

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**761174Orig1s000**

**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.

<b>Application Type</b>	BLA
<b>Application Number(s)</b>	761174
<b>Priority or Standard</b>	Priority
<b>Submit Date(s)</b>	December 19, 2019
<b>Received Date(s)</b>	December 19, 2019
<b>PDUFA Goal Date</b>	August 19, 2020
<b>Division/Office</b>	Division of Oncology 1/Office of Oncologic Diseases
<b>Review Completion Date</b>	<i>Electronic Stamp Date</i>
<b>Established Name</b>	Dostarlimab-gxly
<b>(Proposed) Trade Name</b>	JEMPERLI
<b>Pharmacologic Class</b>	Programmed death-1 (PD-1) Blocking Antibody
<b>Code name</b>	TSR-042
<b>Applicant</b>	GlaxoSmithKline LLC
<b>Formulation(s)</b>	500 mg/10 mL, single-dose vial
<b>Dosing Regimen</b>	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
<b>Applicant Proposed Indication(s)/Population(s)</b>	 (b) (4)
<b>Recommendation on Regulatory Action</b>	<i>Accelerated Approval</i>
<b>Recommended Indication(s)/Population(s) (if applicable)</b>	<p>JEMPERLI is indicated for the treatment of adult patients with mismatch repair deficient (dMMR) recurrent or advanced endometrial cancer, as determined by an FDA-approved test, that has progressed on or following prior treatment with a platinum-containing regimen.</p> <p>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).</p>

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### LIST OF ABBREVIATIONS

3R	reduce/refine/replace
AC	advisory committee
ADA	anti-drug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
ADME	absorption, distribution, metabolism, and excretion
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALC	absolute lymphocyte count
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
BICR	blinded independent central review
BLA	biologics license application
BMI	body mass index
BOR	best overall response
BPCA	Best Pharmaceuticals for Children Act
BRF	benefit risk framework
BTB	breakthrough therapy designation
CBER	Center for Biologics Evaluation and Research
C <sub>avg</sub>	average concentration
CBC	complete blood count
CDC	complement-dependent cytotoxicity
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	cross-discipline team leader
CFR	Code of Federal Regulations
CI	confidence interval
CL	clearance
CL <sub>ss</sub>	steady-state clearance
C <sub>max</sub>	maximum concentration
CMC	chemistry, manufacturing, and controls
C <sub>min</sub>	minimum concentration
CNS	central nervous system
COA	clinical outcome assessment
COSTART	coding symbols for thesaurus of adverse reaction terms
CR	complete response

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CRC	Colorectal cancer
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	controlled substance staff
CT	computerized tomography
CV	cardiovascular
DCR	disease control rate
DDI	drug-drug interaction
DHOT	division of hematology, oncology, and toxicology
DMC	data monitoring committee
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
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FIGO	International Federation of Gynecology and Obstetrics
GCP	good clinical practice
GLP	good laboratory practice
GRMP	good review management practice
hERG	human ether-a-go-go-related gene
HIV	human immunodeficiency virus
ICH	International Conference on Harmonization
ICPI	immune checkpoint inhibitor
IDMC	independent data monitoring committee
IgG	Immunoglobulin G
IHC	immunohistochemistry
IL	interleukin
IMM	immune modulatory medications

IND	Investigational New Drug
INR	international normalized ratio
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
irSD	immune-related stable disease
ISE	integrated summary of effectiveness
ISPD	important and significant protocol deviations
ISS	integrated summary of safety
ITT	intent to treat
IV	intravenous
KM	Kaplan-Meier
LDH	lactate dehydrogenase
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
NME	new molecular entity
NOAEL	no observed adverse effect level
NSCLC	non-small cell lung cancer
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OR	overall response
ORR	objective response rate
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation

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PBMC	peripheral blood mononuclear cell
PBRER	periodic benefit-risk evaluation report
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PDy	pharmacodynamic
PFS	progression-free survival
PI	prescribing information
PK	pharmacokinetics
PMC	post-marketing commitment
PMR	post-marketing requirement
PP	per protocol
PPI	patient package insert
PR	partial response
PREA	Pediatric Research Equity Act
PRO	patient-reported outcome
PSUR	periodic safety update report
PT	preferred term
PTT	partial thromboplastin time
Q1	first quartile
Q3	third quartile
QTc	corrected QT interval
RECIST	response evaluation criteria in solid tumors
REMS	risk evaluation and mitigation strategy
RO	receptor occupancy
RTD	recommended therapeutic dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SGE	special government employee
SI	International Standard (of Units)
SLDR	sum of diameters of measurable target lesions in mm per RECIST
SOC	system organ class
TEAE	treatment emergent adverse event
TILs	tumor infiltrating lymphocytes
TK	toxicokinetic
ULN	upper limit of normal
US	united states
V1	central volume of distribution
WBC	white blood cell
WHO	World Health Organization

## REVIEWERS OF MULTI-DISCIPLINARY REVIEW AND EVALUATION

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## 1. EXECUTIVE SUMMARY

### 1.1. Product Introduction

Dostarlimab-gxly is a humanized monoclonal antibody of the IgG4 isotype that binds to Programmed cell death receptor 1 (PD-1) and blocks PD-1/and its ligand (PD-L1) and PD-1/PD-L2 receptor-ligand interactions. 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 antitumor response. Dostarlimab-gxly is an original biologic.

The Applicant's proposed indication at the time of BLA submission on 12/19/19 was:

(b) (4)

The recommended indication for accelerated approval is:

Dostarlimab-gxly is indicated for the treatment of adult patients with mismatch repair deficient (dMMR) recurrent or advanced endometrial cancer, as determined by an FDA-approved test, that has progressed on or following prior treatment with a platinum-containing regimen.

This indication is approved under accelerated approval based upon tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in ongoing confirmatory trials.

The recommended dose for dostarlimab-gxly is:

- Dose 1 through 4: 500 mg IV every 3 weeks.
- Subsequent dosing beginning 3 weeks after Dose 4 (Dose 5 onwards): 1,000 mg IV every 6 weeks.

### 1.2. Conclusions on the Substantial Evidence of Effectiveness

The review team recommends dostarlimab-gxly for accelerated approval in accordance with Title 21 of the Code of Federal Regulations (21CFR601.41, subpart E), supported by evidence of safety and effectiveness provided by submitted data from an expansion cohort (Part 2B, Cohort A1) in a Phase 1b study of dostarlimab-gxly in subjects with metastatic tumor types, including mismatch repair deficient (dMMR) endometrial cancer. (b) (4)

(b) (4) There are no agents with regular FDA approval for patients with dMMR endometrial cancer who have progressed following platinum-containing therapy, and patients are generally offered single-agent cytotoxic chemotherapy or hormonal therapy with low response rates and brief responses based upon evidence from small studies.

The expansion cohort A1 on study 4010-01-001 (GARNET) enrolled patients with dMMR endometrial cancer that had progressed on or after platinum-based chemotherapy, and who had received no more than 2 lines of therapy for advanced, recurrent disease. Patients were required to have measurable disease. There were 104 subjects with dMMR endometrial cancer (determined by immunohistochemistry, IHC) enrolled to cohort A1, and this group comprised the safety analysis population. All subjects in the safety analysis set who had measurable disease at baseline by RECIST 1.1 by blinded independent central review (BICR) and had received at least one dose of dostarlimab on or before the cutoff date of February 1, 2019 were included in the primary efficacy analysis set, and this included 71 subjects with dMMR endometrial cancer. The primary endpoint for the study was objective response rate (ORR) and duration of response (DOR) as assessed by BICR according to RECIST v.1.1.

Tumor tissue for MMR/MSI status was required for enrollment in Cohort A1. Local testing was allowed to determine eligibility, and acceptable assays could have utilized polymerase chain reaction (PCR), immunohistochemistry (IHC), or next-generation sequencing (NGS). When local MSI test results were available, the quality of the sample was checked and cleared by central laboratory during screening. When local MMR/MSI test results were not available, tumor tissue samples were submitted for MSI testing by central laboratory, which utilized the FoundationOne<sup>®</sup> NGS-based test. However, under protocol version 6.0 (amendment 5), the requirement was changed so that MMR testing could only be determined by central IHC testing. Through the course of the trial, the Applicant partnered with Ventana Medical Systems, Inc. and a premarket authorization (PMA) was submitted to CDRH with the goal for contemporaneous approval of the VENTANA MMR RxDx Panel as a companion diagnostic device. CDRH issued an approvable letter for the VENTANA MMR RxDx Panel on 12/2/20, and the PMA for this companion diagnostic will be approved on the same day as the BLA for dostarlimab-gxly.

Efficacy results from cohort A1 on study 4010-01-001 demonstrated that patients with dMMR endometrial cancer treated with dostarlimab had a BICR-confirmed ORR of 42.3% (95% CI: 30.6%, 54.6%), with 12.7% of patients achieving a complete response (CR) and 30% of patients achieving a partial response (PR). The median duration of response (DOR) was not reached but ranged from 2.6 to 22.4 months. Twenty-eight out of 30 responders (93.3%) had a DOR lasting at least 6 months. The ORR and DOR of dostarlimab for the recommended indication are considered an improvement over available therapies, which generally include off-label used single agent cytotoxic chemotherapy or hormonal therapy with short lived responses ranging from 7 to 14%.

The safety of dostarlimab was assessed in 104 patients with dMMR endometrial cancer from cohort A1, and was supplemented by an assessment of safety in 444 patients with various advanced solid tumors treated in Cohort A2 (mismatch repair proficient endometrial cancers), Cohort F (dMMR non-endometrial cancers), and Cohort E (non-small cell lung cancers) of Study 4010-01-001 (GARNET), who had received dostarlimab monotherapy. Common toxicities for patients treated with dostarlimab included fatigue/asthenia, nausea, diarrhea, anemia and

constipation, anemia, and transaminase elevation. Immune related adverse events irAEs (including all types), which are an adverse event of special interest associated with PD-1/PD-L1 therapies, occurred in 33% of patients with dMMR endometrial cancer treated on cohort A1 and in 39% of patients in the n=444 safety population. When considering the incidence of organ-specific irAEs, the incidence associated with dostarlimab seems relatively similar to the incidence reported with other checkpoint inhibitor therapies. Based upon review of the data submitted, the safety profile of dostarlimab is considered to be acceptable, in the context of the proposed indication.

This BLA is approved with one post-marketing requirement (PMR). The Accelerated Approval PMR requires submission of the final report and datasets for ORR and DOR for additional dMMR endometrial cancer patients from the ongoing 4010-01-001 study of dostarlimab. The report is to include additional follow-up (at least 12 months) from onset of response. Alternatively, the Accelerated Approval PMR could be fulfilled by submission of the final report and datasets from a randomized Phase 3 trial, verifying the clinical benefit (based on progression free survival) of dostarlimab, compared to chemotherapy, in patients with advanced or recurrent endometrial cancer.

Given the impressive ORR and DOR seen with dostarlimab compared with currently available therapies in this patient population with unmet medical need and no therapies with regular approval, as well as the acceptable safety profile of dostarlimab, all disciplines were in agreement with this accelerated approval. There are no outstanding issues that preclude this approval.

In summary, dostarlimab-gxly 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 demonstrates a favorable benefit-risk profile with sufficient evidence to recommend accelerated approval.

### 1.3. Benefit-Risk Assessment

#### **Benefit-Risk Summary and Assessment**

Dostarlimab-gxly is a programmed death receptor-1 (PD-1) blocking antibody indicated for the treatment of adult patients with mismatch repair deficient (dMMR) recurrent or advanced endometrial cancer, as determined by an FDA approved test, that has progressed on or following prior treatment with a platinum-containing regimen.

Endometrial cancer is the most common gynecologic malignancy in the United States. In 2019, 61,880 new cases were estimated, with 12,160 deaths from the disease<sup>1</sup>. Approximately 75% of endometrial cancers are diagnosed at an early stage (FIGO Stage I-II) and these are typically curable with total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO). Advanced disease (FIGO Stage III-IV) is present in approximately 25% of cases at diagnosis, and these patients are treated with TAH/ BSO, as well as radiation and chemotherapy (carboplatin + paclitaxel). For patients with recurrent disease after local therapy or metastatic disease, first-line systemic therapy with platinum-containing chemotherapy (carboplatin and paclitaxel) is the standard of care and affords response rates from 40-62% and an overall survival ranging from 13 to 29 months. Upon progression after initial systemic therapy, pembrolizumab has accelerated approval (for patients with relapsed/refractory dMMR endometrial cancer based upon an objective RECIST ORR of 36% (5 of 14 subjects). Combination of pembrolizumab plus lenvatinib is under accelerated approval for the treatment of patients with advanced endometrial carcinoma that is not MSI-H or dMMR and who have disease progression following prior systemic therapy. While not FDA approved, trastuzumab in combination with carboplatin and paclitaxel is used for treatment of patients with HER2-positive recurrent endometrial cancer. Other treatments commonly used off-label in the setting of progressive disease after platinum-containing chemotherapy typically include single agent chemotherapy, including paclitaxel, albumin-bound paclitaxel, platinum, doxorubicin, liposomal doxorubicin, topotecan, docetaxel, bevacizumab, tamoxifen, and temsirolimus. The objective response rate for most of these agents ranges from 7-14%, and the median overall survival ranges from 9-11 months. In conclusion, there are no FDA-approved products (regular approval) for the treatment of adult patients with recurrent or advanced endometrial cancer including those with mismatch repair deficient (dMMR) tumors.

Genomic and transcriptional analyses of endometrial cancers defined that 25-30% of tumors express a high frequency of somatic mutations that are attributable to deficiencies in DNA mismatch repair (dMMR), which results in chromosomal changes (expansion or reduction in the length of repetitive sequences in tumor DNA compared with normal DNA) referred to as microsatellite instability-high (MSI-H). This alteration in chromosomal biology and resultant high mutation rate is thought to result in the increased expression of tumor-associated neoantigens, making MSI-H tumors attractive targets for the application of immunotherapies such as PD-1 blocking antibodies.

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The safety and efficacy of dostarlimab for the current submission was demonstrated in study 4010-01-001 (GARNET), which was a 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. To be eligible, patients could have received no more than 2 lines of therapy for advanced, recurrent disease, and had to have measurable disease according to BICR assessed RECIST v.1.1 criteria. The primary endpoint was confirmed objective response rate by BICR with duration of response (DOR). Patients were enrolled based upon local testing results of MMR/MSI status by either local immunohistochemistry (IHC), polymerase chain reaction (PCR), or next generation sequencing (NGS). However, the Applicant partnered with Roche Tissue Diagnostics for the development of an MMR IHC CDx test to serve as the companion diagnostic device to select patients for dostarlimab therapy. A PMA (P200019) for the VENTANA MMR RxDx Panel of antibodies as a companion diagnostic (CDx) was submitted to CDRH on 3/16/20. During review of this PMA, CDRH identified several deficiencies communicated to the Applicant, Roche, regarding study data and inter-laboratory reproducibility, which were conveyed during the review cycle. The deficiencies were addressed by Roche and CDRH issued an approvable letter for the PMA on 12/2/20. The PMA will receive contemporaneous approval with the dostarlimab-gxly BLA.

The efficacy population from Cohort A1 of study 4010-01-001 included 71 patients with dMMR/MSI-H relapsed endometrial cancer who had measurable disease by RECIST 1.1 criteria, who had received at least one dose of dostarlimab, and who had at least 24 weeks of tumor assessments as of the data cutoff date of 7/8/19. The primary endpoint for the study was objective response rate (ORR) and the key secondary endpoint was duration of response (DOR) by blinded independent central review (BICR) using response evaluation criteria in solid tumors (RECIST) v1.1. The study demonstrated a RECIST 1.1 confirmed ORR of 42.3% (95% CI: 30.6%, 54.6%), including 9 patients with a complete response (CR) and 21 patients with a partial response (PR). The ORR by investigator assessment using irRECIST revealed similar results, with an immune-related ORR of 44.0% (95% CI: 32.5%, 55.9%). An updated analysis on 12/1/19 revealed that the median DOR by BICR assessment was not reached, but the DOR ranged from 2.6 to 22.4 months. Twenty-eight out of 30 responders (93.3%) had a DOR  $\geq$ 6 months and 15 responders (50.0%) had a DOR  $\geq$ 12 months. The median irDOR by INV assessment was also not reached, and the irDOR ranged from 2.5 months to 19.6 months.

The safety profile of dostarlimab was assessed based upon the safety data from Study 4010-01-001. The FDA review of safety focused mainly on analysis of the safety population including 104 patients with dMMR endometrial cancer treated in cohort A1 of Study 4010-01-001 who had received at least one dose of dostarlimab monotherapy by the data cutoff date. Additionally, the safety analysis included a focused assessment of immune-related adverse events (irAEs) from the 444 patients with various advanced solid tumors treated in Cohort A2 (mismatch repair proficient endometrial cancers), Cohort F (dMMR non-endometrial cancers), and

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Cohort E (non-small cell lung cancers) of Study 4010-01-001 who had received dostarlimab monotherapy at the recommended therapeutic dose.

On Study 4010-01-001 (Cohort A1), fatal adverse reactions (AR) did not occur in any patients. Permanent discontinuation due to adverse reactions occurred in 5 patients (5.8%) and included events of transaminase elevation (n=2), sepsis (n=1), bronchitis (n=1), and pneumonitis (n=1). Serious ARs occurred in 34% of patients, with the most common being sepsis, acute kidney injury, urinary tract infection, abdominal pain, and pyrexia (all occurring in 2.9% of patients). Dose reductions were not allowed, but dose interruptions due to ARs occurred in 23% of patients, with the most common ARs leading to dose interruption ( $\geq 1\%$ ) being anemia, diarrhea, lipase elevation, and pyrexia. Adverse events of special interest, namely immune-mediated adverse reactions, occurred in 33% of dMMR endometrial cancer patients treated on cohort A1. Common grade 1-4 adverse events ( $\geq 20\%$ ) included fatigue/asthenia, nausea, diarrhea, anemia and constipation. The most common grade 3-4 adverse events included anemia and transaminase elevation. The majority of irAEs observed with dostarlimab therapy were Grade 1 or 2 events. IrAEs were managed with treatment interruptions or discontinuations as well as systemic steroids, other immune modulating agents, and hormone supplementation, as needed. The incidence rate and severity of irAEs observed with dostarlimab was generally consistent with those reported with other anti PD-1 agents, although there was some variability.

In the overall safety database, including 444 patients from 3 additional cohorts on Study 4010-01-001, the safety profile was similar to that observed in cohort A1. Fatal ARs occurred in 4% of patients and permanent discontinuation due to AR occurred in 7% of patients. Serious ARs occurred in 37% of patients and immune-mediated ARs occurred in 39% of patients in the safety dataset.

The drug substance (DS) and drug product (DP) facilities for manufacturing of dostarlimab required inspection prior to approval. Due to international travel restrictions as result of COVID-19 pandemic, the onsite inspection of (b) (4) was delayed by approximately 8 months. A review of the (b) (4) DS manufacturing documents was performed under the Agency's authority under Section 704(a)(4) of the FD&C Act in advance or in lieu of an inspection. Subsequent to review of the documents, a pre-license and surveillance inspection was conducted from (b) (4). The IFR of voluntary action indicated (VAI) was issued on 4/6/21, and the recommendation of Approval was made, from the facility standpoint, on 4/6/21.

Patients with recurrent or advanced dMMR endometrial cancer that has progressed following a platinum-containing systemic therapy have a serious and life-threatening disease for which there are currently no therapies with regular FDA approval for this indication. The review team concludes that an ORR of 42.3% with a median DOR not reached at the time of data cutoff and the

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majority of responses durable for at least six months, is of sufficient magnitude to serve as evidence that is reasonably likely to predict clinical benefit over available therapies in support of accelerated approval. All disciplines agree that dostarlimab-gxly has a favorable risk-benefit profile in the indicated population and did not identify any outstanding issues that would preclude approval. The recommendation is for accelerated approval with a post-marketing requirement that the Applicant provide additional clinical trial results to confirm direct clinical benefit.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<b>Analysis of Condition</b>	<p>Endometrial cancer is the most common gynecologic malignancy in the United States. In 2019, an estimated 61,880 new cases were diagnosed and there were 12,160 deaths from the disease.</p> <p>20-30% of endometrial cancers are associated with somatic mutations that can be attributed to deficiencies in DNA mismatch repair (dMMR), leading to microsatellite instability-high (MSI-H) phenotype.</p>	<p><b>Advanced endometrial cancer is a serious and life-threatening disease with a significant unmet medical need for more effective therapies.</b></p> <p><b>Specifically, patients with advanced dMMR endometrial cancer that have progressed following systemic therapy and who are not candidates for curative surgery or radiation have a serious and life-threatening disease.</b></p>
<b>Current Treatment Options</b>	<p>Most patients present with early stage disease, which is often curable with surgery. For patients with advanced (stage III/IV) disease at diagnosis, who are candidates for curative therapy, standard treatment includes surgery, radiation, and adjuvant platinum-based chemotherapy. For patients who relapse after initial multi-modality therapy, systemic therapy options are of limited benefit and include single agent chemotherapy, hormonal therapy, or tamoxifen. Response rates to these therapies are &lt;20% and overall survival is typically less than 1 year.</p>	<p><b>Currently there are few treatment options for patients with relapsed endometrial cancer, including those associated with MSI-H/ dMMR status, these include single agent chemotherapy and hormonal therapies. The existing treatments are not FDA approved and offer limited benefit in terms of duration of responses, when responses are observed. Furthermore, there is no evidence that these existing treatments prolong survival or result in clinically meaningful delays in disease progression. Finally, the toxicity of</b></p>

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	<p>Pembrolizumab is approved under accelerated approval for patients with metastatic/unresectable MSI-h or dMMR solid tumors that had progressed following prior treatment. Patients with advanced MSI-H/dMMR endometrial cancer (n=14) were included in the overall cohort and the ORR for pembrolizumab in these patients was 36%.</p>	<p><b>chemotherapy includes serious and sometimes fatal adverse reactions, particularly in older patients.</b></p> <p><b>There is a need for new effective therapies in this disease space.</b></p>
<b>Benefit</b>	<p>A confirmed ORR of 42.3% (95% CI: 30.6%, 54.6%), with 9 patients achieving a CR and 21 patients achieving a PR.</p> <p>The median DOR by BICR assessment was not reached but ranged from 2.6 to 22.4 months. A total of 28 of the 30 responders (93.3%) had a DOR <math>\geq</math> 6 months.</p>	<p><b>Evidence of effectiveness was supported by an objective response rate and significantly greater DOR than what is seen with standard chemotherapy and hormonal therapy.</b></p> <p><b>A PMR may be required to verify clinical benefit.</b></p>
<b>Risk and Risk Management</b>	<p>The most common adverse reactions experienced by <math>\geq</math> 20% of patients treated with dostarlimab were fatigue/asthenia, nausea, diarrhea, anemia and constipation. Immune-mediated adverse reactions occurred in 33% of patients with dMMR endometrial cancer receiving dostarlimab therapy. Oncologists are well versed in the identification and management of toxicities associated with PD-1/PD-L1 therapies, similar to dostarlimab. Labeling adequately describes dose interruption and discontinuation guidelines, as well as supportive care measures, for the management of treatment-related adverse reactions including immune-mediated adverse reactions.</p>	<p><b>The safety profile of dostarlimab is similar to and consistent with other approved agents in the same class of therapies (anti-PD-1/PD-L1 agents).</b></p> <p><b>The safe use of dostarlimab can be managed through accurate labeling and routine oncology care.</b></p> <p><b>A REMS is not indicated.</b></p>

### 1.4. Patient Experience Data

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

	The patient experience data that was submitted as part of the application included Patient-reported outcomes (PROs) (European Quality of Life scale, 5 Dimensions, 5 Levels [EQ-5D-5L], and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire [EORTC QLQ-C30]) in subjects in Cohorts A1 and F enrolled under protocol amendment 3 or subsequent amendments		Section where discussed, if applicable
	Clinical Outcome Assessment (COA) data, such as PROs:		
X	EORTC QLQ-C30	Patient-reported outcome (PRO)	8.2.5
		Observer-reported outcome (ObsRO)	N/A
		Clinician-reported outcome (ClinRO)	N/A
		Performance outcome (PerfO)	N/A
	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		N/A
	Patient-focused drug development or other stakeholder meeting summary reports		N/A
	Observational survey studies designed to capture patient experience data		N/A
	Natural history studies		N/A
	Patient preference studies (e.g., submitted studies or scientific publications)		N/A
	Other: (please specify)		N/A

X

Gwynn Ison, MD  
 Cross-Disciplinary Team Leader

## 2. THERAPEUTIC CONTEXT

### 2.1. Analysis of Condition

#### The Applicant's Position

The number of newly diagnosed cases of uterine cancer in the United States (US) in 2019 is estimated to be 61,880.<sup>1</sup> Endometrial cancer (EC) is the sixth most common cancer in women worldwide. The majority of patients with EC are diagnosed with Stage I or II disease and receive surgery with curative intent; however, approximately 20% are diagnosed with advanced or metastatic disease (Stage III or IV), for which a surgical cure is unlikely.<sup>2</sup> For these patients, there are no FDA-approved therapies, but adjuvant systemic platinum-based chemotherapy is the standard of care. Nearly 25% of patients diagnosed with early disease will have cancer recurrence within 5 years of initial treatment.<sup>3</sup> Systemic platinum-based chemotherapy is the SOC for these patients as well.

