Criteria

Any of the following was regarded as a criterion for exclusion from the study:

1. Participant had received prior therapy with an anti-PD-1, anti-programmed death-ligand 1 (anti-PD-L1), or anti-programmed death-ligand 2 agent.

2. Participant had known uncontrolled central nervous system metastases and/or carcinomatous meningitis. Note: Participants with previously treated brain metastases may have participated provided they were stable (without evidence of progression by imaging for at least 4 weeks prior to the first dose of study treatment and any neurologic symptoms have returned to baseline), had no evidence of new or enlarging brain metastases, and were clinically stable off corticosteroids for at least 7 days prior to study treatment. Carcinomatous meningitis precluded a participant from study participation, regardless of clinical stability. (Additional provisions for Cohort F only: Participants with primary central nervous system tumors were eligible for Cohort F as long as they were neurologically stable in the absence of systemic corticosteroid use for at least 14 days prior to the first dose of study treatment.)
3. Participant had a known additional malignancy that progressed or required active treatment within the last 2 years. Exceptions included basal cell carcinoma of the skin, squamous cell carcinoma of the skin that had undergone potentially curative therapy, or in situ cervical cancer.
4. Participant was considered a poor medical risk due to a serious, uncontrolled medical disorder, a nonmalignant systemic disease, or an active infection requiring systemic therapy. Specific examples included, but were not limited to, active, noninfectious pneumonitis; uncontrolled ventricular arrhythmia; recent (within 90 days) myocardial infarction; uncontrolled major seizure disorder; unstable spinal cord compression; superior vena cava syndrome; or any psychiatric or substance abuse disorders that would have interfered with cooperation with the requirements of the study (including obtaining informed consent).
5. Participant was pregnant or breastfeeding, or expected to conceive children within the projected duration of the study, starting from the Screening Visit through 150 days after the last dose of study treatment.
6. Participant had a diagnosis of immunodeficiency or was receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment.
7. Participant had a known history of human immunodeficiency virus (HIV) (HIV 1/2 antibodies).
8. Participant had known active hepatitis B (eg, hepatitis B surface antigen reactive) or hepatitis C (eg, hepatitis C virus ribonucleic acid [qualitative] was detected).
9. Participant had an active autoimmune disease that had required systemic treatment in the past 2 years (ie, with the use of disease-modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) was not considered a form of systemic treatment. Use of inhaled steroids, local injection of steroids, and steroid eye drops was allowed.
10. Participant had a history of interstitial lung disease.
11. Participant had not recovered (ie, to Grade ≤1 or to baseline) from radiation- and chemotherapy-induced AEs or received transfusion of blood products (including platelets

or red blood cells) or administration of colony-stimulating factors (including granulocyte colony-stimulating factor, granulocyte macrophage colony-stimulating factor, or recombinant erythropoietin) within 3 weeks prior to the first dose of study drug.

12. Participant had participated in a study of an investigational agent and received study treatment or used an investigational device within 4 weeks prior to the first dose of study drug.
13. Participant had received prior anticancer therapy (chemotherapy, targeted therapies, radiotherapy, or immunotherapy) within 21 days, or less than 5 times the half-life of the most recent therapy prior to study Day 1, whichever was shorter. Note: Palliative radiation therapy to a small field >1 week prior to Day 1 of study treatment may have been allowed.
14. Participant had not recovered adequately (Grade ≤1) from AEs and/or complications from any major surgery prior to starting therapy.
15. Participant had received a live vaccine within 14 days of the planned start of study treatment.
16. Participant had a known hypersensitivity to dostarlimab components or excipients.

8.1.1.4. Treatments Administered

All participants in this study received dostarlimab as a 30-minute IV infusion (with a permitted window of -5 minutes and +15 minutes). In Part 2B, participants received dostarlimab 500 mg Q3W (Day 1 of each 21-day cycle) for the first 4 cycles followed by dostarlimab 1,000 mg Q6W (Day 1 of each 42-day cycle) for all subsequent cycles.

8.1.1.5. Dose Selection

The RTD was determined to be 500 mg dostarlimab Q3W for the first 4 cycles followed by 1,000 mg dostarlimab Q6W for all subsequent cycles. This dosing schedule was used in all cohorts in Part 2B of the study.

The RTD regimen was selected based on the emerging PK and PDy results. A 2-compartment model best described the observed PK data from participants in Part 1 of the study. The PK exposure was related to the RO data from peripheral blood cells and safety data from participants in Part 1 of the study. The effect of body weight on CL of dostarlimab was also explored. In this preliminary analysis, body weight over the range of 45.6 to 145.6 kg was not found to be a significant covariate for CL. At that stage, dosing based on body weight was not warranted.

Part 2A of the study confirmed the PK, safety, and tolerability of dostarlimab at 2 fixed doses (500 mg Q3W and 1,000 mg Q6W). Part 2B evaluated a participant-centric dose and regimen of 500 mg Q3W for 4 cycles followed by 1000 mg Q6W for all subsequent cycles. A PK/PDy model was used to further confirm the projected RTD. Based on the model, concentrations of 54 µg/ml for dostarlimab was estimated to maintain 90% of maximal PD-1 suppression in tumors, assuming a 3-fold tissue dilution for typical mAbs. A dose of 1 mg/kg Q3W did not maintain peripheral PD-1 suppression at maximal levels throughout the dosing interval based on a three-weekly cycle. For dostarlimab at steady-state, both the 500 mg Q3W and 1,000 mg Q6W doses maintained maximal peripheral PD-1 suppression at maximal levels throughout the respective

dosing intervals. In the population PK analysis including data from Part 2B, weight was found to have a statistically significant influence on the dostarlimab PK, though the impact on exposure (AUC_{ss} and $C_{max,ss}$) was minimal, suggesting limited clinical relevance and supporting flat-dosing of dostarlimab (Section 6).

The PK results from Part 1 and Part 2A of the study were described separately. The PDy (RO) results were presented in the Integrated Receptor Occupancy Report (dated 07 November 2019), using a data cutoff date of 08 July 2019. The selection of doses for Part 1 and Part 2A of the study was discussed in the 4010-01-001 CSR - Part 1 and Part 2A (final report), dated 22 November 2019 (4010-01-001 CSR Part 2b, Cohorts A1 and A2 Section 9.4.4).

8.1.1.6. Dose Modification and Dose Discontinuation

Study treatment dosing delays were permitted in the case of medical or surgical events or logistical reasons not related to study treatment (eg, surgery, unrelated medical events, participant vacation, and holidays). Participants should have been placed back on study treatment within 28 days of the scheduled dostarlimab infusion. If a delay was more than 28 days, the participant could have been placed back on study treatment only after discussion with the Sponsor. Reasons for treatment delays of more than 3 days should have been documented in the electronic case report form (eCRF).

In general, dostarlimab must have been withheld for drug-related Grade 3 toxicities but may have been resumed upon recovery to Grade 1 or less; dostarlimab was permanently discontinued for any drug-related Grade 4 event. Dostarlimab was discontinued for some Grade 3 immunologic-mediated AEs, as described in Table 5. For all immune-related adverse events (irAEs) listed in Table 5, dostarlimab should have been held until the participant was clinically and metabolically stable and AEs resolved to Grade 1 or less. If systemic steroids were used as a part of irAE management, the total dose of daily steroids should have been equal to or less than 10 mg prednisone at the time of resuming dostarlimab. The recent joint American Society of Clinical Oncology and NCCN guideline for diagnosis and management of irAEs treated with immune checkpoint inhibitor therapy may be used as a supplement to Table 5 (Brahmer et al. 2018).

All treatment delays (including any missed doses) and discontinuations and the reason for delays or discontinuation of dostarlimab should have been recorded in the eCRF.

Table 5: Guidelines for Treatment of irAEs

Toxicity	Hold Treatment for Grade	Restarting Treatment/Discontinuation
Uveitis	Symptomatic (any grade)	Restart dosing when toxicity resolves to Grade 0.
	Recurrent symptomatic or symptomatic uveitis unresponsive to corticosteroids	Permanently discontinue.
Diarrhea/colitis	2 or 3	Restart dosing when toxicity resolves to Grade 0 or 1.
	4	Permanently discontinue.

Table 5: Guidelines for Treatment of irAEs (Continued)

Toxicity	Hold Treatment for Grade	Restarting Treatment/Discontinuation
AST, ALT, or increased bilirubin	2 (AST or ALT >3 and ≤5×ULN or total bilirubin >1.5 and ≤3×ULN)	Restart dosing when toxicity resolves to Grade 0 or 1.
	3-4 (AST or ALT >5×ULN or total bilirubin >3×ULN)	Permanently discontinue (see the exception below).[a]
T1DM or hyperglycemia	3 or 4 hyperglycemia or T1DM (associated with metabolic acidosis or ketonuria)	Restart dosing in appropriately managed, clinically and metabolically stable subjects; insulin replacement therapy is required.
Immune-related encephalitis	Any grade	Permanently discontinue.
Hypophysitis	2-4	For Grade 2 or 3, hold until hormonal therapy results return to adequate levels by laboratory values, and restart dosing when toxicity resolves to Grade 0 or 1. For recurrence or worsening of Grade ≥2 hypophysitis after steroid taper has been completed and is on adequate hormone replacement therapy, permanently discontinue. For Grade 4, permanently discontinue.
Adrenal insufficiency	2-3	Hold until hormonal therapy results in return to adequate levels by laboratory values, and restart dosing when toxicity resolves to Grade 0 or 1. For recurrent or worsening Grade ≥2 adrenal insufficiency while adequate hormonal replacement is continuing, permanently discontinue study drug.
	4	Permanently discontinue.
Hypothyroidism and hyperthyroidism	3	Hold until hormonal therapy results in return to adequate levels by laboratory values and restart dosing when toxicity resolves to Grade 0 or 1.
	4	Permanently discontinue.
Infusion-related reaction	2[b]	Restart dosing when toxicity resolves to Grade 0 or 1.
	3-4	Permanently discontinue.
Pneumonitis	2	Restart dosing when toxicity resolves to Grade 0 or 1. If Grade 2 recurs, permanently discontinue.
	3-4	Permanently discontinue.

Table 5: Guidelines for Treatment of irAEs (Continued)

Toxicity	Hold Treatment for Grade	Restarting Treatment/Discontinuation
Rash	3	Restart dosing when toxicity resolves to Grade 0 or 1.
	4	Permanently discontinue.
Renal failure or nephritis	2	Restart dosing when toxicity resolves to Grade 0 or 1.
	3-4	Permanently discontinue.
Recurrence of AEs after resolution to Grade ≤1	3-4	Permanently discontinue.

Source: CSR 4010-01-001 - Part 2B, non-endometrial cancer (Cohorts A1 and A2)
Abbreviations: AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CSR=clinical study report; hr=hour; irAE=immune-related adverse event; T1DM=type 1 diabetes mellitus; ULN=upper limit of normal.
[a] For subjects with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by ≥50% relative to baseline and lasts for at least 1 week, then the subject should be discontinued.
[b] Upon resolution within 1 hr of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise, dosing will be held until symptoms resolve, and the subject should be premedicated for the next scheduled dose; refer to Section 5.6.4 of the protocol for further management details.

8.1.1.7. Administrative Structure

TESARO, Inc., subsequently acquired by GlaxoSmithKline LLC (GSK), initiated the study. The Applicant was responsible for study oversight, vendor oversight, database development and maintenance, storage and distribution of clinical supplies to sites, and site and vendor audits for this study. To ensure subjects' safety during Part 2B of the study, safety data were reviewed by an Independent Data Monitoring Committee (IDMC) on an ongoing basis.

8.1.1.8. Procedures and Schedule

Radiographic evaluations (CT [preferred method] or MRI [if clinically indicated]) of the chest, abdomen, and pelvis were conducted according to immune-related response evaluation criteria in solid tumors (irRECIST) at screening to determine the extent of the disease and confirm the presence of measurable disease. MRI was only used when CT was contraindicated or for imaging of the brain, and the same imaging technique was used throughout the study. Appropriate testing of serum-based tumor markers, where applicable (eg, cancer antigen 125 [CA-125] for participants with ovarian cancer), was conducted at screening and throughout the study.

In Part 2, the first radiographic evaluation occurred at Week 12 (84±10 days), following the first dostarlimab dose and Q6W (42±10 days) thereafter, independent of cycle delays and/or dose interruptions. After 1 year (48 weeks) of radiographic assessments, participants in Part 2B had imaging and assessment of serum-based tumor markers performed every 12 weeks (84±10 days)

until PD. After Week 48, the next scan is at Week 60. Imaging should not be delayed for any dose or cycle interruptions.

If a participant discontinued treatment for any reason other than PD, death, withdrawal of consent, or lost to follow-up, radiographic scans and appropriate testing of serum-based tumor markers continued at the specified intervals until PD was confirmed or an alternate anticancer therapy was started, whichever occurred first. In Part 2B, all radiographic images/scans were sent to a central imaging vendor upon acquisition and archived for future evaluation, if needed.

Investigators used irRECIST-based assessment to make clinical decisions. Per irRECIST, immune-related complete response (irCR) or immune-related partial response (irPR) was confirmed by repeat radiographic evaluation, at the earliest, 4 weeks after the first indication of response or at the next scheduled scan, whichever was clinically indicated. PD was confirmed by radiographic evaluation at a minimum of 4 weeks and up to 6 weeks after the first PD assessment.

The FDA's Assessment:

The FDA agrees with the Applicant's presentation of the trial design of Study 4010-01-001 (GARNET). The study design is appropriate for investigation of efficacy and safety of dostarlimab for the proposed indication.

8.1.1.9. Study Endpoints

The Applicant's Position:

The primary objectives of Cohorts A1 and F of Part 2B of this study were as follows:

- to evaluate the safety and tolerability of dostarlimab at the RP2D in participants with recurrent and advanced solid tumors
- to evaluate the antitumor activity of dostarlimab in participants with recurrent and advanced dMMR/MSI-H EC and non-EC, in terms of ORR and DOR by blinded independent central review (BICR) using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1)

ORR was selected as a primary endpoint (together with DOR) in Study 4010-01-001 because it is an accepted surrogate endpoint to measure clinical benefit in oncology studies. Because ORR can be directly attributed to the drug administered, single-arm studies can be used to assess the efficacy of the drug in subjects with refractory tumors where no available therapy exists (Pazdur 2008). ORR has been used to support accelerated (in the US) and conditional (in the EU) approvals with single-arm studies. According to the European Medicines Agency (EMA) Guideline on the Evaluation of Anticancer Medicinal Products in Man (EMA 2017). ORR is a rather convincing measure of antitumor activity because, for most tumors, spontaneous regression-fulfilling criteria for at least PR is a rare phenomenon. In accordance with the FDA and EMA guidances, ORR was calculated based on tumor assessments by BICR (EMA 2018; FDA 2018). The tumor assessments by BICR were done according to the revised RECIST v1.1, which represents standardized World Health Organization (WHO) response criteria (Eisenhauer et al. 2009 Because immune-stimulating agents such as anti-PD-1 antibodies are associated with a recognized phenomenon of transient tumor flare or pseudo-progression followed by long-lasting PR or SD, Investigators were allowed to manage treatment decisions using tumor

assessments based on irRECIST v1.1 during the study (Wolchok et al. 2009; Chiou et al. 2015). This was to prevent subjects from being withdrawn from study treatment prematurely in the case of pseudo-progression.

The primary efficacy endpoints for Cohort A1 and Cohort F were ORR (defined as the proportion of patients achieving a BOR of CR or PR, as assessed per RECIST v1.1 based on BICR) and DOR according to RECIST v1.1 assessed by BICR. ORR was programmatically derived based on reported time point response assessments as determined by a central reader at different evaluation time points from the first dose date until the first documented PD. DOR was defined as the time from first documentation of CR or PR until the time of first documentation of PD or death due to any cause.

Secondary efficacy endpoints for Cohort A1 and Cohort F were:

- DCR, defined as the proportion of patients achieving BOR of confirmed CR, PR, or SD, as assessed per RECIST v1.1.
- PFS, defined as the time from date of first dose to the earlier date of assessment of disease progression or death by any cause in the absence of progression based on the time of first documentation of PD per RECIST v1.1 based on BICR.
- OS, defined as the time from date of first dose of study treatment to the date of death by any cause.
- Immune-related objective response rate (irORR), defined as the proportion of patients achieving immune-related best overall response (irBOR) of irCR or irPR, as assessed per irRECIST based on Investigator's assessment.
- Immune-related duration of response (irDOR), defined as the time from first documentation of irCR or irPR, as assessed per irRECIST based on Investigator's assessment, until the time of first documentation of immune-related progressive disease (irPD) (subsequently confirmed), as assessed per irRECIST based on Investigator's assessment, or death.
- Immune-related disease control rate (irDCR), defined as the proportion of patients achieving irBOR of irCR, irPR, or immune-related SD, as assessed per irRECIST based on Investigator's assessment.
- Immune-related progression-free survival (irPFS), defined as the time from date of first dose to the earlier date of assessment of irPD or death by any cause in the absence of progression based on the time of first documentation of irPD (subsequently confirmed) per irRECIST based on Investigator's assessment.
- PRO is an exploratory endpoint for Cohort A1 and Cohort F. The European Quality of Life scale, 5 Dimensions, 5 Levels and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30) were used to assess cancer-specific health-related quality of life. PRO assessments were added to the study under protocol amendment 3.

The FDA's Assessment:

The FDA review focused primarily on efficacy results in a pooled population of patients from Cohort A1 (participants with recurrent or advanced dMMR EC) and Cohort F (participants with recurrent or advanced dMMR non-EC) in Part 2B of Study 4010-01-001, since these cohorts enrolled patients with dMMR solid tumors, regardless of tumor type. The analysis of the primary efficacy population focused on ORR and DoR as assessed per RECIST v1.1 based on BICR in patients with measurable disease at baseline. Although the Applicant included additional secondary endpoints including PFS and OS, analyses of these time-to-event endpoints are not interpretable in a single-arm trial, without a control group. Additionally, FDA does not consider disease control rate (DCR) to be an interpretable efficacy endpoint for single-arm studies because it incorporates stable disease, which is highly driven by underlying disease natural history and because DCR does not reflect treatment effect as reliably as ORR does.

8.1.1.10. Statistical Analysis Plan

The Applicant's Position:

The determination of the sample size is described in Protocol 4010-01-001, Section 8.9.

Data from Cohorts A1 and F were combined to derive an estimation of ORR in this population. The null hypothesis for the combined cohorts that the true response rate is ≤20% (H0: p≤0.20) was tested against a 1-sided alternative of ≥30% (Ha: p≥0.3). With a total of 165 participants (65 from Cohort A1 and 100 from Cohort F), the study would provide 85% power to rule out ORR ≤20% (null hypothesis) when the true ORR is 30% at the 1-sided 2.5% type I error rate.

Per protocol Amendment 6 (07 Jan 2020), there will be 3 planned interim analysis for dMMR patients combined for administrative purposes. The interim analysis will occur when enrollment reaches approximately 100, 200 and 300 patients and enrolled patients have been followed for at least 6 months.

8.1.1.11. Analysis Sets

The safety analysis set was defined as all participants who received any amount of study drug.

The primary efficacy analysis set by RECIST v1.1 per BICR was defined as all participants in the safety analysis set with measurable disease at baseline (defined as the existence of at least 1 target lesion at baseline tumor assessment by BICR) whose first dose of dostarlimab administration was on or prior to 15 September 2019. These patients had the opportunity for at least 24 weeks of tumor assessment at the time of analysis.

The secondary efficacy analysis set by irRECIST per Investigators' assessment was defined as all participants in the safety analysis set with measurable disease at baseline (defined as the existence of at least 1 target lesion at baseline tumor assessment by Investigators' assessment) whose first dose of dostarlimab administration was on or prior to 15 September 2019. These participants had the opportunity for at least 24 weeks of tumor assessment at the time of analysis.

8.1.1.11.1. Subgroup analysis

Exploratory analysis of ORR and DOR based on RECIST v1.1 was performed for each of the following subgroups:

- MSI status by FoundationOne NGS test: MSI-H vs MSS vs unknown/missing
- number of prior anticancer therapy regimens: 1 vs ≥2
- prior radiation therapy: yes vs no
- prior bevacizumab use: yes vs no
- BOR from last platinum-containing prior anticancer therapy (CR/PR, SD, PD, or missing)
- Progression-free interval from last platinum-containing prior anticancer therapy (less than 6 months vs 6 months or greater vs missing)
- Cohorts A1 and A2: histology (participants with dMMR EC or MMR-proficient EC)
- Cohort F: tumor type: CRC vs Other

8.1.1.12. Handling of Dropouts or Missing Data

No subjects from Cohort A1 and Cohort F were replaced during Part 2B. All data recorded on the eCRF are included in the data listings of this CSR.

In general, missing observations were treated as missing at random and were not imputed. The handling of missing disease history, AE, concomitant medication, and follow-up anticancer treatment dates is described in Section 12.3 of the statistical analysis plan (SAP) for Part 2B.

8.1.1.13. Interim Analyses and Data Monitoring

Interim Analysis-1, performed using a data cutoff date of 08 July 2019, was based on combined enrollment from Cohort A1 and Cohort F of approximately 100 participants who had measurable disease at Baseline and at least 24 weeks of follow-up. Results for Cohort A1 and Cohort A2 were described in interim CSR 4010-01-001 - Part 2B, endometrial cancer (Cohorts A1 and A2; dated 02 December 2019) and results for Cohort F were described in interim CSR 4010-01-001 - Part 2B, non-endometrial cancer (Cohort F; dated 02 December 2019), both using a data cutoff date of 08 July 2019.

The current interim CSRs present the results from Interim Analysis-2, which is based on combined enrollment from Cohort A1 and Cohort F of approximately 200 participants who had measurable disease at Baseline and whose first dose of dostarlimab administration was on or prior to 15 September 2019. These patients had least 24 weeks of follow-up, with a data cutoff date of 01 March 2020.

8.1.1.14. Multiple Comparisons/Multiplicity

Adjustments for multiplicity were not made because this was an estimation study. Separate inferences were drawn for each tumor cohort.

The FDA's Assessment:

Per the SAP, the sample size of Cohort F increased to 200 patients from the originally planned 100 sample size.

The FDA does not use inferential procedures (testing procedures, performance goals, type I error control, etc.) to evaluate single-arm trial results. FDA efficacy evaluation is based on the estimated magnitude of ORR and adequate duration of response. This review focused primarily on efficacy results from Interim Analysis 2 based on the pooled population of patients from Cohort A1 and Cohort F with a data cutoff date of March 1, 2020.

8.1.1.15. Protocol Amendments

The Applicant's Position:

The original protocol was finalized on 03 December 2015. During the conduct of the study, the protocol was amended 6 times, although versions 4.0 and 5.0 were never implemented. Participants in Part 2B of the study were enrolled only under protocol versions 3.0, 4.1, 5.1, and 6.0 (amendments 2, 3, 4, and 5, respectively). No participants were enrolled under protocol version 7.0 by the data cutoff date for this second interim CSR.

8.1.1.15.1. Global Amendment 2 (Protocol Version 3.0; Dated 31 October 2016)

The primary reasons for this global amendment were the following:

- The EC cohort was split into 2 cohorts based on MSI status: Cohort A1 and Cohort A2. Sample size justifications were added for the cohorts.
- Inclusion Criterion 2c was modified to provide information on the 2 EC cohorts, clarify previous anticancer therapy allowances, exclude endometrial sarcoma histology, and require known tumor MSI status prior to the first dose of study treatment.
- Assessment of tumor imaging from Cohort A1 and Cohort A2 by central radiologists based on RECIST v1.1, in addition to Investigators' assessment based on irRECIST, was specified and the parameters used to evaluate clinical activity for these cohorts were separated.
- IDMC review of safety data for Part 2B was defined.

8.1.1.15.2. Protocol Version 4.0 (Dated 29 September 2017)

The primary reasons for this global amendment were the following:

- Assessment of PROs was added to support analyses of health-related quality of life in Cohort A1 and Cohort F subjects.
- A plan was added for an interim analysis of the subjects with MSI-H cancer from Cohort A1 and Cohort F, combined, for administrative purposes.

Protocol version 4.0 was not implemented because an error in the footnotes lettering of Table 6 was discovered prior to distribution. These typographical errors were corrected in protocol version 4.1.

8.1.1.15.3. Protocol Version 4.1 (Dated 09 October 2017)

No substantial changes were made to the protocol in this amendment. Typographical errors found in protocol version 4.0 were corrected. Amendment 3 was implemented as protocol version 4.1.

8.1.1.15.4. Global Amendment 4 (Protocol Version 5.1; Dated 03 July 2018)

The primary reasons for this global amendment were the following:

- The enrollment in Cohort A2 was increased to enroll approximately 125 subjects, with the potential for up to 250 subjects, based on encouraging clinical activity seen from the interim analysis (6 irPRs and 7 immune related stable disease out of 25 subjects). The increase in sample size of Cohort A2 allowed more precise testing of the estimate of ORR, with the lower limit of the exact 95% CI excluding a response rate of 15% or less. The overall sample size of the study was not changed.
- The ex-vivo analysis of PD-1 RO on circulating blood cells was removed. The requirement for a blood sample for PDy was removed for subjects enrolled under Amendment 4 and subsequent amendments.
- Clinically stable subjects without major safety issues were allowed to remain on treatment after confirmation of PD, if the Investigator believed there was clinical benefit and following discussion with the Medical Monitor.

Protocol version 5.0 was not implemented. The protocol title, which had been revised in protocol version 5.0, was reverted back to the original title. Amendment 4 was implemented as protocol version 5.1.

8.1.1.15.5. Global Amendment 5 (Protocol Version 6.0; Dated 10 May 2019)

The primary reasons for this global amendment were the following:

- The definitions of Cohort A1 and Cohort A2 were updated based on a preliminary efficacy analysis (data cutoff date: 21 January 2019), as well as feedback from FDA during the Type C meeting held on 25 February 2019 and Scientific Advice meetings with EU National Authorities during March and April 2019. Tumor status requirements in the EC cohorts were revised to specify that subject eligibility can only be determined by MMR status based on results from IHC testing. Subjects with dMMR EC or, in the absence of known MMR status, MSI-H EC are included in Cohort A1, and subjects with MMR-proficient EC or, in the absence of known MMR status, MSS EC are included in Cohort A2.
- The sample size of Cohort A1 was increased to 100 subjects, with the potential for up to 165 subjects.
- Assessment of PROs was revised from a secondary to an exploratory objective

8.1.1.15.6. Global Amendment 6 (Protocol Version 7.0; Dated 07 January 2020)

The primary reasons for this global amendment were as follows:

- A new cohort, Cohort G, was added to evaluate the efficacy and safety of dostarlimab at the RTD in participants with PROC without a known breast cancer susceptibility gene mutation who have been previously treated with bevacizumab.
- The primary objectives for Part 2B of the study were updated to include an evaluation of the safety and tolerability of dostarlimab.
- Two interim analyses were added, to take place when the combined enrollment in Cohort A1 and Cohort F reached 200 and 300 participants, respectively, and each of the 200 or 300 participants have measurable disease at Baseline and at least 24 weeks of follow-up.

FDA's Assessment:

The FDA agrees with the Applicant's summary of protocol amendments. The key changes made by the protocol amendments above did not affect the interpretation of the results of the trial.

8.1.1.16. Study Results

8.1.1.16.1. Compliance with Good Clinical Practices

The Applicant's Position:

This study was designed and monitored in accordance with Applicant procedures, which comply with the ethical principles of Good Clinical Practice (GCP) as required by the major regulatory authorities, and in accordance with the Declaration of Helsinki. This BLA includes data from sites in the US as well as data from foreign sites that were not part of the IND. For US sites, the study was conducted in accordance with the Code of Federal Regulations (CFR) governing the protection of human subjects (21 CFR part 50), Institutional Review Boards (21 CFR part 56) and the obligations of Clinical Investigators (21 CFR 312.50 to 312.70) in accordance with GCP. Foreign clinical sites complied with the requirements of 21 CFR 312.120 and in accordance with GCPs, with a statement of compliance provided in Module 1.11.3.