The overall prognosis of EC is mainly dependent on the stage at diagnosis and tumor histology. Earlier stages and endometrioid histology are associated with better prognosis, whereas advanced stages and non-endometrioid histologies such as serous, clear cell, and mixed are known to be associated with a worse prognosis.<sup>4</sup>

EC can be classified as mismatch repair-deficient (dMMR) or mismatch repair-proficient (MMRp) based on the absence or presence of proteins that play a critical role in the MMR process. The resulting accumulation of mismatches interferes with DNA replication and drives genome instability.<sup>5</sup> Genome instability can manifest within microsatellites, which are repetitive DNA sequences (1 to 6 bases in length) found in coding and noncoding regions throughout the genome, a finding referred to as microsatellite instability (MSI).<sup>6</sup> In general, patients with dMMR/MSI-high (MSI-H; up to 33%) tumors have a high number of tumor infiltrating lymphocytes (TILs) compared to patients with MMR proficient/microsatellite stable tumors. Anti-programmed cell death protein 1 (PD-1) agents such as dostarlimab alleviate tumor-induced T cell inhibition; therefore, the increased presence of TILs may lead to increased anti-tumor response of dostarlimab in patients with dMMR/MSI-H tumors

EC is one of the cancers with a high observed rate of dMMR/MSI-H, although the incidence varies depending on histology and tumor grade.<sup>7</sup> The rate of dMMR/MSI-H is lower in low-grade endometrial tumors (28.6%) than in high-grade endometrial tumors (54.3%). Although data on MMR/MSI status in the metastatic setting are limited, the rate of dMMR/MSI-H 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%.<sup>8</sup>

Patients with recurrent or advanced EC who have progressed on platinum-based chemotherapy have limited options for treatment and prognosis is poor. National Comprehensive Cancer Network (NCCN) guidelines recommend single-agent intravenous (IV) chemotherapy or bevacizumab based on small, uncontrolled studies conducted in heterogeneous patient populations that provide objective response rates (ORRs) of ~7% to 13.5% (all PRs) and a median overall survival (OS) of 9 to 11 months. In the dataset supporting the accelerated

approval of pembrolizumab in patients with metastatic or advanced dMMR/MSI-H solid tumors, based on data derived from a very limited number of patients (N=14), pembrolizumab has an ORR of 36% in patients with dMMR/MSI-H EC. However, the benefit of treatment with pembrolizumab in this setting is still to be confirmed, thus leaving the treatment of patients with dMMR EC an area of high unmet medical need.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment of mismatch repair deficient endometrial cancer (dMMR EC).

## 2.2. Analysis of Current Treatment Options

The Applicant's Position:

For patients with recurrent or advanced EC who have progressed on or after treatment with a platinum-containing regimen, the NCCN guidelines recommend single-agent chemotherapy.<sup>9</sup> Data for these agents, which are derived from small single-arm, non-registrational studies, are limited and demonstrate that overall clinical benefit is very limited and invariably short-lived, with ORRs of approximately 7% to 14% and median OS of 6 to 11 months.<sup>10</sup>

Even for the agents with a higher ORR (13.5%) such as bevacizumab, the reported median OS remained at <1 year. Additionally, long-term treatment with these agents is challenging even for the patients who achieve responses or disease stabilization due to cumulative chemotherapy related toxicities. Hormone therapies including megestrol acetate are recommended for patients with low-grade recurrent or advanced EC, but megestrol acetate is intended as palliative and not curative treatment. Thus, there is a crucial need to develop new therapeutic options that can address the limitations of currently available therapies that have meaningful and durable clinical activity in these patients.

Pembrolizumab received accelerated approval in May 2017 for the treatment of patients with unresectable or metastatic dMMR/MSI-H tumors, including dMMR/MSI-H EC, who have progressed following prior treatment and who have no satisfactory alternative treatment options. The efficacy of pembrolizumab was evaluated in patients with dMMR/MSI-H solid tumors enrolled in 1 of 5 uncontrolled, open-label, multicohort, multicenter, single-arm studies. Patients received either pembrolizumab 200 mg every 3 weeks (Q3W) or 10 mg/kg every 2 weeks (Q2W) (Keytruda USPI, 2019). The ORR was 39.6% in the pooled population (which included 14 patients with EC; ORR=36%). Currently, there are no anti-PD-1 treatments with full approval for patients with dMMR EC tumors.

Given the lack of fully approved treatment options and the poor prognosis of patients with recurrent or advanced dMMR EC whose disease has progressed following treatment with a platinum containing regimen, new effective treatment options are urgently needed.

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**Table 1: Summary of Treatment Armamentarium Relevant to the Treatment of Endometrial Cancer**

Agent	Approval	Indication	Scope of Approval	Endpoint	Summary of Results	Reference
<b>Therapies approved for the treatment of endometrial cancer</b>						
Megestrol Acetate	Regular approval 1971	Palliative treatment of advanced carcinoma of the endometrium	N/A	N/A	N/A	N/A
Pembrolizumab	Accelerated approval 05/23/2017	Unresectable or metastatic, MSI-H or dMMR solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options	Five uncontrolled, open-label, multicohort, multicenter, single-arm studies	ORR	ORR=39.6% in the pooled population (14 patients with EC)	KEYNOTE-016, KEYNOTE-158, KEYNOTE-164, KEYNOTE-12, KEYNOTE-28
Pembrolizumab + lenvatinib	Accelerated approval 09/16/2019	Advanced EC that is not MSI-H or dMMR after disease progression following prior systemic therapy and not eligible for curative surgery or radiation	Phase 2, multicohort, multicenter, open-label, single-arm trial	ORR	N=108 ORR=38.3% Median DOR (mos) NR (range 1.2+ to 33.1+)	Study 111/ KEYNOTE-146
<b>Other therapies used after platinum-based therapy (not approved)</b>						
Liposomal doxorubicin	N/A	N/A	N/A	ORR	N=45 ORR =9.5% Median DOR (mos.) 2.7 Median OS (mos) 9.2	GOG 129H

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**Table 1: Summary of Treatment Armamentarium Relevant to the Treatment of Endometrial Cancer (Continued)**

Agent	Approval	Indication	Scope of Approval	Endpoint	Summary of Results	Reference
Oxaliplatin	N/A	N/A	N/A	ORR	N=52 ORR=13.5% Median DOR 10.9+ (range 4.1 to 50.3+)	GOG 129-K
Docetaxel	N/A	N/A	N/A	ORR	N=26 ORR=7.7% Median OS (mos) 6.4	GOG 129-N
Topotecan	N/A	N/A	N/A	ORR	N=28 ORR=9% Median DOR 4.5 (N=2 responses) Median OS N/A	GOG 129J
Bevacizumab	N/A	N/A	N/A	ORR	N=52 ORR=13.5% Median DOR 6 Median OS 10.6	GOG 229-E

Abbreviations: dMMR=mismatch repair deficient; DOR=duration of response; EC=endometrial cancer; mos=months; MSI-H=microsatellite instability-high; N=number of patients; N/A=not applicable; NR=not reached; ORR=objective response rate; OS=overall survival.

**The FDA's Assessment:**

FDA conducted its own literature review in determining therapies commonly used for the treatment of patients with recurrent or advanced endometrial cancer who have progressed on or after treatment with a platinum-containing regimen. The FDA's assessment includes the agents described by the Applicant, but also includes additional agents used off label. The FDA assessment of available therapies is shown in Table 2. FDA agrees that, there are no FDA-approved products (under regular approval) for the treatment of adult patients with recurrent or advanced endometrial cancer including those with dMMR tumors. The existing treatments offer limited benefit in terms of duration of responses, when responses are observed. Furthermore, there is no evidence that these existing

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treatments prolong survival or result in clinically meaningful delays in disease progression. Finally, the toxicity of chemotherapy includes serious and sometimes fatal adverse reactions, particularly in older patients. FDA agrees that there is a need for new effective therapies in this disease space.

**Table 2 FDA consideration of therapies for second line endometrial cancer**

Agent	N	ORR	Median DOR (m)	Median OS	Reference
Doxil	45	9.5%	2.7 m	8.2 m	GOG129H
Oxaliplatin	52	13.5%	10.9+ m (range 4-50+)	NA	GOG129K
Docetaxel	26	7.7%	NA	6.4 m	GOG129N
Topotecan	28	9%	4.5 m (2 responses)	NA	GOG129J
Bevacizumab	52	13.5%	6 m	10.6 m	GOG 229E
Temsirolimus	27	4%	4.9 m	NA	Oza, et al. JCO
Tamoxifen/ SERM	-	18-20%	-	-	Ethier, et al. Gynecologic Oncol75%

### 3. REGULATORY BACKGROUND

#### 3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Dostarlimab (TSR-042) is not currently registered (or approved) in the US or in any other part of the world.

The FDA's Assessment:

As of April 9, 2021, dostarlimab has no marketing approvals in any country.

#### 3.2. Summary of Pre-Submission/Submission Regulatory Activity

The Applicant's Position:

The clinical trials included in this application were conducted under [IND 126472](#).

Key regulatory activities relevant to the proposed indication in this original Biologic License Application (BLA) are summarized in [Table 3](#).

**Table 3: 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	Type C Meeting	CMC development
May 2018	CMC Type C Meeting	CMC development
September 2018	Type B Meeting	Discussed the pivotal Phase III study design of dostarlimab in combination with chemotherapy in 1L EC
February 2019	Type C Meeting	Discussed a data package and organization of proposed BLA to support accelerated approval
May 2019	BTD granted	BTD for dMMR EC granted
June 2019	CMC Type C Meeting	CMC development
October 2019	Pre-BLA Meeting	Discussed the plan for BLA submission for dostarlimab as a 2L agent with recurrent dMMR EC

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;

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dMMR=mismatch repair-deficient; EC=endometrial cancer; FDA=US Food and Drug Administration;  
IND=Investigational New Drug; US=United States

**The FDA's Assessment:**

The 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). The study Applicant Tesaro Inc., a wholly owned subsidiary of GSK, and three clinical investigators, Dr. Jubilee Brown (Site 840071), Dr. Cara Mathews (Site 840035), and Dr. Lucy Gilbert (Site 124017), were selected for clinical inspections. The inspections of Dr. Brown, Dr. Mathews, and the study Applicant Tesaro were performed, and there were no objectionable regulatory violations identified at the three entities. The scheduled inspection of Dr. Gilbert in Canada was cancelled by the FDA Office of Regulatory Affairs (ORA) due to the COVID-19 related international travel restrictions.

Based on the results of the three completed inspections, the Applicant's oversight and management of this ongoing study was found to be adequate, and the clinical data generated from the two inspected investigator sites appear to be reliable and acceptable in support of this BLA. Details of these inspections are below.

#### **Site 840071: Dr. Jubilee Brown**

Dr. Brown was inspected on February 25-27, 2020, as a data audit for Study 4010-01-001. This was the first FDA inspection of the investigator. The investigator site enrolled 8 subjects into the study, with 5 subjects to Cohort A1. Of the 5 subjects in Cohort A1, four were included, as of the data cutoff date, in the current submission. Source records for all enrolled subjects were reviewed and compared with the Applicant's submitted Cohort A1 data listings for the site during the inspection. The reviewed records included the informed consent, eligibility criteria, CT/MRI scans performed and their submissions to the BICR, laboratory reports, efficacy endpoints' documentation, adverse events, concomitant medications, and electronic case report forms (eCRFs). Regulatory documents related to the conduct and oversight of the study at the site were also reviewed, including the Institutional Review Board (IRB) approvals of the protocol/amendments and informed consent, financial disclosures, monitoring visits and site's responses to inquiries, reporting to the Applicant, protocol deviations, study drug accountability, and retention of study records. The inspection found no significant regulatory violation in the investigator's conduct of this study at the site. The submitted data listings for this site were verifiable and supported by source documents. There was no evidence of under reporting of adverse events. At the conclusion of this inspection, no Form FDA 483 was issued to the investigator. One discussion item was that for three instances, dispensation of study treatment was not recorded contemporaneously on the drug accountability log. The investigator acknowledged the finding and understood the importance of record keeping per the procedures.

#### **Site 840035: Dr. Cara Mathews**

Dr. Mathews was inspected from January 9 through January 17, 2020, as a data audit for Study 4010-01-001. This was the second FDA inspection of the investigator. The previous inspection was conducted between October 30 and November 2, 2018, and the compliance classification was No Action Indicated. This investigator site enrolled 8 subjects into the study, with 4 subjects in Cohort A1. Of the 4 subjects in Cohort A1, two subjects met the criteria for the interim efficacy analysis in the current submission. Source records for all subjects in Cohort A1 were reviewed and compared with the data listings for this site. Records reviewed during this inspection included, but were not limited to, the informed consent forms, source documentation, subject data, eCRFs, IRB's correspondence and approvals, study protocol and amendment, Applicant monitor correspondence, and drug accountability records. The inspection revealed no objectionable observations at the site, with no Form FDA 483 issued to the investigator at the end of this inspection. The Applicant's submitted data listings were verifiable with source records. All the scans performed before the data cutoff date were submitted to the Applicant's designated central laboratory for BICR. The inspection found no evidence of unreported adverse events. A discrepancy was identified and reported for Subject (b) (6). This was related to an adverse event (Grade 1 fatigue). The reported start date was (b) (6) in the subject data listings. This date was found not to be consistent with the documented ongoing fatigue in the progress notes dated (b) (6). In review of these source documents, Dr. Mathews agreed that the onset date for the reported fatigue for this subject should be earlier than the originally reported date. The investigator assured to communicate with the study Applicant and submit the correct onset date for this adverse event.

**Reviewer's Comments:** *The above-described discrepancy regarding the start date of Grade 1 fatigue does not appear to impact the safety profile of study treatment. Fatigue has been reported as one of the common treatment-emergent adverse events (≥15%) in the clinical study report.*

**Tesaro Inc. (Study Applicant)**

The study Applicant was inspected from May 6 through May 12, 2020, to evaluate its oversight and management of Study 4010-01-001, with a primary focus on Cohort A1. This was the second inspection of the Applicant. The first inspection was conducted in January 2017 and the compliance classification was No Action Indicated. Currently, the established inspection report is not available. Based on the inspector's preliminary summary, the inspection included a review of the Applicant's organizational charts, work orders and agreements with contract research organizations (CRO) involved in the study, Standard Operating Procedures (SOPs), investigators' FDA 1572s and financial disclosures, monitoring plan, monitor qualifications, monitoring reports, test article accountability records, clinical management plan, safety management plan, adverse event reporting, electronic case report forms. Regarding the use of BICR for Cohort A1, the inspector also reviewed the CRO (b) (4) Review Charter and related data transfer documents, including the data that was transferred from (b) (4) to the Applicant. The inspection reported no objectionable observations, with no Form FDA 483 issued to the Applicant at the conclusion of the inspection. For Cohort A1, the BICR data for all 70 subjects that were included in the analysis set were verifiable at the Applicant's site. For the above three

investigator sites, subjects' tumor response results in the submitted data listings were consistent with those conveyed to the Applicant from the BICR. There were no issues identified regarding the adverse event reporting. Overall, this inspection showed that the study Applicant has had proper management and adequate oversight of the ongoing Study 4010-01-001.

**Reviewer's Comments:** *An amendment to this clinical inspection summary will be introduced if the EIR for the study Applicant Tesaro contains substantial differences that can alter the current GCP assessments.*

## 4.2. Product Quality

The Office of Pharmaceutical Quality (OPQ), CDER, reviewed the product quality submission of STN 761174 for Jemperli (dostarlimab-gxly) manufactured by GSK. The data submitted in this application are adequate to support the conclusion that the manufacture of Jemperli is well controlled and leads to a product that is pure and potent.

The drug substance (DS) facility (b) (4) for manufacturing of dostarlimab required inspection prior to approval. Due to international travel restrictions as a result of the COVID-19 pandemic, the onsite inspection of (b) (4) was delayed. A review of the (b) (4) DS manufacturing documents was performed under the Agency's authority under Section 704(a)(4) of the FD&C Act in advance or in lieu of an onsite inspection. Subsequent to review of the documents, a pre-license and surveillance inspection was conducted from (b) (4). The final recommendation of voluntary action indicated (VAI) was issued on 4/6/21, and the recommendation of Approval for the BLA application was made, from the facility standpoint, on 4/6/21.

Refer to the OPQ full review in Panorama.

## 4.3. Clinical Microbiology

Refer to the OPQ Executive Summary and full review in Panorama.

## 4.4. Devices and Companion Diagnostic Issues

The Applicant submitted Premarket Approval (PMA) application (P200019) to the Center for Devices and Radiological Health (CDRH) on March 16, 2020, to seek approval for the VENTANA MMR RxDx Panel of antibodies as a companion diagnostic (CDx) to select patients with dMMR Endometrial cancer (EC) eligible for treatment with dostarlimab. CDRH has completed its review of the PMA and issued an approvable letter on December 2, 2020. The PMA will be contemporaneously approved with the BLA.

## 5. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

### 5.1. Executive Summary

#### FDA's Assessment:

Dostarlimab-gxly (TSR-042, dostarlimab) is a human IgG4 monoclonal antibody that binds the programmed death receptor-1 (PD-1); its established pharmacologic class is programmed death receptor-1 (PD-1) blocking antibody. PD-1 is expressed on activated T and B cells, natural killer cells, and myeloid lineage cells. Binding of PD-1 to its ligands programmed death-ligand (PD-L)1 and PD-L2 inhibits T-cell activity, T-cell proliferation, and cytokine production. In the tumor microenvironment, PD-1 signaling contributes to the inhibition of T cell-mediated immune surveillance of tumors. Thus, blockade of PD-1 signaling in the tumor microenvironment is intended to enhance tumor immunosurveillance and anti-tumor immune responses.

Dostarlimab is indicated for the treatment of adult patients with recurrent or advanced endometrial cancer (EC) that has progressed on or following prior treatment with a platinum-containing regimen whose tumors are mismatch repair deficient (dMMR), as determined by an FDA-approved test. Based on data from published literature (Boland, et al., 2008; Hecht and Mutter, 2006), up to 25% of endometrial cancer demonstrates disruption of the DNA MMR pathway, manifesting as high levels of microsatellite instability (MSI-H) and/or loss of MMR protein expression by immunohistochemistry (IHC).

In pharmacology studies, dostarlimab bound to human and cynomolgus monkey PD-1 with similar affinity but did not bind to mouse PD-1 as measured using surface plasmon resonance. When assessed using flow cytometry, dostarlimab also bound to freshly isolated peripheral blood mononuclear cells (PBMCs) from cynomolgus monkey, human, beagle dog, mouse, and rat; however, higher staining was observed in human and cynomolgus monkey PBMCs compared to dog, mouse, and rat PBMCs. In tissue cross reactivity studies, dostarlimab showed comparable staining profiles between human and monkey tissues. Therefore, the cynomolgus monkey is considered a pharmacologically relevant species for the toxicology assessment.

In in vitro studies, dostarlimab also competed with human PD-1 ligands for binding to PD-1. Following incubation with human dendritic cells and allogenic CD4<sup>+</sup> T cells in a mixed lymphocyte reaction assay, dostarlimab induced a dose-dependent increase in human CD4<sup>+</sup> T-cell proliferation with EC<sub>50</sub> value of 0.13-2 nM. The Applicant did not directly assess dostarlimab for ADCC or CDC activity but demonstrated that dostarlimab bound to human FcγRI CD46 with lower affinity than a control IgG1 antibody and did not bind to C1q. Furthermore, in an in vitro cytokine release assay, dostarlimab did not induce cytokine release at concentrations up to 400 µg/well.

Because dostarlimab did not bind to mouse PD-1, the Applicant developed a mouse surrogate anti-PD-1 antibody (RMP1-14) to investigate the effects of PD-1 pathway inhibition on tumor growth. Intraperitoneal injection of RMP1-14 at 5 mg/kg twice weekly resulted in delayed tumor growth in an MC38 syngeneic mouse colon tumor model when compared to vehicle control.

The Applicant evaluated the safety of dostarlimab in cynomolgus monkeys in GLP-compliant repeat-dose toxicity studies of up to 13 weeks duration. In the 13-week study, monkeys received once weekly intravenous (IV) administration of dostarlimab at doses up to 100 mg/kg. One male in the 10 mg/kg dose group was euthanized on Day 89 due to unresolved skin inflammation and secondary findings of enlarged lymph nodes and increased cellularity in lymphoid organs. Exposure in this animal was approximately 6 times the human exposure at the recommended starting dose of 500 mg. In surviving animals, there were no remarkable effects on clinical signs, body weight, food consumption, body temperature, ophthalmoscopy, ECG parameters, coagulation parameters, cytokine analysis, and immunophenotyping analysis. In T-cell dependent antibody response assay (anti-KLH IgM and IgG), dostarlimab did not induce any remarkable changes in the primary or secondary anti-KLH IgM and IgG response when compared to vehicle control group.

The majority of microscopic findings in surviving animals was minimal mononuclear cell infiltration in numerous tissues, consistent with the mechanism of action. Other major target organs of toxicity identified in monkeys administered  $\geq 30$  mg/kg/week ( $\geq 15$  times the human exposure at the recommended starting dose of 500 mg) for 13 weeks included thymus (minimal to mild decreased lymphoid cellularity), stomach (mild mucosal degeneration of stomach), bone marrow (minimal increased lymphoid cellularity), heart (minimal myocardial degeneration), , adrenal gland (minimal hypertrophy/hyperplasia), and salivary gland (minimal zymogen depletion). In clinical trials, toxicities associated with dostarlimab were primarily immune-mediated adverse reactions that are predicted by its mechanism of action. Exposure multiples were calculated using  $C_{avg}$ , where  $C_{avg}$  for monkeys is  $AUC_{0-168}/168$  h and  $C_{avg}$  for human is  $AUC_{0-504h}/504$  h. At the clinical starting dose of 500 mg, human  $AUC_{0-504}$  was 35730  $\mu\text{g}\cdot\text{h}/\text{mL}$ .

Based on data from the literature and its mechanism of action, treatment with dostarlimab has the potential for enhanced immune response to infection or impaired antimicrobial immune responses. PD-1 deficient C57BL/6 mice infected with *M. tuberculosis* exhibited decreased survival compared to wild-type mice, which correlated with uncontrolled bacterial proliferation and an increased inflammatory response in the lungs (Lazar-Molnar, et al., 2010). It is unclear whether decreased survival resulted from an inability to mount an appropriate antibacterial response or a failure to control the immune response leading to normal tissue destruction and organ failure. In addition, PD-L1 deficient mice died early after chronic systemic lymphocytic choriomeningitis virus (LCMV) infection (Barbar, et al., 2006). Moreover, the absence of PD-1 pathway signaling led to fatal  $\text{CD8}^+$  T cell-mediated killing of virally infected vascular endothelial cells, systemic vascular leakage, and ultimately cardiovascular collapse in mouse models of LCMV infection (Frebel, et al., 2012; Mueller, et al., 2010). The Applicant included a brief description of these data in Section 13.2 of the label to convey these potential risks to prescribers.

No reproductive and developmental toxicity studies were conducted with dostarlimab. The Applicant provided a literature-based assessment of the potential reproductive toxicity of dostarlimab, consistent with the alternative approach described in ICH S6 (R1) and ICH S9. Data from the literature demonstrate that the PD-1/PD-L1 pathway plays a critical role in maintaining maternal immunological tolerance to the fetus during pregnancy. Blockade of PD-

1/PD-L1 signaling resulted in an increased incidence of fetal loss but no fetal malformations in allogeneic mouse models of pregnancy; however, there was a report that late onset autoimmunity can occur in PD-1 deficient mice. In addition, published literature also demonstrate that down regulation of PD-1/PD-L1 pathway may be associated with pregnancy loss in patients with early recurrent miscarriage compared to woman with healthy pregnancies. Based on these findings, potential risks of administering JEMPERLI during pregnancy include increased rates of abortion or stillbirth and an increased risk in offspring of developing immune-related disorders or altering the normal immune response. The product label states that JEMPERLI can cause fetal harm if administered during pregnancy based on its mechanism of action. The current approach in the Office of Oncologic Diseases is to recommend patients use effective contraception during treatment and for 5-half-lives or approximately 4 months following the last dose of dostarlimab-gxly. Because of the potential for serious adverse reactions in a breastfed child, the Pharmacology/Toxicology team also recommended that women not breastfeed during treatment with dostarlimab-gxly and for 4 months after the final dose.

No genetic toxicology or carcinogenicity studies were conducted or warranted to support this BLA submission, as dostarlimab-gxly is a biotechnology-derived pharmaceutical and the proposed indication is for advanced cancer.

The nonclinical data submitted in this BLA are adequate to support approval of dostarlimab-gxly for the proposed indication.

## 5.2. Referenced NDAs, BLAs, DMFs

### The Applicant's Position:

None.

## 5.3. Pharmacology

### 5.3.1. Primary Pharmacology

#### The FDA's Assessment:

Results of primary pharmacology studies were reviewed previously under IND 126472.

When determined using surface plasmon resonance, dostarlimab (TSR-042) bound to human and cynomolgus monkey PD-1 with similar affinity ( $K_D = 1.8$  and  $1.5$  nM, respectively) but did not bind to mouse PD-1, supporting the use of cynomolgus monkey as the single pharmacologically relevant species for toxicity assessment. Dostarlimab competed with human PD-1 ligands in binding to PD-1 with  $IC_{50}$  values of  $1.8$  nM for PD-L1 and  $1.5$  nM for PD-L2, respectively. In a mixed lymphocyte reaction (MLR) assay, human dendritic cells and allogenic  $CD4^+$  T cells were incubated in the presence of dostarlimab or isotype control for 7 days ( $n = 4$ ). Dostarlimab induced a dose-dependent increase in human  $CD4^+$  T-cell proliferation with  $EC_{50}$  values of  $0.13$ - $2$  nM (Study no. ANA011.002-RES-20130429).

In addition, binding of dostarlimab to freshly isolated PBMCs from cynomolgus monkey, human ( $n=2$  donors), beagle dog, mouse, and rat was evaluated using flow cytometry. FITC-TSR-042

was incubated with PBMCs for 15 minutes at room temperature, and the number of TSR-042<sup>+</sup> cells was determined using flow cytometry. Dostarlimab bound to freshly isolated PBMCs from all tested species in vitro with higher staining in cynomolgus monkeys and human PBMCs compared to beagle dog, mouse, and rat PBMCs (Study no. XLB-065).

Due to lack of cross-reactivity between dostarlimab and mouse PD-1, a surrogate anti-mouse PD-1 antibody (RMP1-14) was used to assess the potential for PD-1 inhibition to suppress tumor growth in an MC38 syngeneic mouse colon tumor model. In this model, tumors were measured twice a week for up to 60 days. The time-to-endpoint (TTE) for each mouse was defined as the time when the tumor reached a volume of 2000 mm<sup>3</sup> and the animal was *ethanized or on the final day (Day 60)*, whichever came first. Intraperitoneal injection of RMP1-14 at 5 mg/kg twice weekly (Days 1, 4, 8, and 11) resulted in 78% tumor growth delay compared to Phosphate-Buffer saline (PBS) vehicle control (n=6-9/group), calculated as percent increase in median TTE for treated versus control mice. To investigate whether PD-1 blockade would induce an adaptive anti-tumor immune response, mice bearing tumors from the anti-PD-1 antibody treated group that remained tumor free on Day 81 were re-challenged with four times the number of MC38 tumor cells used for the original inoculation. The results demonstrated that after re-challenge, no tumors grew in animals previously treated with anti-PD-1 while 100% tumor growth was observed in the naïve control group. Thus, anti-PD1 treated mice appear to induce an adaptive tumor immune response and rejected tumor growth upon rechallenge (Study no. ANA011.E004-RES-20150327).

### 5.3.2. Secondary Pharmacology

#### The Applicant's Position:

Dostarlimab is unlikely to independently induce cytokine release, as incubation of dostarlimab with donor peripheral blood mononuclear cells (PBMCs) in vitro did not induce significant production of interferon-gamma, tumor necrosis factor-alpha, interleukin (IL)-2, IL-4, IL-6, and IL-10).

Dostarlimab is also unlikely to induce complement-dependent cytotoxicity (CDC) as it did not bind to C1q. Additionally, because dostarlimab has a lower affinity for the Fc-γ receptor CD64 than a control IgG1 antibody, it is considered less likely to induce antibody-dependent cell-mediated cytotoxicity (ADCC) than IgG1 antibodies.

#### The FDA's Assessment:

Results of secondary pharmacology studies were reviewed previously in IND 126472.

The in vitro cytokine release assay was conducted by incubating human PBMCs (n =3 donors) with soluble dostarlimab (up to 400 μg/well) for 3 days, and the release of cytokines (IL-2, IL-4, IL-6, IL-10, IFN-γ, and TNF-α) was determined using multiplex analysis. Dostarlimab did not directly stimulate human PBMCs, and there was no significant release of cytokine levels when compared to RPMI-1640 media control group (Study no. XLB-069).

As determined using a Bio-Layer Interferometry (BLI) method (n=3), the average dissociation

constant ( $K_D$ ) of dostarlimab to the Fc- $\gamma$  receptor CD64 was 2 times higher than IgG1 control (16.42 nM VS. 6.94 nM). Thus, TSR-042 has a lower affinity to Fc- $\gamma$  receptor CD64 than a control IgG1 antibody (Study no. 8324038).

In an ELISA-based C1q binding assay in vitro, the results showed that dostarlimab did not bind to recombinant human complement C1q following incubation for 2 hours, whereas the  $EC_{50}$  value for a human IgG1 control was 3.44  $\mu$ g/mL (Study no. 8324-037).

Based on available nonclinical data, the FDA agrees that dostarlimab has a low potential to induce cytokine release. FDA agrees that dostarlimab does not bind to human C1q and binds to Fc- $\gamma$  receptor CD64 with lower affinity than a control human IgG1. The Applicant did not directly test for ADCC or CDC activities.

### 5.3.3. Safety Pharmacology

#### Data

1. In vitro: An in vitro human ether-à-go-go-related gene (hERG) assay was not conducted with dostarlimab. Monoclonal antibodies (mAbs) such as dostarlimab have a very low potential to interact with the extracellular or intracellular domains on the hERG channel, and they would be highly unlikely to inhibit hERG channel activity.
2. In vivo: No stand-alone in vivo safety pharmacology studies were conducted with dostarlimab. Safety pharmacology endpoints assessing major organ system function, covering the cardiovascular (CV) system (electrocardiography and blood pressure), respiratory system, and central nervous system (CNS), were evaluated as part of the 4-week cynomolgus monkey repeat-dose toxicity study. The administration of dostarlimab by a weekly IV dose for 4 weeks (5 total doses) to cynomolgus monkeys at dose levels of 0, 10, 30, or 100 mg/kg did not result in any dostarlimab-related effects on function of the CV system, respiratory system, or CNS (Study 273-0022-TX).

#### The Applicant's Position

Overall, there were no clinically relevant findings in safety pharmacology endpoints that examined the potential effects of dostarlimab on the CV system, respiratory system, and CNS.

#### The FDA's Assessment:

The FDA agrees with the Applicant's conclusions.

### 5.4. ADME/PK

#### Data:

**Table 4: ADME/PK**

#### **Absorption**

*A 13-week Once Weekly Intravenous Toxicity Study in Cynomolgus Monkeys with an 8-week Recovery Period (Study 4010-09-003)*

Absorption is considered to be 100% due to the intravenous administration of dostarlimab. In the 13-week, repeat-dose TK study, 32 male and female cynomolgus monkeys (4 animals/sex/group in the main study) received multiple doses of vehicle or dostarlimab administered with IV bolus doses of 10 and 30 mg/kg/week or 15-minute IV infusion at doses of 0 and 100 mg/kg/week once a week for a total of 14 doses (Study 4010-09-003). Serum samples for TK analysis were collected at 0 (predose), 5 minutes, and 1, 4, 8, 24, 48, 96, and 168 hours postdose on Study Days 1 and 85.

The observed  $t_{max}$  ranged from 5 minutes postdose to 168 h postdose on Study Day 1 and from 5 minutes postdose to 96 h postdose on Study Day 85. Steady-state serum dostarlimab concentration was achieved by Study Day 85 in males and females at all dose levels tested. Exposure of dostarlimab as defined by  $AUC_{0-168h}$  increased in an approximately dose-proportional manner in males and females on Study Days 1 and 85 across all dose levels tested. Exposure ( $AUC_{0-168h}$ ) increased in males and females on Study Day 85 relative to Study Day 1 in all dose groups, suggesting accumulation of dostarlimab following repeated weekly dosing. Mean accumulation ratios for  $AUC_{0-168h}$  ranged from 2.2 to 3.6 in male and female animals across all dose groups.

No relevant sex-related difference was observed in dostarlimab exposure ( $AUC_{0-168h}$ ) across all dose levels tested, and sex ratios ( $AUC_{0-168h}$  male/ $AUC_{0-168h}$  female) ranged from 0.660 to 1.47. The  $t_{1/2}$ ,  $V_{d,ss}$ , and CL could not be estimated for any dose levels tested on Study Days 1 and 85 because of the sustained serum dostarlimab concentration within the dosing interval. Overall, dose-proportional TK were noted.

Abbreviations: ADME=absorption, distribution, metabolism, and excretion; AUC=area under the concentration time curve; CL=clearance; h=hour(s); IV=intravenous; PK=pharmacokinetics; TK=toxicokinetic;  $t_{1/2}$ =terminal half-life;  $t_{max}$ =time to maximum concentration;  $V_{d,ss}$ =volume of distribution at steady state.

#### The Applicant's Position:

The PK properties of dostarlimab were characterized from TK studies performed in cynomolgus monkeys following IV administration as part of the general toxicity studies. Traditional distribution, metabolism, and excretion studies were not conducted with dostarlimab because it is a monoclonal antibody.

#### The FDA's Assessment:

The FDA agrees with the results of the PK parameters summarized by the Applicant. Additional study results are summarized in the table below.

PK data from the repeat dose toxicity study in cynomolgus monkeys
<b>Study Title/Study no.:</b> A 13-week once weekly intravenous toxicity study in cynomolgus monkeys with an 8-week recovery period/4010-09-003

Text Table 26  
 Summary of Toxicokinetic Parameters in Male and Female Monkeys Following Intravenous Administration of  
 TSR-042

Gender:	Males			Females		
	10	30 <sup>a</sup>	100	10	30	100
TSR-042 Dose (mg/kg/week):	10	30 <sup>a</sup>	100	10	30	100
<u>Parameter (Units)</u>	<u>Day 1</u>					
T <sub>max</sub> (h)	42.5	3.50	1.71	1.29	24.3	0.236
C <sub>max</sub> (µg/mL)	437	1080	2450	405	874	2850
C <sub>168</sub> (µg/mL)	181	287	924	95.1	403	1000
AUC <sub>(0-168)</sub> (hr*µg/mL)	34500	80100	212000	23500	81700	235000
AUC <sub>(0-168)/D</sub> (hr*µg/mL/(mg/kg))	3450	2670	2120	2350	2720	2350
	<u>Day 85</u>					
T <sub>max</sub> (h)	13.3	0.0833	17.0	0.0833	2.27	1.54
C <sub>max</sub> (µg/mL)	937	1760	6510	805	3020	5960
C <sub>168</sub> (µg/mL)	338	803	3600	395	1390	3310
AUC <sub>(0-168)</sub> (hr*µg/mL)	69200	180000	725000	79800	272000	632000
AUC <sub>(0-168)/D</sub> (hr*µg/mL/(mg/kg))	6920	5990	7250	7980	9070	6320
R <sub>AUC</sub> (Ratio)	2.54	2.22	3.60	3.41	3.62	2.99

RAUC = AUC<sub>(0-168)</sub> on Day 85 / AUC<sub>(0-168)</sub> on Day 1; - = not applicable.

T<sub>1/2</sub>, Vd and CL were not reported because R-square less than 0.8 or extrapolation exceeded 20%.

<sup>a</sup> Animal No. 3004 was excluded from mean and SD calculation due to potential impact from ATA.

(Excerpted from Applicant's submission)

## 5.5. Toxicology

### 5.5.1. General Toxicology

#### Data:

#### A 13-week Once Weekly Intravenous Toxicity Study in Cynomolgus Monkeys with an 8-week Recovery Period/Study 4010-09-003

#### Key Study Findings:

- Dostarlimab was well tolerated in cynomolgus monkeys following once weekly IV administration for 13 weeks (14 doses in total) at mid-dose (30 mg/kg/week) and high-dose (100 mg/kg/week) levels.
- One male animal dosed at 10 mg/kg/week was euthanized on Day 89 due to chronic, unresolved, generalized skin findings and secondary swollen and firm inguinal lymph nodes; although consistent with the features of an immune reaction, relationship of these findings to dostarlimab was uncertain since it was not seen in any other animals.
- For the remaining animals that were sacrificed at terminal necropsy, microscopic findings were sporadically observed in the kidney (mild to moderate mononuclear infiltrates), liver (mild mixed cell inflammation) and heart (mild mononuclear cell myocardial infiltrates accompanied by minimal multifocal myocardial degeneration) at all dose levels. Given the slightly increased severity (mild to moderate in dostarlimab-dosed animals versus minimal in control animals) and the mechanism of action of dostarlimab, the microscopic findings could be a result of the

pharmacological effects (immune mediated in nature) of dostarlimab or dostarlimab-related exacerbation of background findings.

**Conducting Laboratory and Location:**

(b) (4)

**GLP Compliance:** Yes

**Methods:**

See [Table 5](#).

**Table 5: General Toxicology - Methods**

Dose and frequency of dosing:	0 (vehicle), 10, 30, or 100 mg/kg/dose once weekly for 13 weeks (14 doses in total)
Route of administration:	Intravenous (IV) infusion
Formulation/Vehicle:	(b) (4) mM citrate, pH (b) (4) mM arginine drochloride, (b) (4) mM sodium chloride and (b) (4) w/v polysorbate 80
Species/Strain:	Cynomolgus monkey
Number/Sex/Group:	4/sex/group (main) 2/sex/group (8-week recovery period) assigned to control and high-dose groups
Age:	2.5 to 5.1 years old
Satellite groups/Unique design:	None/cytokine analysis, immunophenotyping, ADA, TDAR
Deviation from study protocol affecting interpretation of results:	No

Abbreviations: ADA=anti-drug antibody; TDAR=T-dependent antigen response; w/v weight by volume.

**Observations and Results: Changes from Control**

See [Table 6](#).

**Table 6: General Toxicology - Observations and Results: Changes from Control**

Parameters	Major Findings
<b>Mortality</b>	<p>One male dosed at 10 mg/kg/week (#2002) was euthanized on Day 89 due to chronic and unresolved skin findings with secondary swollen and firm inguinal lymph nodes. Correlated microscopic findings in the skin were consistent with the features of an immune reaction. The relationship of these findings to dostarlimab was uncertain since it was not seen in any other animals.</p> <p>The skin findings could be a result of the pharmacological effects of dostarlimab based on the mechanism of action, but unlikely to be related to the anti-drug antibody (ADA), given the low titer of ADA and the lack of correlation between the titer and progression of skin findings.</p> <p>The dostarlimab exposure in this animal was comparable to the exposure observed in the others of the group.</p>
<b>Clinical Signs</b>	<p>Although observed in all groups, including control, liquid feces were considered a possible dostarlimab-related effect at <math>\geq 30</math> mg/kg/week, given the increased incidence and timing relative to dosing. However, this transient, sporadic, and dose-independent clinical sign was not considered adverse since there were no associated changes in food consumption or body weight as well as lack of associated pathology findings.</p> <p>Other clinical observations, including abrasions, decreased activity, laceration, bruising, shallow breathing, missing digit, and partially closed eyes, were considered incidental, related to study procedures, or transient and did not persist.</p>

**Table 6: General Toxicology - Observations and Results: Changes from Control (Continued)**

Parameters	Major Findings
<b>Body Weights and Food Evaluation (Qualitative)</b>	Unremarkable
<b>Body Temperature, Blood Pressure, and Heart Rate</b>	Unremarkable
<b>Ophthalmoscopy</b>	Unremarkable
<b>ECG</b>	Unremarkable
<b>Hematology and Coagulation</b>	Unremarkable
<b>Clinical Chemistry</b>	<p>No definitive dostarlimab-related changes were noted. There were dose-independent, minimally increased globulins for females at <math>\geq 10</math> mg/kg/week on Day 30 (1.13x to 1.17x). Globulins remained minimally increased at 100 mg/kg/week on Day 92 (1.13x) and on Day 168 (1.17x) compared to control but were comparable to baseline values. These changes did not attain statistical significance and were considered of uncertain relationship to dostarlimab due to the small magnitude of change, the lack of a dose response and the absence of a clear change in the male animals.</p>
<b>Urinalysis</b>	Unremarkable

Parameters	Major Findings
Gross Pathology	No dostarlimab-related gross findings were noted.
Organ Weights	Unremarkable
Histopathology	<p>For the animals that survived to their scheduled terminal necropsies, possible test article-related changes were observed in the kidney, liver, and heart in animals dosed at <math>\geq 10</math> mg/kg/week:</p> <p>Mild to moderate mononuclear cell infiltrates were observed in the kidney of 1 male at 10 mg/kg/week and 1 female at 30 mg/kg/week.</p> <p>Mild mixed cell inflammation was observed in the liver of 1 male at 30 mg/kg/week.</p> <p>Mild mononuclear cell myocardial infiltrates accompanied by minimal multifocal myocardial degeneration was observed in the heart of 1 female at 100 mg/kg/week.</p> <p>In addition, mild mononuclear cell myocardial infiltrates accompanied by minimal multifocal myocardial degeneration were also noted in the heart of 1 male at 100 mg/kg/week following the 8-week recovery.</p>

**Table 6: General Toxicology - Observations and Results: Changes from Control (Continued)**

Parameters	Major Findings
Toxicokinetics	<p>In males and females across all dose levels tested, <math>T_{max}</math> ranged from 5 minutes post dose to 168 hours post dose on Day 1 and ranged from 5 minutes post dose to 96 hours post dose on Day 85. By Day 85, steady state serum dostarlimab concentration was achieved in males and females in all dose levels tested.</p> <p><math>T_{1/2}</math>, <math>V_d</math>, and CL could not be estimated in any dose levels tested on Days 1 and 85 because of the sustained serum dostarlimab concentration within the dosing interval.</p> <p><math>AUC_{0-168h}</math> increased in a roughly dose-proportional manner in males and females across all dose levels tested on Days 1 and 85. <math>AUC_{(0-168)}</math> increased in males and females on Day 85 relative to Day 1 in all dose groups, suggesting dostarlimab accumulation following repeated weekly dosing. Mean accumulation ratios for <math>AUC_{0-168h}</math> ranged from 2.22 to 3.62 in males and females across all dose groups.</p> <p>No relevant gender difference was observed in dostarlimab exposure, as defined by <math>AUC_{0-168h}</math>, across all dose levels tested and gender ratios (male/female) ranged from 0.660 to 1.47.</p>
<b>Other Evaluations</b>	
Anti-therapeutic Antibody	Unremarkable; no ATA-related toxicity was observed in this study.
Cytokine Analysis	Unremarkable; no dostarlimab-related changes to the plasma concentrations of IFN $\gamma$ , IL-1 $\beta$ , IL-2, IL-6, IL-8, IL-10, TNF $\alpha$ , and IL-17.
Immunophenotyping	Unremarkable; no dostarlimab-related alterations in absolute counts or relative percentages of CD3+ T-lymphocytes, CD3+/CD4+ T-helper, CD3+/CD8+ T-cytotoxic, CD20+ B-lymphocytes, and CD3-/CD16+ NK cells as well as CD3-/CD14+ monocytes.

Parameters	Major Findings
<b>T-cell Dependent Antibody Response</b>	Unremarkable; no alterations in the primary, secondary, or tertiary anti-KLH IgM and IgG responses that could be attributed to administration of dostarlimab.

Abbreviations: ADA=anti-drug antibody; ATA=anti-therapeutic antibody; AUC=area under the concentration time curve; CD=cluster of differentiation; CL=clearance; h=hours(s); IFN $\gamma$ =interferon gamma; IgG=immunoglobulin G; IgM=immunoglobulin M; IL=interleukin; KLH=keyhole limpet hemocyanin; NK=natural killer;  $t_{1/2}$ =half life  $T_{max}$ =time to maximum concentration; TNF $\alpha$ =tumor necrosis factor alpha;  $V_d$ =volume of distribution.

The Applicant's Position:

Dostarlimab was well tolerated in cynomolgus monkeys following once weekly IV administration for 13 weeks at dose levels of 30 and 100 mg/kg.

One male dosed at 10 mg/kg/week was euthanized for humane reasons due to chronic, unresolved, generalized skin findings and secondary swollen and firm inguinal lymph nodes. Correlated microscopic findings noted in the skin were consistent with the features of an immune reaction. It was uncertain whether they were dostarlimab-related, as they were not seen in any other dostarlimab-dosed animals. However, they could be a result of the pharmacological effects based on the mechanism of action.

For the animals survived to their scheduled terminal necropsies, sporadic and dose-unrelated macroscopic and/or microscopic findings of an immune-mediated nature were observed in the kidney, liver, or heart of 1 to 2 animals/group dosed with dostarlimab. It was uncertain whether these findings were dostarlimab-related as these findings are commonly observed in cynomolgus monkeys and the incidence or severity of these findings was not dose-related. However, based on the mechanism of action, these findings could be a result of the pharmacological effects.

The nonclinical toxicology studies in monkeys are considered to adequately support the toxicological assessment of dostarlimab for registration.

The FDA's Assessment:

In general, the FDA agrees with the Applicant's conclusions.

Other target organs of toxicity included thymus, stomach, bone marrow, adrenal gland, salivary gland, and minimal inflammation in several organs. Additional study results are summarized in the table below.

<b>Mortality</b>	<p>Additional findings for the early mortality in the 10 mg/kg dose group include:</p> <ul style="list-style-type: none"> <li>• Macroscopic findings included generalized pale tan scaling of the skin and dark black thickening of the ears (pinna).</li> <li>• Microscopic findings included changes in skin (moderate mononuclear cell inflammation), lymph nodes (mild to moderate increased lymphoid cellularity in the axillary, mandibular, and inguinal lymph nodes), spleen (minimal increased cellularity), site injection (minimal degeneration/regeneration of myofiber and inflammation), and thyroid gland (minimal histiocytic infiltration in follicular lumen). In</li> </ul>
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	<p>addition, minimal inflammation was observed in kidney, tongue and heart.</p> <ul style="list-style-type: none"> <li>For skin inflammation, affected skin areas were treated with silver sulfadiazine cream once daily for 5 days (Days 27 through 31). Omega sandwich was given once daily for 33 days (Days 56 through 88); dermal bath was performed, and Aveeno lotion was applied on Day 66; clavomax (27 mg, twice daily) was given orally for 15 days (Days 74 through 88). The animal was not responsive to the treatments and was euthanized on Day 89.</li> </ul>																																																
<p><b>Blood pressure and Heart Rate (measured within 1 hour post-dose)</b></p>	<p><u>Terminal Sacrifices (compared to control on Day 85)</u></p> <ul style="list-style-type: none"> <li>A 22% decrease in heart rate was observed in M at HD.</li> <li>A dose-dependent increase in mean arterial blood pressure was observed in M from MD to HD and ranged from 31-87%. The mean increase is primarily due to variation of a single animal in these groups.</li> <li>A 39% decrease in systolic blood pressure was observed in M at HD.</li> <li>An increase in heart rate was observed in all dose groups (up to 11%) in F.</li> </ul> <p><u>Recovery (HD only)</u>          All changes in blood pressure and heart rate parameters were either reversible or trending towards recovery at end of recovery period.</p>																																																
<p><b>Hematology</b></p>																																																	
<p><u>Terminal Sacrifices</u></p>																																																	
<table border="1"> <thead> <tr> <th rowspan="2">Parameters</th> <th colspan="6">% Change from control at sacrifices (Day 92)</th> </tr> <tr> <th colspan="3">Males</th> <th colspan="3">Females</th> </tr> </thead> <tbody> <tr> <td>Sex</td> <td></td><td></td><td></td> <td></td><td></td><td></td> </tr> <tr> <td>Dose levels (mg/kg/day)</td> <td>10</td><td>30</td><td>100</td> <td>10</td><td>30</td><td>100</td> </tr> <tr> <td>Total number of animals</td> <td>3</td><td>4</td><td>4</td> <td>4</td><td>4</td><td>4</td> </tr> <tr> <td>Absolute reticulocytes</td> <td></td><td></td><td></td> <td></td><td>-19</td><td>-16</td> </tr> <tr> <td>Absolute basophils</td> <td></td><td></td><td></td> <td></td><td>-11</td><td>-33</td> </tr> </tbody> </table>		Parameters	% Change from control at sacrifices (Day 92)						Males			Females			Sex							Dose levels (mg/kg/day)	10	30	100	10	30	100	Total number of animals	3	4	4	4	4	4	Absolute reticulocytes					-19	-16	Absolute basophils					-11	-33
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<p><b>Clinical Chemistry</b></p>	<p>Unremarkable</p>																																																
<p><b>Urinalysis</b></p>	<p><u>Terminal Sacrifices (compared to VH control)</u></p> <ul style="list-style-type: none"> <li>A decrease in urine volume was observed in all dose group in M (18% at LD, 52% at MD, and 44% at HD).</li> </ul> <p><u>Recovery (HD only)</u>          All changes in urinalysis parameters were either reversible or trending towards recovery at end of recovery period.</p>																																																
<p><b>Gross Pathology</b></p>	<p><u>Terminal Sacrifices</u></p> <ul style="list-style-type: none"> <li>Dark red color of subcutaneous tissue was observed in 1/4 M at HD and 2/4 F at LD.</li> <li>Gelatinous of urinary bladder was observed in 1/4 M at HD.</li> </ul> <p><u>Recovery (HD only)</u>          All changes in gross pathology parameters were reversible at end of recovery period.</p>																																																
<p><b>Organ Weights</b></p>	<p><u>Terminal Sacrifices (compared to VH control)</u></p>																																																

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	<ul style="list-style-type: none"> <li>An increase in spleen weight was observed in all dose groups ranged from 16-45%.</li> </ul> <p><u>Recovery (HD only)</u>          All changes in organ weight were reversible or trending towards recovery except the following;</p> <ul style="list-style-type: none"> <li>A decrease in thymus was observed in both M (19%) and F (32%) at HD.</li> </ul>
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**Histopathology**  
**Adequate battery:** Yes

Terminal sacrifices (excluded early moribund sacrificed animal)

Dose (mg/kg/week)	Males				Females			
	0	10	30	100	0	10	30	100
N	4	3	4	4	4	4	4	4
<b>Bone marrow</b> Increased cellularity; lymphoid Minimal			1	1				
<b>Gland, adrenal</b> Hypertrophy/hyperplasia; cortical Minimal			1	1				
<b>Gland, salivary</b> Depletion; zymogen Minimal			1	1			1	1
<b>Heart</b> Degeneration; myocardial Minimal								1
<b>Stomach</b> Degeneration/regeneration; mucosa; epithelial Mild				1				
<b>Thymus</b> Decreased cellularity; lymphoid Minimal Mild							1	1

Additional findings of minimal mixed cell/mononuclear cell infiltration were observed in multiple organs including epididymis, GI tract, eye, gallbladder, adrenal gland, mammary gland, parathyroid gland, salivary gland, thyroid, injection site, heart, kidney, liver, sciatic nerve, pancreas, spinal cord, and uterus.

Recovery (only at HD)

All histopathology findings were either reversible or trending towards recovery at end of recovery period except the following:

- Minimal myocardial degeneration in heart (1/2 M)
- Minimal mucosal congestion in cecum (1/2 F).
- Minimal ectasia crypt of stomach (1/2 M)
- Minimal eosinophilic infiltration in uterus (1/2 F)
- Minimal mononuclear cell infiltration in choroid plexus and meninges of brain, ciliary body of eyes, thyroid gland, lung, mesenteric lymph node, nerve sciatic, spinal cord, and stomach.

**Anti-drug antibody (ADAs)**

- No animal from the control group was screened positive.

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- ADAs were observed in 3 pre-dose animals on Day 1 (3103 (M at MD), 4006 (M at HD), and 4506 (F at HD) with baseline titer result of 5-10. According to the Applicant, these results were likely either false negative or non-specific signals.
- On Day 15 and beyond, ADAs specific for the dostarlimab were observed at  $\geq 10$  mg/kg dose level.