Before each subject was enrolled in the clinical study, written informed consent was obtained from the subject according to the regulatory and legal requirements of the participating country.

The FDA's Assessment:

The FDA agrees with the Applicant's position on compliance with good clinical practices during conduct of this study.

8.1.1.16.2. Financial Disclosure

The Applicant's Position:

In accordance with 21 CFR 54, the Sponsor submitted a financial disclosure certification document in Module 1.3.4. The document includes three tables listing all Investigators who participated in the covered study supporting BLA 761223: those with disclosable financial

interests, no disclosable interests, and those whose financial disclosure information is missing or incomplete.

Three total Investigators, of whom 2 were sub-investigators, in two centers participated in Study 4010-01-001 and received varying amounts of compensation from TESARO/GSK for activities, such as speaking engagements and consultations in the form of Advisory Board meetings. A total of (b) (6) subjects were enrolled in these centers, (b) (6) GSK has determined that there is no impact from potential bias or influence on the data originating from these investigators.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment.

8.1.1.16.3. Patient Disposition

The Applicant's Position:

Participant disposition is presented in Table 6. The primary efficacy analysis set included 209 participants with dMMR solid tumors who had measurable disease at baseline by RECIST v1.1 per BICR and received their first dose of dostarlimab administration on or prior to 15 September 2019.

At the time of data cutoff, 53.6% of participants had discontinued treatment, and 34.0% had discontinued the study. The most common reason for treatment discontinuation was confirmed PD (77 participants), and the most common reason for study discontinuation was death (58 participants).

Table 6: Participant Disposition – Participants with dMMR Solid Tumors (Primary Efficacy Analysis Set)

Variable Reason, n (%)	dMMR EC (N=103)	dMMR NEC (N=106)	dMMR Overall (N=209)
Discontinued treatment	64 (62.1)	48 (45.3)	112 (53.6)
Confirmed PD	45 (43.7)	32 (30.2)	77 (36.8)

Table 6: Participant Disposition – Participants with dMMR Solid Tumors (Primary Efficacy Analysis Set) (Continued)

Variable Reason, n (%)	dMMR EC (N=103)	dMMR NEC (N=106)	dMMR Overall (N=209)
AE	12 (11.7)	8 (7.5)	20 (9.6)
Based on clinical criteria by the Investigator	5 (4.9)	4 (3.8)	9 (4.3)
Other	1 (1.0)[a]	3 (2.8)[b]	4 (1.9)
Participant request	1 (1.0)	1 (0.9)	2 (1.0)
Discontinued study	44 (42.7)	27 (25.5)	71 (34.0)

Variable Reason, n (%)	dMMR EC (N=103)	dMMR NEC (N=106)	dMMR Overall (N=209)
Death	35 (34.0)	23 (21.7)	58 (27.8)
Withdrawal of consent	7 (6.8)	3 (2.8)	10 (4.8)
Lost to follow-up	1 (1.0)	1 (0.9)	2 (1.0)
Other	1 (1.0)[c]	0	1 (0.5)

Source: Module 2.5 Table 14.1.2e
Abbreviations: AE=adverse event; CRF=case report form; CSR=clinical study report; dMMR=mismatch repair-deficient; EC=endometrial cancer; NEC=non-endometrial cancer; PD=progressive disease.
Note: Reasons for discontinuation were based on the Discontinuation of Treatment and Discontinuation of Study CRF page.

[a] This participant died due to the progression of her disease before the decision to stop treatment; no End of Treatment Visit or Safety Follow-up Visit was done (CSR 4010-01-001, Part 2B Cohorts A1 and A2, Listing 16.1.2a).

[b] The reasons for treatment discontinuation in the 3 participants were confirmation of disease progression on exitus, death due to disease progression, and death (CSR 4010-01-001, Part 2B Cohort F, Listing 16.1.2c).

[c] This participant returned to her country of origin (CSR 4010-01-001, Part 2B Cohorts A1 and A2, Listing 16.1.2a).

The FDA's Assessment:

The FDA agrees with the Applicant's assessment that the most common reason for treatment discontinuation in patients with dMMR solid tumors was disease progression. Death was the main reason for study discontinuation. Dostarlimab was permanently discontinued due to adverse reactions in 20 (9%) of patients, the most common adverse reaction (≥1%) leading to discontinuation was increased alanine aminotransferase (1.1%).

8.1.1.16.4. Protocol Violations/Deviations

The Applicant's Position:

The Sponsor's Medical Monitor reviewed, assessed, and classified protocol deviations in consultation, as needed, with Pharmacovigilance, the Biostatistician, the Clinical Trial Manager, and as appropriate, Clinical Pharmacology and/or other Study Team members throughout the clinical study at intervals defined in the Medical Data Review Plan.

Important and significant categories were summarized. A by-participant listing of Important and Significant Protocol Deviations (ISPDs), including deviation visit, deviation type, deviation description, and any relevant comments, was generated. Protocol deviations resulting from the coronavirus disease 2019 (COVID-19) pandemic were listed separately. No COVID-19-related contingency measures were implemented in the study prior to the data cutoff date of 01 March 2020 for this second interim CSR.

A protocol deviation was classified as important if there was the potential for any of the following:

- failure to obtain informed consent for participation in the clinical study
- enrollment of an ineligible participant
- a participant to develop withdrawal criteria during the study but not be withdrawn

- a participant to receive incorrect treatment
- incorrect or noncompliant dosing of a participant (ie, dosing that was inconsistent with the protocol)
- administration of an excluded concomitant treatment to a study participant
- impact on the completeness, accuracy, and/or reliability of the study data
- an effect on a participant's rights, safety, or well-being

A protocol deviation was classified as significant if it was confirmed to adversely impact the completeness, accuracy, and/or reliability of the study data or affect a participant's rights, safety, or well-being.

4010-01-001 (GARNET) Part 2B, Cohorts A1 and A2

A total of 367 important protocol deviations were recorded for 149 participants (51.4%) in the safety analysis set (CSR 4010-01-001, Part 2B Cohorts A1 and A2, Table 13). Of 126 participants with dMMR EC, 168 important protocol deviations were recorded for 75 participants (59.5%). Most of these important deviations were related to study visits or procedures, including missing safety laboratory assessments, missing tumor assessments, and delayed reporting of serious adverse events (SAEs).

In the safety analysis set, a total of 26 significant protocol deviations were recorded for 18 participants (6.2%), including 17 significant protocol deviations in 11 participants with dMMR EC (8.7%) and 9 significant protocol deviations in 7 participants with MMR-proficient EC (4.8%). Most of these significant deviations were related to inclusion/exclusion criteria and included the following (4010-01-001 Part 2B, Cohorts A1 and A2 CSR Listing 16.1.3a and data on file):

- Deviation of inclusion criterion 2 (n=7): progression following more than 2 prior lines of therapy (n=2 [2 participants with dMMR EC]), no prior platinum-based therapy(n=1 [1 participant with dMMR EC]), no central radiological confirmation of PD before dosing/no measurable disease at baseline (n=1 [1 participant with dMMR EC]), and participants with carcinosarcoma (n=3 [3 participants with MMR-proficient EC]; for 1 participant, this was recorded as 2 different significant protocol deviations).
- Deviation of exclusion criterion 11: participant received transfusion of red blood cells within 3 weeks prior to the first dose of study drug (n=1 [1 participant with MMR-proficient EC]; recorded as 2 different significant protocol deviations). A participant with dMMR EC also received transfusion of red blood cells within 3 weeks prior to the first dose of study drug; this participant was summarized under disallowed medications.
- Deviation of exclusion criterion 13: no washout period of 21 days for paclitaxel/carboplatin treatment prior to dosing (n=1 [1 participant with dMMR EC]).
- Deviation of inclusion criterion 7 (n=2): laboratory assessment was not done within 72 hours of first dose of study drug (n=2 [2 participants with dMMR EC]). One of

these 2 participants with dMMR EC was also summarized twice under study visit/procedure deviation.

- Participant enrolled without meeting conflicting study eligibility criteria (n=1 [1 participant with dMMR EC]).
- Prohibited medications (n=4): megestrol acetate (hormone) (n=1 [1 participant with dMMR EC]), radiotherapy (n=1 [1 participant with dMMR EC]), packed red blood cells (n=1 [1 participant with dMMR EC]), and palliative radiation therapy (n=1 [1 participant with MMR-proficient EC]).
- SAE (n=2): SAE was not reported within 24 hours (n=1 [1 participant with dMMR EC]), and an SAE was reported 12 days out of window (n=1 [1 participant with MMR-proficient EC]).
- Study visit/procedures (n=2): laboratory assessment was not done within 72 hours of first dose of study drug/adequate organ function eligibility not met (n=1 [1 participant with dMMR EC]), and participant received dostarlimab before central MSI status confirmation (n=1 [1 participant with MMR-proficient EC]).

4010-01-001 (GARNET) Part 2B, Cohort F

A total of 303 important protocol deviations were recorded for 96 participants (60.8%) in Cohort F of Part 2B (CSR 4010-01-001, Part 2B Cohort F, Table 13). Most of the deviations were related to study visits or procedures, including missing safety laboratory assessments, missing tumor assessments, and delayed reporting of SAEs (4010-01-001 Part 2B, Cohort F CSR Table 14.1.4.1c).

A total of 27 significant protocol deviations were recorded for 22 participants (13.9%). Fifteen of these significant deviations were related to inclusion/exclusion criteria (4010-01-001 Part 2B, Cohort F CSR Listing 16.1.3c):

- Deviation of inclusion criterion 2 (n=7):
  - progression following more than 2 prior lines of therapy (n=2)
  - no prior irinotecan treatment for CRC participant (n=1)
  - no central radiological confirmation of PD from the latest systemic anticancer therapy based on RECIST v1.1 before dosing (n=3). These participants had central radiological confirmation of PD performed after dosing.
  - no check of tumor sample quality by central laboratory prior to Cycle 1/Day 1 (n=1)
- Deviation of inclusion criterion 7 (n=6)
- Deviation of exclusion criterion 11 (n=1)
- Deviation of inclusion criterion 7 and exclusion criteria 3 and 9 (n=1). The Medical Monitor allowed this participant to continue treatment.

None of these significant protocol deviations were considered to affect the participants' safety or well-being or the overall integrity of the study.

No important or significant protocol deviations related to COVID-19 were reported in the safety analysis set (Table 14.1.4.2a).

A by-participant listing of all protocol deviations recorded in the safety analysis set is provided in 4010-01-001 Part 2B, Cohort F CSR Listing 16.1.3a.

The FDA's Assessment:

The FDA agrees that the significant protocol deviations did not affect the efficacy and safety outcomes of the trial.

8.1.1.16.5. Table of Demographic Characteristics

The Applicant's Position:

The demographic characteristics for participants with dMMR solid tumors are summarized in Table 7.

Within the population, 161 participants were female (77.0%), 132 participants were White (63.2%), and 110 participants were <65 years old (52.6%). Participants with dMMR non-EC were approximately evenly distributed by sex (45.3% male and 54.7% female), while all participants with dMMR EC (100%) were female. Median age in participants with dMMR solid tumors was 63.0 years, and median body mass index was 25.72 kg/m^2 (range: 13.6 to 53.9 kg/m^2). A baseline ECOG performance status of 1 and 0 was reported in 60.8% and 39.2% of participants, respectively.

Table 7: Demographic Characteristics – Participants with dMMR Solid Tumors (Primary Efficacy Analysis Set)

Characteristic	dMMR EC (N=103)	dMMR NEC (N=106)	dMMR Overall (N=209)
Sex, n (%)			
Female	103 (100)	58 (54.7)	161 (77.0)
Male	0	48 (45.3)	48 (23.0)
Race, n (%)			
White	80 (77.7)	52 (49.1)	132 (63.2)
Black	2 (1.9)	2 (1.9)	4 (1.9)
Asian	4 (3.9)	2 (1.9)	6 (2.9)
American Indian or Alaska Native	3 (2.9)	0	3 (1.4)
Other	0	1 (0.9)	1 (0.5)

Table 7: Demographic Characteristics – Participants with dMMR Solid Tumors (Primary Efficacy Analysis Set) (Continued)

Characteristic	dMMR EC (N=103)	dMMR NEC (N=106)	dMMR Overall (N=209)
Unknown	0	2 (1.9)	2 (1.0)
Not reported	14 (13.6)	47 (44.3)	61 (29.2)
Age (years)			
n	103	106	209
Mean (StDev)	63.5 (8.87)	60.5 (12.33)	62.0 (10.84)
Median	65.0	61.5	63.0
Q1, Q3	59.0, 70.0	53.0, 70.0	57.0, 70.0
Min, max	39, 80	24, 85	24, 85
Age group, n (%)			
<65 years	51 (49.5)	59 (55.7)	110 (52.6)
≥65 years to <75 years	41 (39.8)	38 (35.8)	79 (37.8)
≥75 years	11 (10.7)	9 (8.5)	20 (9.6)
Weight (kg)			
n	103	105	208
Mean (StDev)	74.2 (21.08)	69.3 (15.74)	71.7 (18.70)
Median	71.0	67.0	68.8
Q1, Q3	57.0, 87.0	59.0, 77.7	57.3, 83.2
Min, max	34.0, 141.4	39.0, 120.0	34.0, 141.4
BMI (kg/m^2)			
n	100	104	204
Mean (StDev)	28.98 (7.794)	24.82 (5.422)	26.86 (6.992)
Median	27.97	23.76	25.72
Q1, Q3	22.83, 34.00	21.38, 28.08	21.82, 31.26
Min, max	13.6, 53.9	13.8, 47.5	13.6, 53.9
ECOG performance status, n (%)			
0	40 (38.8)	42 (39.6)	82 (39.2)
1	63 (61.2)	64 (60.4)	127 (60.8)

Source: Module 2.7.3 Table 14.1.3e

Abbreviations: BMI=body mass index; dMMR=mismatch repair deficient; EC=endometrial cancer; ECOG=Eastern Cooperative Oncology Group; max=maximum; min=minimum; NEC=non-endometrial cancer; Q1=first quartile; Q3=third quartile; StDev=standard deviation.

8.1.1.16.6. Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The Applicant's Position:

The baseline disease characteristics for participants with dMMR solid tumors included in the primary efficacy analysis set are summarized in Table 8.

At baseline, 82.8% of participants with dMMR solid tumors were FIGO Stage IV at most recent assessment.

Table 8: Primary Cancer History – Participants with dMMR Solid Tumors (Primary Efficacy Analysis Set)

Category, (n [%])	dMMR EC (N=103)	dMMR NEC (N=106)	dMMR Overall (N=209)
FIGO Stage at first diagnosis			
Stage I	40 (38.8)	4 (3.8)	44 (21.1)
Stage II	7 (6.8)	10 (9.4)	17 (8.1)
Stage III	36 (35.0)	35 (33.0)	71 (34.0)
Stage IV	20 (19.4)	55 (51.9)	75 (35.9)
Unknown	0	2 (1.9)	2 (1.0)
Most recent FIGO stage			
Stage I	12 (11.7)	0	12 (5.7)
Stage II	3 (2.9)	0	3 (1.4)
Stage III	16 (15.5)	3 (2.8)	19 (9.1)
Stage IV	70 (68.0)	103 (97.2)	173 (82.8)
Unknown	2 (1.9)	0	2 (1.0)

Source: Module 2.7.3 Table 14.1.4e
Abbreviations: dMMR=mismatch repair deficient; EC=endometrial cancer; FIGO=International Federation of Gynecology and Obstetrics; NEC=non-endometrial cancer.

The FDA's Assessment:

FDA generally agrees with the Applicant's assessment of baseline characteristics. In the efficacy analysis population (N=209), median age was 63 years (47% aged 65 years or older); majority of patients were female (77%); 63% White, 3% Asian, 2% Black; and Eastern Cooperative Oncology Group Performance Status 0 (39%) or 1 (61%). At time of trial entry, 97% of patients (103/106) with non-endometrial dMMR solid tumors had TNM Stage IV disease, and 68% (70/103) of patients with dMMR endometrial tumors had FIGO Stage IV disease.

Overall the demographics of patients with dMMR EC in cohort A1 (N=103) and those with non-EC dMMR in cohort F (69 out of 106 were patients with colorectal cancer) in the GARNET trial were consistent with the US population demographics.

The tumor types that comprised the efficacy analysis population in GARNET are listed in Table 9.

Table 9: Tumor types in efficany analysis population with dMMR solid tumors

Tumor Type	Efficacy population N=209
dMMR EC	103
dMMR Non EC	106
CRC	69
Small intestinal cancer	12
Gastric cancer	8
Pancreatic carcinoma	4
Liver cancer	2
Ovarian cancer	2
Adrenal cortical	1
Biliary neoplasm	1
Breast cancer	1
Esophageal cancer	1
Gallbladder	1
Genital neoplasm malignant female	1
Pleural	1
Renal cell carcinoma	1
Unknown origin (possibly GI tract)	1

8.1.1.16.7. Prior Anticancer Treatment

Prior anticancer treatment for participants with dMMR solid tumors included in the primary efficacy analysis set is summarized in Table 10.

All participants had received at least 1 prior anticancer treatment (100%). Approximately 57% had received >1 prior anticancer regimens, 16% had received 3 prior regimens, and 5% had

received 4 or more prior regimens. The majority of participants with dMMR EC had received 1 prior anticancer regimen (63.1%), while participants with dMMR non-EC most often received 2 prior anticancer regimens (45.3%).

Nearly all participants with dMMR solid tumors had received prior anticancer surgery (88.5%), and 45.0% had received prior anticancer radiotherapy. The majority of participants with dMMR EC had received prior anticancer radiotherapy (70.9%), while about one-fifth of participants with dMMR non-EC had received prior anticancer radiotherapy (19.8%). Prior bevacizumab use was reported in 27.4% of participants with dMMR non-EC, compared to 4.9% of participants with dMMR EC. Approximately three-fourths of participants had received prior anticancer regimens for metastatic disease.

Table 10: Prior Anticancer Treatment – Participants with dMMR Solid Tumors (Primary Efficacy Analysis Set)

Variable, n (%)	dMMR EC (N=103)	dMMR NEC (N=106)	dMMR Overall (N=209)
Any prior anticancer treatment	103 (100)	106 (100)	209 (100)
Any prior surgery for study indication	93 (90.3)	92 (86.8)	185 (88.5)
Any prior anticancer radiotherapy	73 (70.9)	21 (19.8)	94 (45.0)
Prior bevacizumab use	5 (4.9)	29 (27.4)	34 (16.3)
Any prior adjuvant/neo-adjuvant anticancer treatment	54 (52.4)	46 (43.4)	100 (47.8)
Number of prior anticancer regimen			
1	65 (63.1)	25 (23.6)	90 (43.1)
2	27 (26.2)	48 (45.3)	75 (35.9)
3	8 (7.8)	25 (23.6)	33 (15.8)
≥4	3 (2.9)	8 (7.5)	11 (5.3)
Number of prior anticancer regimen for metastatic disease[a]			
0	45 (43.7)	11 (10.4)	56 (26.8)
1	48 (46.6)	35 (33.0)	83 (39.7)
2	9 (8.7)	47 (44.3)	56 (26.8)
3	1 (1.0)	11 (10.4)	12 (5.7)
≥4	0	2 (1.9)	2 (1.0)

Source: Module 2.7.3 Table 14.1.6e
Abbreviations: dMMR=mismatch repair deficient; EC=endometrial cancer; max=maximum; min=minimum; NEC=non-endometrial cancer; Q1=first quartile; Q3=third quartile; StDev=standard deviation.
[a] Excluding neo-adjuvant, adjuvant regimens, and hormonal agents.

The FDA's Assessment:

FDA generally agrees with the Applicant's assessment of prior anticancer therapies. When considering the entire cohort of 209 patients, approximately 43% of patients had received 1 prior line of systemic anticancer treatment, 36% had received 2 prior lines, and 21% had received 3 or more prior lines. Patients with dMMR endometrial cancer must have progressed on or after treatment with a platinum-containing regimen. Patients with dMMR colorectal cancer must have progressed after or been intolerant to a fluoropyrimidine, oxaliplatin, and irinotecan.

8.1.1.16.8. Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant's Position:

Treatment Compliance

The study drug was administered by qualified study staff members at the study centers.

The Investigator or designee was responsible for maintaining accurate dispensing records of the study treatments throughout the clinical study.

Details of maintaining drug accountability, including information on the accountability log, were provided in the Study Manual.

All dispensation and accountability records were available for Sponsor review. The Study Monitor assumed the responsibility to reconcile the study treatment accountability log. The pharmacist dispensed study treatment for each subject according to the protocol and Study Manual, if applicable.

From Cycle 1 through Cycle 4, 3 missed infusions (2.4%), 11 infusion delays (8.7%), and no infusion interruptions were reported in participants with dMMR EC (4010-01-001 Part 2B, Cohorts A1 and A2 CSR Table 14.1.15a). From Cycle 5 through the end-of-treatment (EOT), 7 missed infusions (5.6%), 25 infusion delays (19.8%), and 1 infusion interruption (0.8%) were reported in participants with dMMR EC.

When treatment compliance data from participants with MMR-unknown but MSI-H tumors are pooled with those of participants with dMMR tumors, the results remain similar.

In participants with dMMR non-EC, 1 participant (0.7%) missed an infusion, 12 participants (8.3%) had infusion delays, and 2 participants (1.4%) had an infusion interruption from Cycle 1 through Cycle 4 (4010-01-001 Part 2B, Cohort F CSR Table 14.1.15c). From Cycle 5 through the EOT, 1 participant (0.7%) missed an infusion, 10 participants (6.9%) had infusion delays, and 1 participant (0.7%) had an infusion interruption.

When treatment compliance data from participants with MMR-proficient or MMR-unknown but MSI-H non-EC tumors are pooled with those of participants with dMMR non-EC tumors, the results remain similar.

Prior and Concomitant Medication

Medications collected at screening and during the study were coded using the current version of the WHO Drug Dictionary (version WHODrug-DDE-B2\201809). The medications were categorized as prior or concomitant using the following definitions:

- Prior medications were defined as any medications that started and ended prior to the first dose date of study treatment.

- Concomitant medications were defined as any medications, other than study treatments, that started prior to first dose of study treatment and was ongoing at first dose of study treatment, and was being taken on or after the initial study treatment dosing date through 90 days after the EOT Visit or until the start of subsequent antitumor therapy.

Both prior medications and concomitant medications were summarized by anatomical therapeutic chemical level 3 classification drug class and WHO preferred name using the number and percentage of participants for each cohort. A participant reporting the same medication more than once was counted only once when calculating the number and percentage of participants who received that medication in a given time category (prior or concomitant). The summaries of prior and concomitant medications were ordered by descending frequency with respect to drug class and then by descending frequency of preferred name in total within the drug class. For drugs with the same frequency, sorting was done alphabetically. Summaries were based on the safety analysis set.

All prior and concomitant medications were provided in a by-participant listing sorted by participant ID number and administration date in chronological order.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment.

8.1.1.16.9. Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

Objective Response Rate

Tumor response assessed by BICR using RECIST v1.1 is summarized in Table 11 for participants with dMMR solid tumors and presented graphically in Figure 4.

At the data cutoff, the ORR was 41.6%, including 9.1% with CR and 32.5% with PR. Clinical activity was consistent across EC (N=103), CRC (N=69), and other tumor types (non-CRC; N=37): with ORRs of 44.7%, 36.2%, and 43.2%, respectively (Table 12). A total of 18.7% of participants with dMMR solid tumors had a BOR of SD, and 34.0% had a BOR of PD (Table 11).

Table 11: Tumor Response Summary – RECIST v1.1 Assessed by BICR in Participants with dMMR Solid Tumors (Primary Efficacy Analysis Set)

Variable	dMMR EC (N=103)	dMMR NEC (N=106)	dMMR Overall (N=209)
BOR by RECIST v1.1, n (%)			
CR	11 (10.7)	8 (7.5)	19 (9.1)
PR	35 (34.0)	33 (31.1)	68 (32.5)
SD	13 (12.6)	26 (24.5)	39 (18.7)
PD	39 (37.9)	32 (30.2)	71 (34.0)
NE	3 (2.9)	0	3 (1.4)

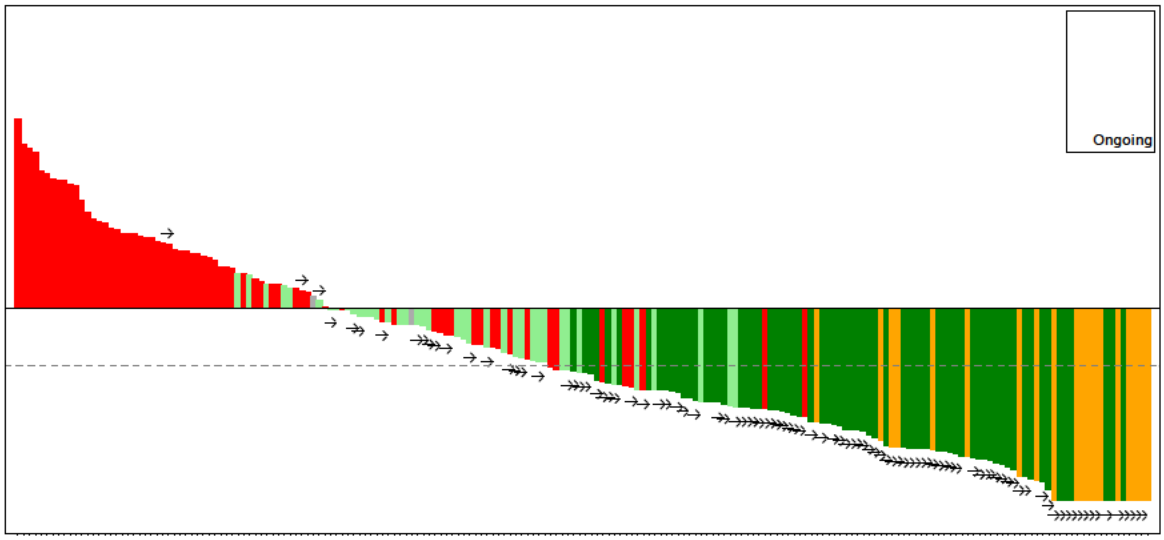
Variable	dMMR EC (N=103)	dMMR NEC (N=106)	dMMR Overall (N=209)
Not done	2 (1.9)	7 (6.6)	9 (4.3)
Confirmed ORR by RECIST v1.1, n (%)	46 (44.7)	41 (38.7)	87 (41.6)
95% CI[a]	34.9, 54.8	29.4, 48.6	34.9, 48.6
Response ongoing[b]	41 (89.1)	38 (92.7)	79 (90.8)

Table 11: Tumor Response Summary – RECIST v1.1 Assessed by BICR in Participants with dMMR Solid Tumors (Primary Efficacy Analysis Set) (Continued)

Variable	dMMR EC (N=103)	dMMR NEC (N=106)	dMMR Overall (N=209)
DCR by RECIST v1.1, n (%)	59 (57.3)	67 (63.2)	126 (60.3)
95% CI[a]	47.2, 67.0	53.3, 72.4	53.3, 67.0

Source: Module 2.7.3 Table 14.2.1e
Abbreviations: BICR=blinded independent central review; BOR=best overall response; CI=confidence interval; CR=complete response; DCR=disease control rate; dMMR=mismatch repair deficient; EC=endometrial cancer; NE=not evaluable; NEC=non-endometrial cancer; ORR=objective response rate; PD=progressive disease; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors; SD=stable disease.
Note: ORR was defined as the percentage of participants with a RECIST v1.1-confirmed CR or PR. DCR was defined as the percentage of participants with a RECIST v1.1-confirmed PR, CR, or SD. Response assessments are based on BICR.
[a] Exact 2-sided 95% CI for the binomial proportion.
[b] All responders who have not yet died or progressed (including clinical progression); the denominator for percentage is number of responders.

Figure 4: Waterfall Plot of the Maximum Percentage Change from Baseline in Target Lesion Size - RECIST v1.1 Based on BICR in Participants with dMMR Solid Tumors (Primary Efficacy Analysis Set)



Source: Module 2.7.3 Figure 14.1.5e
Abbreviations: BICR=blinded independent central review; CR=complete response; dMMR=mismatch repair-deficient; NE=not evaluable; PD=progressive disease; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors; SD=stable disease.
Note: Best change in target lesion size is the maximum reduction from baseline or the minimum increase from baseline in the absence of a reduction. Horizontal reference ranges are defined by -30 for PR.

Table 12: ORR Summary by Tumor Type in Participants with dMMR Solid Tumors

Cancer Type	n	Confirmed ORR	
		n (%)	95% CI[a]
dMMR EC	103	46 (44.7)	34.9, 54.8
dMMR NEC	106	41 (38.7)	29.4, 48.6
dMMR CRC	69	25 (36.2)	25.0, 48.7
Other dMMR non-CRC	37	16 (43.2)	27.1, 60.5
Small intestinal cancer	12	4 (33.3)	9.9, 65.1
Gastric cancer	8	3 (37.5)	8.5, 75.5
Pancreatic carcinoma	4	0	0.0, 60.2
Liver cancer	2	PD, PR	NA
Ovarian cancer	2	PR, SD	NA
Adrenal cortical	1	PR	NA
Biliary neoplasm	1	CR	NA
Breast cancer	1	CR	NA
Esophageal cancer	1	PD	NA
Gallbladder	1	CR	NA
Genital neoplasm malignant female	1	PR	NA
Pleural	1	PR	NA
Renal cell carcinoma	1	SD	NA
Unknown origin (possibly GI tract)	1	PR	NA

Source: Module 2.7.3 Table 14.2.1e and CSR 4010-01-001, Part 2B Cohort F, Table 14.2.9.1c
Abbreviations: BICR=blinded independent central review; CI=confidence interval; CR=complete response; CRC=colorectal cancer; CSR=clinical study report; dMMR=mismatch repair deficient; EC=endometrial cancer; GI=gastrointestinal; NA=not applicable; NEC=non-endometrial cancer; ORR=objective response rate; PD=progressive disease; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors; SD=stable disease.
Note: ORR was defined as the percentage of participants with a RECIST v1.1-confirmed CR or PR. Response assessments are based on BICR.
[a] Exact 2-sided 95% CI for the binomial proportion.

Duration of Response

The KM analysis of BICR-assessed DOR using RECIST v1.1 criteria for participants with dMMR solid tumors is summarized in Table 13.

At the time of data cutoff, the median duration of follow-up was 13.5 months, and the median DOR had not been reached. The DOR in these participants ranged from 1.74+ to 28.09+ months, with DOR ≥6 months in 68 participants (78.2% of responders). The probability of maintaining a response based on KM estimates for 6, 12, and 18 months was 97.4%, 90.6%, and 79.4%, respectively. At the time of data cutoff, 90.8% of responders with dMMR solid tumors had ongoing response (Table 11).

The DOR was consistent across tumor types. At the time of data cutoff, the median DOR had not been reached in any tumor type. Response was ongoing in 89.1% of responders with dMMR EC (N=46), 96.0% of responders with dMMR CRC (N=25), and 87.5% of responders with other tumor types (non-CRC; N=16) (CSR 4010-01-001, Part 2B Cohorts A1 and A2, Table 14.2.1a and CSR 4010-01-001, Part 2B Cohort F, Table 14.2.21c).

The DOR ranged from 2.63 to 28.09+ months in responders with dMMR EC, 1.7+ to 21.9+ months in responders with dMMR CRC, and 5.6+ to 21.4+ months in responders with other tumor types (CSR 4010-01-001, Part 2B Cohorts A1 and A2, Table 14.2.12a and CSR 4010-01-001, Part 2B Cohort F, Table 14.2.21c). A DOR ≥6 months was observed in 78.3% of responders with dMMR EC, 68.0% of responders with dMMR CRC, and 93.8% of responders with other tumor types.

For participants with dMMR EC, the probability of maintaining a response based on KM estimates for 6, 12, and 18 months was 97.8%, 90.6%, and 79.2%, respectively (CSR 4010-01-001, Part 2B Cohorts A1 and A2, Table 14.2.12a). For participants with dMMR CRC, the probability of maintaining a response based on KM estimates for 6, 12, and 18 months was 94.7%, each (CSR 4010-01-001, Part 2B Cohort F, Table 14.2.21c). For participants with other tumor types, the probability of maintaining a response based on KM estimates for 6, 12, and 18 months was 100%, 83.3%, and 66.7%, respectively.

Table 13: KM Analysis of DOR – RECIST v1.1 Based on BICR in Participants with dMMR Solid Tumors (Primary Efficacy Analysis Set – Participants with Objective Response)

Variable	dMMR EC (N=46)	dMMR NEC (N=41)	dMMR Overall (N=87)
Median duration of follow-up (months)	16.3	12.4	13.5
DOR status, n (%)			
Events observed	5 (10.9)	3 (7.3)	8 (9.2)
Censored	41 (89.1)	38 (92.7)	79 (90.8)
DOR (months)			
Min, max	2.63, 28.09+	1.74+, 21.88+	1.74+, 28.09+
Quartile (95% CI[a])			
25%	NR (9.8, NR)	NR (11.0, NR)	NR (12.6, NR)
50%	NR (NR, NR)	NR (12.6, NR)	NR (NR, NR)
75%	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)

Variable	dMMR EC (N=46)	dMMR NEC (N=41)	dMMR Overall (N=87)
Duration ≥6 months, n (%)	36 (78.3)	32 (78.0)	68 (78.2)
DOR distribution function (95% CI)			
Month 6	97.8 (85.6, 99.7)	97.1 (80.9, 99.6)	97.4 (90.0, 99.4)
Month 12	90.6 (72.9, 97.0)	91.0 (66.1, 97.9)	90.6 (78.1, 96.1)
Month 18	79.2 (54.9, 91.3)	80.9 (46.9, 94.2)	79.4 (60.9, 89.8)

Source: Module 2.7.3 Table 14.2.11e
Abbreviations: BICR=blinded independent central review; CI=confidence interval; dMMR=mismatch repair deficient; DOR=duration of response; EC=endometrial cancer; KM=Kaplan-Meier; max=maximum; min=minimum; NEC=non-endometrial cancer; NR=not reached; RECIST=Response Evaluation Criteria in Solid Tumors.
Note: DOR per RECIST v1.1 based on BICR. A "+" indicates that the participant's response is ongoing.
[a] 95% CIs generated using the method of Brookmeyer and Crowley (1982).

The Applicant's Position:

Dostarlimab treatment provided meaningful clinical benefit, as defined by BICR assessed ORR and DOR in patients with dMMR solid tumors. In 209 patients with dMMR tumors from Study 4010-01-001 Cohort A1 and F, the ORR was 41.6% (87 of 209 patients) with 9.1% CRs (19 of 209 patients). At the time of the data cutoff date (01 March 2020), the median DOR had not been reached, and 78.2% of responders had a DOR ≥6 months. Based on KM estimates, the probability of maintaining a response for 6, 12, and 18 months in patients with dMMR tumors was 97.4%, 90.6%, and 79.4%, respectively. At the time of the data cutoff date, 90.8% of responders had ongoing response.

The FDA's Assessment:

The efficacy analysis population was defined as patients with measurable disease at baseline per BICR who received at least one dose of dostarlimab on or before September 15, 2019. There were 209 patients in the efficacy analysis population, 103 from Cohort A1 and 106 from Cohort F. There were 87 responders out of 209 patients. The confirmed ORR by BICR was 41.6% (95% CI: 34.9, 48.6).

There were a total of 15 different tumor types presented in the ORR analysis dataset. Some of the tumor types are only represented by 1 or 2 patients. Under the postmarketing requirement to verify benefit, the confirmatory data would be based on ORR and DoR analyses for patients with dMMR recurrent or advanced solid tumors in the clinical trial 4010-01-001, Part 2B (Cohorts A1 and F) containing at least 300 patients across all tumor types, and including a sufficient number of patients and representation of tumor types (other than endometrial and gastrointestinal (GI) tumors).

The following table summarizes the results of ORR analyses by demographic subgroups and baseline disease characteristics subgroups.

Table 14: Subgroup Analyses of ORR

Subgroup	N	# responders (%)	95% CI of ORR
All	209	87 (41.6)	34.9, 48.6
Gender			
Male	48	20 (41.7)	27.6, 56.8
Female	161	67 (41.6)	33.9, 49.6
Age group (years)			
<65	110	47 (42.7)	33.3, 52.5
≥65	99	40 (40.4)	30.7, 50.7
Race			
White	132	52 (39.4)	31.0, 48.3
Asian	6	3 (50.0)	11.8, 88.2
Black/African American	4	4 (100)	39.8, 100
American Indian/Alaska native	3	2 (66.7)	9.4, 99.2
Other/unknown/not reported	64	26 (40.6)	NA
ECOG			
0	82	49 (59.8)	48.3, 70.4
1	127	38 (29.9)	22.1, 38.7
Number of prior therapies			
1	90	42 (46.7)	36.1, 57.5
≥ 2	119	45 (37.8)	29.1, 47.2
Prior radiation			
Yes	94	39 (41.5)	31.4, 52.1
No	115	48 (41.7)	32.6, 51.3
Prior bevacizumab use			
Yes	34	11 (32.4)	17.4, 50.5
No	175	76 (43.4)	36.0, 51.1

The subgroup analyses presented above are considered exploratory, and no formal inference can be drawn. No outlier subgroups with respect to response rate were observed among the subgroups analyzed.

As agreed between the Applicant and the FDA during the pre-BLA meeting, an update to the DoR data was provided by the Applicant on March 17, 2021 (Sequence Number 008). The data cut-off date for this updated analysis is November 1, 2020. The median DOR was 34.7 months. The DoR ranged from 2.6 months to 35.8 months. Eighty-three out of 87 responders (95.4%) have a DoR ≥6 months and 65 responders (74.7%) have a DoR ≥12 months. No updates to the response were provided with the November 1, 2020 update.

FDA conducted the following subgroup analyses of DoR based on the data cutoff date of November 1, 2020.

Table 15: DoR Summary by Tumor Type in Participants with dMMR Solid Tumors (DCO November 1, 2020)

Cancer Type	n	Confirmed ORR		DoR
		n (%)	95% CI[a]	
dMMR EC	103	46 (44.7)	34.9, 54.8	2.6, 35.8+
dMMR NEC	106	41 (38.7)	29.4, 48.6	5.6, 30.1+
dMMR CRC	69	25 (36.2)	25.0, 48.7	5.6, 30.1+
Other dMMR non-CRC	37	16 (43.2)	27.1, 60.5	8.4+, 28.0+
Small intestinal cancer	12	4 (33.3)	9.9, 65.1	11.1+,28.0+
Gastric cancer	8	3 (37.5)	8.5, 75.5	8.4+, 17.5
Pancreatic carcinoma	4	0	0.0, 60.2	NA
Liver cancer	2	PD, PR	NA	13.8+
Ovarian cancer	2	PR, SD	NA	25.1+
Adrenal cortical	1	PR	NA	19.5+
Biliary neoplasm	1	CR	NA	8.4+
Breast cancer	1	CR	NA	16.8+
Esophageal cancer	1	PD	NA	NA
Gallbladder	1	CR	NA	13.5+
Genital neoplasm malignant female	1	PR	NA	22.2+
Pleural	1	PR	NA	15.2+
Renal cell carcinoma	1	SD	NA	NA
Unknown origin (possibly GI tract)	1	PR	NA	20.4+

"+" denotes ongoing

8.1.1.16.10. Data Quality and Integrity

The Applicant's Position:

The case report forms and clinical source data has not yet been audited by any government authority.

The FDA's Assessment:

There were no concerns regarding the quality and integrity of the submitted data and datasets during the review of this BLA.

8.1.1.16.11. Efficacy Results – Secondary and Other Relevant Endpoints

The Applicant's Position:

Disease Control Rate

At the time of data cutoff, the DCR in participants with dMMR solid tumors, including CR, PR, and SD, was 60.3%.

Progression-free Survival

The KM analysis of PFS by RECIST v1.1 for participants with dMMR solid tumors is summarized in Table 16.

At the time of data cutoff, with a median follow-up duration of 13.5 months (Table 13), the median PFS in participants with dMMR solid tumors was 8.1 months (Table 16). A total of 96 participants with dMMR solid tumors (45.9%) were censored at this time, and 113 PFS events had been observed. Based on these results, the probability of being progression-free at Month 6, Month 9, and Month 12 was estimated to be 50.6%, 47.9%, and 47.2%, respectively.

Table 16: KM Analysis of PFS – BICR Assessed using RECIST v1.1 in Participants with dMMR Solid Tumors (Primary Efficacy Analysis Set)

Variable	dMMR EC (N=103)	dMMR NEC (N=106)	dMMR Overall (N=209)
PFS status, n (%)			
Events observed	57 (55.3)	56 (52.8)	113 (54.1)
Censored	46 (44.7)	50 (47.2)	96 (45.9)
PFS (months)			
Quartile (95% CI)[a]			
25%	2.7 (2.5, 2.9)	2.7 (2.5, 2.8)	2.7 (2.6, 2.8)
50%	5.5 (3.1, 18.0)	8.2 (4.1, NR)	8.1 (4.2, 16.6)
75%	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)
PFS distribution function (95% CI)			
Month 6	48.1 (38.0, 57.4)	53.0 (43.0, 62.1)	50.6 (43.6, 57.3)
Month 9	46.9 (36.9, 56.4)	48.8 (38.8, 58.0)	47.9 (40.8, 54.6)
Month 12	46.9 (36.9, 56.4)	47.5 (37.5, 56.8)	47.2 (40.1, 53.9)

Source: Module 2.7.3 Table 14.2.9e
Abbreviations: BICR=blinded independent central review; CI=confidence interval; dMMR=mismatch repair deficient; EC=endometrial cancer; KM=Kaplan-Meier; NEC=non-endometrial cancer; NR=not reached; PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumors.
Note: PFS per RECIST v1.1 based on BICR.
[a] 95% CIs generated using the method of Brookmeyer and Crowley (1982).

Overall Survival

The KM analysis of OS for participants with dMMR solid tumors is summarized in Table 17.

At the time of data cutoff, with a median follow-up duration of 13.5 months (Table 13), the median OS for participants with dMMR solid tumors was not reached, and only 58 OS events had been observed (Table 17). Based on these results, the probability of survival at Month 6, Month 9, and Month 12 was estimated to be 82.5%, 77.8%, and 73.8%, respectively.

Table 17: KM Analysis of OS Participants with dMMR Solid Tumors (Primary Efficacy Analysis Set)

Variable	dMMR EC (N=103)	dMMR NEC (N=106)	dMMR Overall (N=209)
OS status, n (%)			
Events observed	35 (34.0)	23 (21.7)	58 (27.8)

Table 17: KM Analysis of OS Participants with dMMR Solid Tumors (Primary Efficacy Analysis Set) (Continued)

Variable	dMMR EC (N=103)	dMMR NEC (N=106)	dMMR Overall (N=209)
Censored	68 (66.0)	83 (78.3)	151 (72.2)
OS (months)			
Quartile (95% CI[a])			
25%	8.9 (5.2, 15.4)	16.5 (7.9, NR)	9.5 (7.9, 17.1)
50%	NR (17.1, NR)	NR (18.0, NR)	NR (19.7, NR)
75%	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)
OS distribution function (95% CI)			
Month 6	80.7 (71.4, 87.2)	84.3 (75.7, 90.1)	82.5 (76.5, 87.1)
Month 9	74.9 (64.8, 82.4)	80.7 (71.3, 87.3)	77.8 (71.1, 83.0)
Month 12	68.5 (57.8, 77.1)	79.3 (69.7, 86.2)	73.8 (66.8, 79.6)

Source: Module 2.7.3 Table 14.2.17e
Abbreviations: CI=confidence interval; dMMR=mismatch repair deficient; EC=endometrial cancer; KM=Kaplan-Meier; NEC=non-endometrial cancer; NR=not reached; OS=overall survival.
[a] 95% CIs generated using the method of Brookmeyer and Crowley (1982).

8.1.1.16.12. Supportive Efficacy Data

At the time of data cutoff date of 01 March 2020, tumor response in Study 4010-01-001 was not only assessed by BICR using RECIST v1.1 (primary efficacy analysis set, N=209), but also by the Investigator using irRECIST (secondary efficacy analysis set, N=219). Participants with dMMR solid tumors had an irORR of 45.2%, with 5.9% immune-related CRs and 39.3% immune-related PRs (Module 2.7.3 Table 14.2.2e). These results are similar to the results obtained by BICR using RECIST v1.1 (Module 2.7.3 Table 6). The KM analysis of irPFS is presented in Module 2.7.3 Table 14.2.8e, and the KM analysis of irDOR is presented in Module 2.7.3 Table 14.2.10e.

The FDA's Assessment:

PFS and OS analyses results are not interpretable in a single-arm study. These analyses

are considered as exploratory. FDA does not consider DCR an interpretable efficacy endpoint for single-arm studies because it incorporates stable disease, which is highly driven by underlying disease natural history. DCR does not reflect treatment effect as reliably as ORR does.

8.1.1.16.13. Dose/Dose Response

Data:

See results in Section 8.1.1.16.

The FDA's Assessment:

No additional analysis was performed by the FDA.

8.1.1.16.14. Durability of Response

Data:

Not performed.

The FDA's Assessment:

No additional analysis was performed by the FDA.

8.1.1.16.15. Persistence of Effect

The Applicant's Position:

No analyses to assess the persistence of efficacy after treatment discontinuation have been conducted. There are no known tolerance effects of dostarlimab.

The FDA's Assessment:

No additional analysis was performed by the FDA.

8.1.1.16.16. Efficacy Results – Secondary or Exploratory Clinical Outcome Assessment (PRO) Endpoints

The Applicant's Position:

Completion rates for PRO questionnaires were similarly balanced for both Cohort A1 and Cohort F and remained relatively stable throughout the study period.

In general, compliance was consistent across the five functional domains in the EORTC Quality of Life Questionnaire Core 30 (EORTC QLQ-C30). Overall, the patient-reported outcomes included in the analysis suggest that treatment with dostarlimab does not decrease functioning or QoL. The PRO data support that patients who receive dostarlimab maintain QoL during their treatment.

The FDA's Assessment:

See FDA comments in Section 8.2.6 of this review regarding the PRO Endpoints.

8.1.1.16.17. Integrated Review of Effectiveness

The FDA's Assessment:

Not applicable.

8.1.1.16.18. Assessment of Efficacy Across Trials

The data to support this BLA is from one single study, 4010-01-001, and thus an analysis of efficacy across trials in not applicable.

The FDA's Assessment:

FDA agrees.

8.1.1.16.19. Integrated Assessment of Effectiveness

The Applicant's Position:

A confirmed combined ORR of 41.6% as assessed by RECIST v1.1 by BICR was observed with dostarlimab treatment in participants with dMMR solid tumors (87 of 209 participants), with clinical activity observed across various tumor types.

The FDA's Assessment:

The FDA's efficacy review and assessment for this BLA was based on data from 209 adult patients with mismatch repair deficient (dMMR) recurrent or advanced solid tumors who have progressed following systemic therapy and have no satisfactory alternative treatment options. Dostarlimab demonstrated efficacy in the GARNET trial (Study 4010-01-001) for the treatment of this patient population. The confirmed ORR per RECIST v1.1 by BICR was 41.6% (95% CI: 34.9, 48.6), with a 9.1% complete response rate and a 32.5% partial response rate. The median DoR was 34.7 months. The DoR ranged from 2.6 to 35.8+ months. Eighty-three out of 87 responders (95.4%) have a DoR ≥6 months and 65 responders (74.7%) have a DoR ≥12 months. This durable objective response rate is of sufficient magnitude to serve as an endpoint reasonably likely to predict clinical benefit to patients, and is acceptable to support granting the accelerated approval of dostarlimab for the treatment of adult patients with recurrent or advanced dMMR solid tumors who have progressed following systemic therapy and have no satisfactory alternative treatment options.

8.2. Review of Safety

The Applicant's Position:

The safety population included all participants who received at least 1 dose of dostarlimab treatment as of the data cutoff date of 01 March 2020. All safety analyses were performed on the as-treated principle, where participants were allocated to the treatment that they actually received.

Data from the following 4 study cohorts from GARNET were included in the safety analyses:

- Cohort A1: Participants with recurrent or advanced dMMR/MSI-H EC (N=129)

- Cohort A2: Participants with recurrent or advanced mismatch repair-proficient/microsatellite stable EC (N=161)
- Cohort E: Participants with non-small cell lung cancer (N=67)
- Cohort F: Participants with recurrent or advanced dMMR/MSI-H solid tumors or polymerase epsilon-mutated solid tumors, except EC (N=158)

The FDA's Assessment:

To support the safety evaluation of dostarlimab for this BLA, the Applicant submitted safety data from multiple cohorts of Part 2B of the GARNET trial (Study 4010-01-001), including patients from cohorts A1, A2, E, and F, who had received at least one dose of dostarlimab monotherapy at the recommended therapeutic dose by the data cutoff date.

8.2.1. Safety Review Approach

The Applicant's Position:

Safety data for dostarlimab monotherapy are organized into the following 2 groups, which comprises patients who were treated with the 500 mg every 3 weeks (Q3W) for 4 cycles followed by 1,000 mg every 6 weeks (Q6W) regimen in GARNET:

- participants with recurrent or advanced dMMR solid tumors (participants from Cohorts A1 and F whose tumors were dMMR by immunohistochemistry testing) (N=267)
- participants treated with dostarlimab at the RTD (Cohorts A1, A2, E, and F combined) (N=515).

The following sections, excluding immune-related adverse events (irAEs) and infusion-related reactions, include a discussion of safety in the group of participants with recurrent or advanced dMMR solid tumors (participants from Cohorts A1 and F whose tumors were dMMR by immunohistochemistry testing) (N=267).

In the Analysis of Submission-Specific Safety Issues, including irAEs and infusion-related reactions, the discussion of safety data is focused on the patients treated with dostarlimab at the RTD (N=515).

The FDA's Assessment:

The FDA's independent safety analysis for this BLA was based on the safety data from 267 patients with dMMR recurrent or advanced solid tumors from cohorts A1 and F in Part 2B of the GARNET trial, who had received at least one dose of dostarlimab monotherapy at the recommended therapeutic dose by the data cutoff date. This population included data from the 104 patients with dMMR endometrial cancer in cohort A1 who made up the safety population in the accelerated approval of dostarlimab for dMMR endometrial cancer, but also included additional patients with dMMR endometrial cancer enrolled to cohort A1, as well as patients with other dMMR solid tumors enrolled to cohort F.

Safety analyses of immune-related adverse events (irAEs) and infusion related reactions were also performed, which included 515 patients with a variety of advanced solid tumors in Part 2B of Study 4010-01-001 (GARNET), who had received at least one dose of dostarlimab monotherapy at the recommended therapeutic dose. The FDA evaluated the datasets submitted

by the Applicant and no obvious discrepancies were identified between the datasets and the data submitted in the Clinical Study Report (CSR).

The FDA also reviewed the 90-day safety update analysis and datasets provided by the Applicant and did not identify any new safety signals.

8.2.2. Review of the Safety Database

8.2.2.1. Overall Exposure

The Applicant's Position:

As of the data cutoff date, 267 participants with dMMR solid tumors (126 with dMMR EC and 141 with dMMR non-EC) had received at least 1 dose of dostarlimab in Study 4010-01-001 and were included in the safety analysis set.

The overall median treatment duration for participants with dMMR solid tumors was 25.0 weeks (range: 1 to 139 weeks; Table 18). Just over half of all participants (51.3%) were still on study treatment at the time of the data cutoff (Module 2.7.4 Table 1).

The median relative dose intensity of 100% from the first dose through Week 12 and from Week 13 through the End of Treatment indicates that the majority of participants received doses as planned, without delays or interruptions (Table 18).

Table 18: Treatment Exposure (Safety Analysis Set – Participants with dMMR Solid Tumors)

Parameter	dMMR EC (N=126)	dMMR NEC (N=141)	dMMR Overall (N=267)
Duration of exposure (weeks)			
n	126	141	267
Mean (StDev)	40.6 (36.47)	34.7 (27.14)	37.5 (31.96)
Median	25.6	24.1	25.0
Min, max	3, 139	1, 113	1, 139
First dose through Week 12			
Total number of doses received			
n	126	141	267
Mean (StDev)	3.5 (0.95)	3.5 (1.01)	3.5 (0.98)
Median	4.0	4.0	4.0
Min, max	1, 4	1, 4	1, 4
Cumulative dose (mg)			
n	126	141	267
Mean (StDev)	1,773.8 (475.85)	1,731.0 (514.67)	1,751.2 (496.26)
Median	2,000.0	2,000.0	2,000.0

Parameter	dMMR EC (N=126)	dMMR NEC (N=141)	dMMR Overall (N=267)
Min, max	500; 2,000	500; 2,000	500; 2,000
Relative dose intensity (%)			
n	126	141	267
Mean (StDev)	97.7 (6.96)	97.8 (7.77)	97.8 (7.39)

Table 18: Treatment Exposure (Safety Analysis Set – Participants with dMMR Solid Tumors) (Continued)

Parameter	dMMR EC (N=126)	dMMR NEC (N=141)	dMMR Overall (N=267)
Median	100.0	100.0	100.0
Min, max	57, 107	38, 111	38, 111
Week 13 through EOT			
Total number of doses received			
n	87	97	184
Mean (StDev)	6.9 (5.68)	5.7 (3.83)	6.3 (4.82)
Median	5.0	6.0	6.0
Min, max	1, 21	1, 15	1, 21
Cumulative dose (mg)			
n	87	97	184
Mean (StDev)	6,919.5 (5,681.91)	5,726.6 (3,836.45)	6,290.7 (4,821.78)
Median	5,000.0	6,000.0	6,000.0
Min, max	1,000; 21,000	1,000; 15,000	1,000; 21,000
Relative dose intensity (%)			
n	87	97	184
Mean (StDev)	98.2 (4.30)	99.0 (3.71)	98.6 (4.01)
Median	100.0	100.0	100.0
Min, max	77, 108	77, 104	77, 108

Source: Module 2.7.4 Table 14.3.5
Abbreviations: dMMR=mismatch repair-deficient; EC=endometrial cancer; EOT=End of Treatment; max=maximum; min=minimum; NEC=non-endometrial cancer; StDev=standard deviation.

The FDA's Assessment:

The FDA agrees with the Applicant's assessments of duration of exposure and dose intensity in Table 188.

8.2.2.2. Relevant Characteristics of the Safety Population (Patients with dMMR Solid Tumors)

The Applicant's Position:

Most participants with dMMR solid tumors were female (75.7%) and White (64.0%). Participants with dMMR non-EC were approximately evenly distributed by sex (46.1% male and 53.9% female), while all participants with dMMR EC (100%) were female. The median age was 63.0 years (range: 24 to 85 years); just over half of the participants were <65 years old (54.7%) and had an ECOG performance status of 1 at study entry (58.8%).

Dostarlimab has been administered to participants with various dMMR tumor types; the most common of these were EC (47.2%) and colon cancer (33.3%).

The median body mass index (BMI) of participants with dMMR solid tumors was 25.72 kg/m^2 (range: 13.6 to 53.9 kg/m^2). Participants with dMMR EC had a higher incidence of obese BMI status (≥30 kg/m^2) than participants with dMMR non-EC (43.7% vs 12.8%, respectively), while participants with dMMR non-EC had a higher incidence of normal BMI status (≥18.5 to <25 kg/m^2) than participants with dMMR EC (47.5% vs 27.0%, respectively).