Dose (mg/kg/week)	VH		10		30		100	
	M	F	M	F	M	F	M	F
Study Day								
1	0/6	0/6	0/4	0/4	1/4	0/4	1/6	1/6
15	0/6	0/6	1/4	1/4	3/4	2/4	3/6	2/6
29	0/6	0/6	1/4	3/4	4/4	2/4	4/6	3/6
57	0/6	0/6	1/4	3/4	4/4	0/4	2/6	3/6
85	0/6	0/6	1/4	2/4	2/4	0/4	1/6	3/6
92	0/6	0/6	0/4	2/4	1/4	0/4	0/6	2/6
99	0/2	0/2	NA	NA	NA	NA	0/2	1/2
106	0/2	0/2	NA	NA	NA	NA	0/2	2/2
113	0/2	0/2	NA	NA	NA	NA	0/2	1/2
120	0/2	0/2	NA	NA	NA	NA	0/2	1/2
134	0/2	0/2	NA	NA	NA	NA	0/2	1/2
148	0/2	0/2	NA	NA	NA	NA	0/2	2/2
Sub-total	0/6	0/6	1/4	3/4	4/4	2/4	5/6	4/6
Positive Rate (%)	0%	0%	25%	75%	100%	50%	83.33%	67%

**T-cell dependent antigen testing  
(anti-KLH IgM and IgG)**

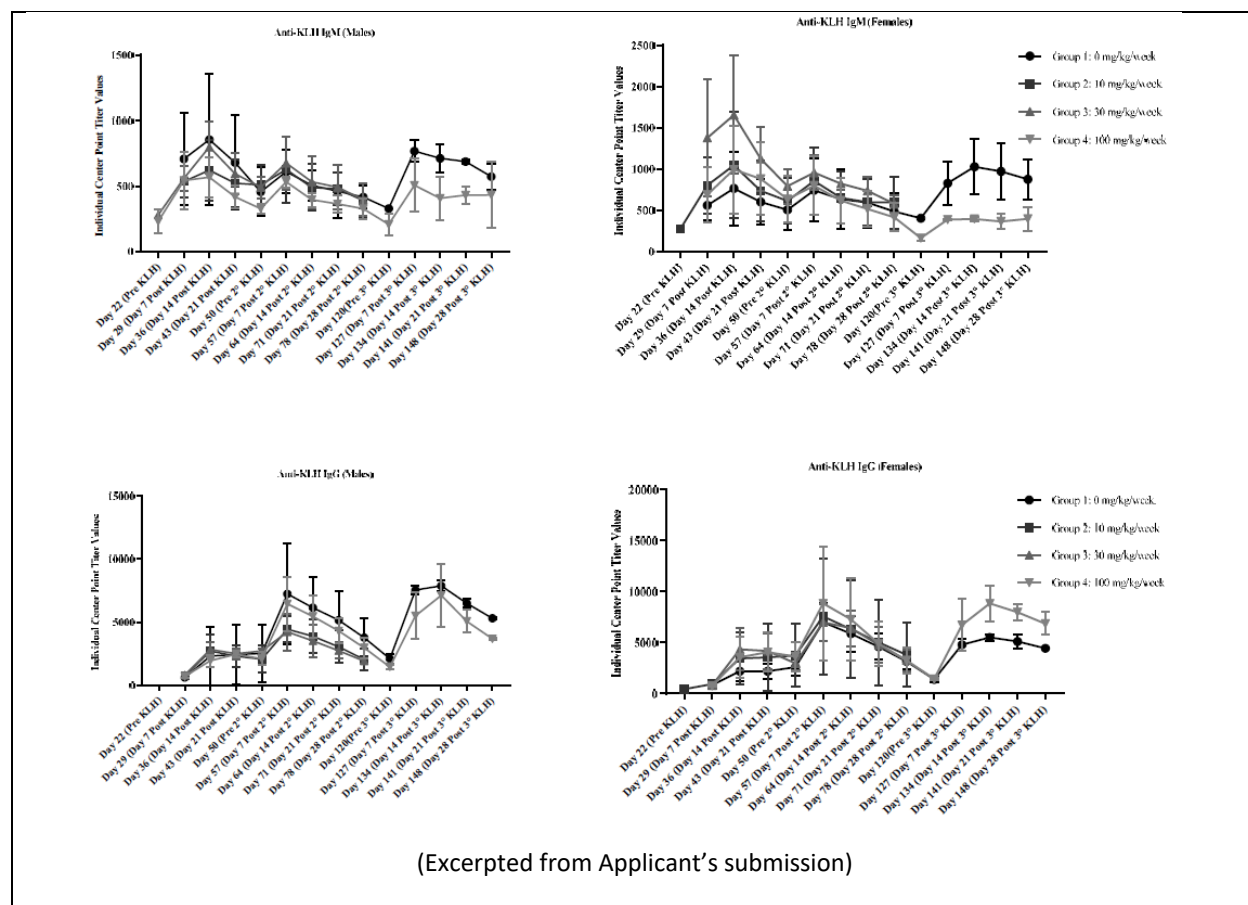
Anti-KLH IgM and IgG antibodies in monkey serums were analyzed by ELISA.

Terminal Sacrifices

- All main study and recovery animals produced primary and secondary humoral anti-KLH IgM and IgG responses after immunization with KLH on Days 22 and 50.
- Dostarlimab did not induce any remarkable changes in the primary or secondary anti-KLH IgM and IgG responses when compared to vehicle control group.

Recovery (only HD)

- The recovery animals produced a tertiary humoral anti-KLH IgM and IgG responses after immunization with KLH on Day 120.
- Dostarlimab did not induce any remarkable changes in the tertiary anti-KLH IgM and IgG responses.



**General Toxicology; additional studies**

Data:

**4-week Repeated Intermittent Intravenous Infusion GLP Toxicity, Toxicokinetics and Safety Pharmacology Study in the Cynomolgus Monkey with 4-week Recovery/Study 273-0022-TX**

A 4-week, GLP, repeat-dose, IV toxicity study was performed in cynomolgus monkeys to evaluate the potential systemic toxicity, TK, and immunogenicity of dostarlimab (Study 273-0022-TX). Safety pharmacology endpoints assessing major organ system function, covering the cardiovascular (CV) system (electrocardiography and blood pressure), respiratory system, and central nervous system (CNS), were evaluated as part of the study. Cynomolgus monkeys (6 animals/sex/group) were administered an IV dose of 0 (vehicle control), 10, 30, or 100 mg/kg dostarlimab once weekly for 4 weeks. The administration of dostarlimab as a weekly IV dose (5 total doses) to cynomolgus monkeys at 10, 30, or 100 mg/kg was well tolerated and did not result in any dostarlimab-related effects on clinical signs, body weight, food consumption, electrocardiography, ophthalmology, safety pharmacology parameters, and clinical or anatomic pathology. The NOAEL was considered to be 100 mg/kg, the top dose tested. At 100 mg/kg, the Day 22 C<sub>max</sub> and area under the concentration-time curve from time 0 to 168 hours (AUC<sub>0-168h</sub>) were 4,070 µg/mL and 419,000 µg•h/mL, respectively

The Applicant's Position:

No findings of toxicological significance were observed in the 4-week repeat-dose toxicity study with dostarlimab, and the NOAEL was determined to be 100 mg/kg, which was the highest dose tested.

The FDA's Assessment:

Results of 4-week repeated dose toxicity studies were reviewed previously in IND 126472.

In general, the FDA agrees with the Applicant's conclusions. Histopathology findings included minimal chronic hypertrophy/hyperplasia of the heart (1/4 male at 100 mg/kg), kidneys (1/4 male at 30 mg/kg and 1/4 male at 100mg/kg), pancreas (1/4 male at 100 mg/kg), and thyroid gland (1/4 male at 100 mg/kg). Changes in histopathology findings were reversible at end of 4-week recovery period. In addition, immunogenicity was confirmed in ~25% animals (1/24 male and 5/24 females); however, there was no evidence of compromised exposures.

### 5.5.2. Genetic Toxicology

The Applicant's Position:

Genotoxicity studies with dostarlimab have not been conducted as these studies are not required for biotechnology-derived products according to ICH S6 (R1).<sup>11</sup>

The FDA's Assessment:

The FDA agrees that genotoxicity studies are not warranted for this BLA submission.

### 5.5.3. Carcinogenicity

The Applicant's Position:

Carcinogenicity studies with dostarlimab have not been conducted as these studies are not required for biotechnology-derived products according to ICH S6(R1). In addition, ICH S9 states that carcinogenicity studies are not warranted for therapeutics intended to treat patients with advanced cancer.<sup>12</sup>

The FDA's Assessment:

The FDA agrees that carcinogenicity studies are not warranted for this BLA submission.

### 5.5.4. Reproductive and Developmental Toxicology

The Applicant's Position:

No reproductive and developmental studies were conducted because of potential adverse effects of the blockade of PD-1/programmed death-ligand 1 (PD-L1) pathway on the immune tolerance at the fetomaternal interface. Consistent with the ICH S9 guidance, fertility assessments are not typically expected for products intended for the treatment of patients with cancer.

Based on a review of the available literature on the functions of the PD-1/PD-L1 pathway, blockade of the PD-1/PD-L1 pathway may disrupt the immune tolerance at the fetomaternal

interface. This could result in pregnancy disorders and complications. Therefore, there is an inherent risk to the embryo or fetus associated with the administration of dostarlimab, which blocks the PD-1/PD-L1 pathway.

Dostarlimab is, however, not expected to affect the intrauterine fetal growth and development because the viability and intrauterine growth and development of fetuses are not affected in PD-L1 knockout mice. Additionally, dostarlimab is not active in any animal species other than nonhuman primates. Reproductive and developmental toxicity studies would therefore have to be conducted in monkeys. Considering the high rate of spontaneous abortion in the monkey and the anticipated increased risk of abortion associated with PD-1/PD-L1 blockade, a reproductive and developmental toxicity study would require the use of many animals to be able to deliver interpretable results. In accordance with the 3R (reduce/refine/replace) principles, reproductive and developmental toxicity studies have, therefore, not been performed with dostarlimab.<sup>13</sup>

#### The FDA's Assessment:

The FDA agrees that dedicated reproductive and developmental toxicity studies are not needed to support this BLA submission, and the Applicant's literature-based assessment of the potential reproductive toxicity of dostarlimab is acceptable.

Studies in the literature demonstrate that the PD-1/PD-L1 pathway plays a critical role in maintaining maternal immunological tolerance to the fetus during pregnancy. PD-L1 is expressed on trophoblast cells in the placenta throughout pregnancy in humans (Petroff, et al., 2003). Based on results from Guleria et al. (2005), the fetomaternal tolerance was studied in a mouse abortion-prone allogeneic pregnancy model (CBA x C57BL/6). PD-L1 expression was detected at the utero-placental interface of the placenta as early as 10.5 days post-conception. An increased incidence of abortion rates and pregnancy loss (86%) were observed in the allogeneic pregnant mice administered 250-500 µg of a murine anti-PD-L1 monoclonal antibody intraperitoneally on Day 6.5, 8.5, 10.5, and 12.5 post-conception when compared to isotype control (18%). However, anti-PD-L1 treatment in a syngeneic (C57BL/6 x C57BL/6) mouse model did not cause resorption. In addition, the results showed that allogeneic fetal rejection was T-cell dependent but not B-cell dependent because PD-L1-specific antibody treatment caused fetal rejection in B-cell deficient but not in Recombination Activating Gene (RAG)-1-deficient females (lack T cells and B cells but have antigen-presenting cells). Moreover, increased rates of abortion occurred in female PD-L1 homozygous knockout (PD-L1 -/-) mice compared to female PD-L1 heterozygous knockout mice. Increases in IFN-γ-producing Th1 cells at the maternal-fetal interface were observed in pregnant PD-L1 -/- mice as well as mice administered an anti-PD-L1 antibody compared to appropriate controls.

Other published nonclinical studies also suggest that PD-L1 expressing Tregs are responsible for tolerance to fetal alloantigens. In an allogeneic pregnancy C57BL/6 mouse model, depletion of Tregs before mating abrogated the effect of PD-L1 blockade on fetal resorption and fetal survival rate when compared to isotype control, whereas adoptive transfer of Tregs from wild-type mice to PD-L1-/- mice improved fetal survival (Habicht, et al, 2007).

In an alloantigen-specific CD4<sup>+</sup> TCR transgenic mouse model (ABM-tg mouse), PD-L1 blockade resulted in an increase in embryo resorption (34% VS 1.4%) and a reduction in litter size (5.8 VS 8.5) when compared to isotype control group (D'Addio, et al., 2011). In the same model, neutralization of IL-17 abrogated the anti-PD-L1 effect on fetal survival rate (increase in litter size and decrease fetal resorption) and restored Treg number. In addition, PD-L1 blockade increased the frequency of IL-17-producing cells from CD4<sup>+</sup>Foxp3<sup>-</sup> cells in a dose-dependent manner; however, when CD4<sup>+</sup>Foxp3<sup>+</sup> Tregs were cultured in the presence of anti-PD-L1, they failed to convert to Th17 producing cells (D'Addio, et al., 2011). These results suggest that IL-17-producing cells are derived mainly from CD4<sup>+</sup>Foxp3<sup>-</sup> cells and not Tregs. In pre-eclampsia patients, it was found that the percentage of Treg cells significantly decreased and the percentage of Th17 cells increased compared with normal pregnancy (Tian, et al., 2016 and Darmochwal-Kolarz, et al., 2012). These results suggested that Treg and Th17 cells play a critical role in the maternal-fetal tolerance, including in pregnant women with pre-eclampsia, and altering the PD-1/PD-L1 pathway contributed to Treg/Th17 imbalance.

Collectively, published literature suggests the importance of the PD-1/PD-L1 pathway in maintaining maternal-fetal tolerance; however, blockade of PD-1/PD-L1 signaling in PD-L1<sup>-/-</sup> mice or via an anti-PD-1/PD-L1 antibody did not result in overt malformations in offspring (Guleria, et al, 2005; Habicht, et al., 2007; and Wafula, et al., 2009). The maternal-fetal interface of mice is similar to that of humans, suggesting that findings from mouse models of allogeneic pregnancy are applicable to humans. A study from Li, et al., 2015 demonstrated that mRNA expression of PD-L1, but not PD-1, was significantly decreased (~2-fold lower than control) in decidual tissues isolated from 19 patients with early recurrent miscarriage compared to woman with healthy pregnancies (n=22). In addition, flow cytometry analysis showed that decidual CD4<sup>+</sup> T cells from patients with recurrent miscarriage (n= 23) had a significant, approximately 4-fold lower co-expression of PD-1 and T-cell immunoglobulin mucin (Tim)-3 when compared to decidual CD4<sup>+</sup> T cells from women with normal pregnancies (n=28) (Wang, 2016). In another ex vivo study, PD-1 and PD-L1 expression on Th17 cells as well as PD-1 expression on Th1 cells were significantly down regulated (≥ 65%) in women with recurrent pregnancy losses (n=45) when compared to 20 women who had at least one or more live-born infants (Wang, et al., 2020). Thus, down regulation of PD-1/PD-L1 pathway may be associated with pregnancy loss.

Dostarlimab is a humanized IgG4 antibody. Human IgG4 is known to cross the placenta. Thus, dostarlimab may be transmitted from the mother to the fetus. Based on its mechanism of action and findings from murine models of pregnancy, administration of dostarlimab is likely to disrupt the maintenance of normal pregnancy. Potential risks associated with administration of dostarlimab during pregnancy include increased rates of abortion and stillbirth. In addition, fetal exposure to dostarlimab may alter the normal immune response or increase the risk of developing immune-related disorder because PD-1<sup>-/-</sup> mice develop late onset autoimmune phenotypes (Okazaki and Honjo 2007). Thus, a warning for embryo-fetal toxicity is recommended for JEMPERLI. Based on a half-life of approximately 25 days, females of reproductive potential are advised to use effective contraception during treatment with JEMPERLI and for at least 4 months after the final dose.

Fertility studies have not been conducted with dostarlimab and are not needed to support a BLA for the proposed indication. In 3-month repeat-dose toxicity studies in monkeys, there were no notable effects in the male and female reproductive organs at doses up to the highest dose tested, 100 mg/kg/week ( $\geq 53$  times the human exposure based on AUC at the clinical starting dose of 500 mg); however, many animals in these studies were not sexually mature.

#### 5.5.5. Other Toxicology Studies

##### Data:

##### **GLP Tissue Cross-reactivity Study in a Full Panel of Normal Human Tissues (Study 4010-09-001)**

##### **Tissue Cross-reactivity Study in Normal Cynomolgus Monkey Tissues (Study 4010-09-002)**

GLP tissue cross-reactivity studies were performed with fluorescein-labeled dostarlimab and full panels of normal human tissue (Study 4010-09-001) and normal cynomolgus tissue (Study 4010-09-002). Specific binding of dostarlimab was observed on plasma membrane elements of lymphocytes (including intravascular, perivascular, interstitial, and migrating lymphocytes) in a large number of tissues and to monocytes in peripheral blood. Dostarlimab did not bind to other tissue elements examined in the human and cynomolgus monkey tissue panels. PD-1 is expressed on CD4+ T cells, CD8+ T cells, natural killer T cells, B cells, and monocytes following activation of these cell types.<sup>14,15</sup> Dostarlimab stained cell types as anticipated, suggesting that off-target toxicity is unlikely.

##### The Applicant's Position:

No findings of toxicological relevance were observed in the in-vitro tissue cross-reactivity studies using human and cynomolgus monkey tissues.

##### The FDA's Assessment:

Results of tissue cross-reactivity studies were reviewed previously in IND 126472.

The FDA agrees that dostarlimab demonstrated overall comparability in staining between frozen cynomolgus monkey and human tissue panels, and there was no unexpected staining.

##### ***Other toxicity studies also included:***

##### **Literature Based Assessment of Potential for Effects on Infection**

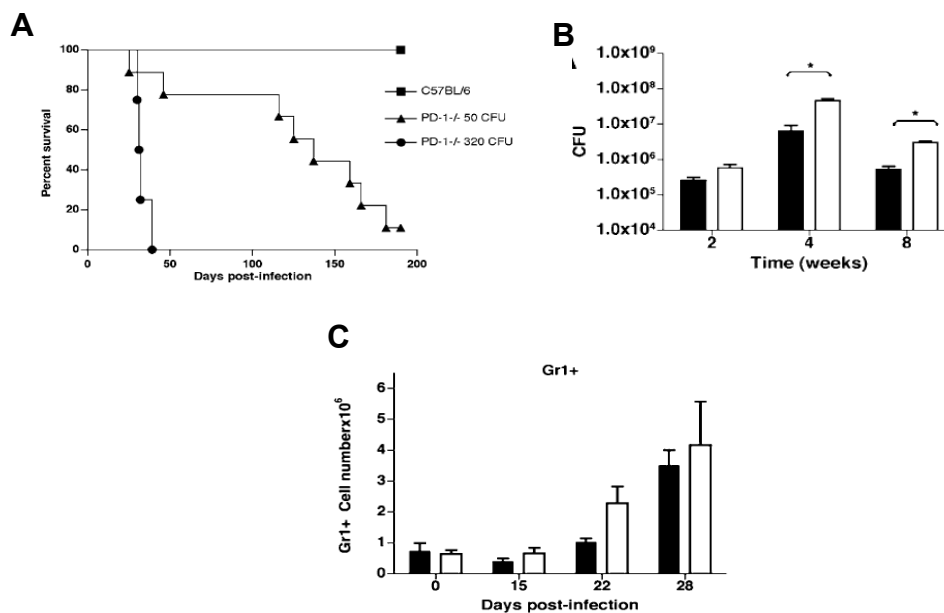
(Reviewed by Dr. Shawna Weis)

Published literature demonstrated that the absence of PD-1 signaling can increase susceptibility to certain pathogens such as tuberculosis and lymphocytic choriomeningitis virus (LCMV) in some animal models.

A significant decrease in survival as early as 28 days post-infection (Figure 1A) was observed in a PD-1-deficient C57BL/6 mouse model infected with *M. tuberculosis*, which correlated with a

higher number of bacterial proliferation (Figure 1B; dark bars = wild-type) and a larger inflammatory response in the lungs of PD-1-deficient mice compared with wild-type controls (Figure 1D; dark bars = wild-type). Therefore, PD-1 appears to play an essential role in controlling the excessive inflammatory responses in the lungs of mice infected with *M. Tuberculosis* (Lazar-Molnar, et al., 2010); however, the pathogenesis of this observation has not been clearly defined. Especially, it is unclear whether the decreased survival reflects uncontrolled bacterial growth resulting from an inability to mount appropriate antibacterial responses and/or whether it is a failure to downregulate the immune reaction that leads to massive tissue destruction and organ failure.

**Figure 1 Decreased survival, increase bacterial proliferation and increased inflammation in PD-deficient mice infected with *M. tuberculosis***



(Derived from Lazar-Molnar, et al., 2010)

PD-L1 deficient mice died early after chronic systemic LCMV infection (Barber et al., 2006). In mouse models of LCMV infection, the absence of PD-1 pathway signaling resulted in fatal CD8<sup>+</sup> T cell-mediated pathology due to killing of virally infected endothelial cells, systemic vascular leakage, and ultimately cardiovascular collapse (Frebel et al., 2012; Mueller et al., 2010).

These data suggest that there is concern that treatment with dostarlimab may increase susceptibility to these pathogens (i.e., tuberculosis infection or viral infection). In addition, infected patients with these pathogens may develop more severe disease in the presence of dostarlimab.

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Wimolnut Manheng  
Primary Reviewer

Tiffany K. Ricks  
Supervisor

## 6. CLINICAL PHARMACOLOGY

### 6.1. Executive Summary

#### The FDA's Assessment:

Dostarlimab is an anti-programmed cell death protein 1 (PD-1) humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) produced by recombinant DNA technology using a stable Chinese hamster ovary (CHO) cell line. The Applicant seeks an accelerated approval of dostarlimab for the treatment of adult patients with recurrent or advanced endometrial cancer (EC) that has progressed on or following prior treatment with a platinum-containing regimen whose tumors are mismatch repair (MMR) deficient (dMMR), as determined by an FDA-approved test. The proposed clinical dose of 500 mg given every 3 weeks (Q3W) for 4 cycles followed by 1000 mg every 6 weeks (Q6W) thereafter.

The Clinical Pharmacology Review evaluated the immunogenicity, population pharmacokinetic (PPK) and exposure-response (E-R) data obtained from the ongoing first-in-human (FIH) Study 4010-01-001 (GARNET). The incidence of treatment-emergent positive anti-dostarlimab antibodies (ADAs) is generally low at the proposed clinical dose (2.5%, n=8/315). The impact of immunogenicity on each of efficacy, safety or PK of dostarlimab is inconclusive because of the limited number of ADAs observed in the study. Dostarlimab has an elimination half-life of 25.4 days. There are 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 dose of 500 mg given every 3 weeks (Q3W) for 4 cycles followed by 1000 mg every 6 weeks (Q6W) thereafter is acceptable based on the clinically significant improvement in ORR (42%, N=71) and an acceptable safety profile obtained in the GARNET study.

#### **Recommendations**

The Office of Clinical Pharmacology has reviewed the information and data submitted in BLA 761174. This BLA is approvable from a clinical pharmacology perspective with no major review issues as seen in the table below.

<b>Review Issues</b>	<b>Recommendations and Comments</b>
<b>Supportive evidence of effectiveness</b>	The primary evidence of effectiveness comes from the FIH phase 1 Study 4010-01-001 (GARNET) in 71 patients with recurrent or advanced endometrial cancer (EC) whose tumors are mismatch repair deficient (dMMR). An ORR of 42% was observed at the proposed clinical dose. Refer to Section 7 of this review for further details.
<b>General dosing instructions</b>	The proposed dose is 500 mg every 3 weeks (Q3W) for 4 cycles, followed by 1000 mg every 6 weeks (Q6W), thereafter starting from Cycle 5 until disease progression or unacceptable toxicity. This dosing regimen is supported by the clinically significant improvement in ORR (42%, N=71) and an acceptable safety profile

	observed in GARNET Study. Refer to Section 7 of this review for further details.
<b>Dosing in patient subgroups (intrinsic and extrinsic factors)</b>	The PPK analysis of data from GARNET Study indicates that the various covariates such as age (24-86 years), sex (male = 101, females = 376), race/ethnicity, body weight (range = 40-86 kg), ADAs, alkaline phosphatase (ALP), tumor type, tumor size, normal renal function (RF) to moderate renal impairment (RI) (normal RF = 173, mild RI = 210, moderate RI = 90, severe RI = 3, ESRD=1]) or normal hepatic function (HF) to mild hepatic impairment (HI) (normal HF = 425, mild HI = 48, moderate HI = 4) have no clinically significant effect on dostarlimab PK. No dosage adjustments are needed for any intrinsic or extrinsic factors.
<b>Labeling</b>	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.
<b>Bridge between the to-be marketed and clinical trial formulations</b>	No <i>in vivo</i> comparability studies have been conducted. There were no changes to the formulation during clinical development. The only changes during clinical development were to scale-up of drug substance (DS) and to change the manufacturing facility. The scaled-up DS manufacturing process at (b) (4) was compared to the original 2000 L process manufactured at (b) (4) through a formal comparability assessment.

**Post-marketing requirements (PMRs) or post-marketing commitments (PMCs):**

None.

## 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 of dostarlimab, based on data following single and repeated IV administration from 477 patients with various cancers enrolled in the first-in-human Study 4010-001-01 (GARNET).

Dostarlimab is administered by a 30-minute intravenous (IV) infusion. In a population PK analysis, a 2-compartment model with non-linear, time-dependent elimination, and weight as an allometric factor on clearance (CL) and central volume of distribution (V1) fit the data well. Clearance and volume of distribution values are consistent to that seen with other monoclonal antibodies. Based on the population pharmacokinetic analysis, dostarlimab had a mean steady

state systemic clearance of 0.00742 L/hr, a steady-state volume of distribution of 5.34 L, and an elimination half-life of 25.4 days. Over time, the clearance was reduced 15.5% due to time dependent changes in this parameter. Based on model simulations of exposure parameters following either 500 mg Q3W or 1,000 mg Q6W dosing, the comparability of dostarlimab steady state  $C_{avg}$  suggests similar overall dostarlimab exposure following either the 500 mg Q3W or 1,000 mg Q6W dosing regimens.