The most frequently reported (>50% of participants) medical history condition system organ classes (SOCs) were gastrointestinal disorders (59.2%) and vascular disorders (51.3%). Medical history conditions in the SOCs of eye disorders, general disorders and administration site conditions, immune system disorders, musculoskeletal and connective tissue disorders, psychiatric disorders, renal and urinary disorders, and reproductive system and breast disorders were reported more frequently (>10% difference in frequencies) in participants with dMMR EC than in participants with dMMR non-EC. Medical history conditions in the SOC of surgical and medical procedures were reported more frequently (>10% difference in frequencies) in participants with dMMR non-EC than participants with dMMR EC.

The most frequently reported (>30% of participants) medical history condition preferred term (PT) was hypertension (39.0%). Medical history conditions in the PTs of anxiety, back pain, constipation, fatigue, insomnia, and vaginal haemorrhage were more common (>10% difference in frequencies) in participants with dMMR EC than in participants with dMMR non-EC. Diarrhoea was the only medical history condition PT reported more frequently (>10% difference in frequencies) in participants with dMMR non-EC than in participants with dMMR EC.

The FDA's Assessment:

The FDA agrees with the demographics and baseline characteristics presented by the Applicant.

8.2.2.3. Adequacy of the Safety Database

The Applicant's Position:

The safety population consists of all patients who received at least 1 dose of dostarlimab treatment prior to the data cutoff date, including the 515 patients who have been treated with dostarlimab monotherapy in Part 2B of Study 4010-01-001 (GARNET). The size of the safety database is considered adequate to define the risks of dostarlimab treatment, which will be managed via labeling.

The size of the safety database, the pooling strategy, and parameters to be analyzed were discussed at the Type C meeting on September 2, 2020. As agreed with the Agency, data from combination studies with dostarlimab were excluded from the integrated summary of safety because they are not anticipated to influence the overall safety profile of dostarlimab as a single agent.

Observed AEs included events that were in line with those expected in subjects with recurrent or advanced solid tumors, as well as those consistent with reported safety profiles of monoclonal antibodies blocking the PD-1 interactions (Keytruda SmPC 2019; Keytruda® USPI 2020; Opdivo® USPI 2020; Opdivo SmPC 2020; Libtayo® USPI 2020; Libtayo SmPC 2019).

The Applicant agreed to submit an updated safety analysis with corresponding datasets to supplement the summary of clinical safety as part of a Day 90 update.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

8.2.3.1.1. Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:

No meaningful concerns are anticipated in the quality and integrity of the submitted datasets and individual case narratives; these were sufficiently complete to allow for a thorough review of safety.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment.

8.2.3.1.2. Categorization of Adverse Event(s)

The Applicant's Position:

The overall analysis of safety included treatment emergent adverse event (TEAEs) (SAEs, ≥Grade 3 AEs, treatment-related AEs), adverse events of special interest (irAEs and infusion-related reactions), deaths, clinical laboratory assessments (hematology and chemistry), ECOG performance status evaluations, immunogenicity evaluation, and ECG findings. Additional analysis was performed on disposition of subjects, demographics/baseline characteristics, prior anticancer therapy, medical history, previous/concomitant medication, and treatment exposure.

AEs were summarized by Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 by SOC and PT. Unless otherwise stated, the sort order was SOC and PT by descending frequency of the "overall" column and then alphabetical order.

The analyses of AEs were based on all subjects in the safety analysis set. The incidence rate of AEs was expressed as a percentage of the number of subjects experiencing an AE to the number of subjects at risk (i.e., number of subjects treated).

Only TEAEs were summarized. For each PT, a subject was included only once, even if they experienced multiple events in that PT. TEAEs were new AEs that began, or any preexisting condition that worsened in severity, after at least 1 dose of study treatment was administered and

throughout the treatment period until 90 days after the End of Treatment (or until the start of alternate anticancer therapy, whichever occurred earlier). Treatment-related AEs refer to any TEAE assessed by the Investigator as related to study treatment ("Related," "Possibly Related," or missing).

The FDA's Assessment:

The FDA agrees with the Applicant's assessment.

8.2.3.1.3. Routine Clinical Tests

The Applicant's Position:

Clinical laboratory assessments for hematology and blood chemistry, including potential liver toxicities, are presented in the following sections.

Laboratory values were primarily based on International Standard (of units) units. Laboratory result toxicity grades were based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03.

All patients in the safety population were included. NCI CTCAE v. 4.03 grades were applied for hematology, chemistry and coagulation laboratory parameters where applicable. Laboratory data were summarized both as continuous data and by severity by NCI-CTCAE grade. Multiple measurements taken during the visit for a patient were represented by the most severe value for each test. A summary of maximum severity observed on-study treatment was generated for the coded hematology and chemistry laboratory parameters. Additional laboratory results that were not part of NCI-CTCAE were presented according to the categories: below normal limit, within normal limits and above normal limit (according to the laboratory normal ranges). A shift summary of baseline to maximum severity on-study treatment was also produced. A categorical summary of liver function tests was also produced. Vital signs, physical examinations, ECOG parameters, and ECG results were summarized descriptively.

The FDA's Assessment:

Routine clinical testing of patients enrolled in the trial was adequate.

8.2.4. Safety Results

8.2.4.1. Deaths

The Applicant's Position:

A total of 65 participants with dMMR solid tumors died while on study (Table 19). The overall most common primary reason for death was disease progression (58 of 65 participants). Three participants (1.1%) died due to a TEAE during the active treatment period, and 4 participants (1.5%) died due to a TEAE during the 90-day safety follow-up period.

Of the 65 participants with dMMR solid tumors who died while on study, 7 participants had a treatment-unrelated TEAE leading to death (Module 2.7.4Table 21). All TEAEs leading to death (aspiration, cerebrovascular accident, pleural effusion, pneumonia, respiratory failure, sepsis, and shock) were reported in 1 participant (0.4%) each. Of all 7 TEAEs leading to death, 3 were in the SOC of Respiratory, thoracic, and mediastinal disorders

Table 19: Deaths (Safety Analysis Set – Participants with dMMR Solid Tumors)

Reason, n (%)	dMMR EC (N=126)	dMMR NEC (N=141)	dMMR Overall (N=267)
Overall deaths	36 (28.6)	29 (20.6)	65 (24.3)
Deaths during active treatment[a]	6 (4.8)	3 (2.1)	9 (3.4)
Primary reason of death			
Disease progression	5 (4.0)	1 (0.7)	6 (2.2)
AE	1 (0.8)	2 (1.4)	3 (1.1)

Table 19: Deaths (Safety Analysis Set – Participants with dMMR Solid Tumors) (Continued)

Reason, n (%)	dMMR EC (N=126)	dMMR NEC (N=141)	dMMR Overall (N=267)
Deaths during 90-day safety follow-up[b]	13 (10.3)	18 (12.8)	31 (11.6)
Primary reason of death			
Disease progression	9 (7.1)	18 (12.8)	27 (10.1)
AE	4 (3.2)	0	4 (1.5)
Deaths during long-term follow-up[c]	17 (13.5)	8 (5.7)	25 (9.4)
Primary reason of death			
Disease progression	17 (13.5)	8 (5.7)	25 (9.4)
AE	0	0	0

Source: Module 2.7.4 Table 14.3.1.14
Abbreviations: AE=adverse event; dMMR=mismatch repair-deficient; EC=endometrial cancer; EOT=End of Treatment; NEC=non-endometrial cancer.
[a] If the last cycle of the dostarlimab treatment was ≤4 cycles, the active treatment period was calculated from the date of first dose to the date of last dose of dostarlimab +21 days; otherwise, the active treatment period was calculated from the date of first dose to date of last dose of dostarlimab +42 days.
[b] Within 90 days after EOT Visit of dostarlimab and first follow-up anticancer therapy, whichever was earlier.
[c] After the EOT Visit of dostarlimab+ 90 days or first follow-up anticancer therapy, whichever was earlier.

The FDA's Assessment:

The FDA conducted an independent analysis of deaths in patients with dMMR recurrent or advanced solid tumors in the GARNET trial based on the death narratives submitted by the Applicant. All-cause death had occurred in 65/267 (24%) patients with dMMR recurrent or advanced solid tumors as of the time of data cutoff. The majority (89%) of deaths were due to disease progression (58 out of 65 patients). Seven patients had an adverse event with an outcome of death. During the review, FDA requested additional death narratives for treatment-emergent Grade 5 adverse events that were not included in the original BLA submission. The FDA reviewed the on-study deaths that occurred during study treatment or within 30 days after the last dose of study drug. It was determined that one of the seven deaths (respiratory failure) that occurred in the setting of an adverse event could be attributed to dostarlimab, and dostarlimab

product labeling was revised to add this fatal adverse event. Narratives of each event and reviewer assessment is captured below.

1- Patient (b) (6) Respiratory failure. 62-years-old female patient diagnosed with Stage IV colorectal cancer (T, N, and M stage unknown), and the most recent stage was Stage IV metastatic colorectal cancer. The subject's past medical history is significant for depression, ALT/AST increased, back pain, and decreased appetite. (b) (6) (Cycle 1 Day 1). Patient began treatment with dostarlimab on (b) (6) (Cycle 1 Day 1), and received the second and last dose of dostarlimab on (b) (6) (Cycle 2 Day 1). Within 17 days of the last dose of study drug, the patient experienced the serious adverse event (SAE) of respiratory failure on (b) (6); on the same day, the subject died. Concomitant medications at the time of the respiratory failure event included betamethasone sodium phosphate (4 mg IM QD), dexamethasone (16 drops PO QD), duloxetine hydrochloride (60 mg PO QD), fentanyl (75 µg transdermal frequency not reported), omeprazole sodium (20 mg PO QD), ondansetron (8 mg IM PRN), paracetamol (1,000 mg PO BID), and pregabalin (75 mg PO BID). Per Applicant submitted narrative, on (b) (6), the subject experienced a nonserious adverse event (AE) of Grade 3 respiratory failure; treatment medication included betamethasone sodium phosphate (4 mg IM QD). The subject died the next day on (b) (6) (b) (6), due to Grade 5 SAE of respiratory failure. Additional details were not provided. The event of respiratory failure was considered not related to study treatment by the Investigator.

FDA requested additional information from the Applicant regarding the clinical course of the respiratory failure that resulted in death, including an updated narrative describing extent of under metastatic cancer (e.g., lung metastases, etc.), relevant AEs leading up to the event of respiratory failure (pneumonia, respiratory infections, etc.), vital signs, all laboratory results, all testing results (imaging, biopsies, etc.), particularly starting with C2D1 (b) (6) through the date of death (b) (6) and an autopsy report, if performed. The updated narrative by Applicant included the following additional information:

At baseline, the patient had an ECOG performance status of 0, with physical exam remarkable for an abdominal scar and colostomy, and abnormal baseline liver function tests. The baseline imaging assessment indicated the patient had 5 target lesions: 1 peritoneal (43mm), 2 liver lesions (one measuring 30mm and the second 31mm); 2 lung lesions (measuring 16mm and 17mm in diameter), and with a sum of longest dimension of 137mm. Patient had no non-target lesions. No follow-up scans available while on treatment as the next timepoint for assessment per protocol was not reached. The patient received dostarlimab Cycle 2 Day 1 on (b) (6) (b) (6) Patient did not have investigator site visits between (b) (6) On (b) (6) the patient experienced dyspnea with Grade 3 respiratory failure assessed by the investigators to be unlikely related to study treatment. The patient declined to call emergency services and received betamethasone 4 mg by intramuscular injection at home with improvement in the condition. On (b) (6) patient's symptoms worsened despite betamethasone 4 mg IM injection treatment. The patient was evaluated by emergency medical services at home including an emergency service physician, the clinical impression was the event was due to disease progression and the patient declined hospital transport and passed away at home on the same day. The Grade 5 event was assessed by the investigator to be not related to

study treatment and likely due to disease progression. The site provided the following information on the SAE report regarding the event of respiratory failure:

"ON (b) (6) HAD WORSENING OF PERFOMANCE STATUS DUE TO RESPIRATORY FAILURE PROBABILY RELATED TO THE PROGRESSION OF DISEASE. THJEREFORE BETAMETASONE 4MG IM WAS PRESCRIBED WITH IMPROVEMENT OF SYMPTONS. 24 HOURS LATER (b) (6) HAD A NEW EPISODE AND BETAMETASONE WAS PRESCRIBED AGAIN BUT (b) (6) WAS REFRATTORY TO THE TRATMENT AND THE EVENT WAS FATAL." The investigator site indicated that no autopsy was performed.

Reviewer comments: This reviewer does not agree with the investigator's assessment of death due to disease progression. This patient had no comorbidities and no risk factors for respiratory failure and death, and no clear evidence of disease progression was provided. Based on the original narrative and the updated details submitted by the Applicant, there is temporal association between dostarlimab administration and the onset of respiratory failure and death within 24 hours (respiratory failure occurred 17 days from the second dose of dostarlimab). The patient's past medical history is not significant for any respiratory condition/disease or predisposing factors. Per the updated narrative, the patient's clinical course including vital signs, lab results, lack of hospitalization, and most recent adverse events leading up to the event of respiratory failure and death does not indicate any occurrence of any respiratory condition possibly contributing to death (e.g. pneumonia, respiratory infections, etc.). In addition, the patient did not have extensive lung involvement with underlying cancer that could have contributed to the respiratory event and death and there were only two small tumor lesions in the lungs (<2 cm in measurement)documented, per last imaging performed prior to the event of death. No imaging or lab tests were performed upon the onset of dyspnea and respiratory failure on (b) (6), which resulted in death on (b) (6), so no further information could be used to further elucidate the etiology for the adverse events of dyspnea and respiratory failure. Finally, fatal respiratory events are events listed under the Warnings and Precautions section of the anti PD-1 Class of Drugs.

Based on the known findings above, the adverse reaction of respiratory failure that resulted in death was reasonably associated with dostarlimab therapy and the contribution of dostarlimab cannot be ruled out. Dostarlimab product labeling was revised to add this fatal adverse event.

2- Patient (b) (6) Cerebrovascular accident. 67-year-old female with Stage IV colorectal cancer who received the first and last dose of dostarlimab on (b) (6) The reported adverse event leading to death per investigator was cerebrovascular accident/stroke. The subject's medical history was significant for thrombosis, thrombophlebitis, asthma, anemia, diarrhea, asthenia, abdominal pain, and decreased appetite. Concomitant medications at the time of the CVA included nefopam hydrochloride (2 mL IV PRN), paracetamol (1 g PO QD), salbutamol (100 µg inhalation PRN), and fluticasone/salmetrol (500 µg inhalation QD). On (b) (6) the subject experienced a nonserious adverse event (AE) of Grade 2 rectal haemorrhage, which led to discontinuation of tinzaparin sodium on the same day. No treatment was administered for the rectal haemorrhage.

On (b) (6) the subject fell while trying to stand up and noticed an isolated deficiency of her left lower limb; the subject was subsequently hospitalized for an SAE of Grade 3 cerebrovascular accident and nonserious AEs of Grade 2 fall and Grade 3 hemiplegia were reported. CT scans showed cerebrovascular accident, and a nuclear magnetic resonance imaging scan showed a right anterior cerebral artery infarction involving the right precentral gyrus. CT scans of the chest, abdomen, and pelvis showed hypoplasia of right segment A1. Treatment for the SAE of cerebrovascular accident included midazolam (dose not reported IV QD), morphine (dose not reported IV QD), and furosemide (dose not reported PO QD). The subject also received enoxaparin sodium (0.4 mL IV QD) as prophylaxis for thrombosis and acetylsalicylate lysine/glycine (250 mg PO QD) as prophylaxis for pain. No treatment was administered for the nonserious AEs of fall, dyspnoea, and hemiplegia. On (b) (6) the subject had difficulty with mobility. The common, superficial, and bilateral popliteal femoral veins were patent and compressible. There was no venous thrombosis of the lower limbs at both left and right popliteal arteries. On (b) (6) the subject's respiratory status degraded with an episode of respiratory distress. Study treatment was discontinued due to the cerebrovascular accident. On the same day, the SAE of cerebrovascular accident worsened to Grade 5 and the subject died due to this SAE. The nonserious AEs of hemiplegia and dyspnoea were ongoing at the time of subject's death. The event of cerebrovascular accident was considered unlikely related to the study treatment by the Investigator.

Reviewer comments: This patient had a history of ongoing thrombosis and thrombophlebitis (since (b) (6)). Considering that this patient had multiple comorbidities and multiple risk factors, it is unclear whether this death may be related to study therapy.

Note: The following death narrative reviews for patients (b) (6) (b) (6) were conducted during FDA review of the Original BLA761174 application submitted by the Applicant for the indication of dMMR recurrent or advanced endometrial cancer. This application was granted accelerated approval in April, 2021. These patients were part of the safety population submitted to both BLA761174 and BLA761223.

3- Patient (b) (6) Bronchial aspiration. The 76-year-old white female received a total of 6 doses of dostarlimab. The reported adverse event leading to death was bronchial aspiration. The subject's other relevant medical history included aortic valve stenosis, Cataract, Type 2 diabetes mellitus, Upper limb fracture. The subject received the first dose of dostarlimab on (b) (6) (Cycle 1 Day 1). The subject received the last dose of dostarlimab (Cycle 6 day 1) (b) (6) Twenty-four days after the last dose of study treatment, the subject experienced an SAE of Grade 5 bronchial aspiration and a nonserious adverse event (AE) of Grade 1 pyrexia (no vital signs or additional information were available on this date). Treatment for pyrexia included levofloxacin (500 mg IV bolus QD) and paracetamol (1 g IV TID). No treatment was reported for the bronchial aspiration. Concomitant medications at the time of the bronchial aspiration included lorazepam (1 mg PO BID), metamizole (575 mg PO PRN), omeprazole (20 mg PO QD), carbohydrates not otherwise specified (NOS) w/fats NOS/minerals (200 mL PO BID), almagate (1,000 mg PO PRN), and vildagliptin (50 mg PO BID). No additional information about the hospitalization was provided. On the same day, the subject died

due to bronchial aspiration. The event of bronchial aspiration was considered not related to study treatment by the investigator.

Reviewer comments: FDA agrees with the investigator's assessment.

4- Patient (b) (6) Sepsis. The 64-year-old White female with the most recent stage of Stage IV T3aN2M received a total of 2 doses of dostarlimab. The reported adverse event leading to death was sepsis. The subject received the first dose of dostarlimab on (b) (6) (Cycle 1 Day 1). The subject received the last dose of dostarlimab on (b) (6) (Cycle 2 Day 1). On (b) (6) the patient reported G1 diarrhea, then on (b) (6) (twenty-three days after the last dose of study treatment), the subject presented to the emergency room with increasing abdominal pain, hypotension, bradycardia, and lactic acidosis (vital sign measurements and laboratory test results not provided). Laboratory results showed white blood cell 21.4×109/L (reference range 3.1 to 9.7×109/L) and absolute neutrophil count 18.4×109/L (reference range 1.2 to 6×109/L). Blood cultures and urine cultures showed no infection or growth over a period of 5 days. Treatment for the event included ceftriaxone (2 g IV once) and methylprednisolone sodium succinate (125 mg IV QID). The subject died on (b) (6). A previous CT scan on (b) (6) documented an enlarging uterine mass with central gas and necrosis, with the mid sigmoid colon draped over the superior margin of the mass and demonstrating abnormal mural thickening that was suspicious for invasion. The cause of sepsis was assessed by investigator to be related to the necrosis occurring within the uterine cancer, and its close proximity to the sigmoid colon. The event of sepsis was considered unlikely related to the study treatment. No autopsy was performed.

Reviewer comments: FDA initially disagreed with the investigator's assessment. Since there was no imaging performed at the time of hospitalization, immune-mediated colitis causing bowel perforation and sepsis leading to death was considered a possibility and it was thought that the role of dostarlimab treatment in the AE leading to death could not be ruled out. The FDA requested additional information on this patient. There was not further information available, including that there was no colonoscopy performed, which would have potentially confirmed colitis. Based upon the CT scan report, showing the uterine mass possibly invading the colon, and lack of definitive story to corroborate a diagnosis of immune-mediated colitis, FDA determined that the most likely diagnosis was colonic perforation resulting from progression of uterine cancer, and subsequently leading to sepsis and death. It was determined that this event would not be considered a study-treatment related adverse event leading to death.

5- Patient (b) (6) Pneumonia/ respiratory failure. The 65-year-old White female received a total of 15 doses of dostarlimab. The reported adverse event leading to death per investigator was bronchitis. The subject was initially diagnosed with Stage IB T1bN0 endometrial cancer, and the most recent stage was Stage IVB T1aN0. The subject's medical history is significant for atrial fibrillation, constipation, depression, diabetes mellitus, gastro-oesophageal reflux disease, hypothyroidism, urinary incontinence, blurred vision, arthritis, hypertension, headache, peripheral swelling (right leg), back pain, anemia, vaginal haemorrhage hypomagnesaemia. The subject received the first dose of dostarlimab on (b) (6) (Cycle 1 Day 1). The subject received the last dose of dostarlimab on (b) (6) (Cycle 15 Day 1). Forty-four days after the last dose of study treatment, the subject was hospitalized for a serious adverse event (SAE) of Grade 3 bronchitis. On the same day, the subject experienced a nonserious AE of Grade 3

syncope and hit her head. The preceding symptoms included light-headedness, fainting, and loss of consciousness. No seizure activity, incontinence, or apnea were noted. Upon admission, the subject had a productive cough, fever, chills, and myalgia with decreased oral intake. The subject also had dizziness due to excessive coughing. An electrocardiogram (ECG) revealed sinus tachycardia at the time of admission, which progressed to atrial fibrillation with rapid ventricular response. Vital signs included systolic blood pressure ranging between 140 to 160 mmHg, temperature 38.6°C, and respiratory rate 20 breaths per minute. Laboratory results showed absolute neutrophil count of 87×109/L (reference range 42 to 75×109/L) and lymphocyte count of 0.3×109/L (reference range 0.6 to 4.9×109/L). An ECG showed atrial fibrillation with nonspecific ST-T wave abnormalities. A chest X-ray showed mild increased density within right and left infrahilar regions, subsegmental atelectasis versus scar, clear lung peripheries, and no peripheral airspace disease and pulmonary edema. A CT scan of the brain without contrast showed mild mucosal membrane thickening of ethmoid air cells and right and left maxillary antrum, small fluids within the right and left sphenoid air cells, clear mastoid air cells, unremarkable intracranial anatomy, enlarged ventricles and extra-axial spaces suggesting generalized atrophy, deep white matter disease most likely related to chronic microangiopathy, and no evidence of acute intracranial process (hemorrhage or edema). Influenza A and B antigens were negative. The subject received treatment with azithromycin (500 mg IV drip QD), guaifenesin (600 mg PO BID), levosalbutamol (0.53 mg nasogastric QID), and ceftriaxone sodium (1 g IV once and QD) for bronchitis. On (b) (6) an ECG showed mildly dilated left and right atriums and mild degree of sclerosis of the aortic valve without stenosis. A Doppler study showed mild tricuspid regurgitation and pulmonary artery systolic pressure estimated at 39 mmHg, with mild bilateral enlargement. On (b) (6) a posteroanterior lateral chest X-ray showed multifocal airspace disease and interstitial thickening, which was new; pulmonary edema and pneumonitis versus combination would be in the differential. A CT scan of chest without contrast showed diffusely patchy multifocal airspace disease, which might represent pneumonitis and less likely pulmonary edema. Throat swab had no group A Streptococcus isolated at 48 hours, and urine culture showed no growth at 48 hours. The subject received treatment with prednisone (10 mg PO PRN) and methylprednisolone (40 mg IV drip TID) for bronchitis. On (b) (6) the subject experienced a nonserious AE of Grade 3 pneumonia. A chest X-ray (single view) showed interval worsening of bilateral consolidation, most pronounce in the left-mid and lower lung zones; results were likely related to pneumonia with no layering pleural fluid seen. Additional treatment for bronchitis included vancomycin (125 mg PO BID), paracetamol (1,000 mg IV drip PRN), and piperacillin (3.375 g IV drip QID). Blood cultures were negative. On (b) (6) the subject experienced a nonserious AE of Grade 3 increased bronchial secretion, for which she received atropine (3 gtts SL PRN). Per investigator, on the same day, the SAE of bronchitis worsened to Grade 5 leading to study treatment withdrawal; the nonserious AEs of syncope, atrial fibrillation, pneumonia, and increased bronchial secretion remained ongoing. The event of bronchitis was considered not related to the study treatment by the Investigator. Autopsy was not performed.

Reviewer comments: FDA initially disagreed with the investigator's assessment, and considered that immune-mediated pneumonitis associated with dostarlimab therapy could not be ruled out as a possible cause of death in this patient. FDA requested additional information from the Applicant, which was provided as follows:

In the case of fatal bronchitis (Patient (b) (6)), the subject in question developed bronchitis in (b) (6) approximately 18 months after initiation of dostarlimab. The investigator assessed the fatal event of bronchitis as not related to dostarlimab. While other potential causal factors could be considered, based on results from radiographic workups performed during the hospitalization which showed worsening air space disease, the Applicant agrees with the investigator's assessment that this event was likely from pulmonary infection manifested as bronchitis and pneumonia. Furthermore, the event occurred in the winter, and the subject had a history of previous episodes of bronchitis (in (b) (6) neither of which were related to dostarlimab, and both of which resolved) prior to the fatal event of bronchitis. Moreover, the subject also had a history of type 2 diabetes mellitus which is known to be associated with infectious complications, and gastroesophageal reflux disease which has been associated with chronic bronchitis. GSK agrees with the Investigator and does not attribute the fatal event of bronchitis to dostarlimab based on the patient's medical history and likelihood of pulmonary infection.

FDA ultimately determined that, based upon the radiology report favoring infiltrates and pneumonia, and given that she developed increasing secretions and clinical worsening when steroids were started, the diagnosis of pneumonia leading to death seemed most likely. This was not considered to be a dostarlimab related adverse event leading to death.

6- Patient (b) (6) Pleural effusion. The 70-year-old White female received only one dose of dostarlimab on (b) (6) The reported adverse event leading to death per investigator was pleural effusion. The subject's medical history was significant for ascites, dyspnea exertional, obesity, pleural effusion, hypertension, depression, deep vein thrombosis. Per investigator, this subject had a history of ongoing pleural effusion and exertional dyspnea. Eleven days after the first (and last dose) of dostarlimab, the subject went to the emergency department with Grade 2 dyspnea and was subsequently hospitalized for an SAE of Grade 3 pleural effusion confirmed with a chest X-ray; the sodium level was 116.8 mmol/L, for which the subject received hypertonic infusion (fluid replacement). Thoracentesis was performed and a chest drainage system (Pleur-evac) was placed on the same day. Treatment medications for pleural effusion included hydrocortisone (200 mg IV continuous), methylprednisolone (40 mg IV continuous), ipratropium bromide (inhalation, PRN), and salbutamol (inhalation PRN). On an unspecified date in (b) (6) the subject underwent pleurodesis with talc. On (b) (6) the hyponatremia resolved. On (b) (6) a chest X-ray result continued to show massive pleural effusion. On (b) (6) improvement of symptoms was noted and the SAE of pleural effusion improved to a nonserious Grade 2 adverse event (AE). On the same day, the subject was discharged from the hospital. On (b) (6) study treatment was withdrawn due to the pleural effusion. On (b) (6) the subject presented to the emergency room and was hospitalized with dyspnea and cough; and a Grade 3 pleural effusion. A chest X-ray showed the persistence of massive pleural effusion. Laboratory results included sodium 13.3 mmol/L, N-terminal prohormone brain natriuretic peptide 936 pg/mL (reference range 0 to 125 pg/mL), and blood fibrinogen >740 mg/dL (reference range 150 to 450 mg/dL). No further treatment was administered for the pleural effusion. On an unspecified date, total protein was 5.7 g/dL (reference range 6.4 to 8.3 g/dL). On (b) (6) the subject died due to pleural effusion. The pleural effusion was considered not related to the study treatment by the Investigator. No autopsy was performed.

Reviewer comments: FDA agrees with the investigator's assessment that the event leading to death was unlikely to be related to dostarlimab and was more consistent with disease progression leading to death.