Statistically significant covariates included: albumin, alkaline phosphatase (ALP), sum of diameters of measurable target lesions in mm per RECIST (SLDR), anti-drug antibodies (ADA), and age on CL and ALP and sex as covariates on V1. 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. Further, there was no effect of tumor type, lactate dehydrogenase (LDH), lymphocyte count, Eastern Cooperative Oncology Group (ECOG) status, race, ethnicity, geographic location and use of systemic glucocorticoids found on dostarlimab PK.

The overall immunogenicity risk for dostarlimab is low; current clinical data are consistent with this assessment. Treatment emergent anti-drug antibody (ADA) incidence has been low (13/349 participants [3.7%]) with no obvious effects on dostarlimab safety, efficacy or pharmacokinetics. A total 349 out of 478 enrolled patients (73.0%) were evaluable for treatment-emergent antibodies to dostarlimab, with 315 patients from Part 2B included in this analysis. Thirteen patients (3.7%) developed ADA during the entire study, and for patients receiving the recommended therapeutic dose, the overall incidence of treatment-emergent ADA was only 2.5%, with 1.3% being neutralizing antibody (NAb) positive.

The results of the concentration-QTc analysis as well as the central tendency analysis demonstrated that dostarlimab does not have a clinically meaningful effect on electrocardiogram (ECG) changes or QT prolongation at the recommended therapeutic dose.

Receptor occupancy (cRO and fRO) was measured in Study 4010-01-001 to evaluate dostarlimab binding to its receptor and the subsequent downstream functional effects. Dostarlimab produces a sustained, consistent engagement of the receptor and functional effects at all dose levels studied, and the RTD regimen of 500 mg Q3W followed by 1,000 mg Q6W is expected to result in full target engagement for the duration of treatment.

An exposure-response analysis was conducted using both safety and efficacy endpoints. Results did not suggest any change of the recommended therapeutic dose and regimen in the intended treatment population.

No significant relationship was seen between dostarlimab average concentration ( $C_{avg}$ ) dose and overall response (OR) in any of the populations studied. There was also no significant relationship between dostarlimab  $C_{min}$  and OR among mismatch repair-deficient (dMMR) endometrial cancer (EC) patients. For the EC and pan tumor populations however, a statistically significant 2.4- and 2.6-fold increase in the likelihood of overall response was apparent with a doubling of  $C_{min}$ .

In terms of exposure-safety, there was no correlation between dostarlimab  $C_{max}$  and the increase of the probability of the top 5 most prevalent drug-related adverse events (fatigue, diarrhea, asthenia, nausea, and hypothyroidism). Increased  $C_{avg}$  was, however, associated with reduced odds of diarrhea and nausea and with increased odds of asthenia. It is noted that no statistically significant relationships were detected between either  $C_{avg}$  or  $C_{max}$  and the top 5 prevalent drug-related adverse events (AEs) when NSCLC patients were excluded from the analysis.

The FDA's Assessment:

The FDA agrees with Applicant's position that similar overall dostarlimab--gxly exposure following either the 500 mg Q3W or 1000 mg Q6W dosing regimens based on the population PK analysis; however, the Applicant's exposure-response (ER) analyses for efficacy and safety are limited and inconclusive due to limited exposure range of dostarlimab--gxly and other confounding factors. The ER relationships for dostarlimab-a-gxly have not been fully characterized.

## **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 for the duration of treatment based on the PDy analysis. Although only one dose regimen was evaluated in the intended target population, the results of the exposure-response analysis did not suggest any necessary changes of the recommend therapeutic dose and regimen in the intended treatment population at the RTD to improve safety or efficacy. This combined with meaningful efficacy responses in dMMR EC patients (Section 8.1.2) 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 pharmacokinetic 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:** Dostarlimab is administered intravenously. Maximum concentrations of dostarlimab were observed at or shortly after the end of the infusion. Estimates of absorption are not applicable.

**Distribution:** Dostarlimab has a relatively small volume of distribution approximately equal to blood volume (5.34 L), consistent with the volume of distribution of endogenous IgG and other mAbs.

**Metabolism:** The anticipated metabolic pathway for dostarlimab is non-specific degradation to peptides, amino acids and small carbohydrates by lysosome through fluid-phase or receptor-mediated endocytosis.

**Excretion:** Dostarlimab had a steady state clearance ( $CL_{ss}$ ) of 0.00742 L/hr, and a terminal half-life of 25.4 days. The clearance estimate was approximately 15.5% lower at steady state when compared to single dose due to time-dependent changes in this parameter.

**Clinical Pharmacokinetics:** In a population pharmacokinetic analysis, a 2-compartment model with non-linear, time-dependent elimination, and weight as an allometric factor on clearance (CL) and V1 fit the data well. Body weight is known to influence the clearance and volume of distribution of therapeutic mAbs, therefore body weight was included in base model development. However, it should be noted that the body weight covariate estimate was within the range of reported values for monoclonal antibodies, in which fixed dosing approaches have been shown to perform similarly to body weight-based dosing, and even compare favorably, possibly resulting in lower interpatient variability in exposure.

Statistically significant covariates included: albumin, ALP, SLDR, ADA, and age on CL and ALP and sex as covariates on V1. No statistically significant effects of mild to moderate renal impairment and mild hepatic impairment were found, with insufficient data from more severely impaired patients to draw conclusions. However, an effect in impaired renal or hepatic function would not be expected, as dostarlimab is anticipated to be catabolized into amino acids by general protein degradation processes. Further, there was no effect of tumor type, lactate dehydrogenase (LDH), lymphocyte count, Eastern Cooperative Oncology Group (ECOG) status, race, ethnicity, geographic location and use of systemic glucocorticoids found on dostarlimab PK.<sup>16</sup>

The population clearance estimate was approximately 15.5% lower at steady state when compared to single dose due to time-dependent changes in this parameter. Based on model simulations of exposure parameters following either 500 mg Q3W or 1,000 mg Q6W dosing, both  $C_{min}$  and  $C_{avg}$  were similar across the two treatments. In particular, the comparability of dostarlimab steady state  $C_{avg}$  suggests similar overall dostarlimab exposure following either the 500 mg Q3W or 1,000 mg Q6W dosing regimens.

**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, 477 of 478 patients (99.8%) had at least one immunogenicity sample result and were included in the analysis of prevalence. A total 349 out of 478 enrolled patients (73.0%) were evaluable for treatment-emergent antibodies to dostarlimab, with 315 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 (3.7%) developed ADA during the entire study, and for patients receiving the recommended therapeutic dose, the overall incidence of treatment-emergent ADA was only 2.5%, with 1.3% 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 inference regarding the effect of ADA was proved inconclusive. Importantly, there was no evidence of a clinically-meaningful impact of ADA formation on any safety or efficacy measures.

**Exposure-Response for Safety and Efficacy Endpoints:** In support of the efficacy and safety endpoints, an exposure-response analysis was conducted using both safety and efficacy endpoints as the response variables, and model-predicted exposures following the first 1,000 mg Q6W dose (Cycle 5) of dostarlimab. The Cycle 5 exposure was selected as it coincided with the efficacy assessments and  $C_{max}$  covers the maximum concentration during the treatment process for safety evaluation. Exposure variables included  $C_{min}$  and average concentration over a dosing interval ( $C_{avg}$ ) for the exposure-efficacy relationship, and  $C_{max}$  and  $C_{avg}$  for the exposure-safety relationship.

A single dose and regimen were studied in the expansion cohort, and consequently the range in exposures used in the analysis is limited to the variability in PK at the recommended therapeutic dose. The challenge of interpreting exposure-response relationships when data from only a single dose level is available should be noted, particularly for a molecule with time-dependent CL. Emerging science has posited a potential relationship between higher CL and worse outcome.<sup>17</sup> At Cycle 5, CL may be decreased for responders, resulting in an apparent relationship that is a function of multiple factors, particularly when looking for relationships with efficacy variables. It is also important to note that the linear model used for the analysis cannot be extrapolated beyond the range of data used.

**Efficacy:** No significant relationship was seen between average concentration ( $C_{avg}$ ) following the first 1,000 mg Q6W dose (Cycle 5) and overall response (OR) in any of the populations studied. There was also no significant relationship between dostarlimab  $C_{min}$  and OR among mismatch repair-deficient (dMMR) endometrial cancer (EC) patients. For the EC and pan tumor populations however, a statistically significant 2.4- and

2.6-fold increase in the likelihood of overall response was apparent with a doubling of  $C_{min}$ .

**Exposure-Response for Safety Endpoints:** There was no correlation between dostarlimab  $C_{max}$  and the increase of the probability of the top 5 most prevalent drug-related adverse events (fatigue, diarrhea, asthenia, nausea, and hypothyroidism) when the total safety population (Part 2B) was used in the analysis. Increased  $C_{avg}$  was, however, associated with reduced odds of diarrhea and nausea and with increased odds of asthenia; increased  $C_{max}$  was associated with reduced odds of nausea. It is noted, however, that when the safety dataset excluded patients with NSCLC, no statistically significant relationships were detected between either  $C_{avg}$  or  $C_{max}$  and the top 5 prevalent drug-related adverse events (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 electrocardiogram (ECG) changes or QT prolongation at the recommended therapeutic dose.

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).

The FDA's Assessment:

The FDA agrees with Applicant's population PK model for dostarlimab--gxly and overall conclusions from the population PK analysis; however, the exposure-response (ER) analyses for efficacy and safety are limited due to factors mentioned above by the Applicant and can only be considered as exploratory. The ER analysis for efficacy and safety have not been fully characterized.

**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 receptor occupancy for the duration of treatment based on the PDy analysis. Although only one dose regimen was administered in the intended target population, the results of the exposure- response analysis did not suggest any necessary changes of the recommend therapeutic dose and regimen in the intended treatment population at the RTD to improve safety or efficacy. Specifically, no relationship was seen between average concentration ( $C_{avg}$ ) following the first 1,000 mg Q6W dose (Cycle 5) and overall response (OR) in any of the populations studied. There was also no significant relationship between dostarlimab  $C_{min}$  and OR among mismatch repair-deficient (dMMR) endometrial cancer (EC) patients (Section 6.3.1), the relevant population.

The Applicant's Position:

The clinical pharmacology program provides supportive evidence of effectiveness.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

**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 dMMR EC 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 preliminary population PK modeling and RO data, and confirmed based on the clinical results of the dMMR EC cohort of Study 4010-001-01 as well as PDy and exposure-response analyses for efficacy and safety endpoints.

Study 4010-001-01 was not designed to assess efficacy or safety at different dose levels, however, the findings from the 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 EC patients (Section 8.1.2) 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 EC 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 pharmacokinetic analyses, potential covariates influencing the pharmacokinetics of dostarlimab have been evaluated (Section 6.3.1). Statistically significant covariates included: albumin, ALP, SLDR, ADA, and age on CL and ALP and sex as covariates on V1. 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. Further, there was no effect of tumor type, lactate dehydrogenase (LDH), lymphocyte count, Eastern Cooperative Oncology Group (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 or extrinsic patient factors based on the results of population pharmacokinetic 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 interaction has been performed.

No specific clinical studies to assess potential drug-drug interactions (DDIs) have been performed. Concomitant use of corticosteroids was assessed as a potential covariate in the population PK model but was not found to be significant. Because dostarlimab is a monoclonal antibody, it has a low risk of DDIs in general.

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.

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X

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Primary Reviewer

Team Leader

Safaa Burns

Atiqur Nam Rahman

X

X

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Primary Reviewer

Team Leader

Fang Li

Jingyu (Jerry) Yu

**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 7](#).

**Table 7: Listing of Clinical Trials Relevant to This BLA**

Trial Identity, NCT Number	Trial Design	Regimen/Schedule/Route	Study Endpoints	Treatment Duration/Follow Up	Number of Patients	Study Population	Number of Centers and Countries
<b><i>Uncontrolled Studies to Support Efficacy and Safety</i></b>							
4010-01-001 (GARNET), NCT 02715284	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)	<b>Primary:</b> ORR and DOR by BICR for Cohorts A1/F and A2, irORR by Investigators' assessment for Cohort E  <b>Secondary:</b> PK, immunogenicity, ORR, irORR, DCR, irDCR, DOR, irDOR, PFS, irPFS, and OS	Up to 2 years, or until the subject meets protocol specific discontinuation criteria	Part 1: 21  Part 2A: 13  Part 2B: Cohort A1 – 10 Cohort A2 – 161 Cohort E – 67 Cohort F - 109	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 NSCLC  Cohort F - Patients with dMMR/MSI-H or POLE-mut solid tumors	Part 1/2A: 3 sites across 1 country  Part 2B: Cohorts A1 and A2 - 84 sites across 8 countries Cohort E - 22 across 6 countries Cohort F - 49 sites across 8 countries

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**Table 7: Listing of Clinical Trials Relevant to This BLA (Continued)**

Trial Identity, NCT Number	Trial Design	Regimen/Schedule/Route	Study Endpoints	Treatment Duration/ Follow Up	Number of Patients	Study Population	Number of Centers and Countries
<b>Studies to Support Safety</b>							
4020-01-001 <sup>a</sup> (AMBER), NCT 02817633	Multi-center, open-label, first-in-human, 2-part dose escalating and expansion study	<p>Part 1C (dose escalation): Dostarlimab 500 mg Q3W IV + TSR-022 100, 300, or 900 mg Q3W IV</p> <p>Part 1D (dose escalation): Dostarlimab 500 mg Q3W IV + TSR-022 300 or 900 mg Q3W IV + TSR-033 3 or 10 mg/kg Q3W IV</p> <p>Part 1E: Dostarlimab 500 mg Q3W IV + TSR-022 300 or 900 mg Q3W IV</p> <p>Part 2 (expansion): RP2D from Part 1</p>	<p><b>Primary:</b> ORR as assessed by the Investigators for Part 1e and Part 2</p> <p><b>Secondary:</b> PK, immunogenicity, ORR by RECIST v1.1 and by irRECIST, DOR, DCR by RECIST v1.1 and by irRECIST, PFS by RECIST 1.1 and by irRECIST, and OS</p>	Up to 2 years or until the subject meets protocol specific discontinuation criteria	Part 1C: 51 Part 1D: 11 Part 1E: 9 Part 2: 149	Part 1: Patients with advanced solid tumors Part 2: Patients with melanoma, NSCLC, or colorectal cancer	63 sites across 2 countries

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**Table 7: Listing of Clinical Trials Relevant to This BLA (Continued)**

Trial Identity, NCT Number	Trial Design	Regimen/Schedule/Route	Study Endpoints	Treatment Duration/ Follow Up	Number of Patients	Study Population	Number of Centers and Countries
<b>Studies to Support Safety</b>							
3000-01-002 <sup>b</sup> (IO Lite), NCT 03307785	Multi-center, open-label, 9-part study	<p>Part A: Dostarlimab 500 mg Q3W IV for 4 cycles followed by 1,000 mg Q6W IV for subsequent cycles + niraparib 200 or 300 mg QD PO</p> <p>Part B: Dostarlimab 500 mg Q3W IV for 4 cycles followed by 1,000 mg Q6W IV for subsequent cycles + carboplatin AUC of 5 or 6 IV/paclitaxel 175 mg/m<sup>2</sup> Q3W IV for 4 to 6 cycles</p> <p>Part C: Dostarlimab 500 mg Q3W IV for 4 cycles followed by 1,000 mg Q6W IV for subsequent cycles + niraparib 200 or 300 mg QD PO + bevacizumab 15 mg/kg Q3W IV up to 15 months</p> <p>Part D: Dostarlimab 500 mg Q3W IV for 4 cycles followed by 1,000 mg Q6W IV for subsequent cycles + carboplatin AUC of 5 or 6 IV/paclitaxel 175 mg/m<sup>2</sup> Q3W IV for 4 to 6 cycles + bevacizumab 15 mg/kg Q3W IV up to 15 months</p>	<p><b>Primary:</b> Evaluate DLTs</p> <p><b>Secondary:</b> ORR, DOR, DCR and PFS as assessed by the Investigators, PK, ADAs</p>	Up to 2 years or until the subject meets protocol specific discontinuation criteria	Part A: 22 Part B: 14 Part C: 13 Part D: 6	Patients with advanced or metastatic cancer	7 sites across 1 country

Abbreviations: ADA=anti-drug antibody; AUC=area under the concentration time curve; BICR=blinded independent central review; DCR=disease control rate; DLT=dose-limiting toxicity; dMMR=mismatch repair-deficient; DOR=duration of response; EC=endometrial cancer; irDCR=immune-related disease control rate; irDOR=immune-related duration of response; irORR=immune-related objective response rate; irPFS=immune-related progression-free survival; irRECIST=immune-related response evaluation criteria in solid tumors; IV=intravenous; MMRp=mismatch repair proficient; MSI-H=microsatellite instability-

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high; MSS=microsatellite stable; NCT=national clinical trial; NSCLC=non-small cell lung cancer; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PK=pharmacokinetic; PO=by mouth; POLE-mut=DNA polymerase epsilon mutation; QD=daily; QxW=every x weeks; RECIST=response evaluation criteria in solid tumors; RP2D=recommended phase II dose; TSR-022=anti-T-cell immunoglobulin and mucin-domain containing-3 antibody; TSR-033=anti-lymphocyte-activation gene 3 antibody.

<sup>a</sup> Parts 1A and 1B not included as no patients in these parts were treated with dostarlimab.

<sup>b</sup> Parts E through I are not included as no patients in these parts were treated with dostarlimab.

### The FDA's Assessment:

In this NME BLA application, the clinical data for the FDA's analysis of efficacy was based on the efficacy data from 71 patients with dMMR EC in Cohort A1 in Part 2B of Study 4010-01-001 (GARNET), a phase 1 dose-escalation/cohort-expansion, non-randomized, multicenter, open-label, multi-cohort clinical trial that enrolled patients with advanced solid tumors. For the FDA's analysis of safety, data from 444 patients with a variety of advanced solid tumors in the expansion cohorts of Part 2B of Study 4010-01-001 (GARNET) were submitted to support this BLA; the expansion cohorts included: Cohort A1, Cohort A2, Cohort E, and Cohort F, which are described in Table 7.

## **8. STATISTICAL AND CLINICAL EVALUATION**

### **8.1. Review of Relevant Individual Trials Used to Support Efficacy**

#### **8.1.1. Study 4010-01-001 (GARNET)**

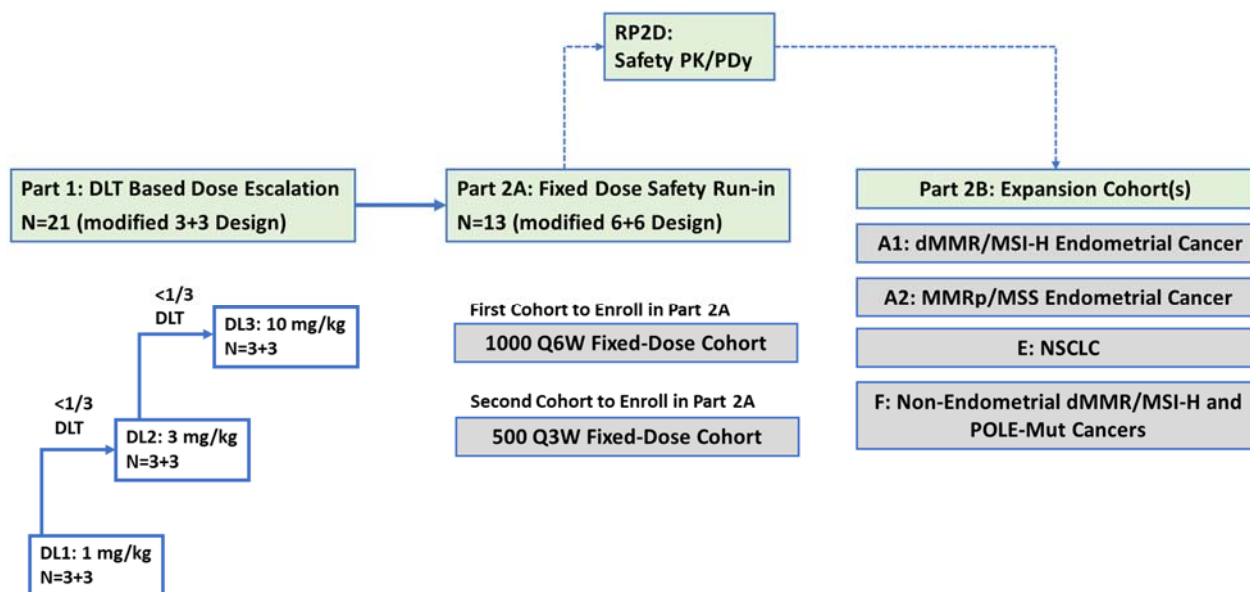
##### The Applicant's Description:

Study 4010-01-001 is an ongoing, multicenter, open-label, first-in-human, Phase I, dose escalation study with expansion cohorts designed to assess the safety, PK, PDy, and clinical activity of the anti-PD-1 antibody, dostarlimab, as monotherapy in patients with recurrent or advanced solid tumors who experienced disease progression on or after treatment with available anticancer therapies.

The study is being conducted in 2 parts. 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 recommended therapeutic dose (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 2: Study 4010-01-001 (GARNET) Schema**



Abbreviations: DLT=dose-limiting toxicity; dMMR=mismatch repair-deficient; MMRp=mismatch repair proficient; MSI-H=microsatellite instability-high; MSS=microsatellite stable; N=number of patients; NSCLC=non-small cell lung cancer; PDy=pharmacodynamic; PK=pharmacokinetic; QxW=every x weeks; RP2D=recommended Phase 2 dose.

Efficacy data in support of this BLA are derived primarily from Part 2B Cohort A1 of Study 4010-01-001, which included subjects with dMMR/MSI-H EC tumors.

Study enrollment was based on local laboratory test results of MMR/MSI status, which were to be confirmed by central laboratory testing. Local testing included polymerase chain reaction (PCR) and next-generation sequencing (NGS) to determine MSI status and immunohistochemistry (IHC) to detect dMMR. Central laboratory testing was performed using an NGS (FoundationOne) assay. Preliminary efficacy analysis demonstrated that local test results obtained with IHC were better at identifying patients more likely to respond to dostarlimab treatment than central test results obtained with NGS. Therefore, test results from local IHC testing were used for the final determination of dMMR status for all efficacy and safety analyses.

### Trial location

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

### Inclusion Criteria

The patients who were included in the primary efficacy population were  $\geq 18$  years of age with recurrent or advanced dMMR EC that had progressed following treatment with a platinum-containing regimen,

The inclusion criteria for Cohort A1 or Cohort A2 of Part 2B are listed below:

1. Subject was at least 18 years old

2. Subject 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 part of the study they participated in.
  - a. Part 2B: Histologically or cytologically proven recurrent or advanced solid tumor with measurable lesion(s) per RECIST v1.1 and met one of the following disease types:

The criteria below were met for subjects participating in

    - Cohort A1 – Subjects with dMMR/MSI-H EC
    - Cohort A2 – Subjects with MMRp/MSS EC
    - Subjects had progressed on or after platinum doublet therapy.
    - Subjects had received no more than 2 lines of anticancer therapy for recurrent or advanced ( $\geq$ Stage III B) 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).
    - Subjects 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: Subjects could be screened based on local MMR/MSI testing results using IHC, PCR, or NGS performed in a certified local laboratory, but subject eligibility was determined by MMR IHC results. For subjects 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 subjects without available local MMR IHC test results (ie, subjects with local PCR or NGS test results), tumor samples were submitted directly to a central IHC laboratory, and the 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 sent to a central NGS laboratory for further testing.
3. Part 2B: Subjects had archival tumor tissue available that was formalin fixed and paraffin embedded.
  - a. For subjects who did not have archival tissue, a new biopsy was performed to obtain a tissue sample prior to study treatment initiation. For subjects 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 subjects 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.  $\geq 45$  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, MRI, or CT scan. Tubal ligation must have been confirmed with medical records of the actual procedure; otherwise, the subject must have fulfilled Inclusion Criterion 5. Information must have been captured appropriately within the site's source documents.
5. Female subjects of childbearing potential (see above) must have agreed to use 1 highly effective form of contraception with their partners starting with the Screening Visit through 150 days after the last dose of study treatment.
6. Subject had an Eastern Cooperative Oncology Group (ECOG) performance status of  $\leq 2$  for Part 1 and  $\leq 1$  for Part 2.
7. Subject had adequate organ function, defined as follows:
  - a. absolute neutrophil count (ANC)  $\geq 1,500/\mu\text{L}$
  - b. platelets  $\geq 100,000/\mu\text{L}$
  - c. hemoglobin  $\geq 9$  g/dL or  $\geq 5.6$  mmol/L
  - d. serum creatinine  $\leq 1.5 \times$  upper limit of normal (ULN) or calculated creatinine clearance  $\geq 50$  mL/min using the Cockcroft-Gault equation for subjects with creatinine levels  $>1.5 \times$  institutional ULN
  - e. total bilirubin  $\leq 1.5 \times$ ULN AND direct bilirubin  $\leq 1 \times$ ULN
  - f. aspartate aminotransferase (AST) and alanine aminotransferase (ALT)  $\leq 2.5 \times$ ULN, unless liver metastases were present, in which case they must be  $\leq 5 \times$ ULN
  - g. international normalized ratio (INR) or prothrombin time  $\leq 1.5 \times$ ULN, unless the subject 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)  $\leq 1.5 \times$ ULN, unless the subject was receiving anticoagulant therapy or as long as prothrombin time or PTT was within the therapeutic range of intended use of anticoagulants

### Exclusion Criteria

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

1. Subject had received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.

2. Subject had known uncontrolled central nervous system metastases and/or carcinomatous meningitis. Note: Subjects 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 subject from study participation, regardless of clinical stability.
3. Subject 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. Subject 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. Subject was pregnant or breastfeeding, or expected to conceive children within the projected duration of the study, starting with the Screening Visit through 150 days after the last dose of study treatment.
6. Subject 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. Subject had a known history of HIV (HIV 1/2 antibodies).
8. Subject had known active hepatitis B (e.g., hepatitis B surface antigen reactive) or hepatitis C (e.g., hepatitis C virus ribonucleic acid [qualitative] was detected).
9. Subject 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 (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc) was not considered a form of systemic treatment. Use of inhaled steroids, local injection of steroids, and steroid eye drops were allowed.
10. Subject had a history of interstitial lung disease.
11. Subject had not recovered (ie, to Grade  $\leq$ 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. Subject 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. Subject 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. Subject had not recovered adequately (Grade  $\leq 1$ ) from AEs and/or complications from any major surgery prior to starting therapy.
15. Subject had received a live vaccine within 14 days of the planned start of study treatment.
16. Subject had a known hypersensitivity to dostarlimab components or excipients.