7- Patient (b) (6): Gastrointestinal obstruction/ rectovaginal fistula/ shock. The 43-year-old White female with the most recent stage of Stage III T1BNXM0 received a total of 2 doses of dostarlimab. The reported adverse event leading to death was gastroenteritis. The subject's medical history is significant for peripheral edema, peripheral sensory neuropathy, arthralgia, constipation, and vaginal discharge. Concomitant medications at the time of the gastroenteritis included ibuprofen (400 mg PO PRN), lactulose (10 g PO PRN), and paracetamol (500 mg PO PRN).The subject received the first dose of dostarlimab on (b) (6) (Cycle 1 Day 1). The subject received the last dose of dostarlimab on (b) (6) (Cycle 2 Day 1). On (b) (6) the subject presented to the emergency department with a 3- to 4-week history of nausea, vomiting, and diarrhea, and was hypotensive (blood pressure not reported). She was given 2 L of sodium chloride intravenous (IV) and was subsequently admitted due to an SAE of gastroenteritis. The subject was transferred to the intensive care unit. She was started on norepinephrine 1,000 mL IV and 2 L more of IV fluids, and was aggressively fluid resuscitated and vasopressin was started. The subject's condition remained unchanged. Epinephrine infusion and further IV fluids were given. The subject complained of shortness of breath and her blood pressure continued to drop, followed by bradycardia and cardiac arrest. Resuscitation was initiated, IV fluids were increased, and she was given epinephrine and bicarbonate. After multiple rounds of resuscitation for approximately 50 minutes without return of spontaneous circulation and no response to epinephrine, resuscitation was stopped. On the same day, the subject died due to the SAE of gastroenteritis. The event of gastroenteritis was considered not related to the study treatment by the investigator. An autopsy was performed and the coroner reported that the cause of death was natural.

Reviewer comments: The reason for study drug discontinuation on (b) (6) was unclear. Initially, no information was provided by the Applicant regarding patient's status between (b) (6) (b) (6) and the AE of gastroenteritis leading to death on (b) (6)

FDA sent an information request to the Applicant for further information. The Applicant submitted the following update to the patient narrative:

On (b) (6) the subject had a planned surgery to treat rectovaginal fistula and ureterovaginal fistula which involved laparotomy and colostomy. Per the treating physician, post-op complication included wound dehiscence, which started 1 week after surgery. On (b) (6) (b) (6) the subject was seen in the clinic to be evaluated for possibility of resuming study treatment. However, on account of delayed wound healing and fatigue, subject was considered not fit to resume study therapy through the last clinic visit on (b) (6) (b) (6) The predominant reason for delayed wound healing was assessed as morbid obesity (height of 162cm, weight of 141.4kg, BMI 53.8 at screening). Delayed wound healing was deemed unrelated to study drug. On (b) (6) the subject attended the emergency department presenting with nausea/ vomiting / diarrhea (grade and treatment unknown). Neither blood cultures nor CT scans were conducted at either visit. Upon her presentation on (b) (6) she was in shock. Attempts to resuscitate were made but were unsuccessful; no investigation into her decline was conducted.

The Applicant contacted the investigator to obtain additional information on the SAE and the investigator stated that the patient was seen in ED on (b) (6) for her symptoms of nausea, vomiting, and diarrhea and when she came back to ED on (b) (6) the patient was found be in shock. Possible differential diagnosis included partial bowel obstruction, ischemic, infectious and inflammatory. Neither blood cultures nor CT scans were conducted and the cause of the subject's decline was not clearly identified. The Applicant requested the site to update the safety data and SAE report form accordingly."

Based on the updated patient narrative provided by the Applicant, FDA concluded that due to the time lapse between the last dose of dostarlimab and the event of death, and in the absence of blood cultures and imaging, there was not enough evidence to consider this case to be dostarlimab related adverse event leading to death.

8.2.4.2. Serious Adverse Events

The Applicant's Position:

SAEs reported in participants with dMMR solid tumors are summarized in Table 20. SAEs were experienced by 91 participants (34.1%) with dMMR solid tumors. The most frequently reported SAEs (>2% of participants) were abdominal pain, sepsis, and acute kidney injury. Other than gastrointestinal-related SAEs, there was no apparent pattern of distribution by PT, organ, or organ system for the observed SAEs in participants with dMMR solid tumors.

Treatment-related SAEs were experienced by 21 participants (7.9%) with dMMR solid tumors. Colitis and pneumonitis were the only treatment-related SAEs reported in >1 participant with dMMR solid tumors (2 participants [0.7%] each).

Table 20: SAEs by SOC and PT (≥1% of Participants) (Safety Analysis Set – Participants with dMMR Solid Tumors)

System Organ Class Preferred Term, n (%)	dMMR EC (N=126)	dMMR NEC (N=141)	dMMR Overall (N=267)
Participants with at least 1 SAE	43 (34.1)	48 (34.0)	91 (34.1)
Gastrointestinal disorders	13 (10.3)	18 (12.8)	31 (11.6)

Table 20: SAEs by SOC and PT (≥1% of Participants) (Safety Analysis Set – Participants with dMMR Solid Tumors) (Continued)

System Organ Class Preferred Term, n (%)	dMMR EC (N=126)	dMMR NEC (N=141)	dMMR Overall (N=267)
Abdominal pain	4 (3.2)	5 (3.5)	9 (3.4)
Vomiting	0	3 (2.1)	3 (1.1)
Infections and infestations	12 (9.5)	16 (11.3)	28 (10.5)
Sepsis	4 (3.2)	3 (2.1)	7 (2.6)
Pneumonia	2 (1.6)	3 (2.1)	5 (1.9)
Urinary tract infection	3 (2.4)	0	3 (1.1)

System Organ Class Preferred Term, n (%)	dMMR EC (N=126)	dMMR NEC (N=141)	dMMR Overall (N=267)
General disorders and administration site conditions	9 (7.1)	4 (2.8)	13 (4.9)
Pyrexia	3 (2.4)	2 (1.4)	5 (1.9)
General physical health deterioration	2 (1.6)	1 (0.7)	3 (1.1)
Respiratory, thoracic and mediastinal disorders	8 (6.3)	3 (2.1)	11 (4.1)
Pulmonary embolism	3 (2.4)	0	3 (1.1)
Renal and urinary disorders	6 (4.8)	3 (2.1)	9 (3.4)
Acute kidney injury	4 (3.2)	2 (1.4)	6 (2.2)

Source: Module 2.7.4 Table 14.3.1.11
Abbreviations: dMMR=mismatch repair-deficient; EC=endometrial cancer; NEC=non-endometrial cancer; PT=preferred term; SAE=serious adverse event; SOC=system organ class.
Note: For each SOC and PT, participants were included only once even if they experienced multiple events in that SOC or PT.

The FDA's Assessment:

FDA agrees with the serious adverse event (SAE) data presented by the Applicant in Table 20. The incidence rate of SAEs in the safety population with dMMR solid tumors who received dostarlimab was 34%. The most common SAEs with an incidence rate of > 2% included abdominal pain (3.7%), sepsis (2.6%), and acute kidney injury (2.2%).

8.2.4.3. Dropouts and/or Discontinuations Due to Adverse Events

The Applicant's Position:

TEAEs leading to permanent discontinuation of study treatment reported for participants with dMMR solid tumors are summarized in Table 21.

TEAEs that led to permanent discontinuation of study treatment were experienced by 25 participants (9.4%) with dMMR solid tumors. The most frequently reported TEAEs that led to permanent discontinuation of study treatment (≥0.5% of participants) were alanine aminotransferase increased, aspartate aminotransferase increased, pneumonitis, and transaminases increased.

Treatment-related TEAEs that led to permanent discontinuation of study treatment were experienced by 10 participants (3.7%) with dMMR solid tumors. Alanine aminotransferase increased, aspartate aminotransferase increased, and transaminases increased were the only treatment-related TEAEs reported in >1 participant with dMMR solid tumors (2 participants [0.7%] each; Module 2.7.4 Table 14.3.1.10).

It should be noted that Grade ≥3 irAEs of transaminases increased and pneumonitis required permanent discontinuation of study treatment per protocol. irAEs leading to permanent discontinuation of study treatment reported for participants with dMMR solid tumors are presented in Section 8.2.5.1.

Table 21: TEAEs Leading to Permanent Discontinuation of Study Treatment by SOC PT (Safety Analysis Set – Participants with dMMR Solid Tumors)

System Organ Class Preferred Term, n (%)	dMMR EC (N=126)	dMMR NEC (N=141)	dMMR Overall (N=267)
Participants with at least 1 TEAE leading to permanent treatment discontinuation	15 (11.9)	10 (7.1)	25 (9.4)
Investigations	4 (3.2)	1 (0.7)	5 (1.9)
Alanine aminotransferase increased	2 (1.6)	1 (0.7)	3 (1.1)
Aspartate aminotransferase increased	1 (0.8)	1 (0.7)	2 (0.7)
Transaminases increased	2 (1.6)	0	2 (0.7)
Gamma-glutamyltransferase increased	1 (0.8)	0	1 (0.4)
Respiratory, thoracic and mediastinal disorders	3 (2.4)	2 (1.4)	5 (1.9)
Pneumonitis	1 (0.8)	1 (0.7)	2 (0.7)
Aspiration	1 (0.8)	0	1 (0.4)
Pleural effusion	1 (0.8)	0	1 (0.4)
Respiratory failure	0	1 (0.7)	1 (0.4)
Gastrointestinal disorders	2 (1.6)	1 (0.7)	3 (1.1)
Intestinal obstruction	1 (0.8)	0	1 (0.4)
Nausea	0	1 (0.7)	1 (0.4)
Pancreatitis	1 (0.8)	0	1 (0.4)
Vomiting	0	1 (0.7)	1 (0.4)
Infections and infestations	2 (1.6)	0	2 (0.7)
Bronchitis	1 (0.8)	0	1 (0.4)
Pneumonia	1 (0.8)	0	1 (0.4)
Sepsis	1 (0.8)	0	1 (0.4)
Nervous system disorders	1 (0.8)	1 (0.7)	2 (0.7)
Apraxia	1 (0.8)	0	1 (0.4)
Cerebrovascular accident	0	1 (0.7)	1 (0.4)
Renal and urinary disorders	2 (1.6)	0	2 (0.7)
Acute kidney injury	1 (0.8)	0	1 (0.4)
Tubulointerstitial nephritis	1 (0.8)	0	1 (0.4)
Hepatobiliary disorders	0	1 (0.7)	1 (0.4)
Cholangitis	0	1 (0.7)	1 (0.4)

Table 21: TEAEs Leading to Permanent Discontinuation of Study Treatment by SOC PT (Safety Analysis Set – Participants with dMMR Solid Tumors) (Continued)

System Organ Class Preferred Term, n (%)	dMMR EC (N=126)	dMMR NEC (N=141)	dMMR Overall (N=267)
Immune system disorders	0	1 (0.7)	1 (0.4)
Hypersensitivity	0	1 (0.7)	1 (0.4)
Injury, poisoning, and procedural complications	0	1 (0.7)	1 (0.4)
Pelvic fracture	0	1 (0.7)	1 (0.4)
Metabolism and nutrition disorders	0	1 (0.7)	1 (0.4)
Hyperlipasaemia	0	1 (0.7)	1 (0.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (0.7)	1 (0.4)
Transitional cell carcinoma	0	1 (0.7)	1 (0.4)
Vascular disorders	1 (0.8)	0	1 (0.4)
Shock	1 (0.8)	0	1 (0.4)

Source: Module 2.7.4 Table 14.3.1.9
Abbreviations: dMMR=mismatch repair-deficient; EC=endometrial cancer; NEC=non-endometrial cancer; PT=preferred term; SOC=system organ class; TEAE=treatment-emergent adverse event.
Note: For each SOC and PT, participants were included only once even if they experienced multiple events in that SOC or PT.

The FDA's Assessment:

FDA conducted an independent analysis of TEAEs leading to dropouts and treatment discontinuations and agree with the Applicant's assessment presented in Table 21.

8.2.4.4. Dose Interruption/Reduction Due to Adverse Events

The Applicant's Position:

TEAEs leading to treatment interruption reported for ≥2 participants with dMMR solid tumors are summarized in Table 22.

TEAEs leading to treatment interruption were experienced by 60 participants (22.5%) with dMMR solid tumors. The most frequently reported TEAEs leading to treatment interruption (>1% of participants) were anaemia, pneumonitis, diarrhoea, adrenal insufficiency, alanine aminotransferase increased, and aspartate aminotransferase increased.

Table 22: TEAEs Leading to Treatment Interruption by SOC and PT (≥2 Participants) (Safety Analysis Set – Participants with dMMR Solid Tumors)

System Organ Class Preferred Term, n (%)	dMMR EC (N=126)	dMMR NEC (N=141)	dMMR Overall (N=267)
Participants with at least 1 TEAE leading to treatment interruption	31 (24.6)	29 (20.6)	60 (22.5)

Table 22: TEAEs Leading to Treatment Interruption by SOC and PT (≥2 Participants) (Safety Analysis Set – Participants with dMMR Solid Tumors) (Continued)

System Organ Class Preferred Term, n (%)	dMMR EC (N=126)	dMMR NEC (N=141)	dMMR Overall (N=267)
Gastrointestinal disorders	9 (7.1)	6 (4.3)	15 (5.6)
Diarrhoea	3 (2.4)	1 (0.7)	4 (1.5)
Abdominal pain	0	2 (1.4)	2 (0.7)
Colitis	2 (1.6)	0	2 (0.7)
Infections and infestations	4 (3.2)	6 (4.3)	10 (3.7)
Pneumonia	2 (1.6)	0	2 (0.7)
Sepsis	1 (0.8)	1 (0.7)	2 (0.7)
Investigations	4 (3.2)	4 (2.8)	8 (3.0)
Alanine aminotransferase increased	1 (0.8)	2 (1.4)	3 (1.1)
Aspartate aminotransferase increased	1 (0.8)	2 (1.4)	3 (1.1)
Blood creatinine increased	1 (0.8)	1 (0.7)	2 (0.7)
Lipase increased	2 (1.6)	0	2 (0.7)
Respiratory, thoracic and mediastinal disorders	2 (1.6)	6 (4.3)	8 (3.0)
Pneumonitis	1 (0.8)	4 (2.8)	5 (1.9)
Blood and lymphatic system disorders	5 (4.0)	2 (1.4)	7 (2.6)
Anaemia	4 (3.2)	1 (0.7)	5 (1.9)
Endocrine disorders	3 (2.4)	4 (2.8)	7 (2.6)
Adrenal insufficiency	0	3 (2.1)	3 (1.1)
General disorders and administration site conditions	3 (2.4)	4 (2.8)	7 (2.6)
Asthenia	0	2 (1.4)	2 (0.7)
Fatigue	0	2 (1.4)	2 (0.7)
Injury, poisoning and procedural complications	2 (1.6)	0	2 (0.7)

System Organ Class Preferred Term, n (%)	dMMR EC (N=126)	dMMR NEC (N=141)	dMMR Overall (N=267)
Gastroenteritis radiation	2 (1.6)	0	2 (0.7)
Musculoskeletal and connective tissue disorders	1 (0.8)	1 (0.7)	2 (0.7)
Arthralgia	1 (0.8)	1 (0.7)	2 (0.7)

Source: Module 2.7.4 Table 14.3.1.6
Abbreviations: dMMR=mismatch repair-deficient; EC=endometrial cancer; NEC=non-endometrial cancer; PT=preferred term; SOC=system organ class; TEAE=treatment-emergent adverse event.
Note: For each SOC and PT, participants were included only once even if they experienced multiple events in that SOC or PT.

The FDA's Assessment:

FDA conducted an independent analysis of dose interruptions due to adverse events. Dosage interruptions due to an adverse reaction occurred in 23% of patients who received dostarlimab. Adverse reactions that required dosage interruption in ≥1% of patients were anemia, pneumonitis, diarrhea, adrenal insufficiency, increased alanine aminotransferase, and increased aspartate aminotransferase.

8.2.4.5. Treatment Emergent Adverse Events and Adverse Reactions

The Applicant's Position:

Treatment Emergent Adverse Events

Most participants with dMMR solid tumors experienced at least 1 TEAE (96.3%; Table 23). Treatment-related TEAEs were reported in 65.9% of participants. The majority of TEAEs were not severe or serious and did not require treatment interruption or discontinuation. TEAEs leading to death were reported in 7 participants (2.6%); none of these TEAEs were assessed by the Investigator as related to study treatment or considered to be an irAE.

Table 23: Overview of TEAEs (Safety Analysis Set - Participants with dMMR Solid Tumors)

Events, n (%)	dMMR EC (N=126)	dMMR NEC (N=141)	dMMR Overall (N=267)
Any TEAEs	120 (95.2)	137 (97.2)	257 (96.3)
Any treatment-related TEAEs	80 (63.5)	96 (68.1)	176 (65.9)
Any Grade ≥3 TEAEs	61 (48.4)	61 (43.3)	122 (45.7)
Any treatment-related Grade ≥3 TEAEs	17 (13.5)	12 (8.5)	29 (10.9)
Any TEAEs leading to permanent treatment discontinuation	15 (11.9)	10 (7.1)	25 (9.4)
Any treatment-related TEAEs leading to permanent treatment discontinuation	5 (4.0)	5 (3.5)	10 (3.7)
Any serious TEAEs	43 (34.1)	48 (34.0)	91 (34.1)

Events, n (%)	dMMR EC (N=126)	dMMR NEC (N=141)	dMMR Overall (N=267)
Any treatment-related serious TEAEs	12 (9.5)	9 (6.4)	21 (7.9)
Any TEAE leading to study treatment interruption	31 (24.6)	29 (20.6)	60 (22.5)
Any treatment-related TEAE leading to study treatment interruption	18 (14.3)	16 (11.3)	34 (12.7)
Any TEAEs leading to death	5 (4.0)	2 (1.4)	7 (2.6)
Any treatment-related TEAEs leading to death	0	0	0
Any treatment-emergent irAE	44 (34.9)	45 (31.9)	89 (33.3)

Table 23: Overview of TEAEs (Safety Analysis Set - Participants with dMMR Solid Tumors) (Continued)

Events, n (%)	dMMR EC (N=126)	dMMR NEC (N=141)	dMMR Overall (N=267)
Any treatment-related treatment-emergent irAE	27 (21.4)	27 (19.1)	54 (20.2)
Any dostarlimab infusion-related reactions	0	2 (1.4)	2 (0.7)

Source: Module 2.7.4 Table 14.3.1.1.1
Abbreviations: AE=adverse event; CTCAE=Common Terminology Criteria for Adverse Events; dMMR=mismatch repair-deficient; EC=endometrial cancer; irAE=immune-related adverse event; NEC=non-endometrial cancer; TEAE=treatment-emergent adverse event.
Note: For each category, participants were included only once even if they experienced multiple events in that category. AE severity was graded using CTCAE v4.03.

The most frequently reported TEAEs (≥20%) in participants with dMMR solid tumors were anaemia, diarrhoea, asthenia, and nausea (Table 24). The most frequently reported TEAEs were Grade 1 or Grade 2 in severity in most participants for whom the TEAEs were reported.

Table 24: Common TEAEs by System Organ Class and Preferred Term (≥10% of Participants) (Safety Analysis Set – Participants with dMMR Solid Tumors)

System Organ Class Preferred Term, n (%)	dMMR EC (N=126)	dMMR NEC (N=141)	dMMR Overall (N=267)
Any TEAEs	120 (95.2)	137 (97.2)	257 (96.3)
Gastrointestinal disorders	79 (62.7)	90 (63.8)	169 (63.3)
Diarrhoea	35 (27.8)	31 (22.0)	66 (24.7)
Nausea	40 (31.7)	19 (13.5)	59 (22.1)
Vomiting	24 (19.0)	21 (14.9)	45 (16.9)
Constipation	25 (19.8)	17 (12.1)	42 (15.7)
Abdominal pain	21 (16.7)	19 (13.5)	40 (15.0)

System Organ Class Preferred Term, n (%)	dMMR EC (N=126)	dMMR NEC (N=141)	dMMR Overall (N=267)
General disorders and administration site conditions	81 (64.3)	75 (53.2)	156 (58.4)
Asthenia	28 (22.2)	36 (25.5)	64 (24.0)
Fatigue	31 (24.6)	22 (15.6)	53 (19.9)
Pyrexia	13 (10.3)	18 (12.8)	31 (11.6)
Investigations	48 (38.1)	56 (39.7)	104 (39.0)
Aspartate aminotransferase increased	9 (7.1)	19 (13.5)	28 (10.5)
Musculoskeletal and connective tissue disorders	55 (43.7)	42 (29.8)	97 (36.3)

Table 24: Common TEAEs by System Organ Class and Preferred Term (≥10% of Participants) (Safety Analysis Set – Participants with dMMR Solid Tumors) (Continued)

System Organ Class Preferred Term, n (%)	dMMR EC (N=126)	dMMR NEC (N=141)	dMMR Overall (N=267)
Arthralgia	18 (14.3)	17 (12.1)	35 (13.1)
Back pain	19 (15.1)	12 (8.5)	31 (11.6)
Metabolism and nutrition disorders	41 (32.5)	51 (36.2)	92 (34.5)
Decreased appetite	16 (12.7)	16 (11.3)	32 (12.0)
Skin and subcutaneous tissue disorders	40 (31.7)	50 (35.5)	90 (33.7)
Pruritus	18 (14.3)	21 (14.9)	39 (14.6)
Rash	13 (10.3)	15 (10.6)	28 (10.5)
Blood and lymphatic system disorders	40 (31.7)	49 (34.8)	89 (33.3)
Anaemia	35 (27.8)	41 (29.1)	76 (28.5)
Respiratory, thoracic, and mediastinal disorders	42 (33.3)	36 (25.5)	78 (29.2)
Cough	19 (15.1)	16 (11.3)	35 (13.1)

Source: Module 2.7.4 Table 14.3.1.2
Abbreviations: dMMR=mismatch repair-deficient; EC=endometrial cancer; NEC=non-endometrial cancer; PT=preferred tem; SOC=system organ class; TEAE=treatment-emergent adverse event.
Note: For each SOC and PT, participants were included only once even if they experienced multiple events in that SOC or PT.

Twenty-nine participants (10.9%) had Grade ≥3 TEAEs of anaemia, 5 participants (1.9%) had Grade 3 TEAEs of asthenia, 4 participants (1.5%) had Grade 3 TEAEs of diarrhoea, and 1 participant (0.4%) had a Grade 3 TEAE of nausea (Table 33). None of the participants had Grade 4 or Grade 5 diarrhoea, asthenia, or nausea; 1 participant (0.4%) had Grade 4 anaemia. The overall safety profile was similar between participants with dMMR EC and dMMR non EC,

and no clinically significant differences were noted. Nausea and urinary tract infection were reported more frequently (>10% difference in frequencies) in participants with dMMR EC (nausea 31.7%; urinary tract infection 15.1%) than in participants with dMMR non-EC (nausea 13.5%; urinary tract infection 4.3%).

A total of 122 participants (45.7%) with dMMR solid tumors experienced a Grade ≥3 TEAE. The most frequently reported Grade ≥3 TEAEs (≥3%) in participants with dMMR solid tumors were anaemia, abdominal pain, and hyponatraemia. Grade 4 TEAEs reported in >1% of participants with dMMR solid tumors were sepsis, reported in 4 participants (1.5%), and hyponatraemia, reported in 3 participants (1.1%) (Table 25).

Table 25: Grade ≥3 TEAEs by SOC and PT (≥2% of Participants) (Safety Analysis Set – Participants with dMMR Solid Tumors)

System Organ Class Preferred Term, n (%)	dMMR EC (N=126)	dMMR NEC (N=141)	dMMR Overall (N=267)
Participants with at least 1 Grade ≥3 TEAE	61 (48.4)	61 (43.3)	122 (45.7)
Gastrointestinal disorders	18 (14.3)	17 (12.1)	35 (13.1)
Grade ≥3 Abdominal pain	7 (5.6)	4 (2.8)	11 (4.1)
Grade 3 Abdominal pain	7 (5.6)	4 (2.8)	11 (4.1)
Blood and lymphatic system disorders	20 (15.9)	14 (9.9)	34 (12.7)
Grade ≥3 Anaemia	19 (15.1)	10 (7.1)	29 (10.9)
Grade 3 Anaemia	19 (15.1)	9 (6.4)	28 (10.5)
Grade 4 Anaemia	0	1 (0.7)	1 (0.4)
Infections and infestations	12 (9.5)	15 (10.6)	27 (10.1)
Grade ≥3 Sepsis	4 (3.2)	3 (2.1)	7 (2.6)
Grade 3 Sepsis	0	2 (1.4)	2 (0.7)
Grade 4 Sepsis	3 (2.4)	1 (0.7)	4 (1.5)
Grade 5 Sepsis	1 (0.8)	0	1 (0.4)
Grade ≥3 Pneumonia	3 (2.4)	3 (2.1)	6 (2.2)
Grade 3 Pneumonia	2 (1.6)	3 (2.1)	5 (1.9)
Grade 5 Pneumonia	1 (0.8)	0	1 (0.4)
Metabolism and nutrition disorders	9 (7.1)	13 (9.2)	22 (8.2)
Grade ≥3 Hyponatraemia	4 (3.2)	4 (2.8)	8 (3.0)
Grade 3 Hyponatraemia	3 (2.4)	2 (1.4)	5 (1.9)
Grade 4 Hyponatraemia	1 (0.8)	2 (1.4)	3 (1.1)
Renal and urinary disorders	7 (5.6)	2 (1.4)	9 (3.4)
Grade ≥3 Acute kidney injury	4 (3.2)	2 (1.4)	6 (2.2)

System Organ Class Preferred Term, n (%)	dMMR EC (N=126)	dMMR NEC (N=141)	dMMR Overall (N=267)
Grade 3 Acute kidney injury	4 (3.2)	2 (1.4)	6 (2.2)

Source: Module 2.7.4 Table 14.3.1.4
Abbreviations: AE=adverse event; CTCAE=Common Terminology Criteria for Adverse Events; dMMR=mismatch repair-deficient; EC=endometrial cancer; NEC=non-endometrial cancer; PT=preferred term; SOC=system organ class; TEAE=treatment-emergent adverse event.
Note: AE severity was graded using CTCAE v4.03. For each PT, participants were included only once even if they experienced multiple events in that PT.

Grade 5 TEAEs were reported in 7 participants (2.6%). TEAEs leading to death are discussed in Section 8.2.4.1. None of the TEAEs leading to death were assessed as related to study treatment by Investigators.

Treatment-related Grade ≥3 TEAEs were experienced by 29 participants (10.9%) with dMMR solid tumors. Anaemia (6 participants [2.2%]), lipase increased (5 participants [1.9%]), and alanine aminotransferase increased and diarrhoea (3 participants [1.1%] each) were the only treatment-related Grade ≥3 TEAEs reported in >2 participants with dMMR solid tumors (see Integrated Summary of Safety [ISS] Outputs, Table 14.3.1.5).

Adverse Reactions

TEAEs that have been determined by the sponsor to be adverse reactions related to dostarlimab in participants with dMMR solid tumors include: anemia, diarrhea, nausea, vomiting, colitis, enterocolitis, enterocolitis hemorrhagic, pancreatitis, pancreatitis acute, pyrexia, chills, myalgia, aspartate aminotransferase increased, alanine aminotransferase increased, transaminases increased, hypertransaminasemia, hepatocellular injury, pruritus, rash, rash maculo-papular, rash macular, rash papular, rash erythematous, toxic skin eruption, pemphigoid, erythema, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, autoimmune thyroiditis, infusion-related reaction, pneumonitis, interstitial lung disease, iridocyclitis, uveitis, nephritis and tubulointerstitial nephritis.

The FDA's Assessment:

FDA independently reviewed all adverse events. Although FDA generally agrees with the Applicant's assessment for most common adverse events (Grade 1-4), this reviewer combined the PT terms fatigue and asthenia resulting in an all-grade fatigue/asthenia incidence rate of 42%. The most common Grades 1-4 adverse reactions occurring in ≥20% of patients were fatigue/asthenia, anemia, diarrhea, and nausea. The most common Grade 3 or 4 adverse reactions (≥2%) were anemia, fatigue/asthenia, increased transaminases, sepsis, and acute kidney injury.

The FDA analysis is presented in Table 26.

Table 26: FDA Analysis of Common Treatment-Emergent Adverse Reactions (≥10%)

Treatment-Emergent Adverse Events	Dostarlimab dMMR solid tumors N= 267 (%) G1-4

Any TEAEs	**257 (96)**
Fatigue/Asthenia	113 (42)
Anemia	79 (30)
Diarrhea	66 (25)
Nausea	59 (22)
Abdominal pain	49 (18)
Vomiting	45 (17)
Constipation	42 (16)
Pruritus	40 (15)
Cough	35 (13)
Decreased appetite	32 (12)
Transaminases increased	32 (12)
Pyrexia	31 (11)

8.2.4.6. Laboratory Findings

The Applicant's Position:

As of the data cutoff date, the median treatment duration for participants with dMMR solid tumors was 25.0 weeks. During this time, fluctuations in mean values for hematology and blood chemistry parameters were observed, but no clinically meaningful trends were identified during the study.

Of the 267 participants with dMMR solid tumors, 1 participant had Grade 3 decreased hemoglobin at baseline and 4 participants had Grade 3 decreased lymphocytes. Grade 3 baseline chemistry values included decreased sodium (7 participants), decreased albumin (2 participants), increased alkaline phosphatase (ALP) (2 participants), decreased potassium (1 participant), and decreased magnesium (1 participant). Grade 4 baseline values included decreased corrected calcium (1 participant).

Laboratory abnormalities that worsened from Baseline to Grade 3 or 4 occurring in at least 1% of participants with dMMR solid tumors are summarized in Table 27.

The most frequent Grade 3 or 4 laboratory abnormalities observed in participants with dMMR solid tumors (≥3% of participants) were lymphopenia, hyponatremia, and increased alkaline phosphatase.

No participant with dMMR solid tumors met the criteria for potential Hy's law (concurrent aspartate aminotransferase [AST] or ALT ≥3×upper limit of normal [ULN], in combination with TBL ≥2×ULN and ALP <2×ULN). ALT or AST ≥10 to <20×ULN was observed in 3 participants with dMMR solid tumors (1.1%), and no participant with dMMR solid tumors had ALT or AST ≥20×ULN.

Table 27: Laboratory Abnormalities that Worsened from Baseline to Grade 3 or 4 Occurring in ≥1% of Participants with dMMR Solid Tumors Receiving Dostarlimab in GARNET (Safety Analysis Set)

Laboratory Test	All Grades %	Grades 3-4 %
Chemistry		
Increased alkaline phosphatase	25.8	3.4
Increased aspartate aminotransferase	25.8	1.5
Hypoalbuminemia	25.5	2.2
Increased alanine aminotransferase	22.1	1.9
Increased creatinine	20.6	1.1
Total bilirubin increased	7.1	1.5
Electrolytes		
Hyponatremia	21.3	4.9
Hypomagnesemia	15.7	1.1
Hyperkalemia	14.2	1.1
Hypokalemia	13.5	1.1
Hypercalcemia	5.6	1.1
Hypermagnesemia	4.1	1.5
Hypocalcemia	2.6	1.5
Hematology		
Lymphopenia	32.6	7.1
Leukopenia	18.4	1.1
Neutropenia	12.0	1.5

Source: Module 2.5 Table 14.3.4.3 and Table 14.3.4.4
Abbreviations: dMMR=mismatch repair-deficient;
Note: Anemia is included in Table 14 in Module 2.5 as an adverse drug reaction and is therefore not included in this table.

The FDA's Assessment:

FDA independently reviewed the laboratory findings, and agrees with the Applicant's assessment.

8.2.4.7. Vital Signs

The Applicant's Position:

Vital signs, including blood pressure, pulse and temperature, were collected per protocol and listed for each patient. Vital signs assessed as clinically significant were to be recorded as an AE or SAE as appropriate.

The FDA's Assessment:

FDA agrees with the Applicant's assessment of vital signs submitted in the CSRs. No clinically relevant changes in vital signs or trends over time were observed.

8.2.4.8. Electrocardiograms and QT

The Applicant's Position:

Electrocardiograms were conducted per protocol and listed for each patient. Electrocardiogram results assessed as clinically significant were to be recorded as an AE or SAE as appropriate.

Cardiac safety analyses were performed on data using the 08 July 2019 data cutoff date (Cardiac Safety Report, report date 19 November 2019, BLA 761174). The cardiac effects of dostarlimab on QT were studied by analysis of central tendency and concentration-Δcorrected QT interval (QTc) analysis in participants with solid tumors dosed at the RTD.

Based on the results of the concentration-ΔQTc modeling, summary statistics, incidence of clinical noteworthy ECG interval values, and rhythm abnormalities, it is reasonable to conclude that dostarlimab administered at 500 mg Q3W and 1,000 mg Q6W does not cause a clinically significant QTcF prolongation.

The FDA's Assessment:

FDA agrees with the Applicant's QTc assessment.

8.2.4.9. Immunogenicity

The Applicant's Position:

As of 01 March 2020, samples from 418 participants in Study 4010-01-001, with 384 participants treated at the RTD, were evaluable for the presence of treatment-emergent ADAs. The overall immunogenicity risk for dostarlimab is low. Post-dostarlimab antibody responses to date have been low in incidence and with no apparent impact on PK, safety, or efficacy.

The incidence of treatment-emergent (treatment-induced or treatment-boosted) ADA was low and comparable to that of other anti-PD-1 antibodies (Keytruda SmPC 2019; Keytruda® USPI 2020; Opdivo® USPI 2020; Opdivo SmPC 2020). The incidence of treatment-emergent ADA in participants receiving the RTD (Part 2B) was 2.1%, with 1.0% being neutralizing antibody (NAb) positive. For all participants tested in Study 4010-01-001, the incidence of treatment-emergent anti-dostarlimab antibodies was similarly low (3.1%; 1.7% NAb positive). The ADA titers were generally low. There was no evidence of a clinically meaningful impact of ADA formation on any safety or efficacy measures.

Overall, the prevalence of baseline-positive samples was 16.8%. In Part 2B, the proportion of participants with positive results decreased temporally from 17.5% at baseline to 4.2% at Cycle 4, 4.1% at Cycle 5, 2.6% at Cycle 8, and further declined to 0.0% by Cycle 12 before increasing slightly to 1.8% at the Safety Follow-up visit.

Based on PK noncompartmental analysis using the 08 July 2019 data cutoff date, there was no apparent visual effect of ADA on PK. However, due to the low number of participants with treatment-emergent ADA, the generally low titer, and the intermittent incidence of ADA

samples, the impact of immunogenicity on PK cannot be assessed conclusively. ADA was therefore evaluated in population PK analysis as a covariate in 3 scenarios (time variant at each time point; participant level never positive or ever positive; and time variant as negative until first positive, then carry forward as positive). No significant effect on dostarlimab clearance was determined. Therefore, an effect of ADA on dostarlimab PK is not apparent.

Analysis of the observed incidence of TEAEs (any TEAE; TEAEs Grade ≥3; treatment-emergent irAEs; treatment-emergent SAEs; or TEAEs leading to study treatment interruption, study treatment discontinuation, or death) in participants positive for ADA or NAb demonstrated no effect of baseline or treatment-emergent ADA or NAb on safety.

Although multivariate logistic regression of ORR identified NAb status to be a significant covariate in participants with dMMR solid tumors, the observed ORR and DOR in participants positive for ADA or NAb were at least comparable to or better than those of participants negative for ADA or NAb. These results demonstrate that there is no effect of baseline or treatment-emergent ADA or NAb on efficacy.

The FDA's Assessment:

The FDA agrees with the Applicant's immunogenicity assessment.

8.2.5. Analysis of Submission-Specific Safety Issues

8.2.5.1. Immune-Related Adverse Events (irAEs)

The Applicant's Position:

In participants treated with dostarlimab as a single agent at the RTD, 179 participants (34.8%) had irAEs (Table 28). Immune-mediated endocrinopathies and immune-mediated gastrointestinal events were the most frequently observed categories of irAEs, with hypothyroidism and diarrhoea (7.2% each) being the most frequently observed PTs in these categories, respectively. The median time to onset of the first hypothyroidism event was 91.0 days, and the median time to onset of the first diarrhoea event was 61.0 days. Although none of the participants with irAEs of diarrhoea were treated with immune modulatory medication (IMM), nearly all of the participants with irAEs of hypothyroidism (36 of 37 participants) were treated with IMMs.

The median time to first onset of any irAE was 2.1 months (95% CI: 1.8, 2.2; see Table 28). Of the 179 participants with an irAE, 70 participants (39.1%) were treated with an IMM; about half of these participants received systemic steroids (36 of 70 participants; 28 of these participants were treated with high-dose prednisone or equivalent; ISS Outputs Table 14.3.1.22.1). irAEs in 38 participants (54.3%) resolved after treatment with an IMM, with a median time to resolution of 84.0 days (range: 1 to 698+ days). One participant (0.6%) was treated with immune suppressants, and 41 participants (22.9%) were treated with thyroid therapy (ie, any type of therapy used to treat hypothyroidism or hyperthyroidism). A total of 109 participants (60.9%) did not require treatment with an IMM; of these, irAEs in 68 participants (62.4%) resolved, with a median time to resolution of 43.0 days (range: 1 to 913+ days).

An overview of irAE categories and subcategories (ie, PT) with an incidence of ≥2% is provided in Table 28. For each of the subcategories, data on the median time to onset and median time to resolution are also provided.

No participant treated with dostarlimab as a single agent at the RTD died due to an irAE (ISS Outputs Table 14.3.1.18.1). A total of 26 participants (5.0%) had a serious irAE, with the most frequently reported serious irAEs (>0.5% of participants) being adrenal insufficiency, pancreatitis, pancreatitis acute, and pneumonitis (3 participants [0.6%] each; Module 2.7.4 Table 42).

Twenty participants (3.9%) treated with dostarlimab as a single agent at the RTD had an irAE that led to permanent discontinuation of study treatment, with the highest incidence (>1%) in the category of immune-mediated hepatic irAEs (Module 2.7.4 Table 43). The most frequently reported irAEs (>0.5% of participants) that led to study treatment discontinuation were alanine aminotransferase increased (4 participants [0.8%]), followed by pneumonitis and transaminases increased (3 participants [0.6%] each).

It should be noted that Grade ≥3 irAEs of transaminases increased (including alanine aminotransferase increased and aspartate aminotransferase increased) and pneumonitis required permanent discontinuation of study treatment per protocol.

Table 28: Overview of irAEs (≥2% Participants) (Safety Analysis Set – Participants Treated with Dostarlimab at the RTD)

Category Preferred Term, n (%)	Overall N=515 n (%)	Median Time to Onset (Days)	Treated with an IMM			Not treated with an IMM		
			n (%)	Resolved n (%)	Median TTR (Days) (Range)	n (%)	Resolved n (%)	Median TTR (Days) (Range)
Any immune-related TEAE	179 (34.8)	–[a]	70 (39.1)	38 (54.3)	84.0 (1, 698+)	109 (60.9)	68 (62.4)	43.0 (1, 913+)
Immune-mediated endocrinopathies	62 (12.0)	72.0	–	–	–	–	–	–
Hypothyroidism	37 (7.2)	91.0	36 (97.3)	13 (36.1)	NE (10, 698+)	1 (2.7)	0	NE (9+, 9+)
Hyperglycaemia	16 (3.1)	71.0	0	0	–	16 (100)	13 (81.3)	22.0 (1, 213+)
Immune-mediated gastrointestinal	42 (8.2)	62.5	–	–	–	–	–	–
Diarrhoea	37 (7.2)	61.0	0	0	–	37 (100)	33 (89.2)	7.5 (1, 347+)
Immune-mediated hepatic	26 (5.0)	76.5	–	–	–	–	–	–
Alanine aminotransferase increased	15 (2.9)	76.0	5 (33.3)	4 (80.0)	15.0 (5, 88)	10 (66.7)	8 (80.0)	11.0 (2, 22)
Aspartate aminotransferase increased	14 (2.7)	38.5	5 (35.7)	3 (60.0)	5.0 (3, 88)	9 (64.3)	3 (33.3)	NE (1, 103)
Immune-mediated pancreatitis	24 (4.7)	84.5	–	–	–	–	–	–
Amylase increased	16 (3.1)	84.5	1 (6.3)	1 (100)	14.0 (14, 14)	15 (93.8)	8 (53.3)	64.0 (16, 655+)
Immune-mediated skin adverse reactions	22 (4.3)	29.0	–	–	–	–	–	–
Rash	11 (2.1)	31.0	4 (36.4)	4 (100)	15.0 (6, 38)	7 (63.6)	6 (85.7)	30.0 (1, 300+)
Immune-mediated renal	19 (3.7)	64.0	–	–	–	–	–	–
Blood creatinine increased	19 (3.7)	64.0	1 (5.3)	1 (100)	1.0 (1, 1)	18 (94.7)	10 (55.6)	57.0 (1, 535+)

Source: ISS Outputs Table 14.3.1.18.1, Table 14.3.1.22.1, and Table 14.3.1.24
Abbreviations: CI=confidence interval; IMM=immune modulatory medication; irAE=immune-related adverse event; ISS=Integrated Summary of Safety; NE=not evaluable; PT=preferred term; RTD=recommended therapeutic dose; TEAE=treatment-emergent adverse event; TTR=time to resolution.
Note: For each PT, participants were included only once even if they experienced multiple events in that PT. If a participant experienced multiple events in a PT, the highest grade was taken. If a participant experienced multiple events of the same grade in a PT, the event that was treated with an IMM was taken. If a participant experienced multiple events of the same grade in a PT that was treated with the same IMM or no treatment, the longer duration to recovery was taken. Percentages were calculated using the number of participants with an irAE as denominator. Resolved percentages were calculated using n (%) of treated/not treated with an IMM.
[a] The median time to first onset of any irAE was 2.1 months (95% CI: 1.8, 2.2; ISS Outputs Table 14.3.1.21.1).

8.2.5.1.1. Infusion-related Reactions

The Applicant's Position:

A total of 7 participants (1.4%) treated with dostarlimab as a single agent at the RTD reported infusion-related reaction TEAEs (ISS Outputs Table 14.3.1.20.1). These infusion-related reaction TEAEs were infusion-related reaction (6 participants [1.2%]) and hypersensitivity (1 participant [0.2%]).

Of the 7 participants treated with dostarlimab as a single agent who experienced infusion-related reaction TEAEs, 1 participant (14.3%) with a Grade ≥3 event of infusion related reaction was treated with IMM. The event resolved after 1.0 day. Six participants (85.7%) were not treated with an IMM. The events in these participants resolved after a median time to resolution of 1.0 day (ISS Outputs Table 14.3.1.22.4 and Table 14.3.1.22.3).

Grade ≥3 infusion-related reaction TEAEs were reported in 1 participant (0.2%), infusion-related reaction TEAEs leading to infusion interruption were reported in 4 participants (0.8%), and infusion-related reaction TEAEs leading to permanent discontinuation of study treatment were reported in 2 participants (0.4%). The 2 participants with an infusion-related reaction leading to permanent discontinuation of study treatment had treatment interrupted due to the infusion-related reaction prior to permanently discontinuing treatment (ISS Outputs Listing 16.2.7.1).

None of the infusion-related reaction TEAEs were serious or led to death (ISS Outputs Table 14.3.1.20.1).

The FDA's Assessment:

FDA agrees with the applicant's assessment of immune-related adverse events. In the pooled safety database (N=515), treated with dostarlimab as a single agent at the recommended therapeutic dose, 179/515 patients (34.8%) reported an irAE. The majority of irAEs, regardless of organ involved, were Grade 1 or 2 in severity. Immune-related AEs were manageable by treatment interruptions or discontinuations, and administration of corticosteroids and other immunomodulators. Thirty six patients (7%) with an irAE required treatment with high dose steroids. Table 29 outlines FDA analysis of immune-related adverse events reported with dostarlimab monotherapy. The incidence rate and severity of irAEs reported with dostarlimab therapy is consistent with those reported with other approved agents in the anti-PD1 class of drugs.

Table 29: FDA Analysis of Immune-Related Adverse Events

Immune mediated AEs	**Dostarlimab dMMR solid tumors N=267 (%) G1-4**	**Dostarlimab Overall Safety Population N= 515 (%) G1-4**
Any immune-related AE	89 (33)	179 (34)
Immune mediated diarrhea	19 (7)	37 (7)
Immune mediated colitis	4 (1.5)	7 (1.4)
Immune mediated gastritis	2 (0.7)	2 (0.4)

Increased transaminases	23 (8)	40 (7)
Immune mediated hypothyroidism	17 (6)	37 (7)
Immune mediated hyperthyroidism	6 (2)	10 (1.9)
Immune mediated skin	5 (1.9)	11 (2.1)
Immune mediated pneumonitis	5 (1.8)	7 (1.4)
Adrenal insufficiency	4 (1.4)	7 (1.4)
Immune mediated pancreatitis	3 (1.1)	6 (1.2)
Immune mediated renal/nephritis	1 (0.4)	2 (0.4)

8.2.6. Clinical Outcome Assessment Analyses Informing Safety/Tolerability

The Applicant's Position:

Patient-reported outcome (PRO) is an exploratory endpoint for Cohort A1 and Cohort F. The European Quality of Life scale, 5 Dimensions, 5 Levels and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30) were used to assess cancer-specific health-related quality of life. PRO assessments were added to the study under protocol amendment 3.

The FDA's Assessment:

FDA disagrees with the Applicant assessment that dostarlimab does not decrease functioning or QoL. FDA considered the PRO analyses as exploratory and descriptive. Although the completion rates for cohorts A1 and F were reasonable for review, given the sample size, design of the trial, and the PRO instruments used, these limitations preclude a definitive conclusion that dostarlimab does not result in patient-reported functioning or QoL detriments. A comprehensive strategy to measure patient-reported aspects of tolerability was not undertaken, and in light of the limitations listed above, FDA does not agree with the Applicant assessment.

8.2.7. Safety Analyses by Demographic Subgroups

The Applicant's Position:

Demographic subgroups evaluated in the RTD are presented in the following sections.

8.2.7.1. TEAEs by Sex

Of the 515 participants treated with dostarlimab single agent at the RTD, 77.3% were female, and 22.7% were male.

The incidence of TEAEs was generally similar between male and female participants treated with dostarlimab as a single agent at the RTD; however, SAEs were more frequent in female participants (41.2%) than in male participants (33.3%; ISS Outputs Table 14.3.1.1.2).

8.2.7.2. TEAEs by Age

Of the 515 participants treated with dostarlimab single agent at the RTD, 50.7% were <65 years, 37.9% were ≥65 to <75 years, 11.1% were ≥75 to <85 years, and 0.4% were ≥85 years old.

Overall safety risks were not observed to be increased in older participants compared to younger participants.

The incidence of TEAEs was generally similar among participants <65 years old (N=261), ≥65 to <75 years old (N=195), and ≥75 to <85 years old (N=57). TEAEs leading to treatment interruption were reported more frequently in the <65 (24.1%) and ≥65 to <75 years old age groups (22.1%) than in the ≥75 to <85 years old age group (15.8%; ISS Outputs Table 14.3.1.1.3). However, due to the low number of participants in the ≥75 to <85 years old age group (57 in total, with 9 experiencing a TEAE leading to treatment interruption), these results should be interpreted with caution.

Due to the small number of participants >85 years old (≤30 participants), a meaningful comparison based on this age group could not be made.

8.2.7.3. TEAEs by Race

Most of the participants treated with dostarlimab as a single agent at the RTD were White (379 participants [73.6%]). For 17.5% of participants, race was not reported. Due to the small number of participants in race subgroups other than White or not reported (≤30 participants), a meaningful comparison based on race could not be made (ISS Outputs Table 14.3.1.1.4).

8.2.7.4. TEAEs by Ethnicity

Most of the participants treated with dostarlimab as a single agent at the RTD were not Hispanic or Latino (398 participants [77.3%]). For 17.9% of participants, ethnicity was not reported. Due to the small number of participants in ethnicity subgroups other than not Hispanic or Latino and not reported (≤30 participants), a meaningful comparison based on ethnicity could not be made (ISS Outputs Table 14.3.1.1.5).

The FDA's Assessment:

FDA generally agrees with the Applicant's assessment.

8.2.8. Specific Safety Studies/Clinical Trials

The Applicant's Position:

Not applicable.

The FDA's Assessment:

Not Applicable.

8.2.9. Additional Safety Explorations

8.2.9.1. Human Carcinogenicity or Tumor Development

The Applicant's Position:

No human carcinogenicity studies were conducted.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

8.2.9.2. Human Reproduction and Pregnancy

The Applicant's Position:

Dostarlimab has not been studied in pregnant or lactating women. No pregnancies were reported during the study.

The FDA's Assessment:

FDA agrees with the Applicant's position.

8.2.9.3. Pediatrics and Assessment of Effects on Growth

The Applicant's Position:

Dostarlimab has not been studied in the pediatric population to date. A waiver for the Pediatric Research Equity Act (PREA) requirement for pediatric evaluation was requested for the proposed indication in dMMR solid tumors based on pediatric studies being highly impractical or impossible given the pediatric prevalence in this indication.

The FDA's Assessment:

FDA is waiving the pediatric study requirement for this application because the necessary studies are impossible or highly impracticable because dMMR EC is rare in the pediatric population.

8.2.9.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant's Position:

There have been no reported cases of overdose, drug abuse, withdrawal or rebound with dostarlimab. There is no known abuse potential as dostarlimab is administered in a hospital setting.

The FDA's Assessment:

FDA agrees with the Applicant's position.

8.2.10. Safety in the Post-Market Setting

8.2.10.1. Safety Concerns Identified Through Post-Market Experience

The Applicant's Position:

Not applicable as dostarlimab is not currently registered or approved in the US or any other part of the world.

The FDA's Assessment:

Dostarlimab was granted accelerated approved by the FDA for the second line treatment of dMMR recurrent or advanced endometrial cancer in April of 2021, after Applicant's submission of this BLA761223 application. No safety concerns identified post-market.

8.2.10.2. Expectations on Safety in the Post-Market Setting

The Applicant's Position:

Routine pharmacovigilance will be conducted to monitor for adverse events. Ongoing and planned clinical studies will further define the safety profile for dostarlimab.

The FDA's Assessment:

FDA will continue to monitor any post-marketing reports including safety reports that are submitted after accelerated approval.

8.2.11. Integrated Assessment of Safety

The Applicant's Position:

Prior to the approval of PD-1 inhibitors in the US and other countries, adult patients with recurrent or advanced dMMR solid tumors that have progressed on or following prior treatment and who have no satisfactory alternative treatments had limited treatment options, and available therapy was typically associated with poor response and limited OS. While pembrolizumab demonstrated favorable outcome in patients with unresectable or metastatic dMMR/MSI-H tumors, at this time, there are no anti-PD-1 treatments with regular approval for this patient population in the US, indicating that an unmet medical need remains.

For patients with recurrent or advanced dMMR solid tumors, Study 4010-01-001 provides a robust source of data from a well-conducted study, where participants were dosed with a uniform dose and schedule and were enrolled with rigorous enrollment criteria, including documented progression prior to enrollment. The data in participants with dMMR solid tumors comprise pooled data from Cohort A1 (participants with recurrent or advanced dMMR EC) and Cohort F (participants with recurrent or advanced dMMR non-EC) of Part 2B of Study 4010-01-001. Some differences were observed in the demographic characteristics and prior anticancer therapies between participants with dMMR non-EC and participants with dMMR EC as a result of the difference in disease characteristics based on the tumor types and available standard-of-care.

Based on the data from the GARNET study (4010-01-001), dostarlimab demonstrated an acceptable safety profile with manageable toxicities. The most frequently reported TEAEs (≥20%) in participants with dMMR solid tumors were anaemia, diarrhoea, asthenia, and nausea. These TEAEs were mild or moderate in severity in most participants with dMMR solid tumors. Of the most frequently reported TEAEs, 1 participant with dMMR solid tumors had a Grade 4 event of anaemia and none had a Grade 5 event. Grade ≥3 TEAEs were reported in 45.7% of participants with dMMR solid tumors. The Grade ≥3 TEAEs with the highest incidence (≥3%) in participants with dMMR solid tumors were anaemia, abdominal pain, and hyponatraemia. The only Grade 4 TEAEs reported in >1% of participants with dMMR solid tumors were sepsis (4 participants [1.5%]) and hyponatraemia (3 participants [1.1%]).

A total of 65 participants (27.9%) with dMMR solid tumors died on study. The primary cause for death for the majority of participants was disease progression (58 of 65 participants). Seven participants (2.6%) had a TEAE that was the primary cause for death: aspiration, cerebrovascular accident, pleural effusion, pneumonia, respiratory failure, sepsis, and shock. None of these events were considered related to study treatment by the Investigator or are considered to be an irAE.

SAEs were experienced by 34.1% of participants with dMMR solid tumors. The most frequently reported SAEs (>2%) were abdominal pain, sepsis, and acute kidney injury. For 16 of

91 participants with dMMR solid tumors who had an SAE, the SAE was considered to be immune related. Colitis, pancreatitis acute, and pneumonitis were the only immune-related SAEs reported in >1 participant with dMMR solid tumors (2 participants [0.7%] each).

Despite being a heavily pretreated patient population, the overall safety profile of dostarlimab at 500 mg Q3W for the first 4 cycles followed by 1,000 mg Q6W thereafter in participants with dMMR solid tumors and participants treated with dostarlimab as a single agent at the RTD in GARNET was consistent with AEs observed in patients with cancer and cancer-related comorbidities and the known safety profile of other antiPD-1 agents (Keytruda® USPI 2020; Keytruda SmPC 2019; Opdivo® USPI 2020; Opdivo SmPC 2019; Libtayo® USPI 2020; Libtayo SmPC 2019). The majority of TEAEs were Grade 1 or Grade 2 and not serious, and few participants discontinued treatment with dostarlimab due to a TEAE. irAEs may be managed by treatment interruptions or discontinuations, or the use of systemic steroids and other IMMs, as clinically indicated. None of the participants treated with dostarlimab as a single agent died from a TEAE that was considered to be treatment related by the Investigator.

The FDA's Assessment:

FDA agrees that dostarlimab demonstrated an acceptable safety profile with manageable toxicities based on data from 267 patients with dMMR recurrent or advanced solid tumors and from a larger safety database of 515 patients with advanced solid tumors treated with dostarlimab monotherapy on Study 4010-01-001 (GARNET). The most common adverse reactions (≥20%) were fatigue/asthenia, anemia, diarrhea, and nausea. The most common Grade 3 or 4 adverse reactions (≥2%) were anemia, fatigue/asthenia, increased transaminases, sepsis, and acute kidney injury. Serious adverse reactions occurred in 34% of patients receiving dostarlimab. Serious adverse reactions in >2% of patients included abdominal pain (3.7%), sepsis (2.6%), and acute kidney injury (2.2%). Fatal adverse reaction occurred in one patient who received dostarlimab, due to respiratory failure. Immune-related adverse events were reported in 179/515 patients (34%) treated with dostarlimab as a single agent at the recommended therapeutic dose. The majority of irAEs, regardless of organ involved, were Grade 1 or 2 in severity, and were manageable by treatment interruptions or discontinuations, and administration of steroids and other immunomodulators. Thirty six patients (7%) with an irAE required treatment with high dose steroids. Overall, the incidence rate and severity of irAEs reported with dostarlimab therapy is consistent with those reported with other approved agents in the anti-PD1 class of drugs.