### **Treatments Administered**

All subjects in this study received dostarlimab as a 30-minute IV infusion (with a permitted window of -5 minutes and +15 minutes). In Part 2B, subjects 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.

### **Dose Selection**

The proposed dosing regimen for dostarlimab as a single agent in the treatment of dMMR EC 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 preliminary population PK modeling and RO data, and confirmed based on the clinical results of the dMMR EC cohort of Study 4010-001-01 as well as PDy and exposure-response analyses for efficacy and safety endpoints.

Study 4010-001-01 was not designed to assess efficacy or safety at different dose levels, however, the findings from the 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 EC patients (Section 8.1.2) and overall manageable safety profile (Section 8.2) of dostarlimab at the RTD supports the choice of recommended therapeutic dose and regimen.

### **Dose Modification and Dose Discontinuation**

Adverse events in the study were managed with appropriate clinical treatment, dosing delays or discontinuations as needed.

In general, dostarlimab was withheld for drug-related Grade 3 toxicities but could be 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 8](#). For all irAEs listed in [Table 8](#), dostarlimab should have been held until the subject 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 prednisone 10 mg at the time of resuming dostarlimab. The recent joint ASCO and NCCN guideline for diagnosis and management of irAEs treated with ICPI therapy were used as a supplement to [Table 8](#).

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.

Study treatment dosing delays were permitted in the case of medical or surgical events or logistical reasons not related to study treatment (e.g., surgery, unrelated medical events, subject vacation, and holidays). Subjects 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 subject could have been placed back on study treatment only after discussion with the Applicant. Reasons for treatment delays of more than 3 days should have been documented in the eCRF.

**Table 8: Guidelines for Treatment of AEs of Interest**

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.
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). <sup>a</sup>
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.

Toxicity	Hold Treatment for Grade	Restarting Treatment/Discontinuation
	4	Permanently discontinue.
Infusion-related reaction	2 <sup>b</sup>	Restart dosing when toxicity resolves to Grade 0 or 1.
	3-4	Permanently discontinue.

**Table 8: Guidelines for Treatment of AEs of Interest (Continued)**

Toxicity	Hold Treatment for Grade	Restarting Treatment/Discontinuation
Pneumonitis	2	Restart dosing when toxicity resolves to Grade 0 or 1. If Grade 2 recurs, permanently discontinue.
	3-4	Permanently discontinue.
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.

Abbreviations: AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; hr=hour; irAE=immune-related adverse event; T1DM=type 1 diabetes mellitus; ULN=upper limit of normal.

<sup>a</sup> 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.

<sup>b</sup> 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.

### Administrative Structure

TESARO was the study Applicant and was responsible for study oversight, vendor oversight, database development and maintenance, storage and distribution of clinical supplies to sites, and site and vendor audits. 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.

### Procedures and Schedule

In Part 2B of the study, radiographic evaluations and appropriate testing of serum-based tumor markers to assess tumor responses are conducted at Week 12 (84±10 days) following the first dostarlimab dose and every 6 weeks thereafter (±10 days), independent of cycle delays and/or dose interruptions. After 1 year on treatment, patients have radiographic evaluations performed every 12 weeks (84 ±10 days). The scans are evaluated for eligibility check and

primary efficacy evaluation. All patients undergo an end-of-treatment (EOT) visit conducted 30 days ( $\pm 7$  days) for the Q3W schedule or 42 days ( $\pm 7$  days) for the Q6W schedule after the last date of study drug administration. Patients also undergo a safety follow-up visit conducted 90 days ( $\pm 7$  days) after the last date of study drug administration. After the 90-day safety follow-up visit, patients enter the post-treatment follow-up period for telephone assessment of survival status every 90 days ( $\pm 14$  days).

Safety assessments conducted throughout the treatment period include symptom-directed physical examinations, vital signs, electrocardiograms (ECGs), Eastern Cooperative Oncology Group (ECOG) performance status, and clinical laboratory assessments, including complete blood count (CBC) with differential (including absolute lymphocyte count [ALC] and absolute neutrophil count [ANC]), coagulation profile, chemistry, thyroid panel, urinalysis, and pregnancy testing. All adverse events (AEs) and serious adverse events (SAEs) are collected and recorded for each patient from the day of signing the informed consent form (ICF) until 90 days after end of treatment visit or until alternate anticancer treatment has been initiated, whichever occurs earlier; any pregnancies that occur within 150 days post-treatment are to be reported (Please see Tables 3 and 4 from Endo CSR).

Serum samples for PK determination as well as antidrug antibody (ADA) assessment are collected prior to, during, and after dostarlimab administration at Day 1 of cycles 1, 4, 5, 8 and 12, and safety follow up.

**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.

**Study Endpoints**

**The Applicant's Position:**

The primary objectives of Cohort A1 of Part 2B of this study were to evaluate the antitumor activity of dostarlimab in subjects with recurrent and advanced dMMR/MSI-H EC, in terms of objective response rate (ORR) and duration of response (DOR) by blinded independent central review (BICR) using response evaluation criteria in solid tumors (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.<sup>17</sup> 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<sup>18</sup>, 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.<sup>18 19</sup> The tumor assessments by BICR were done according to the revised RECIST v1.1, which represents standardized World Health Organization

(WHO) response criteria.<sup>20</sup> 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 stable disease (SD), Investigators were allowed to manage treatment decisions using tumor assessments based on irRECIST v1.1 during the study.<sup>21 22</sup> This was to prevent subjects from being withdrawn from study treatment prematurely in the case of pseudo-progression.

The use of ORR as an endpoint for study 4010-01-001 and to support accelerated approval for dostarlimab in a dMMR EC population was discussed with the Agency in a meeting on July 15, 2017.

Efficacy assessment was performed on the following endpoints for Cohort A1:

- ORR is a primary efficacy endpoint. It is defined as the proportion of subjects achieving best overall response (BOR) of CR or PR, as assessed per RECIST v1.1 based on BICR.
- DOR is a primary efficacy endpoint. It is defined as the time from first documentation of CR or PR, as assessed per RECIST v1.1, until the time of first documentation of PD, as assessed per RECIST v1.1 based on BICR, or death due to any cause.
- Disease control rate (DCR) is a secondary efficacy endpoint. It is defined as the proportion of subjects achieving BOR of CR, PR, or stable disease (SD), as assessed per RECIST v1.1 based on Investigator's assessment.
- Progression-free survival (PFS) is a secondary endpoint. It is defined as the time from date of first dose to the earlier date of assessment of 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 is a secondary endpoint. It is defined as the time from date of first dose of study treatment to the date of death by any cause.
- Immune-related ORR (irORR) is a secondary endpoint. It is defined as the proportion of subjects achieving irBOR of immune-related CR (irCR) or immune-related PR (irPR), as assessed per irRECIST based on Investigator's assessment.
- Immune-related DOR (irDOR) is a secondary endpoint. It is 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 PD (irPD) (subsequently confirmed), as assessed per irRECIST based on Investigator's assessment, or death.
- Immune-related DCR (irDCR) is a secondary efficacy endpoint. It is defined as the proportion of subjects achieving irBOR of irCR, irPR, or immune-related SD (irSD), as assessed per irRECIST based on Investigator's assessment.
- Immune-related progression-free survival (irPFS) is a secondary endpoint. It is 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. The European Quality of Life scale, 5 Dimensions, 5 Levels (EQ-5D-5L) and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) were used to assess cancer-specific health-related quality of life. PRO assessments were added to the study under amendment 3, and only limited data were available at the data cutoff. In addition, because of the nonrandomized nature of the study, interpretation of the PRO data is potentially biased. Therefore, PRO data were not evaluated at this time.

#### The FDA's Assessment:

The FDA review focused primarily on efficacy results in Cohort A1 in Part 2B of Study 4010-01-001, since this cohort is the basis of the indication sought by the Applicant. The analysis of the primary efficacy population will focus on ORR and DoR as assessed per RECIST v1.1 based on BICR in patients with measurable disease at baseline. Analyses for time-to-event endpoints, such as PFS and OS, are not interpretable in a single-arm trial without a control group.

#### **Statistical Analysis Plan**

##### The Applicant's Position:

The determination of the sample size is described in [Protocol 4010-01-001, Section 8.9](#). For Cohort A1 in Part 2B, the null hypothesis that the true response rate was  $\leq 20\%$  ( $H_0: p \leq 0.2$ ) had been planned to be tested against a one-sided alternative of  $\geq 40\%$  ( $H_a: p \geq 0.4$ ). With 65 subjects treated, there was 92% power to rule out a  $\leq 20\%$  ORR (null hypothesis) when the true ORR was 40% at the 2.5% type I error rate (one-sided).

There was a planned interim analysis for administrative purposes for dMMR/MSI-H patients from Cohort A1 and Cohort F combined to occur when enrollment in both cohorts reached approximately 100 patients and enrolled patients had been followed for at least 6 months. The part for Cohort A1 formed the basis of this BLA as agreed with the Agency on the October 17, 2019 pre-BLA meeting.

The statistical analysis plan was finalized prior to data base lock. The statistical analysis was descriptive in nature. In general, categorical data were summarized using number of subjects (n), frequency, and percentages, with the denominator for percentages being the number of subjects in the analysis set. Two-sided exact 95% confidence intervals (CIs) based on the Clopper-Pearson method was provided to summarize the binomial proportion of the ORR/irORR and DCR/irDCR for both RECIST v1.1 and irRECIST assessments, where applicable (Clopper and Pearson 1934).

Continuous data were summarized using the number of subjects, mean, standard deviation, median, first and third quartiles (Q1, Q3), minimum, and maximum. Time-to-event analyses were performed using Kaplan-Meier (KM) methods.

All statistical analyses and data listings were performed using SAS v9.4.

Data presented in this BLA are based on a prospectively defined interim analysis in a single study (4010-01-001) conducted when approximately a total of 100 patients enrolled in two cohorts (Cohort A1 and Cohort F) had at least 6 months of follow up.

### **Analysis Sets**

The safety analysis set: All subjects who received any amount of study drug.

Primary efficacy analysis set (RECIST v1.1 per BICR): All subjects 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) who had the opportunity for at least 24 weeks of tumor assessment at the time of data cutoff (July 8, 2019). Thus, all patients with measurable disease at baseline who received their first dose of dostarlimab 24 weeks prior to data cutoff were included in the primary efficacy analysis set, regardless of whether they had a post-treatment scan.

Secondary efficacy analysis set (irRECIST per Investigators' assessment): All subjects with measurable disease at baseline (defined as the existence of at least 1 target lesion at baseline tumor assessment by the Investigator) who had the opportunity for at least 24 weeks of tumor assessment at the time of analysis.

### **Efficacy Endpoints**

The following parameters will be analyzed for this summary:

- ORR and DOR using RECIST v1.1 based on BICR
- DCR using RECIST v1.1 based on BICR
- PFS using RECIST v1.1 based on BICR
- OS
- irORR and irDOR using irRECIST based on Investigator's assessment
- irDCR using irRECIST based on Investigator's assessment
- irPFS using irRECIST based on Investigator's assessment

The analyses for efficacy endpoints were based on the efficacy population,

### **Subgroup analysis [CO and CSR 11.4.1.8]**

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

- MSI status by FoundationOne NGS test: MSI-H vs MSS vs Unknown
- Number of prior anticancer therapy regimens: 1 vs  $\geq 2$
- Prior radiation therapy: Yes vs No
- Prior bevacizumab use: Yes vs No
- BOR from last platinum-containing prior anticancer therapy

- Progression-free interval from last platinum-containing prior anticancer therapy

No significant effect of local (IHC) vs central (FoundationOne NGS) test results on DOR was observed; patients with tumors classified as dMMR by IHC and MSI-H by NGS demonstrated a similar DOR as the overall dMMR EC population. No significant effect of progression-free interval from the last platinum-containing prior anticancer therapy, number of prior anticancer therapies, prior radiation therapy, BOR from last platinum-containing prior anticancer therapy, or duration of progression-free interval from last platinum-containing prior anticancer therapy on DOR was observed in responders with dMMR EC. There were too few responders with dMMR EC and prior bevacizumab use (N=1) to draw any conclusion on the potential effect of bevacizumab on DOR or DOR range.

### **Handling of Dropouts or Missing Data**

No subjects from Cohort A1 and Cohort A2 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 SAP ([Appendix 16.1.9](#)).

### **Interim Analyses and Data Monitoring**

The pivotal CSR to support this BLA presents the results from an interim analysis based on confirmed response per RECIST v1.1 using BICR with a data cutoff date of 08 July 2019. The data cutoff date for this interim analysis was chosen based on predetermined sample size calculations for Cohort A1.

### **Multiple Comparisons/Multiplicity**

No adjustments for multiplicity were made. Separate inferences were drawn for each tumor cohort.

#### **The FDA's Assessment:**

The FDA does not use inferential procedures (testing procedures, performance goals, type I error control, etc.) to evaluate single-arm trial results. Therefore, FDA efficacy evaluation is based on the estimated magnitude of ORR and adequate duration of response.

In the pre-BLA meeting, the FDA recommended the Applicant to include all patients with measurable disease at baseline who have received at least one dose of dostarlimab by a pre-specified enrollment cutoff date and advised that the Applicant should use a data cutoff date that corresponds to a time when most patients were followed for at least 6 months. In the BLA submission, the enrollment cutoff date and the data cutoff date were February 1, 2019 and July 8, 2019, respectively. In the original BLA submission, the Applicant's efficacy analysis population included 70 patients with measurable disease at baseline who received at least one dose of dostarlimab on or before the enrollment cutoff date (February 1, 2019) and had the opportunity for at least 24 weeks of tumor assessment before the data cutoff date. In the submission, one patient who received the first dose of dostarlimab on January 31, 2019 and

had 24-week tumor scan administered on July 11, 2019, was excluded from the efficacy analysis population by the Applicant.

However, after review, the Agency did not agree with the Applicant's use of the condition that a minimum of 24 weeks of tumor assessment prior to the data cutoff date was required, as this could introduce a selection bias. Therefore, the FDA defined the efficacy analysis population as all patients with measurable disease at baseline who received at least one dose of dostarlimab on or before the cutoff date of February 1, 2019. As a result, the FDA defined efficacy analysis population included 71 patients; this is referred to as the "revised efficacy analysis population" in this review. This is the FDA preferred efficacy analysis population and is the denominator (n=71) that the FDA used in its efficacy analyses for this application.

### **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 5 times, although versions 4.0 and 5.0 were never implemented.

#### **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.

#### **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.

#### **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.

#### **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 irSDs 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 receptor occupancy 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.

#### **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

#### **FDA's Assessment:**

The FDA agrees with the Applicant's summary of protocol amendments.

### 8.1.2. Study Results

#### 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 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 good clinical practice (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.

#### Financial Disclosure

##### The Applicant's Position:

In accordance with 21 CFR 54, the Applicant submitted a financial disclosure certification document in [Module 1.3.4](#). The document includes three tables listing all Investigators who participated in the two covered studies supporting BLA 761174: those with disclosable financial interests, no disclosable interests, and those whose financial disclosure information is missing or incomplete.

Four total Investigators, of whom 2 were sub-investigators, participated in Study 4010-01-001 and received varying amounts of compensation from TESARO/GlaxoSmithKline for activities such as speaking engagements and consultations in the form of Advisory Board meetings. Only one of the four Investigators was involved in the enrollment of two patients (1 in the efficacy population and 1 in the safety population) in Cohort A1. Furthermore, the patient in the efficacy population was a non-responder, and the ORR at this Investigator's site was 0%. Thus, no bias due to financial interest is reported. The Applicant provided a list of all Investigators and sub-investigators from Study 4010-01-001 who had no disclosable interests and a copy of the certification (Option 1 on Form FDA 3454) for these participants. For the Investigators and sub-investigators with missing financial disclosure information, the Applicant submitted certification that TESARO/GlaxoSmithKline acted with due diligence but was unable to obtain the missing information (Option 3 on Form FDA 3454).

##### The FDA's Assessment:

The FDA agrees with the Applicant's assessment.

### Patient Disposition

#### The Applicant's Position:

A summary of disposition for patients with dMMR EC in the revised primary efficacy analysis set is presented in Module 2.7.3; see [Table 9](#). At the time of data cutoff, 60.0% of the subjects with dMMR EC had discontinued treatment, and 34.3% had discontinued the study. The most common reason for treatment discontinuation was confirmed PD (29 patients), and the most common reason for study discontinuation was death (18 patients).

**Table 9: Patient Disposition – Patients with dMMR EC (Primary Efficacy Analysis Set)**

Variable Reason, n (%)	dMMR EC (N=70)
Discontinued treatment	42 (60.0)
Adverse event	9 (12.9)
Confirmed disease progression	29 (41.4)
Patient request	1 (1.4)
Based on clinical criteria by Investigator	3 (4.3)
Discontinued study	24 (34.3)
Withdrawal of consent	4 (5.7)
Lost to follow-up	1 (1.4)
Death	18 (25.7)
Other	1 (1.4)
Patients treated beyond initial disease progression	16 (22.9)
Died while on study	18 (25.7)
Disease progression	12 (17.1)
Adverse event	4 (5.7)
Unknown	2 (2.9)

Source: CSR 4010-01-001 Table 14.1.3.1a

Abbreviations: CRF=case report form; CSR=clinical study report; dMMR=mismatch repair-deficient; EC=endometrial cancer; n=number of patients.

Note: Reasons for discontinuation were based on the Discontinuation of Treatment and Discontinuation of Study CRF page.

#### The FDA's Assessment:

The FDA agrees with the Applicant's assessment that the most common reason for treatment discontinuation in patients with dMMR EC was disease progression. Dostarlimab was permanently discontinued due to adverse reactions in 5 (4.8%) of patients, including 2 patients due to transaminases increased, and sepsis, bronchitis, and pneumonitis (one patient each).

## Protocol Violations/Deviations

### The Applicant's Position:

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

Important and Significant Protocol Deviations (ISPDs) came from the Protocol Deviation Management System and the Clinical Trial Management System. The ISPD categories include, but are not limited to, those described below.

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 subject
- A subject to develop withdrawal criteria during the study but not be withdrawn
- A subject to receive incorrect treatment
- Incorrect or noncompliant dosing of a subject, ie, dosing that was inconsistent with the protocol
- Administration of an excluded concomitant treatment to a study subject
- Impact on the completeness, accuracy, and/or reliability of the study data
- An effect on a subject'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 subject's rights, safety, or well-being. Important and significant categories were summarized. A by-subject listing of ISPDs, including deviation visit, deviation type, deviation description, and any relevant comments, was generated.

Of 104 subjects with dMMR EC, 75 important protocol deviations were recorded for 44 subjects (42.3%). Most of these important deviations were related to study visits or procedures, including missing safety laboratory assessments, missing tumor assessments, and delayed reporting of SAEs. None of these important protocol deviations were considered to affect the subjects' safety or wellbeing or the overall integrity of the study.

In the safety analysis set, a total of 14 significant protocol deviations were recorded for 13 subjects (4.9%), including 7 significant protocol deviations in 6 subjects (5.8%) with dMMR EC. Most of these significant deviations were related to inclusion/exclusion criteria and included the following (Listing 16.1.3a and data on file):

- Deviation of inclusion criterion 2 (n=8), including progression following more than 2 prior lines of therapy (n=2 [2 subjects with dMMR EC]), no prior platinum doublet therapy (n=1 [1 subject with dMMR EC]), no central radiological confirmation of PD

before dosing (n=1 [1 subject with dMMR EC]), no measurable disease at baseline (n=1 [1 subject with dMMR EC]), and subjects with carcinosarcoma (n=3 [3 subjects with MMR-proficient EC]).

- Deviation of exclusion criterion 11: subject has not received transfusion of red blood cells within 3 weeks prior to the first dose of study drug (n=1 [1 subject with MMR-proficient EC]). A second subject with dMMR EC also received transfusion of red blood cells within 3 weeks prior to the first dose of study drug; this subject is 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 subject with dMMR EC]).
- Subject received dostarlimab before central MSI status confirmation (n=1 [1 subject with MMR-proficient EC]).
- SAE was reported 12 days out of window (n=1 [1 subject with MMR-proficient EC]).

None of these significant protocol deviations were considered to affect the subjects' safety or wellbeing or the overall integrity of the study.

#### The FDA's Assessment:

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

#### **Table of Demographic Characteristics**

##### The Applicant's Position:

The demographic characteristics for subjects with dMMR EC in the revised primary efficacy analysis population (n=71) are summarized in [Table 10](#).

All patients were females with EC. Most of the 71 patients with dMMR EC were white (81.7%). The median age was 64.0 years (range: 39,80 years), and half of the patients were <65 years old. Median body mass index (BMI) was 29.21 kg/m<sup>2</sup> (range: 13.6, 53.9 kg/m<sup>2</sup>). A baseline ECOG performance status of 1 and 0 was reported in 67.6% and 32.4% of patients, respectively.

**Table 10: Demographic Characteristics – Subjects with dMMR EC (Revised Primary Efficacy Analysis Set)**

Characteristic	dMMR EC (N=71)
Race, n (%)	
White	58 (81.7)
Asian	2 (2.8)
Black	1 (1.4)
American Indian or Alaska Native	3 (4.2)
Other	0
Unknown	0
Not Reported	0
Age (years)	
n	71
Median	64.0
Min, max	39, 80
Age group, n (%)	
<65 years	36 (50.7)
≥65 years to <75 years	28 (39.4)
≥75 years	7 (9.9)
Weight (kg)	
n	71
Median	72.00
Min, max	34.0, 141.4
BMI (kg/m <sup>2</sup> )	
n	69
Median	29.21
Min, max	13.6, 53.9
ECOG performance status	
0	23 (32.4)
1	47 (67.6)

Source: Abbreviated Efficacy Report Table 14.1.5.3a

Abbreviations: BMI=body mass index; CSR=clinical study report; dMMR=mismatch repair deficient; EC=endometrial cancer; ECOG=Eastern Cooperative Oncology Group; N=number of patients; Q1=first quartile; Q3=third quartile; StDev=standard deviation.

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

The Applicant's Position:

The baseline disease characteristics for subjects with dMMR EC for the revised primary efficacy population (n=71) are summarized in [Table 11](#).

At baseline, 66.2% of the subjects with dMMR EC were International Federation of Gynecology and Obstetrics (FIGO) Stage IV at most recent assessment. A total of 70.4% of subjects with dMMR EC had a histologic diagnosis of endometrioid carcinoma Type I, and the most common disease grade at diagnosis was Grade 2 (40.0%).

**Table 11: Primary Cancer History – Subjects with dMMR EC (Revised Primary Efficacy Analysis Set)**

Category, n (%)	dMMR EC (N=71)
Histology at diagnosis	
Endometrioid carcinoma Type I	50 (70.4)
Serous carcinoma	4 (5.6)
Clear cell carcinoma	0
Squamous carcinoma	1 (1.4)
Undifferentiated carcinoma	2 (2.8)
Carcinosarcoma	0
Mixed carcinoma	2 (2.8)
Other	11 (15.5)
Unknown	1 (1.4)
Grade of disease at diagnosis	
Grade 1	22 (31.0)
Grade 2	29 (40.8)
Grade 3	17 (23.9)
Not assessable	0
Missing	3 (4.2)
Most recent FIGO stage	
Stage I	10 (14.1)
Stage II	2 (2.8)
Stage III	10 (14.1)
Stage IV	47 (66.2)
Unknown	2 (2.8)

Source: Abbreviated Efficacy Report Table 14.1.6.3a

Abbreviations: CSR=clinical study report; dMMR=mismatch repair deficient; EC=endometrial cancer; FIGO=International Federation of Gynecology and Obstetrics; n=number of patients.

**The FDA's Assessment:**

The FDA agrees with the demographics and baseline characteristics data presented by the Applicant. Overall the demographics of patients with dMMR EC in cohort A1 of GARNET Trial were consistent with the US population demographics.

**Prior Anticancer Treatment**

All subjects with dMMR EC had received prior anticancer treatment (100.0%), with 57.7% of subjects having received any prior adjuvant/neo-adjuvant anticancer treatment. The number of prior anticancer regimens received was 1 in 59.2% of subjects. Less than 16% of subjects with dMMR EC had received 3 or more prior regimens. Half of the subjects had received prior regimens for metastatic disease. The majority of subjects had prior surgery (90.1%) and prior anticancer radiotherapy (78.9%).

The most common BOR from the last platinum-containing anticancer therapy was PR (28.2% of subjects with dMMR EC), followed by SD (18.3% of subjects with dMMR EC) and CR (16.9% of subjects with dMMR EC) (Table 14.1.13.2a). The median progression-free interval from the last platinum-containing anticancer therapy was 6.39 months (Q1, Q3: 4.4, 11.7 months).

Prior anticancer treatment for subjects with dMMR EC for the revised primary efficacy population (n=71) is summarized in Table 12.

All patients with dMMR EC had received prior anticancer treatment (100.0%), and as per protocol, all but 1 patient received platinum-containing therapy. 90.1% of patients received prior anticancer surgery and 78.9% received prior anticancer radiotherapy. Approximately 40% had >1 prior anticancer treatment (Module 2.7.3, Table 5); approximately 11% of patients had received 3 regimens, and 4.2% had received 4 or more prior regimens. Half of the patients had received prior anticancer regimens for metastatic disease.