8.3. Statistical Issues

The FDA's Assessment:

Study GARNET is an open-label, single-arm, non-randomized, multicenter study to evaluate the efficacy and safety of single agent dostarlimab. The primary efficacy endpoint was the objective response rate (CR + PR) based on BICR. No inferential procedures (testing procedures) were conducted to evaluate the single-arm trial results. The efficacy evaluation for this application was based on the magnitude of ORR and adequate duration of response from a pooled population of patients from Cohort A1 (participants with recurrent or advanced dMMR EC) and Cohort F (participants with recurrent or advanced dMMR non-EC). The PFS and OS results from a nonrandomized single-arm study without comparators are not interpretable.

There were no major statistical issues identified in this application.

8.4. Conclusions and Recommendations

The FDA's Assessment:

Based upon a favorable risk-benefit profile, the clinical and statistical reviewers recommend accelerated approval of dostarlimab for the following indication:

Dostarlimab is indicated for the treatment of adult patients with mismatch repair deficient (dMMR) recurrent or advanced solid tumors, as determined by an FDA-approved test, that have progressed on or following prior treatment and who have no satisfactory alternative treatment options.

X	X
Hui Zhang, PhD Primary Statistical Reviewer	Erik Bloomquist, PhD Statistical Team Leader
X	X
Sakar Wahby, PharmD Primary Clinical Reviewer	Gwynn Ison, MD Clinical Team Leader

9. ADVISORY COMMITTEE MEETING AND OTHER EXTERNAL CONSULTATIONS

The FDA's Assessment:

No advisory committee discussion or consultations external to the FDA were deemed necessary for this BLA application.

10. PEDIATRICS

The Applicant's Position:

Dostarlimab was not studied in pediatric patients. GSK submitted a Pediatric Study Plan waiver dMMR solid tumors under PREA.

The FDA's Assessment:

The FDA issued waiver of pediatric study requirement for this application because the necessary studies are impossible or highly impracticable because the condition is rare in the pediatric population.

11. LABELING RECOMMENDATIONS

Table 30: Prescription Drug Labeling: Summary of Significant Labeling Changes (High Level Changes and Not Direct Quotations)

Section	Applicant's Proposed Labeling	Approved Labeling
Indications and Usage	1 Solid tumors	FDA agreed to the proposed Indications and Usage.
Dosage and Administration	2.1 Patient Selection	FDA added the following statement to section 2.1 based on emerging data in glioma: "Because the effect of prior chemotherapy on test results for dMMR in patients with high-grade gliomas is unclear, it is recommended to test for this marker in the primary tumor specimen obtained prior to initiation of temozolomide chemotherapy in patients with high-grade gliomas."
Dosage Modifications for Adverse Reactions	None proposed	FDA and Applicants of anti PD-1/PD-L1 products are harmonizing approved PD-1/PD-L1 blocking antibody product labeling. FDA revised section 2.3 of the dostarlimab USPI to reflect the most current harmonized labeling available for these products. For details, please see the approved Full Prescribing Information.
Warnings and Precautions	5.1 Immune-Mediated Adverse Reactions 5.2 Infusion-Related Reactions	FDA revised section 5 of the dostarlimab USPI to reflect the most current harmonized labeling available for PD-1/PD-L1 blocking antibody product labeling. For details, please see the approved Full Prescribing Information.
Adverse Reactions	6.1 Clinical Trials Experience 6.2 Immunogenicity	FDA added fatal adverse reaction due to respiratory failure with dostarlimab therapy to section 6.1. FDA added the list of laboratory abnormalities with dostarlimab therapy. Tables in section 6.1 were revised to provide the adverse reactions in order of decreasing frequency for SOCs. During labeling negotiations, GSK proposed to include in section 6.1 those adverse reactions occurring in less than 10% of patients which were listed in the Warnings and Precautions, as well as other adverse reactions occurring in <10% of patients. FDA agreed with this change.
Use in Specific Populations	8.5 Geriatric	Minor change to section 8.5 were accepted.
Clinical Pharmacology	12.3 Pharmacokinetics	Minor changes were negotiated and agreed upon.

Section	Applicant's Proposed Labeling	Approved Labeling
Clinical Studies	14.1 Mismatch Repair Deficient Recurrent or Advanced Endometrial Cancer 14.2 Mismatch Repair Deficient Recurrent or Advanced Solid Tumors	FDA did not agree with GSK revisions to section 14.1 including updated efficacy results based on 103 patients for the approved dMMR recurrent or advanced endometrial cancer indication, and kept the data based on 71 patients with dMMR recurrent or advanced endometrial cancer that supported the approval. FDA added the name of the companion diagnostic to select patients for treatment with Jemperli to both sections 14.1 and 14.2: "The dMMR tumor status was retrospectively confirmed using the VENTANA MMR RxDx Panel assay." FDA revised Table 8 (b) (4) in section 14.2 of labeling, to add a separate row for including efficacy results for patients with dMMR endometrial cancer (n=103).

The FDA's Assessment:

The table above summarizes significant changes to the proposed prescribing information made by the FDA.

12. RISK EVALUATION AND MITIGATION STRATEGIES

The Applicant's Position:

None.

The FDA's Assessment:

No REMS is recommended for dostarlimab.

13. POSTMARKETING REQUIREMENTS AND COMMITMENT

The FDA's Assessment:

There is one PMR and one PMC associated with the current approval as follows:

PMR 4124-1

Conduct a clinical trial evaluating overall response rate and duration of response to verify and describe the clinical benefit of Jemperli in patients with mismatch repair deficient (dMMR), recurrent or advanced solid tumors, including at least 300 patients across all tumor types, and including a sufficient number of patients and representation of tumor types (other than endometrial and gastrointestinal tumors). In order to characterize response rate and duration of responses, patients should be followed for at least 12 months from the onset of response. Submit the datasets with final report.

Final Protocol Submission:	12/2015 (completed)
Trial Completion:	12/2021
Final Report Submission:	10/2022

PMC 4124-2

Commitment to establish and support the availability of a nucleic acid based in vitro diagnostic device that is essential to support the safe and effective use of Jemperli for patients with tumors that are microsatellite instability high (MSI-H) through and appropriate analytical and clinical validation study using clinical trial data. Summarize the study results in the final report submission.

Final Report Submission: 12/2025

14. DIVISION DIRECTOR (DHOT) (NEW MOLECULAR ENTITY ONLY)

X

John Leighton, PhD

15. DIVISION DIRECTOR (OCP)

X

Nam Atiqur Rahman, PhD

16. DIVISION DIRECTOR (OB)

X

Shenghui Tang, PhD

17. DIVISION DIRECTOR (CLINICAL)

X

Laleh Amiri-Kordestani, MD

18. OFFICE DIRECTOR (OR DESIGNATED SIGNATORY AUTHORITY)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents and approval recommendation for the clinical portion of this application under the OCE.

X

Marc Theoret, MD

19. APPENDICES

19.1. References

The Applicant's References:

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The FDA's References:

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19.2. Financial Disclosure

The Applicant's Position:

All Investigators on Study 4010-01-001 (GARNET) were assessed for significant equity or payments, proprietary interest and other compensation. Three clinical Investigators (less than 1%) had financial information to disclose (3 Investigators for TESARO and 1 of the 3 Investigators also for GSK).

The FDA's Assessment:

Covered Clinical Study: Study 4010-01-001 (GARNET)

Was a list of clinical investigators provided:	**Yes ☒**	**No ☐ (Request list from Applicant)**
Total number of investigators identified: 1514 (TESARO and GSK)		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3		
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: 0 Significant payments of other sorts: 3 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in study: 0 Sponsor of covered study: TESARO/GlaxoSmithKline		
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) 206		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

19.3. Nonclinical Pharmacology/Toxicology

The Applicant's Position:

There are no nonclinical pharmacology/toxicology appendices.

The FDA's Assessment:

None.

19.4. OCP Appendices

The FDA's Assessment:

Pharmacometrics Review

1. Population PK analysis

1.1 Review Summary

In general, the applicant's population PK (PopPK) analysis is considered acceptable for the purpose of characterizing the PK profile of dostarlimab in adult subjects with recurrent or advanced solid tumor including EC (MSS or MMRp and MSI-H or dMMR tumors), NSCLC, and non-endometrial dMMR/MSI-H and polymerase Ɛ-mutated cancer. The applicant's analyses were verified by the reviewer, with no significant discordance identified.

More specifically, the developed model was used to support the current submission as outlined in **Table 31**.

Table 31: Specific Comments on Applicant's Final Population PK model

Utility of the final model			**Reviewer's Comments**
Support applicant's proposed labeling statements about intrinsic and extrinsic factors	**Intrinsic factor**	"No clinically significant differences in the pharmacokinetics of dostarlimab-gxly were observed based on age (24 to 86 years), sex (79% female), race/ethnicity (78% White, 2% Asian, 4% African American, and 16% other), tumor types, and renal impairment based on the estimated creatinine clearance (CL_{CR} mL/min) (normal: CL_{CR} ≥90 mL/min, n = 173; mild: CL_{CR} = 60-89 mL/min, n = 210; moderate: CL_{CR} = 30-59 mL/min, n = 90; severe: CL_{CR} = 15-29 mL/min, n = 3; and end-stage renal disease: CL_{CR} <15 mL/min, n = 1) and hepatic impairment as measured by total bilirubin (TB) and aspartate aminotransferase (AST) (normal: TB and AST less than or equal to upper limit of normal [ULN], n = 425; mild: TB>ULN to 1.5 ULN	The statement is acceptable. Please see details in "Covariate Analysis" under Section 1.3 and **Figure 4.**

		or AST>ULN, n = 48; and moderate: TB>1.5-3 ULN, any AST, n = 4)."	
	Extrinsic factor	N/A	N/A

1.2 Introduction

The primary objectives of applicant's analysis were to:

- To develop a population pharmacokinetics (PK) model of dostarlimab and identify the covariates of clinical interest.
- To evaluate the exposure-response relationship between dostarlimab and ORR and, if data permit, DOR.
- To evaluate the exposure-response relationship between dostarlimab and occurrence of relevant AEs.

1.3 Model development

Data

The analyses were based on PK data from ongoing study No. 4010-01-001. Brief descriptions of the study are presented in **Table 32**.

NONMEM 7.4 was used for PopPK modeling. Post-processing of NONMEM analysis results as well as exposure-response analyses of efficacy and safety were carried out in R version 3.6.2. NONMEM run execution, visual predictive check (VPC), stepwise covariate modeling (SCM) was carried out using Perl-speaks-Nonmem (PsN) version 4.8.0.

The final NONMEM data file for analysis contained 4783 PK observations from 546 subjects. **Table 33** provides summary statistics of the baseline demographic covariates in the analysis dataset. Throughout model development, the estimation method used to analyze the data was the first order conditional estimation (FOCE) with the INTERACTION option.

Table 32: Summary of Study with PK Sampling Included in Population PK Analysis

Study # & Study Design	Dosage Regimen & Study Description	Number of Subjects in PopPK Analysis, Subject Type and Food Status	Dose(s)

4010-01-001 A multicenter, open-label, first-in-human Phase 1 study evaluating dostarlimab in patients with advanced solid tumors who have limited available treatment options as	Part 1: Dose escalation cohorts (Modified 3+3 design) Dose: 1 mg/kg, 3 mg/kg, 10 mg/kg Part 2A: Fix-Dose Safety Evaluation Cohorts (Modified 6+6 design) Dose: 1000 mg Q6W or 500 mg Q3W	Part 1: N = 21 Part 2A: N=13 Part 2B: N = 512 cut on Mar. 1 2020 dMMR/MSI-H Endometrial Cancer: N= 100 up to 165 MMRp/MSS Endometrial Cancer: N= 125 up to 250	Part 1: 1 mg/kg, 3 mg/kg, 10 mg/kg Part 2A: 1000 mg Q6W or 500 mg Q3W Part 2B: 500 mg Q3W 4 cycles followed by 1000 mg Q6W Male and female patients with advanced solid

Source: Table adapted from Applicant's Population PK report (Protocol No. 4010-01-001), Table.1

Table 33: Summary of Baseline Demographic Covariates for Analysis

Covariate	Statistic	Total
Demographic Data		
Body Weight (kg)	N	546
	Mean (SD)	74.4 (20)
	Median (Min, Max)	71.4 (34.0, 182)
Age (yr)	N	546
	Mean (SD)	62.5 (11)
	Median (Min, Max)	64.0 (24.0, 86.0)
Sex		
Male	N (%)	124 (22.7%)
Female	N (%)	422 (77.3%)
Race		

American Indian or Alaska native	N (%)	4 (0.7%)
		13 (2.4%)
Asian	N (%)	19 (3.5%)
Black or African American	N (%)	89 (16.3%)
Not Reported	N (%)	6 (1.1%)
Other	N (%)	5 (0.9%)
Unknown	N (%)	410 (75.1%)
White	N (%)	
Continuous Covariate		
eGFR (mL/min/m2)	N	546
	Mean (SD)	84.6 (29)
	Median (Min, Max)	83.4 (19.5 – 336)
Creatinine Clearance (CLCR, mL/min)	N	546
	Mean (SD)	90.3 (30)
	Median (Min, Max)	86.4 (19.3, 150)
Alanine Aminotransferase (ALT, U/L)	N	546
	Mean (SD)	20.9 (15)
	Median (Min, Max)	17.0 (2.90, 120)
Aspartate Aminotransferase (U/L)	N	546
	Mean (SD)	24.3 (15)
	Median (Min, Max)	20.0 (5.00, 163)
Alkaline phosphatase (IU/L)	N	546
	Mean (SD)	117 (88)
	Median (Min, Max)	94.0 (33.0, 855)
Albumin (ALB, g/L)	Mean (SD)	38.2 (5.1)
	Median (Min, Max)	39.0 (19.0, 51.0)
Bilirubin (BILI, µmol/L)	Mean (SD)	7.81 (4.0)
	Median (Min, Max)	6.84 (1.71, 31.0)

Lactate Dehydeogenase (LDH, U/L)	Mean (SD) Median (Min, Max)	348 (5.7e +02) 222 (86.0, 1.17e+4]
Categorical Covariates		
Hepatic Impairment	Mild Moderate Normal	55 (10.1%) 5 (0.9%) 486 (89.0%)
Renal Impairment	Mild Moderate Normal Severe	235 (43.0%) 100 (18.3%) 209 (38.3%) 2 (0.4%)
Immuno Modulators	No Yes	545 (99.8%) 1 (0.2%)
Immuno Stimulants	No Yes	543 (99.5%) 3 (0.5%)
Corticosteroids	No Yes	340 (62.3%) 206 (37.7%)
ADAs if ever positive	Ever positive Never positive	101 (18.5%) 445 (81.5%)

Source: Table adapted from Applicant's Population PK report (Protocol No. 4010-01-001), Table.2

Base model

The final base model for dostarlimab was a two-compartment model with time-dependent linear elimination. The residual variability was assumed to be a function of normally distributed random effects and the residual error was modeled using a combination of additive and proportional residual error. Body weight were included in the model according to allometric principles and a common exponent for WT on Vc and Vp were kept in the model. The model

incorporated interindividual variability on CL, Vc and Imax as independent random effects and was estimated to be 29.2% coefficient of variation (CV), 17.4% CV, and 82% CV, respectively. All parameters were estimated with acceptable precision (RSE <50%).

Covariate analysis

The effect of body weight was modeled based on the principles of allometry and included as a covariate for CL, Vc and Vp (standardized to a 70-kg person) prior to stepwise covariate model (SCM) building. Additional covariates such as age, sex, tumor diagnosis, sum of diameters of measurable target lesions (SLD), antidrug antibody (ADA), corticosteroids, liver function, ALB, ALT, BILI, LDH, renal impairment, CLCR was tested using the SCM procedure. In the forward inclusion steps: age, gender, time-varying ALB, and time-varying ALT were found to affect the CL and remained statistically significant after the backward elimination step. Similarly, both time-varying ALB and gender were found to affect Vc in the forward inclusion steps and remained statistically significant. Time-varying SLD on CL and tumor diagnosis on Vc were not found statistically significant during the backward elimination step. No covariates were found significant for Vp and Imax.

1.4 Final Model

The final selected model for dostarlimab was a 2-compartment model with time-dependent elimination. A schematic depiction of the model structure is shown in **Figure 5**, and the model is mathematically described as below.

$$\frac{dA_{central}}{dt} = -k_{10} \cdot A_{central} - k_{12} \cdot A_{central} + k_{21} \cdot A_{peripheral}$$
$$\frac{dA_{peripheral}}{dt} = k_{12} \cdot A_{central} - k_{21} \cdot A_{peripheral}$$

with time-dependent elimination

$$CL_{\text{time-base}} = CL_{\text{base}} \cdot exp\left(\frac{Imax \cdot Day^{Hill}}{T50^{Hill} + Day^{Hill}}\right)$$

where the micro-constants of the mass transfer are defined as

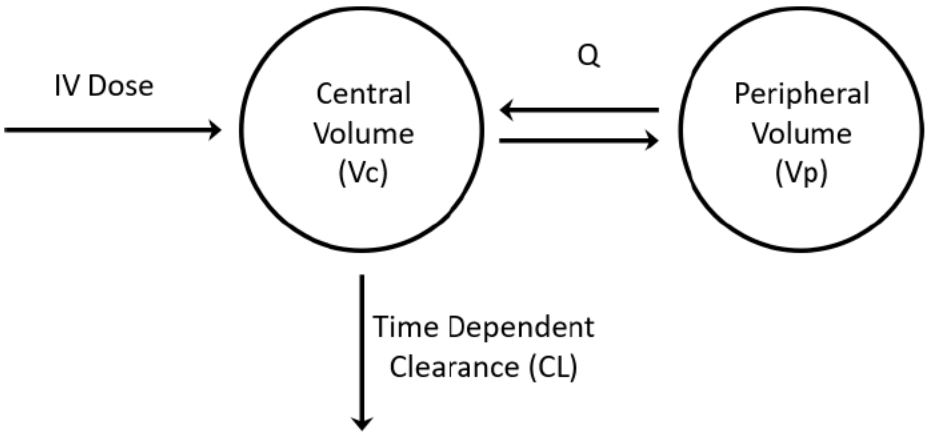
$$k_0 = \frac{CL}{Vc} \quad k_{12} = \frac{Q}{Vc} \quad k_{21} = \frac{Q}{V_P}.$$

The age, ALB, ALT, and gender effects are given by

$$CL = CL_{\text{time-base}} \cdot \left(\frac{WT}{70}\right)^{\theta_{CL,WT}} \cdot \left(\frac{AGE}{64}\right)^{\theta_{CL,AGE}} \cdot \left(\frac{ALB}{39}\right)^{\theta_{CL,ALB}} \cdot \left(\frac{ALT}{18}\right)^{\theta_{CL,ALT}} \cdot (1 + \theta_{CL-SEX}),$$
$$Vc = Vc_{\text{base}} \cdot \left(\frac{WT}{70}\right)^{\theta_{Vcp,WT}} \cdot \left(\frac{ALB}{39}\right)^{\theta_{Vc,ALB}} \cdot (1 + \theta_{Vc-SEX}),$$
$$Vp = Vp_{\text{base}} \cdot \left(\frac{WT}{70}\right)^{\theta_{Vcp,WT}}$$

where θ_{CL-SEX} and θ_{Vc-SEX} are equal to 0 for females (most common) and estimated for males.

Figure 5: Scheme of Final PopPK Model for dostarlimab



Source: Applicant's Population PK report (Protocol No. 4010-01-001), Figure 6

The parameter estimates for the final covariate model are listed in **Table 34**. In general, parameters were estimated with sufficient precision (%RSE were generally <40%). Shrinkage in ETA1(CL), ETA2(Vc) and ETA4(Vp) was 16.2%, 7.37% and 49.2% respectively.

Table 34: Parameter Estimates (RSE) for the Final Model of dostarlimab

Parameter	Alias	Estimate	Relative SE (%)	95% CI
θ_1	Clearance (CL (L·h^{-1}))	0.00745	1.57	(0.00722 - 0.00768)
θ_2	Central volume of distribution (Vc (L))	2.98	0.871	(2.93 - 3.03)
θ_3	Proportional Error	0.133	2.45	(0.126 - 0.139)
θ_4	Additive Error (mg/L)	2.79	14.7	(1.98 - 3.59)
θ_5	Intercompartmental clearance (Q (L·h^{-1}))	0.0228	9.18	(0.0192 - 0.0271)
θ_6	Peripheral volume of distribution (Vp (L))	2.10	2.00	(2.02 - 2.18)
θ_7	Imax	-0.161	8.53	(-0.187 - -0.134)
θ_8	T50 (days)	108	7.47	(92.6 - 124)
θ_9	Hill	5.29	9.12	(4.34 - 6.23)
θ_{10}	Effect of WT on CL	0.470	6.12	(0.414 - 0.527)
θ_{11}	Effect of WT on Vc and Vp	0.419	5.29	(0.376 - 0.463)
θ_{12}	Effect of age on CL	-0.227	29.7	(-0.360 - -0.0951)
θ_{13}	Effect of ALB on CL	-1.01	8.64	(-1.18 - -0.835)
θ_{14}	Effect of ALT on CL	-0.0585	32.4	(-0.0956 - -0.0213)
θ_{15}	Effect of male on CL	0.165	18.4	(0.106 - 0.225)
θ_{16}	Effect of ALB on Vc	-0.153	35.8	(-0.261 - -0.0461)
θ_{17}	Effect of male on Vc	0.162	12.6	(0.122 - 0.202)
$\omega_{1,1}$	ω^2_{CL}	0.0551	7.51	(0.0470 - 0.0632)
$\omega_{2,1}$	$\omega^2_{CL,Vc}$	0.0210	11.1	(0.0164 - 0.0255)
$\omega_{2,2}$	ω^2_{Vc}	0.0258	7.48	(0.0220 - 0.0296)
$\omega_{5,5}$	ω^2_{Imax}	0.537	16.4	(0.365 - 0.710)

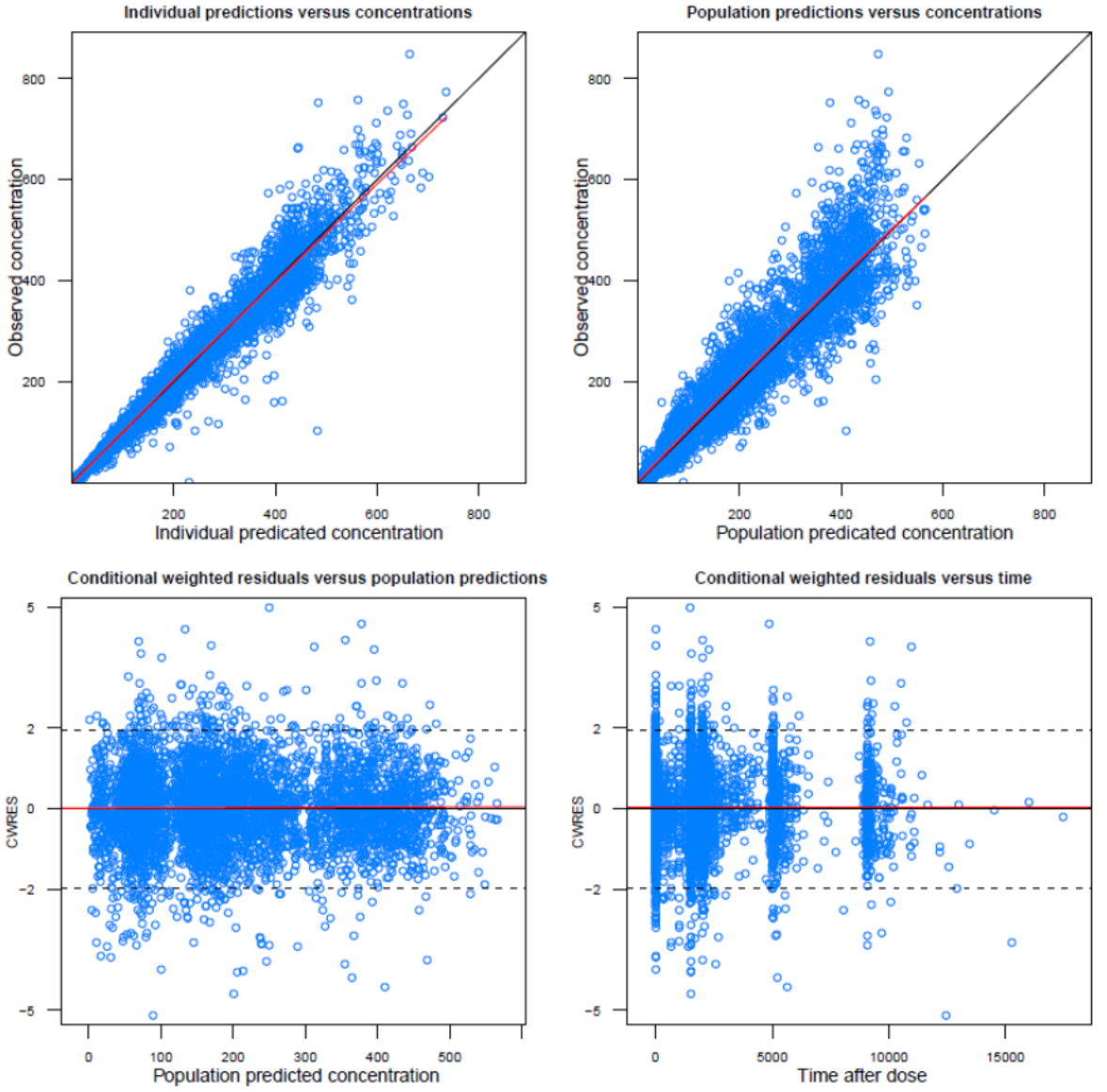
Parameter values for the final PopPK model. **CL:** apparent systemic clearance; **Vc:** apparent central volume of distribution; **Q:** apparent intercompartment clearance; **Vp:** apparent peripheral volume of distribution; **WT:** body weight; **ALB:** albumin; **ALT:** alanine aminotransferase; **Imax:** maximal decrease in clearance relative to baseline; **T50:** time at which 50% of Imax is reached; **RSE:** relative standard error; **CI:** confidence interval; ω^2_X: variance of the IIV of parameter X, IIV is derived from variance according to $\sqrt{\omega^2_X} \cdot 100$.

Source: Applicant's Population PK report (Protocol No. 4010-01-001), Table 14

The goodness-of-fit (GOF) plots for the final covariate model are shown in **Figure 6**. Overall the model predicts the concentration versus time profile reasonably well across the treatments,

except for the lowest dose group (1 mg/kg), where the observations appears to be slightly lower than predicted. The VPC stratified by cycle indicates some over-prediction of the variability at later cycles.

Figure 6: Goodness-of-fit plots for final covariate model of dostarlimab



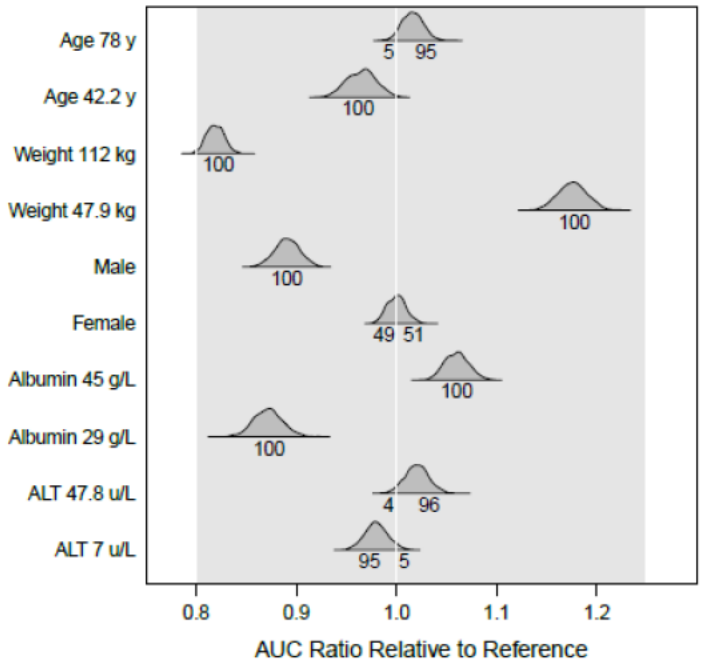
Source: FDA reviewer's analysis

Patients at the lower end of the body weight distribution (47.8 kg) are estimated to have 16.4% lower CL and 14.8% lower Vc and Vp as compared to a reference patient of 70 kg. Patients at higher end of the body weight distribution (111 kg) are estimated to have 24.4% higher CL and 21.5% higher Vc and Vp, respectively compared to a reference patient. ALB was found to have relatively large influence on CL while the impact on Vc was limited. The impact of sex, age, and ALT on CL was relatively limited.

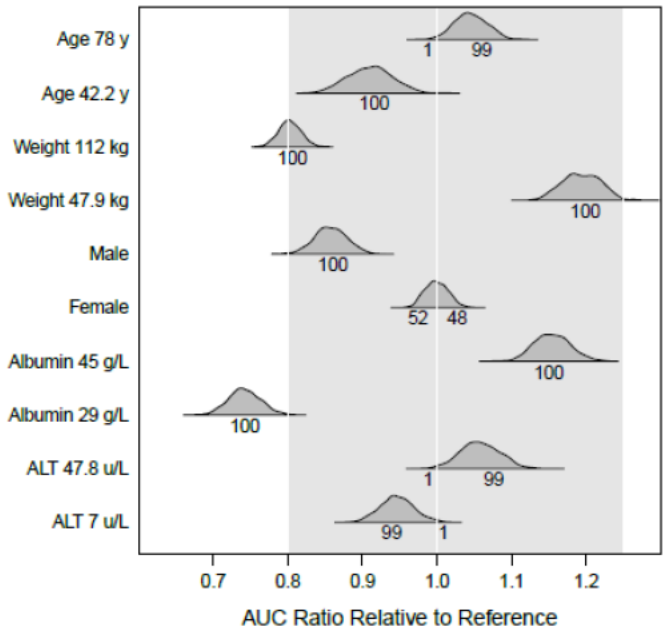
The impact of the included covariates on exposure following the first dose (0-3 weeks) and steady state is illustrated in **Figure 7**. Overall no clinically significant differences in the PK of dostarlimab were observed based on age, sex, and ALT (ratio within 0.8-1.25 boundary).

Figure 7: Forest Plots Illustrating the Covariate Effects on AUC Following First Dose (0-3 weeks) and Steady State

0-3 weeks following first dose



Steady State



Forest plot of AUC ratios as compared to median reference patient (female, 70 kg, age 64, ALB 39 g/dl, and ALT 18 U/L). The distribution represents the ratios based on 1000 set of parameter estimates re-sampled from the variance covariance matrix. Plotted number indicate actual percent of each distribution in a bounded region (central reference line). The grey area represents the 0.8 and 1.25 boundaries.

Individual Dostarlimab concentration versus time profiles for the patients included in the PK analysis were simulated using individual posthoc PK parameter estimates from the final model. A summary of the individual model predicted exposure following the first six weeks treatment are shown in **Table 35**. In addition, Dostarlimab showed approximately a 2-fold accumulation when comparing individual predicted exposure after the first 500 mg dose Q3W with the steady state exposure following 500 mg Q3W dose and 1000 mg Q6W doses, respectively (**Table 36**). No significant differences in predicted exposures for different renal, hepatic status and tumor subgroups (EC dMMR, EC MMRp and dMMR pan tumor).

Table 35: Summary of Individual Predicted Exposure Following the Frist 6 Weeks of Treatment

Treatment Group	$AUC_{0\text{-}6\ weeks}$ (mg*h)/L), (CV%)	$C_{max,\ 0\text{-}6\ weeks}$ (mg/L), (CV%)	Number of Patients
1 mg/kg Q2W	13900 (24.2)	32.7 (23)	6
3 mg/kg Q2W	48000 (10.4)	109 (16)	3
10 mg/kg Q2W	159000 (20.4)	356 (20)	12
1000 mg Q6W	88000 (31.8)	324 (32.3)	7
500 mg Q3W	85300 (21.6)	222 (23.2)	6
500 mg Q3W, 1000 mg Q6W	81200 (20.2)	210 (19.3)	512

$AUC_{0\text{-}6\ weeks}$ area under the concentration versus time curve during the first 6 weeks; Cmax: maximum concentration.

Source: Applicant's Population PK report (Protocol No. 4010-01-001), Table 15

Table 36: Summary of Individual Predicted Exposure at First Dose and Steady State

Dose	$AUC_{0\text{-}tau}$ (mg*h)/L), (CV%)	C_{max} (mg/L), (CV%)
First dose (500 mg)	33550 (18.2)	172 (19.4)
Steady state (500 mg)	73270 (30.1)	286.4 (22.8)
Steady state (1000 mg)	146600 (30.1)	433.6 (21.1)

$AUC_{0\text{-}tau}$: area under the concentration versus time curve for a dosing interval; **Cmax:** maximum concentration. Based on individual predicted exposure for patients in Part 2B

Source: Applicant's Population PK report (Protocol No. 4010-01-001), Table 16

1.5 Listing of analyses codes and output files

File Name	Description	Location in \\cdsnas\pharmacometrics\
NONMEM dataset for the final model	GSK_TSR042_poppk_03SEP2020.csv	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Dostarlimab_BLA761223_YW\PopPK
NONMEM code for the final model	Run2.mod	

2.Exposure-Response (E-R) analysis

2.1 Review Summary

In general, the applicant's exposure-response (E-R) analysis is considered acceptable for the purpose of characterizing the E-R relationships of dostarlimab for efficacy and adverse events (AEs) on efficacy and safety for the adult subjects with recurrent or advanced solid tumor including EC (MSS or MMRp and MSI-H or dMMR tumors), NSCLC, and non-endometrial dMMR/MSI-H and polymerase Ɛ-mutated cancer. However, Dostarlimab-gxly exposure-response relationships have not been fully characterized due to only one dose level studied ER analysis.

2.2 Methods

Efficacy E-R analyses were performed only for patients in Part 2B. The primary efficacy endpoint ORR is defined as the proportion of patients achieving a best overall response of complete response (CR) or partial response (PR) over the entire study.

Safety variables were analyzed for all patients participating the study 4010-01-001 (Part 1, 2A, and 2B). The analysis included safety variables that were the top five occurring drug related AEs as assessed by investigators: asthenia, diarrhea, fatigue, hypothyroidism, and nausea.

The dichotomous response (response/non-response) for ORR was assessed using logistic regression and exposure as the independent predictor. The drug exposure was represented by AUC, C_{max} and C_{min} at cycle 1 (i.e, 21 days), simulated using the planned dosing and individual posthoc parameters from the final PopPK model.

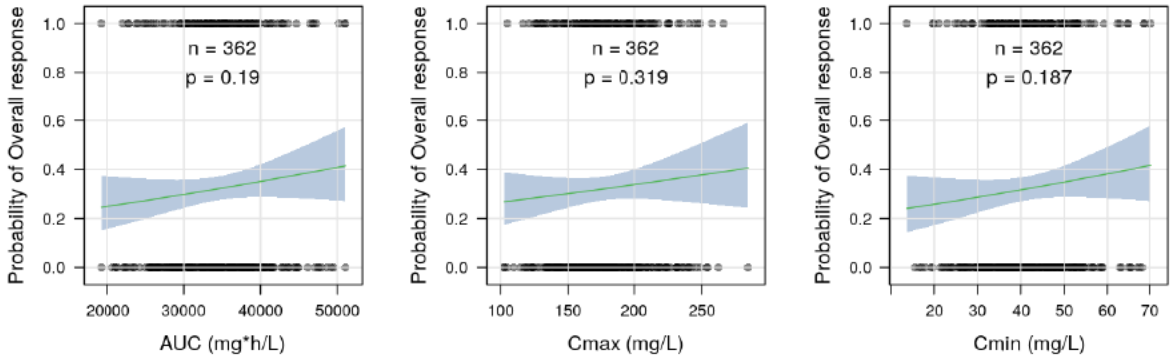
2.3 Results

2.3.1 Efficacy

2.3.1.1 Overall Response

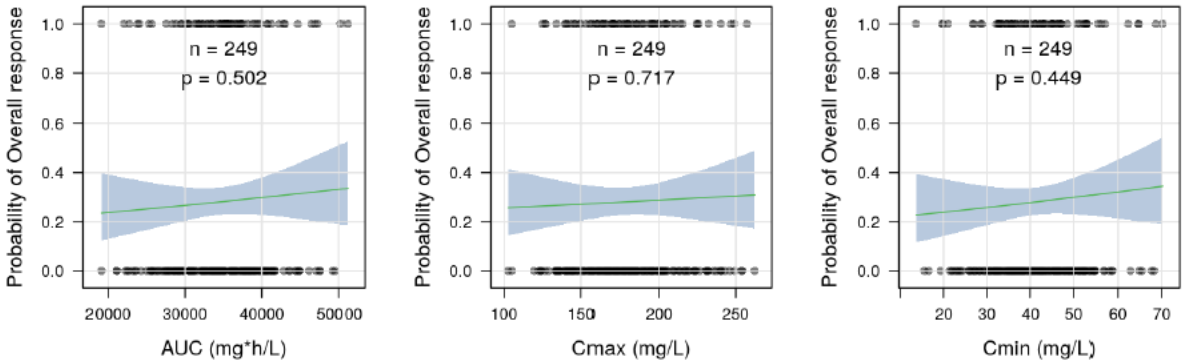
None of AUC, Cmax and Cmin had a statistically significant relationship with ORR with p value of 0.19, 0.319, and 0.187 for AUC, Cmax, and Cmin, respectively (**Figure 8**). Subgroup analysis using patients with tumor type EC (n=249) suggests none of the tested exposure metrics had a statistically significant relationship with ORR with p value of 0.502, 0.717, and 0.449 for AUC, Cmax and Cmin, respectively. Subgroup analysis using patients with tumor type dMMR (n=217) suggests AUC and Cmin were statistically significant with p values of 0.0395 and 0.0451, respectively. Cmax was not significant with a p value of 0.0805.

Figure 8: Overall Response vs Exposure Metrics (Cycle 1), Univariate Analysis



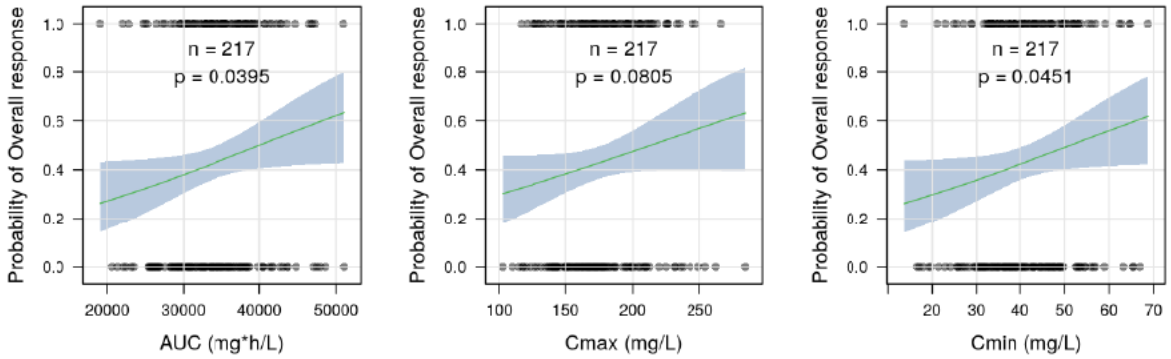
Line: Predicted probability; **Shaded area**: 95% confidence interval; **Circles**: Data

Subgroup: Tumor type EC



Line: Predicted probability; **Shaded area**: 95% confidence interval; **Circles**: Data

Subgroup: Tumor type dMMR



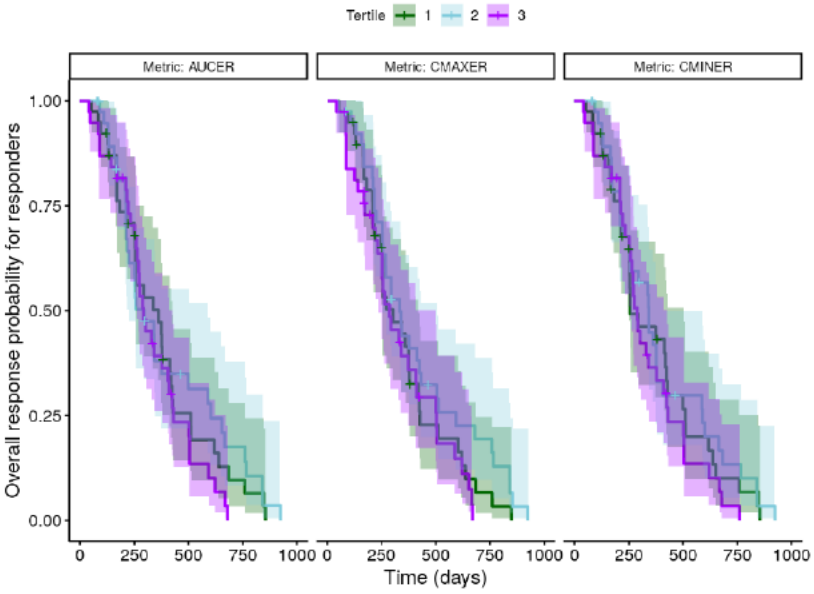
Line: Predicted probability; **Shaded area**: 95% confidence interval; **Circles**: Data

Source: Applicant's Population PK report (Protocol No. 4010-01-001), Figure 18, 20, 22

2.3.1.2 Duration of Overall Response (DOR)

No clear exposure-response with the available DOR data for 116 patients, which is confirmed by applying a Cox Proportional Hazards Model for different exposure metrics, giving p-values of 0.36, 0.73, 0.35 for AUC, Cmax and Cmin, respectively (**Figure 9**).

Figure 9: Kaplan-Meier Plots of Overall Response Duration vs Exposure Metric Tertiles



Line: Mean survival; **Shaded area**: 95% confidence interval

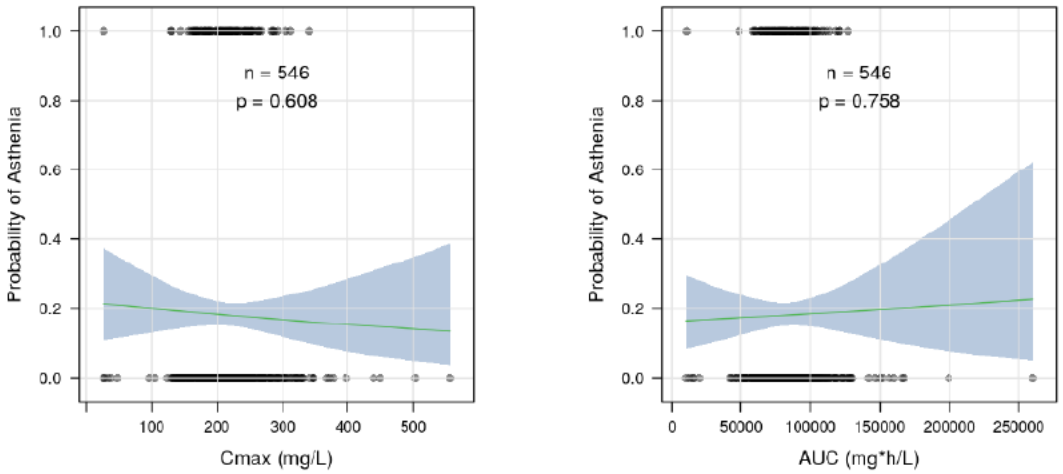
Source: Applicant's Population PK report (Protocol No. 4010-01-001), Figure 24

2.3.2 Safety

Binary data for the five most prevalent drugs related AEs (asthenia, diarrhea, fatigue, hypothyroidism and nausea) from 546 patients in the study were analyzed using univariate logistic regression. None of the tested exposure metrics had a statistically significant relationship with any of the five AEs (**Figure 10**).

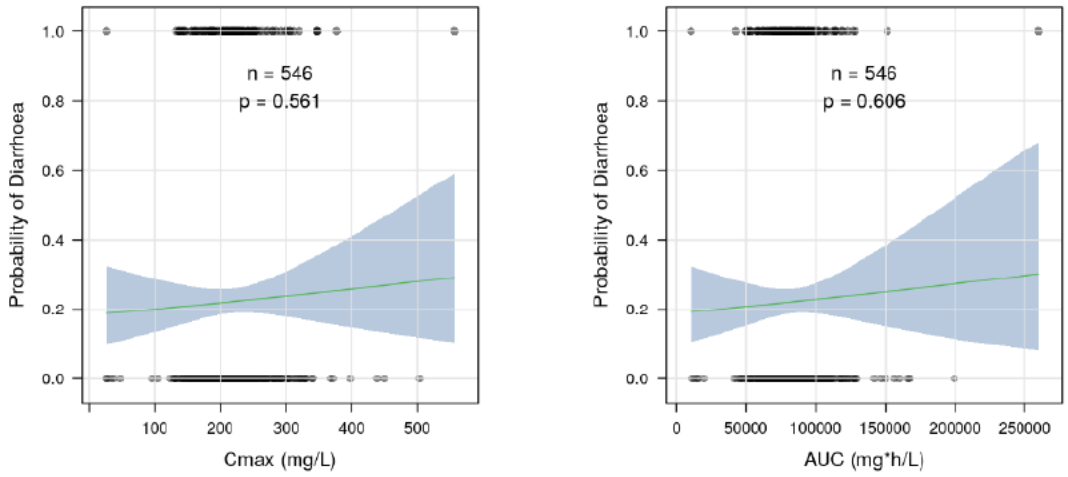
Figure 10: AE vs Exposure Metrics

Asthenia



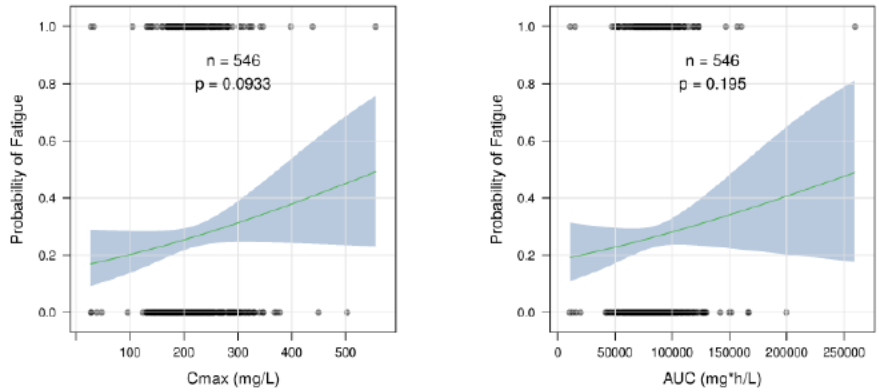
Line: Predicted probability; **Shaded area**: 95% confidence interval; **Points**: Data

Diarrhea



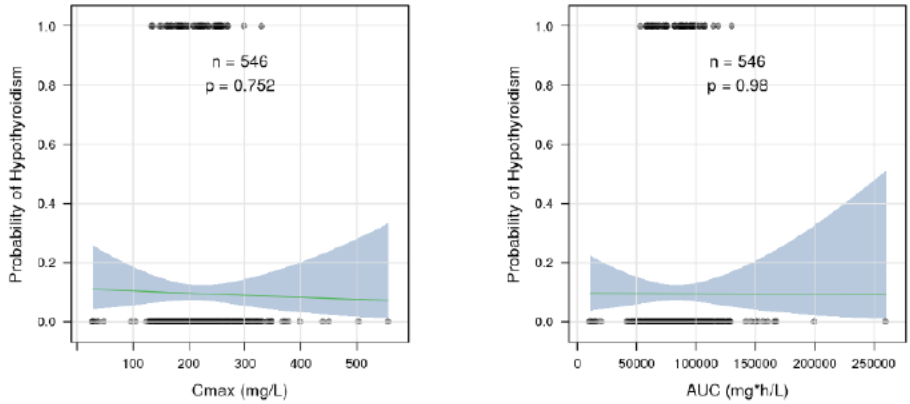
Line: Predicted probability; **Shaded area**: 95% confidence interval; **Points**: Data

Fatigue



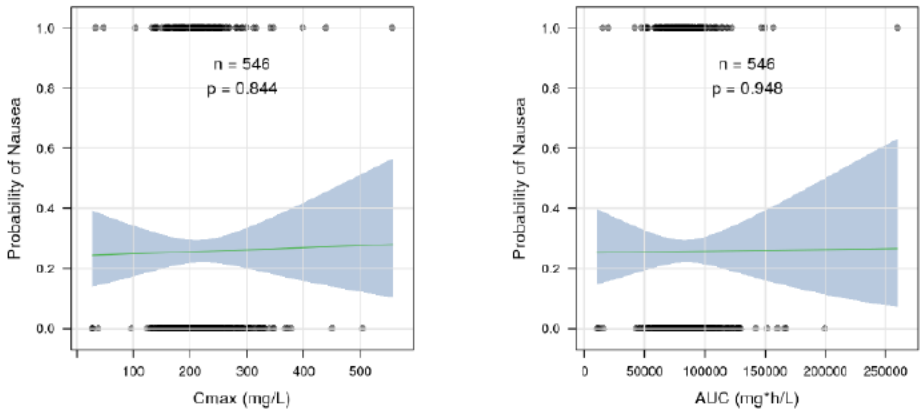
Line: Predicted probability; **Shaded area**: 95% confidence interval; **Points**: Data

Hypothyroidism



Line: Predicted probability; **Shaded area**: 95% confidence interval; **Points**: Data

Nausea



Line: Predicted probability; **Shaded area**: 95% confidence interval; **Points**: Data

Source: Applicant's Population PK report (Protocol No. 4010-01-001), Figure 25, 26, 27, 28, 29]

19.5. Additional Safety Analyses Conducted by FDA

The FDA's Assessment:

None.

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology	Safaa Burns, PhD	OCP/DO1	Sections: 6	Select one: x Authored ___ Approved
	Signature: Safaa Burns -S Digitally signed by Safaa Burns -S DN: c=US, o=U S. Government, ou=HHS, ou=FDA, ou=People, cn=Safaa Burns -S, 0.9.2342.19200300.100.1.1=1300068123 Date: 2021.08.12 11:16:09 -04'00'			
Clinical Pharmacology (TL)	Nam Atiqur Rahman, PhD	OCP	Sections: 6	Select one: ___ Authored x Approved
	Signature: Nam A. Rahman -S Digitally signed by Nam A. Rahman -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Nam A. Rahman -S, 0.9.2342.19200300.100.1.1=1300072597 Date: 2021.08.12 11:21:55 -04'00'			
Pharmacometrics	Yun Wang, PhD	OCP/DPM	Sections: 6,19.4	Select one: X Authored _____ Approved
	Signature: Yun Wang -S Digitally signed by Yun Wang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yun Wang -S, 0.9.2342.19200300.100.1.1=2001408091 Date: 2021.08.12 19:53:23 -04'00'			
Pharmacometrics (TL)	Jerry (Jingyu) Yu, PhD	OCP/DPM	Sections: 6, 19.4	Select one: ___ Authored X Approved
	Signature: Jingyu Yu -S Digitally signed by Jingyu Yu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jingyu Yu -S, 0.9.2342.19200300.100.1.1=2000794699 Date: 2021.08.12 15:34:13 -04'00'			
Pharm/Tox	Wimolnut Manheng, PhD	OOD/DHOT	Sections: 5	Select one: X Authored x Approved
	Signature: Wimolnut Manheng -S Digitally signed by Wimolnut Manheng -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001655153, cn=Wimolnut Manheng -S Date: 2021.08.12 10 56:06 -04'00'			
Pharm/Tox (TL)	Tiffany Ricks, PhD	OOD/DHOT	Sections: 5	Select one: x Authored x Approved
	Signature: Tiffany K. Ricks -S Digitally signed by Tiffany K. Ricks -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000497170, cn=Tiffany K. Ricks -S Date: 2021.08.12 11:01:02 -04'00'			

BLA Multi-disciplinary Review and Evaluation BLA 761223
Jemperli (dostarlimab-gxly) Injection

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Biometrics Reviewer	Hui Zhang, PhD	OB/DBV	Sections: 8.1, 8.3	Select one: X Authored ___ Approved
	Signature: Hui Zhang -S Digitally signed by Hui Zhang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Hui Zhang -S, 0.9.2342.19200300.100.1.1=2000980266 Date: 2021.08.12 11:05:36 -04'00'			
Biometrics (TL)	Erik Bloomquist, PhD	OB/DBV	Sections: 8.1, 8.3	Select one: ___ Authored X Approved
	Signature: Erik W. Bloomquist -S Digitally signed by Erik W. Bloomquist -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000477083, cn=Erik W. Bloomquist -S Date: 2021.08.12 10:42:26 -04'00'			
Clinical Reviewer	Sakar Wahby, PharmD	OOD/DO1	Sections: 2,3,4,7,8,9,10,11 ,12,13, and 19.	Select one: X Authored ___ Approved
	Signature: Sakar M. Wahby -S Digitally signed by Sakar M. Wahby -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Sakar M. Wahby -S, 0.9.2342.19200300.100.1.1=0013507760 Date: 2021.08.13 08:49:12 -04'00'			
Clinical Reviewer (TL)	Gwynn Ison, MD	OOD/DO1	Sections: 2,3,4,7,8,9,10,11 ,12,13, and 19.	Select one: X Authored ___ Approved
	Signature: Gwynn Ison -S Digitally signed by Gwynn Ison -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Gwynn Ison -S, 0.9.2342.19200300.100.1.1=2000205244 Date: 2021.08.12 11:25:27 -04'00'			
Associate Director for Labeling	Elizabeth Everhart, MSN, ACNP signing as proxy for William Pierce, PharmD	OOD	Sections:11	Select one: ___ Authored x Approved
	Signature: Elizabeth E. Everhart -S Digitally signed by Elizabeth E. Everhart -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000363858, cn=Elizabeth E. Everhart -S Date: 2021.08.12 11:03:04 -04'00'			

BLA Multi-disciplinary Review and Evaluation BLA 761223
Jemperli (dostarlimab-gxly) Injection

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Cross-Disciplinary Team Leader (CDTL)	Gwynn Ison, MD	OOD/DO1	Section: 1 Sections 2-19 approved	Select one: x Authored x Approved
	Signature: Gwynn Ison -S Digitally signed by Gwynn Ison -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Gwynn Ison -S, 0.9.2342.19200300.100.1.1=2000205244 Date: 2021.08.12 15:42:44 -04'00'			
Division Director (DHOT)	John Leighton, PhD	OOD/DHOT	Sections: 5	Select one: ___ Authored x Approved
	Signature: John K. Leighton -S Digitally signed by John K. Leighton -S Date: 2021.08.12 10:52:35 -04'00'			
Division Director (OCP)	Nam Atiqur Rahman, PhD	OCP	Sections: 6	Select one: ___ Authored X Approved
	Signature: Nam A. Rahman -S Digitally signed by Nam A. Rahman -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Nam A. Rahman -S, 0.9.2342.19200300.100.1.1=1300072597 Date: 2021.08.12 15:58:08 -04'00'			
Division Director OB	Shenghui Tang, PhD	OB/DBV	Sections: 8.1, 8.3	Select one: ___ Authored X Approved
	Signature: Shenghui Tang -S Digitally signed by Shenghui Tang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Shenghui Tang -S, 0.9.2342.19200300.100.1.1=1300224175 Date: 2021.08.12 10:45:03 -04'00'			
Director	Laleh Amiri-Kordestani, MD	OOD/DO1	Sections: 1-17	Select one: ___ Authored X Approved

Laleh Amiri-kordestani -S Digitally signed by Laleh Amiri-kordestani -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0014338688, cn=Laleh Amiri-kordestani -S Date: 2021.08.12 10:46:59 -04'00'

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/

AMY R TILLEY
08/13/2021 01:15:26 PM

GWYNN ISON
08/13/2021 01:20:39 PM

MARC R THEORET
08/13/2021 03:10:13 PM
My signature indicates that I have considered the FDA assessments and recommendations included in this Review in determining the regulatory action.