For enrollment in Study 4010-01-001, subjects were required to have progressed on or after receiving platinum doublet therapy; therefore, all subjects with dMMR EC had received prior platinum doublet therapy, except for 1 subject who was enrolled in error and did not meet this criterion.

**Table 12: Prior Anticancer Treatment – Subjects with dMMR EC (Revised Primary Efficacy Analysis Set)**

Variable, n (%)	dMMR EC (N=71)
Any prior anticancer treatment	71 (100)
Prior surgery for study indication	64 (90.1)
Any prior anticancer radiotherapy	56 (78.9)
Prior bevacizumab use	4 (5.6)
Any prior adjuvant/neo-adjuvant anticancer treatment	41 (57.7)

Variable, n (%)	dMMR EC (N=71)
Number of prior anticancer regimens	
1	42 (59.2)
2	18 (25.4)
3	8 (11.3)
≥4	3 (4.2)
Number of prior regimens for metastatic disease <sup>a</sup>	
0	35 (49.3)
1	27 (38.0)
2	8 (11.3)
3	1 (1.4)

Source: Abbreviated Efficacy Report Table 14.1.13.3a

Abbreviations: CR=complete response; CSR=clinical study report; dMMR=mismatch repair deficient; EC=endometrial cancer; max=maximum; min=minimum; n=number of patients; PD=progressive disease; PR=partial response; Q1=first quartile; Q3=third quartile; SD=stable disease; StDev=standard deviation.

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#### The FDA's Assessment:

The FDA agrees with the Applicant's assessment.

### **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 Applicant 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 doses (2.9%), 14 infusion delays (13.5%), and no infusion interruptions were reported in subjects with dMMR EC. From Cycle 5 through the end of treatment, 5 missed doses (4.8%), 14 infusion delays (13.5%), and no infusion interruptions were reported in subjects with dMMR EC.

#### **Concomitant Medications in Subjects with dMMR EC**

Medications collected at screening and during the study were coded using the current version of the WHO Drug Dictionary (version WHO Drug-DDE-B2\201709). 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, starting prior to first dose of study treatment and ongoing at first dose of study treatment, 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 ATC (anatomic therapeutic chemical) level 3 classification drug class and WHO preferred name using the number and percentage of subjects for each cohort. A subject reporting the same medication more than once was counted only once when calculating the number and percentage of subjects 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-subject listing sorted by subject ID number and administration date in chronological order.

All subjects with dMMR EC (100%) reported taking concomitant medications. The most common types of concomitant medications (used by  $\geq 40\%$  of subjects) were in the ATC classes of other analgesics and antipyretics (75.0%); opioids (60.6%); drugs for peptic ulcer and gastroesophageal reflux disease (47.1%); antithrombotic agents (46.2%); and anti-inflammatory and antirheumatic products, non-steroids (40.4%).

#### The FDA's Assessment:

The FDA agrees with the Applicant's assessment.

### **Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)**

#### Data:

#### **Objective Response Rate**

Tumor response by RECIST v1.1 for subjects with dMMR EC is summarized in [Table 13](#) and [Figure 3](#).

The ORR in subjects with dMMR EC was 42.3%, with 12.7% of patients having a BOR of CR and 29.6% having a BOR of PR. A BOR of SD was observed in 15.5% of subjects with dMMR EC. A total of 38.0% of subjects with dMMR EC had a BOR of PD. BOR was NE in 4.2% of subjects with dMMR EC.

**Table 13: Tumor Response Summary – RECIST v1.1 Assessed by BICR in Subjects with dMMR EC (Revised Primary Efficacy Analysis Set)**

Variable	dMMR EC (N=71)
BOR by RECIST v1.1, n (%)	
CR	9 (12.7)
PR	21 (29.6)
SD	11 (15.5)
PD	27 (38.0)
NE	3 (4.2)
Not done	0
Confirmed ORR by RECIST v1.1, n (%)	30 (42.3)
95% CI <sup>a</sup>	(30.6, 54.6)
DCR by RECIST v1.1, n (%)	41 (57.7)
95% CI <sup>a</sup>	(45.4, 69.4)

Source: Abbreviated Efficacy Report Table 14.2.1.1a

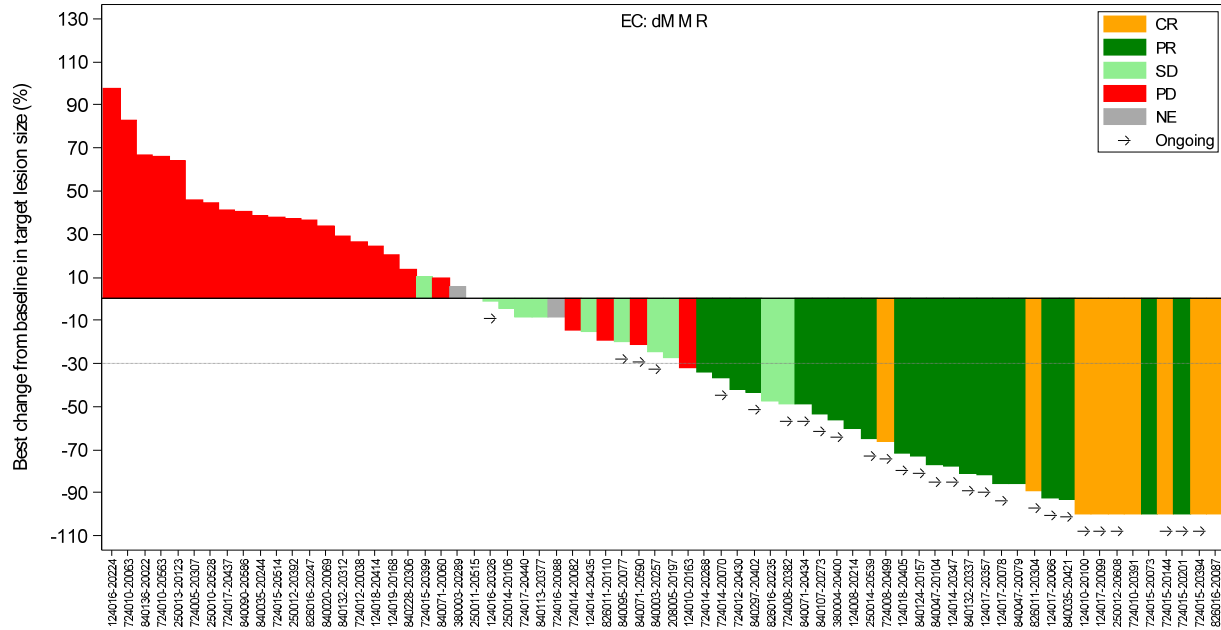
Abbreviations: BICR=blinded independent central review; CI=confidence interval; CR=complete response; CSR=clinical study report; DCR=disease control rate; dMMR=mismatch repair deficient; EC=endometrial cancer; ORR=objective response rate; PD=progressive disease; PR=partial response; RECIST=response evaluation criteria in solid tumors; SD=stable disease.

Note: ORR is defined as the percentage of patients with a RECIST v1.1-confirmed CR or PR. DCR is defined as the percentage of patients with a RECIST v1.1-confirmed PR, CR, and SD. Response assessments are based on BICR.

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**Figure 3: Waterfall Plot of the Maximum Percentage Change from Baseline in Target Lesion Size - RECIST v1.1 Based on BICR in Subjects with dMMR EC (Primary Efficacy Analysis Set)**



Source: CSR 4010-01-001 Figure 14.1.6a

Abbreviations: BICR=blinded independent central review; CR=complete response; CSR=clinical study report; dMMR=mismatch repair-deficient; EC=endometrial cancer; NE=unable to evaluate; 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 reduction. Horizontal reference ranges are defined by -30 for PR.

### Duration of Response

The KM analysis of DOR by RECIST v1.1 for subjects with dMMR EC is summarized in [Table 14](#) and CSR 4010-01-001 [Figure 14.1.3a](#).

At the time of data cutoff, the median DOR had not been reached. The DOR in subjects with dMMR EC ranged from 1.87 to 19.61 months, and 73.3% of subjects had a DOR of ≥6 months. The probability of maintaining a response based on KM estimates for 6, 12, and 18 months in the dMMR EC population was 96.4%, 76.8%, and 61.4%, respectively. At the time of data cutoff, 83.3% of responders with dMMR EC had ongoing response ([Table 13](#)).

**Table 14: Kaplan-Meier Analysis of OR – RECIST v1.1 Based on BICR in Subjects with dMMR EC (Primary Efficacy Analysis Set – Patients with Objective Response)**

Variable	dMMR EC (N=30)
DOR status (n [%])	
Events observed	5 (16.7)
Censored	25 (83.3)
DOR (months)	
Min, max	1.87+, 19.61+
Quartile (95% CI) <sup>a</sup>	
25%	15.2 (8.3, NE)
50%	NE (9.8, NE)
75%	NE (15.2, NE)
Duration ≥6 months (n [%])	22 (73.3)
DOR distribution function (95% CI)	
Month 6	96.4 (77.2, 99.5)
Month 12	76.8 (48.0, 90.9)
Month 18	61.4 (24.6, 84.4)

Source: CSR 4010-01-001 Table 14.2.12a

Abbreviations: BICR=blinded independent central review; CI=confidence interval; CSR=clinical study report; dMMR=mismatch repair deficient; DOR=duration of response; EC=endometrial cancer; max=maximum; min=minimum; N=number of patients; NE=unable to evaluate; RECIST=response evaluation criteria in solid tumors. Note: DOR per RECIST v1.1 based on BICR.

+ indicates subject's response is ongoing.

<sup>a</sup> 95% CIs generated using the method of Brookmeyer and Crowley (1982).

### Applicant Position

Dostarlimab treatment provided meaningful clinical benefit, as defined by BICR assessed ORR and DOR in patients with advanced or recurrent EC. In 71 patients with dMMR EC from Study 4010-01-001 Cohort A1, the ORR was 42.3% (30 of 71 patients) with 12.7% CRs (9 of 71

patients). At the time of the data cutoff date (08 July 2019), the median DOR had not been reached, and 73.3% of responders had a DOR  $\geq$  6 months. Based on KM estimates, the probability of maintaining a response for 6, 12, and 18 months in patients with dMMR EC was 96.4%, 76.8%, and 61.4%, respectively. At the time of the data cutoff date, 83.3% of responders had ongoing response.

DCR, including CR, PR, and SD at 12 weeks, was 57.7% (41 of 71 patients) in the dMMR population.

**The FDA's Assessment:**

The revised 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 February 1, 2019. There are 71 patients in the revised efficacy analysis population, which includes one patient who received the first dose of dostarlimab on January 31, 2019 but had 24-week tumor scan after the data cutoff date.

There were 30 responders out of 71 patients. The confirmed ORR by BICR was 42.3% (95% CI: 30.6, 54.6).

FDA conducted the following subgroup analyses for the primary endpoint of ORR (**Error! Not a valid bookmark self-reference.**).

**Table 15: FDA ORR Subgroup Analyses Based on BICR in Subjects with dMMR EC**

	ORR, % (n) [95% CI]
Overall ORR	
FIGO stage	
I, II, III	40.9% (9/22) [20.7, 63.6]
IV	44.7% (21/47) [30.2, 59.9]
Best overall response from last platinum-containing prior anticancer therapy	
CR/PR	46.9% (15/32) [29.1, 65.3]
SD	61.5% (8/13) [31.6, 86.1]
PD	20.0% (2/10) [2.5, 55.6]
Age	
<65	38.9% (14/36) [23.1, 56.5]
65-74	42.9% (12/28) [24.5, 62.8]
75+	57.1% (4/7) [18.4, 90.1]
Race	
White	41.4% (24/58) [28.6, 55.1]
Black	100% (1/1) [2.5, 100]
Asian	50.0 (1/2) [1.3, 98.7]
American Indian or Alaska native	66.7% (2/3) [9.4, 99.2]
Not reported	28.6% (2/7) [3.7, 71.0]
ECOG performance status	
0	69.6% (16/23) [47.1, 86.8]
1	29.2 (14/48) [17.0, 44.1]

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 19, 2020. The data cut-off date for this updated analysis is December 1, 2019. The median DOR was not reached. The DoR ranged from 2.6 to 22.4 months. Twenty-eight out of 30 responders (93.3%) have a DoR  $\geq 6$  months and 15 responders (50.0%) have a DoR  $\geq 12$  months. No updates to the response were provided with the December 1, 2019 update.

### **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.

### **Efficacy Results – Secondary and Other Relevant Endpoints**

#### The Applicant's Position:

#### **Disease Control Rate**

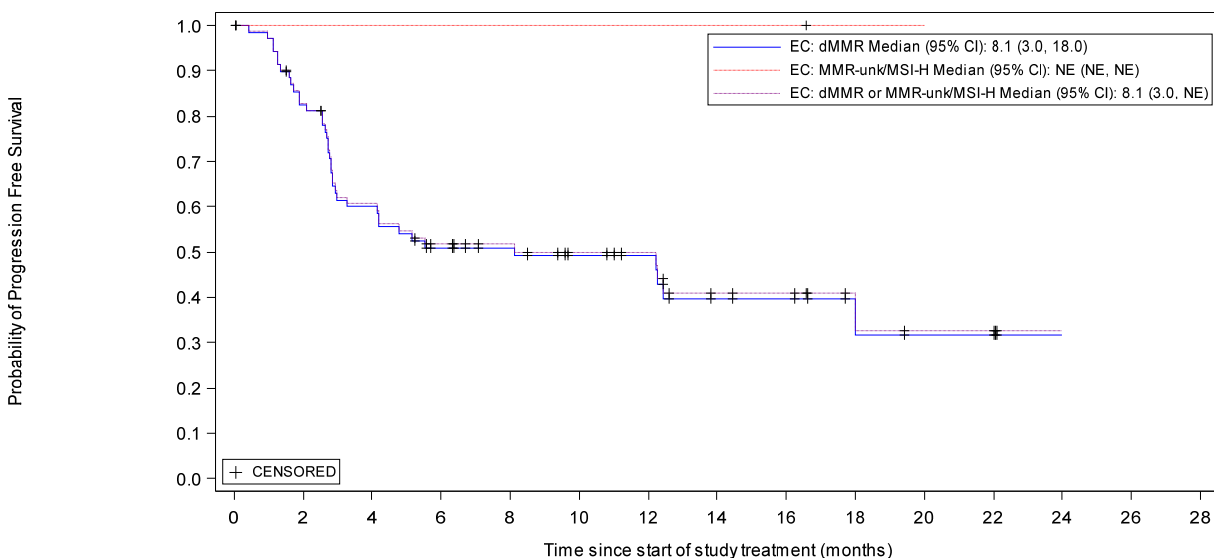
At the time of data cutoff, the DCR in subjects with dMMR EC, including CR, PR, and SD was 57.7% ([Table 13](#)).

#### **Progression-free Survival**

The KM analysis of PFS by RECIST v1.1 for subjects with dMMR EC is presented graphically in [Figure 4](#).

At the time of data cutoff, the median PFS in subjects with dMMR EC was 8.1 months. Just under half of the subjects (45.7%) were censored at this time, and a total of 38 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 51.0%, 49.1%, and 49.1%, respectively.

**Figure 4: Kaplan-Meier Plot for PFS - RECIST v1.1 based on BICR in Subjects with dMMR EC (Primary Efficacy Analysis Set)**



Number of patients at risk															
	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28
EC: dMMR	70	56	40	31	27	20	16	10	9	5	3	3	0	0	0
EC: MMR-unk/MSI-H	2	1	1	1	1	1	1	1	1	0	0	0	0	0	0
EC: dMMR or MMR-unk/MSI-H	72	57	41	32	28	21	17	11	10	5	3	3	0	0	0

Source: CSR 4010-01-001 Figure 14.1.1a

Abbreviations: BICR=blinded independent central review; CI=confidence interval; CSR=clinical study report; dMMR=mismatch repair-deficient; EC=endometrial cancer; MMR-unk=unknown mismatch repair tumor status; MSI-H=microsatellite instability-high; NE=unable to evaluate; PFS=progression-free survival; RECIST=response evaluation criteria in solid tumors.

Note: Medians are presented in months.

### Overall Survival

The KM analysis of OS for subjects with dMMR EC is summarized in [Table 16](#) and presented graphically in [Figure 5](#).

At the time of data cutoff, the median OS for subjects with dMMR EC had not been reached. Most of the subjects (74.3%) were censored at this time, and a total of 18 OS events had been observed. Based on these results, the probability of survival at Month 6, Month 9, and Month 12 was estimated to be 80.5%, 76.7%, and 72.5%, respectively.

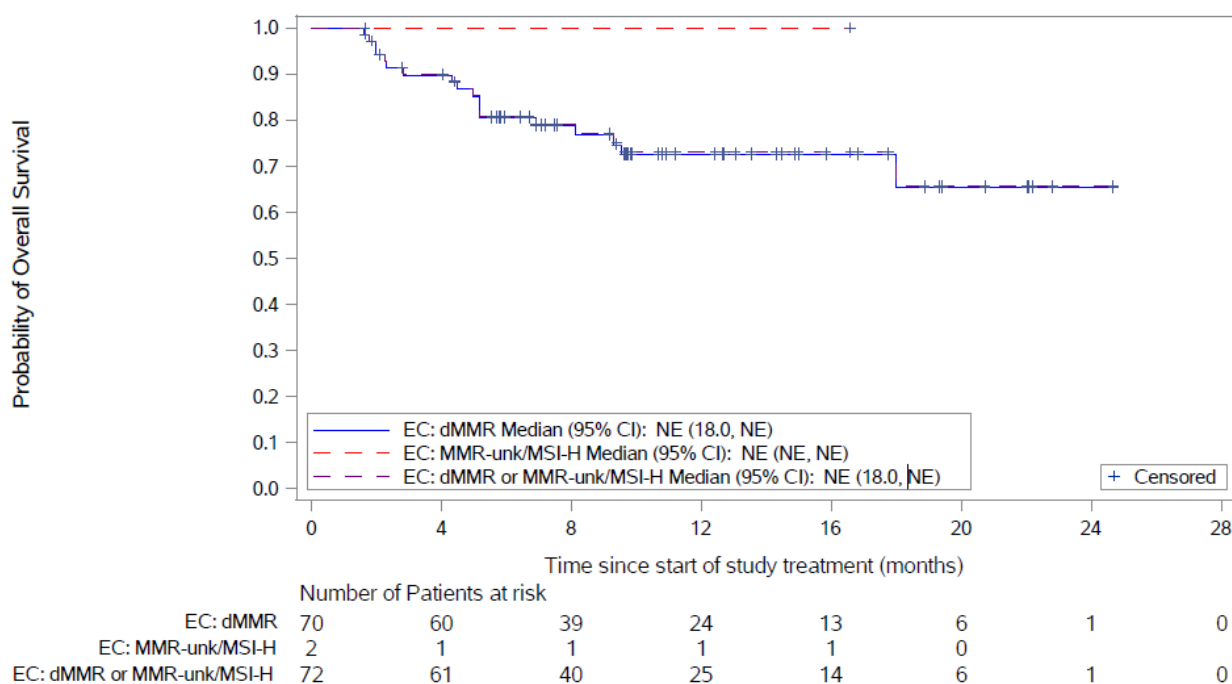
**Table 16: Kaplan-Meier Analysis of OS in Subjects with dMMR EC (Primary Efficacy Analysis Set)**

Variable	dMMR EC (N=70)
OS status (n [%])	
Events observed	18 (25.7)
Censored	52 (74.3)
OS distribution function (95% CI)	
Month 6	80.5 (68.8, 88.2)
Month 9	76.7 (64.2, 85.3)
Month 12	72.5 (59.2, 82.1)

Source: CSR 4010-01-001 Table 14.2.22.1a

Abbreviations: CI=confidence interval; CSR=clinical study report; dMMR=mismatch repair deficient; EC=endometrial cancer; OS=overall survival.

**Figure 5: Kaplan-Meier Plot for OS in Subjects with dMMR EC (Primary Efficacy Analysis Set)**



Source: CSR 4010-01-001 Figure 14.1.5.1a

Abbreviations: CI=confidence interval; CSR=clinical study report; dMMR=mismatch repair-deficient; EC=endometrial cancer; MMR-unk=unknown mismatch repair tumor status; MSI-H=microsatellite instability-high; NE=unable to evaluate; OS=overall survival.

Note: Medians are presented in months.

### Immune-related ORR

Tumor response by irRECIST based on Investigators' assessment for subjects with dMMR is summarized in [Table 17](#).

At the time of data cutoff, the irORR in subjects with dMMR EC was 44.6%, with 5.4% irCRs and 39.2% irPRs. A total of 17.6% of subjects with dMMR EC had an irBOR of irSD, and 36.5% had an irBOR of irPD.

**Table 17: Tumor Response Summary – irRECIST Based on Investigator Assessment in Subjects with dMMR EC (Secondary Efficacy Analysis Set)**

Variable	dMMR EC (N=74)
Best overall response by irRECIST (n [%])	
irCR	4 (5.4)
irPR	29 (39.2)
irSD	13 (17.6)
irPD	27 (36.5)
Not evaluable	1 (1.4)
Not done	0
Confirmed objective response rate per irRECIST	
n (%)	33 (44.6)
95% CI <sup>a</sup>	(33.0, 56.6)
Response ongoing <sup>b</sup>	26 (78.8)
Disease control rate per irRECIST	
n (%)	46 (62.2)
95% CI <sup>a</sup>	(50.1, 73.2)

Source: CSR 4010-01-001 Table 14.2.2a

Abbreviations: CI=confidence interval; CSR=clinical study report; dMMR=mismatch repair deficient; EC=endometrial cancer; irCR=immune-related complete response; irPD=immune-related progressive disease; irPR=immune-related partial response; irRECIST=immune-related response evaluation criteria in solid tumors; irSD=immune-related stable disease.

<sup>a</sup> Exact 2-sided 95% CI for the binomial proportion.

<sup>b</sup> All responders who have not yet died or progressed (including clinical progression), denominator for percentage is number of responders.

### Immune-related DOR

The KM analysis of irDOR by irRECIST for subjects with dMMR EC is summarized in [Table 18](#).

At the time of data cutoff, the median irDOR had not been reached. The irDOR in subjects with dMMR EC ranged from 2.46 to 19.61 months. The probability of maintaining a response based on KM estimates for 6, 12, and 18 months in the dMMR EC population was 96.9%, 70.0%, and

63.0%, respectively. At the time of data cutoff, 78.8% of responders with dMMR EC had ongoing response (Table 17).

**Table 18: Kaplan-Meier Analysis of irDOR – irRECIST Based on Investigator Assessment in Subjects with dMMR EC (Secondary Efficacy Analysis Set – Patients with Objective Response)**

Variable	dMMR EC (N=33)
<i>irDOR</i> status (n [%])	
Events observed	7 (21.2)
Censored	26 (78.8)
<i>irDOR</i> (months)	
Min, max	2.46+, 19.61+
Quartile (95% CI) <sup>a</sup>	
25%	11.3 (6.4, NE)
50%	NE (11.3, NE)
75%	NE (NE, NE)
<i>irDOR</i> distribution function (95% CI)	
Month 6	96.9 (79.8, 99.6)
Month 12	70.0 (43.7, 85.7)
Month 18	63.0 (36.2, 81.1)

Source: CSR 4010-01-001 Table 14.2.13a

Abbreviations: CI=confidence interval; CSR=clinical study report; dMMR=mismatch repair deficient; DOR=duration of response; EC=endometrial cancer; irDOR=immune-related duration of response; irRECIST=immune-related response evaluation criteria in solid tumors; max=maximum; min=minimum; NE=unable to evaluate.

Note: irDOR: DOR per irRECIST.

+ indicates subject's response is ongoing.

<sup>a</sup> 95% CIs generated using the method of Brookmeyer and Crowley (1982)

### Immune-related DCR

At the time of data cutoff, the irDCR in subjects with dMMR EC, including irCR, irPR, and irSD was 62.2% (Table 17).

### Immune-related PFS

The KM analysis of irPFS by irRECIST for subjects with dMMR EC is summarized in Table 19.

At the time of data cutoff, the median irPFS in subjects with dMMR EC was 10.3 months. Just under half of the subjects (43%) were censored at this time, and a total of 42 irPFS 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 54.7%, 51.5%, and 47.4%, respectively.

**Table 19: Kaplan-Meier Analysis of FS – irRECIST Based on Investigator Assessment in Subjects with dMMR EC (Secondary Efficacy Analysis Set)**

Variable	dMMR EC (N=74)
irPFS status (n [%])	
Events observed	42 (56.8)
Censored	32 (43.2)
irPFS (months)	
Quartile (95% CI) <sup>a</sup>	
25%	2.7 (1.7, 3.0)
50%	10.3 (4.2, 17.0)
75%	NE (17.0, NE)
irPFS distribution function (95% CI)	
Month 6	54.7 (42.6, 65.3)
Month 9	51.5 (39.4, 62.3)
Month 12	47.4 (35.0, 58.7)

Source: CSR 4010-01-001 Table 14.2.11a

Abbreviations: CI=confidence interval; CSR=clinical study report; dMMR=mismatch repair deficient; EC=endometrial cancer; irPFS=immune-related progression-free survival; irRECIST=immune-related response evaluation criteria in solid tumors; NE=unable to evaluate.

<sup>a</sup> 95% CIs generated using the method of Brookmeyer and Crowley (1982)

**The FDA’s Assessment:**

The results for the secondary endpoints presented above are based upon the Applicant’s efficacy analysis population which didn’t include the patients who received the first dose of dostarlimab on January 31, 2019 but had 24-week tumor scan after the data cutoff date. Based upon the revised efficacy analysis population, the immune-related ORR per investigators assessments was 44.0% (95% CI: 32.5%, 55.9%). The median irDoR was not reached and the irDoR was ranged from 2.5 months to 19.6 months.

Based upon the revised efficacy analysis population, median PFS was 8.1 months and median OS was not reached.

Note that PFS, and OS analyses results are not interpretable in a single-arm study. These analyses are considered as exploratory.

**Dose/Dose Response**

**Data:**

See results in Section 8.1.2.

**The FDA’s Assessment:**

No additional analysis was performed by the FDA.

### **Durability of Response**

Data:

Not performed

The FDA's Assessment:

No additional analysis was performed by the FDA.

### **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.

### **Efficacy Results – Secondary or Exploratory COA(PRO) Endpoints**

The Applicant's Position:

Data on PRO are not included in this submission

The FDA's Assessment:

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

#### **8.1.3. Integrated Review of Effectiveness**

The FDA's Assessment:

Not applicable.

#### **8.1.4. Assessment of Efficacy Across Trials**

The Applicant's Position:

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

The FDA's Assessment:

FDA agrees.

#### **8.1.5. Integrated Assessment of Effectiveness**

The Applicant's Position:

Clinical activity was consistent across EC, colorectal cancer (CRC), and other tumor types (42.3%, 43.3%, and 44.4% [non-CRC], respectively. A total of 32.7% had a BOR of SD, and 14.3% had a BOR of PD.

The FDA's Assessment:

The FDA's efficacy review and assessment for this BLA is based on data from 71 adult patients with mismatch repair deficient (dMMR) recurrent or advanced endometrial cancer (EC) who progressed on or following prior treatment with a platinum-containing regimen. Dostarlimab demonstrated efficacy in Study 4010-01-001 (GARNET) for the treatment of this patient population. The confirmed ORR by BICR was 42.3% (95% CI: 30.6, 54.6), with a 12.7% complete response rate and a 29.6% partial response rate. The median DoR was not reached by the data cut-off date of December 1, 2019. The DoR ranged from 2.6 to 22.4 months. Twenty-eight out of 30 responders (93.3%) have a DoR  $\geq$ 6 months. and 15 responders (50.0%) have a DoR  $\geq$ 12 months. This durable objective response rate is of sufficient magnitude to serve as an endpoint earlier than survival that improved over that of available therapies and is reasonably likely to predict clinical benefit and is supportive of accelerated approval of dostarlimab for the treatment of adult patients with recurrent or advanced dMMR EC who progressed on or following prior treatment with a platinum-containing regimen.

## 8.2. Review of Safety

The Applicant's Position:

Safety data for dostarlimab are organized into 2 groups:

- Subjects treated with dostarlimab at the recommended therapeutic dose (RTD) (monotherapy and combination therapy)
- Subjects with mismatch repair-deficient (dMMR) and dMMR/microsatellite instability-high (MSI-H) endometrial cancer (EC; Cohort A1; monotherapy)

As presented in [Table 20](#), the "RTD" pool comprises patients who were treated with the 500 mg every 3 weeks (Q3W) for 4 doses followed by 1,000 mg every 6 weeks (Q6W) regimen as well as those who were treated with the 500 mg Q3W regimen throughout the AMBER study. Data from Study 4010-01-001 Parts 1 and 2A were excluded because of the variability in dosing due to the tolerability and dose-finding objectives (1, 3, or 10 mg/kg every 2 weeks in Part 1 and 500 mg Q3W or 1,000 Q6W in Part 2A).

For dostarlimab combination therapy data derived from Study 4020-01-001, a subgroup of patients received TSR-033 in addition to TSR-022. For dostarlimab combination therapy data derived from Study 3000-01-002, a subgroup of patients received bevacizumab in addition to niraparib or chemotherapy agents. However, no combination data is discussed in this review.

For the Analysis of Submission-Specific Safety Issues, including immune-related adverse events (irAEs) and infusion-related reactions, the discussion of safety data for the RTD pool focuses on patients who received dostarlimab as a single agent (N=444).

**Table 20: Summary of Studies for irAEs and Infusion-related Reactions Derived from All Patients Treated with Dostarlimab at the RTD**

	<b>Dostarlimab Single Agent</b>	<b>Dostarlimab in Combination with Niraparib</b>	<b>Dostarlimab in Combination with TSR-022</b>	<b>Dostarlimab in Combination with Chemotherapy Agents</b>	<b>Total</b>
Study	4010-01-001 (GARNET, Part 2B) N=444	3000-01-002 (IOLite, Parts A and C) N=35	4020-01-001 (AMBER, dostarlimab-treated patients) <sup>a</sup> N=220	3000-01-002 (IOLite, Parts B and D) N=20	N=719

Abbreviations: irAE=immune-related adverse event; Q3W=every 3 weeks; Q6W=every 6 weeks; PK=pharmacokinetic; RTD=recommended therapeutic dose.

Note: Dostarlimab was administered at the RTD (ie, 500 mg Q3W for 4 doses followed by 1,000 mg Q6W) in Study 4010-01-001 and Study 3000-01-002. In Study 4020-01-001, dostarlimab was administered at a dose of 500 mg Q3W, which was shown to have an equivalent PK trough to the RTD.

<sup>a</sup> Includes 11 patients who were treated with a combination of dostarlimab, TSR-022, and TSR-033. Four patients who crossed over from dostarlimab monotherapy to dostarlimab + TSR-022 were excluded.

Cohort A1 of Study 4010-01-001 included patients with dMMR/MSI-H EC who received dostarlimab monotherapy. Discussion of this group for all other sections (excluding irAEs and infusion-related reactions) of the safety review, will focus on patients with dMMR EC (N=104), as identified by MMR IHC.

Despite being a heavily pretreated patient population, the safety profile observed was consistent with the known safety profile of other anti-PD-1 agents and AEs that are commonly managed by physicians treating patients with cancer and cancer-related comorbidities. Treatment-related treatment-emergent adverse events (TEAEs) in general were Grades 1 or 2, and few patients discontinued due to a treatment-related TEAE. The irAEs observed with dostarlimab were consistent with those observed with other anti-PD-1 agents. IrAEs may be managed by treatment interruptions or discontinuations, the use of systemic steroids and other IMMs or hormonal therapy, as clinically indicated. None of the patients treated with dostarlimab as single agent died from a treatment-related TEAE. Please refer to Section 8.1.4 for additional details on the safety results.

**The FDA's Assessment:**

To support the safety evaluation of dostarlimab for this BLA, the Applicant submitted safety data from the Study 4010-01-001 (GARNET), which has been described previously as a Phase 1 dose escalation and cohort expansion study of dostarlimab monotherapy in patients with advanced solid tumors. The safety population included 104 patients with dMMR endometrial cancer from cohort A1 of the trial who had received at least one dose of dostarlimab monotherapy by the data cutoff date. Additionally, safety analyses of immune-related adverse events (irAEs) were also performed, which included 444 patients with a variety of advanced solid tumors in Part 2B of Study 4010-01-001 who had received 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). FDA's analyses of deaths and the safety results are discussed in other sections of this review.

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

### **8.2.1. Safety Review Approach**

#### The Applicant's Position:

Safety data and analyses for dostarlimab are presented below. The primary safety concerns for all drugs in the anti-PD-1 class are immune-related adverse events (irAEs) due the mechanism of action of these agents, and infusion-related reactions. Data reviewed for these potential risks include the RTD safety population. In subjects treated with dostarlimab as a single agent at the RTD, the most frequently reported irAEs ( $\geq 5\%$  of the subjects) were diarrhoea (5.9%) and hypothyroidism (5.6%). irAEs are managed with dose interruption, discontinuation and immunomodulatory agents including systemic steroids, immune suppressants, and thyroid therapy when required. These have been effective measures for the PD-1/PD-L1 inhibitors that are currently approved.

For a full description of treatments received in each RTD study, see [Table 7](#).

#### The FDA's Assessment:

The FDA agrees with the Applicant's assessment. Also, see FDA comments in section 8.2 of this review.

### **8.2.2. Review of the Safety Database**

#### **Overall Exposure**

#### The Applicant's Position:

A total of 104 dMMR EC patients had received at least 1 dose of dostarlimab in the GARNET study by the data cutoff date and were included in the safety analysis. As of the data cutoff date, the overall median treatment duration for patients with dMMR EC was 19.6 weeks (range: 3.0 to 105 weeks; [Table 21](#)). The median relative dose intensity during the first 12 weeks of treatment (100.0%) and from 13 weeks of treatment and beyond (100.0%) indicate the majority of patients received doses as planned without delays or interruptions.

**Table 21: Treatment Exposure (Safety Analysis Set – Patients with dMMR EC**

Parameter	dMMR EC (N=104)
Treatment duration (weeks)	
n	104
Mean (StDev)	32.0 (28.10)
Median	19.6
Min, max	3.0, 105.0
<b>First Dose through Week 12</b>	
Actual dose intensity (mg/day)	
n	104
Mean (StDev)	23.3 (1.54)
Median	23.8
Min, max	16.3, 25.6
Cumulative dose (mg)	
n	104
Mean (StDev)	1764.4 (456.65)
Median	2000.0
Min, max	500, 2000
Relative dose intensity (%)	
n	104
Mean (StDev)	97.9 (6.46)
Median	100.0
Min, max	68.3, 107.7
<b>Week 13 through End of Treatment</b>	
Actual dose intensity (mg/day)	
n	65
Mean (StDev)	23.4 (1.25)
Median	23.8
Min, max	17.3, 25.6
Cumulative dose (mg)	
n	65
Mean (StDev)	5415.4 (4369.25)
Median	4000.0
Min, max	1000, 15000
Relative dose intensity (%)	

Parameter	dMMR EC (N=104)
n	65
Mean (StDev)	98.1 (5.25)
Median	100.0
Min, max	72.7, 107.7

Source: CSR 4010-01-001 Table 14.1.14a and Table 14.1.15a

Abbreviations: CSR=clinical study report; dMMR=mismatch repair-deficient; EC=endometrial cancer; max=maximum; min=minimum; StDev=standard deviation.

#### The FDA's Assessment:

The FDA agrees with the Applicant's assessments of duration of exposure and dose intensity in Table 21.

### **Relevant Characteristics of the Safety Population**

#### The Applicant's Position:

This section reflects the relevant characteristics of the 104 patients with dMMR endometrial cancer.

All 104 patients with dMMR EC were female. Most were White (79.8%), the median age was 64.5 years (range: 39 to 80 years), half of the patients were <65 years old, and 61.5% had an ECOG performance status of 1 at study entry.

A total of 67.3% of patients with dMMR EC were International Federation of Gynecology and Obstetrics (FIGO) Stage IV at most recent assessment. The median BMI was 28.01 kg/m<sup>2</sup> (range: 13.6 to 53.9 kg/m<sup>2</sup>).

The most frequently reported (in >50% of patients with dMMR EC) medical history condition system organ classes (SOCs) were gastrointestinal disorders (65.4%), musculoskeletal and connective tissue disorders (57.7%), and psychiatric disorders (51.0%). The most frequently reported (in >40% of patients) medical history condition preferred term (PT) was hypertension (40.4%).

Overall, the demographics and baseline characteristics of subjects in the safety analysis set were similar to those of subjects in the primary efficacy analysis set.

#### The FDA's Assessment:

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

### **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 444 patients who have been treated with dostarlimab monotherapy and an additional 275 patients who received dostarlimab in

combination with other agents. 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, as well as the studies to be included (monotherapy [Study 4010-01-001] and combination therapy [Studies 4020-01-001 and 3000-01-002]), the pooling strategy, and parameters to be analyzed, were discussed at the Type C meeting held on February 25, 2019. As agreed with the Agency, data from Study 4010-01-001 Part 1 and Part 2A and other ongoing, open-label studies with dostarlimab combination therapy, including Study 4040-01-001 (CITRINO), Study 3000-02-001 (JASPER), Study 3000-02-005 (OPAL) and Study 3000-02-006 (MOONSTONE), were excluded from the integrated summary of safety because it was estimated that very few patients in each would have received dostarlimab at the time of the data cutoff date. Data from Study 3000-03-005 (FIRST) were excluded as well, because the study is an ongoing, double-blind study.

Observed AEs included events that were in line with those expected in subjects with recurrent or advanced EC, as well as those consistent with reported safety profiles of monoclonal antibodies blocking the PD-1 interactions.

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

The FDA's Assessment:

The FDA agrees with the Applicant's assessment.

### **8.2.3. Adequacy of Applicant's Clinical Safety Assessments**

#### **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.

#### **Categorization of Adverse Event(s)**

The Applicant's Position:

The overall analysis of safety included TEAEs (SAEs,  $\geq$ Grade 3 AEs, treatment-related AEs), AESIs (potential 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 patients,

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 20.0 by system organ class (SOC) and preferred term (PT). Unless otherwise stated, the sort order was SOC and PT by descending frequency of the “total” column and then alphabetical order.

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

The FDA’s Assessment:

The FDA agrees with the Applicant’s categorization of safety assessments in this trial.

**Routine Clinical Tests**

The Applicant’s Position:

Laboratory values were primarily based on International Standard (SI) units. Laboratory result toxicity grades were based on NCI-CTCAE v4.03. The laboratory parameters analyzed were:

1. Hematology (including hemoglobin, white blood cell count, platelet count, neutrophil count, and lymphocyte count)
2. Blood chemistry (including hepatic profile, renal profile, and metabolic and muscle profile)

Any unscheduled measurements were included in by-visit summaries and were used for the determination of worse grade during treatment.

For those parameters that were graded with 2 toxicities (hyper-, and hypo-), the toxicities were summarized separately. Low direction toxicity grades at baseline and postbaseline were set to 0 when the variables were derived for summarizing high direction toxicity, and vice versa.

Please refer to Section 8.1.1 for additional details on the procedures and schedule for safety assessments.

The FDA’s Assessment:

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

**8.2.4. Safety Results**

**Deaths**

The Applicant’s Position:

A total of 20 patients (19.2%) with dMMR EC died while on study (Table 22).

During the treatment period, 4 patients (3.8%) with dMMR EC died. The primary cause for death for the majority of patients (3 patients [2.9%]) was disease progression. TEAEs (treatment unrelated) were the primary cause for death in 1 patient (1.0%).

During the 90-day safety follow-up period, 10 patients (9.6%) with dMMR EC died. The primary cause for death for the majority of patients (6 patients [5.8%]) was disease progression. TEAEs (treatment unrelated) were the primary cause for death in 4 patients (3.8%).

During the long-term follow-up period, 6 patients (5.8%) with dMMR EC died. The primary cause for death for the majority of deaths (4 patients [3.8%]) was disease progression. The primary cause for death was unknown for 2 patients (1.9%).

**Table 22: Deaths (Safety Analysis Set - Subjects with dMMR Endometrial Cancer)**

Period, n (%)	dMMR EC (N=104)
During the Treatment Period <sup>a</sup>	
Deaths	4 (3.8)
Disease progression	3 (2.9)
Adverse Events	1 (1.0)
During 90-day Safety Follow-up Period <sup>b</sup>	
Deaths	10 (9.6)
Disease Progression	6 (5.8)
Adverse Events	4 (3.8)
Other	0
During Long-term Follow-up Period <sup>c</sup>	
Deaths	6 (5.8)
Disease Progression	4 (3.8)
Unknown	2 (1.9)

Abbreviations: CSR=clinical study report; dMMR=mismatch repair-deficient; EC=endometrial cancer; PD=progressive disease.

<sup>a</sup> If the last cycle of the dostarlimab treatment is ≤4 cycles, it is from first dose to last dose of dostarlimab + 21 days, otherwise it is from first dose to last dose of dostarlimab + 42 days.

<sup>b</sup> Within 90 days after end of treatment visit of dostarlimab and first follow-up anticancer therapy, whichever is earlier.

<sup>c</sup> After end of treatment visit of dostarlimab + 90 days or first follow-up anticancer therapy, whichever is earlier.

Source: CSR 4010-01-001 Table 14.3.1.21a.

**The FDA's Assessment:**

The FDA conducted an independent analysis of deaths in patients with dMMR EC in Study 4010-01-001, based on the death narratives submitted by the Applicant.

All-cause death occurred in 20 patients with dMMR EC (19%) at the time of data cutoff. The majority of deaths were due to disease progression (13 out of 20 patients). Two deaths were due to unknown causes. Five out of 20 patients had an adverse event with an outcome of death including: Patients (b) (6)

During the course of labeling negotiations, additional details on the clinical courses of

the five patients who died was provided by the Applicant. After further assessment by FDA, it was determined that none of the five deaths that occurred in the setting of an adverse event could reasonably be attributed to dostarlimab.

The FDA analysis of the submitted narratives for the five patients who experienced adverse events with an outcome of death is captured below.

1- Patient (b) (6): 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) on (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.*

2- Patient (b) (6): 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  $21.4 \times 10^9/L$  (reference range 3.1 to  $9.7 \times 10^9/L$ ) and absolute neutrophil count  $18.4 \times 10^9/L$  (reference range 1.2 to  $6 \times 10^9/L$ ). 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.*

3- Patient (b) (6): 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  $87 \times 10^9/L$  (reference range 42 to  $75 \times 10^9/L$ ) and lymphocyte count of  $0.3 \times 10^9/L$  (reference range 0.6 to  $4.9 \times 10^9/L$ ). 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 [REDACTED] (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 [REDACTED] (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 [REDACTED] (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 [REDACTED] (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 [REDACTED] (b) (6)), the subject in question developed bronchitis in [REDACTED] (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 ([REDACTED] (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.*

4- Patient (b) (6): 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.*

5- Patient (b) (6): 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 [REDACTED] (b) (6) (Cycle 1 Day 1). The subject received the last dose of dostarlimab on [REDACTED] (b) (6) (Cycle 2 Day 1). On [REDACTED] (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 [REDACTED] (b) (6) was unclear. Initially, no information was provided by the Applicant regarding patient's status between [REDACTED] (b) (6) and the AE of gastroenteritis leading to death on [REDACTED] (b) (6).*

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

*On [REDACTED] (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 [REDACTED] (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 [REDACTED] (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 [REDACTED] (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 [REDACTED] (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 [REDACTED] (b) (6) for her symptoms of nausea, vomiting, and diarrhea and when she came back to ED on [REDACTED] (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.*

### Serious Adverse Events

#### The Applicant's Position:

Treatment-related SAEs were experienced by 10 patients (9.6%) with dMMR EC (Table 23). Colitis was the only treatment-related SAE reported in >1 patient with dMMR EC (2 patients [1.9%]). All other treatment-related SAEs occurred in 1 patient each.

**Table 23: SAEs by PT (Safety Analysis Set - >1% of Patients with dMMR EC)**

Preferred Term, n (%)	dMMR EC (N=104)	
	Any SAE	Treatment-related SAE
Patients with at least 1 SAE	35 (33.7)	10 (9.6)
Abdominal pain	3 (2.9)	0
Acute kidney injury	3 (2.9)	0
Pyrexia	3 (2.9)	1 (1.0)
Sepsis	3 (2.9)	0
Urinary tract infection	3 (2.9)	0
Bronchitis	2 (1.9)	0
Colitis	2 (1.9)	2 (1.9)
General physical health deterioration	2 (1.9)	0
Intestinal obstruction	2 (1.9)	0
Pain	2 (1.9)	0
Pulmonary embolism	2 (1.9)	0
Pyelonephritis	2 (1.9)	0
Tumour pain	2 (1.9)	0

Source: CSR 4010-01-001, Table 14.3.1.11a; CSR 4010-01-001, Table 14.3.1.13a

Abbreviations: CSR=clinical study report; dMMR=mismatch repair-deficient; EC=endometrial cancer; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SAE=serious adverse event.

Note: Adverse events are coded using MedDRA version 20.0.

#### The FDA's Assessment:

The FDA agrees with the serious adverse event (SAE) data presented by the Applicant in Table 23. The incidence rate of SAEs in the safety population with dMMR EC who received

dostarlimab was 34%. The most common SAEs with an incidence rate of > 2% include sepsis, pyrexia, urinary tract infection, acute kidney injury, and abdominal pain.

### Dropouts and/or Discontinuations Due to Adverse Events

#### The Applicant's Position:

TEAEs leading to permanent discontinuation of study treatment reported for patients with dMMR EC are summarized in [Table 24](#).

Transaminases increased was the only TEAE reported in >1 patient (>1%) with dMMR EC that led to permanent discontinuation of study treatment (2 patients [1.9%]); both events were Grade 3 and treatment-related and 1 (1.0%) of these 2 patients experienced treatment-related gamma-glutamyl transferase increased that also led to discontinuation of study treatment. It should be noted that Grade 3 transaminases increased and Grade 3 pneumonitis required permanent discontinuation of study treatment per protocol.

None of the other TEAEs that led to discontinuation of study treatment were considered treatment-related.

**Table 24: TEAEs Leading to Permanent Discontinuation of Study Treatment by SOC and PT (Safety Analysis Set - Subjects with dMMR Endometrial Cancer)**

Preferred Term, n (%)	dMMR EC (N=104)
Any TEAE leading to discontinuation of study treatment	11 (10.6)
Transaminases increased	2 (1.9)
Acute kidney injury	1 (1.0)
Aspiration bronchial	1 (1.0)
Bronchitis	1 (1.0)
Gamma-glutamyl transferase increased	1 (1.0)
Gastroenteritis	1 (1.0)
Intestinal obstruction	1 (1.0)
Nervous system disorder	1 (1.0)
Pleural effusion	1 (1.0)
Pneumonitis	1 (1.0)
Sepsis	1 (1.0)

Source: CSR 4010-01-001 Table 14.3.1.14a

Abbreviations: dMMR=mismatch repair-deficient; EC=endometrial cancer; PT=preferred term; SOC=system organ class; TEAE=treatment-emergent adverse event.

#### The FDA's Assessment:

The Applicant assessed that none of the TEAEs that led to treatment discontinuation were related to dostarlimab. However, FDA conducted an independent analysis of TEAEs leading to

dropouts and treatment discontinuations, and assessed each of the 11 events listed in Table 24. FDA determined that 5 of the events were at least possibly study-treatment related. These included bronchitis (Patient (b) (6)), sepsis (Patient (b) (6)), pneumonitis (Patient (b) (6)), and 2 patients with transaminase elevation (Patient (b) (6) and (Patient (b) (6)). As a result, the product labeling for dostarlimab reflects that there were 5 (4.8%) TEAEs leading to permanent discontinuation of study drug and the adverse events are included in product labeling of dostarlimab.

### Dose Interruption/Reduction Due to Adverse Events

#### The Applicant's Position:

TEAEs leading to treatment interruption reported for patients with dMMR EC are summarized in Table 25. There were no dose reductions due to adverse events.

TEAEs leading to study treatment interruption were experienced by 24 patients (23.1%) with dMMR EC. The most frequently reported TEAEs leading to study treatment interruptions were anaemia (2.9%) as well as diarrhoea, lipase increased, and pyrexia (1.9% each). No other TEAE that led to interruption of study treatment was reported in more than 1 patient (>1%) with dMMR EC.

Treatment-related TEAEs leading to study treatment interruption were reported in 14 patients with dMMR EC, including diarrhoea and lipase increased in 2 patients each. No other treatment-related TEAE that led to interruption of study treatment was reported in more than 1 patient with dMMR EC.

**Table 25: TEAEs Leading to Treatment Interruption by PT (Safety Analysis Set - ≥1% of Total Patients with dMMR Endometrial Cancer)**

Preferred Term, n (%)	dMMR EC (N=104)
Any AE leading to study treatment interruption	24 (23.1)
Anaemia	3 (2.9)
Diarrhoea	2 (1.9)
Lipase increased	2 (1.9)
Pyrexia	2 (1.9)

Source: CSR 4010-01-001 Table 14.3.1.18a.

Abbreviations: AE=adverse event; CSR=clinical study report; dMMR=mismatch repair-deficient; EC=endometrial cancer; PT=preferred term; TEAE=treatment-emergent adverse event.

#### The FDA's Assessment:

The 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 included anemia, diarrhea, increased lipase, and pyrexia.

## Treatment Emergent Adverse Events and Adverse Reactions

### The Applicant's Position:

TEAEs reported for patients with dMMR EC are summarized in [Table 26](#) and [Table 27](#).

**Table 26: Overview of TEAEs (Safety Analysis Set - Patients with dMMR EC)**

Events, n (%)	dMMR EC (N=104)
TEAEs	97 (93.3)
Treatment-related TEAEs	68 (65.4)
Grade $\geq 3$ TEAEs	48 (46.2)
Grade $\geq 3$ treatment-related TEAEs	12 (11.5)
TEAEs leading to permanent treatment discontinuation	11 (10.6)
Treatment-related TEAEs leading to permanent treatment discontinuation	2 (1.9)
TEAEs leading to study treatment interruption	24 (23.1)
Serious TEAEs	35 (33.7)
Treatment-related serious TEAEs	10 (9.6)
TEAEs with outcome of death	5 (4.8)
Treatment-related TEAEs with outcome of death	0
Treatment-emergent irAE <sup>a</sup>	35 (33.7)
Treatment-related treatment-emergent irAE <sup>a</sup>	24 (23.1)
Dostarlimab infusion-related reactions <sup>b</sup>	0

Source: Table 14.3.1.1a

Abbreviations: AE=adverse event; dMMR=mismatch repair-deficient; EC=endometrial cancer; irAE=immune-related adverse event; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; TEAE=treatment-emergent adverse event.

Note: Adverse events are coded using MedDRA version 20.0.

<sup>a</sup> irAEs were defined as any Grade  $\geq 2$  AEs identified by PTs of Appendix C of the integrated summary of safety statistical analysis plan.

<sup>b</sup> Dostarlimab infusion-related reactions were defined as any treatment-related AEs that occurred on or 1 day after dostarlimab infusion and identified by the following PTs: infusion-related reaction, anaphylactic reaction, drug hypersensitivity, hypersensitivity and type I hypersensitivity

The most frequently reported treatment-related TEAEs ( $\geq 10\%$ ) for patients with dMMR EC were asthenia, diarrhoea, fatigue, and nausea. These TEAEs were Grade 1 or 2 in severity in most patients for whom the TEAEs were reported; of these common treatment-related TEAEs, 2 patients (1.9%) had Grade  $\geq 3$  events of diarrhoea and 1 patient (0.9%) had a Grade  $\geq 3$  event of asthenia.

A total of 12 patients (11.5%) with dMMR EC experienced at least 1 Grade  $\geq 3$  treatment-related TEAE ([Table 27](#)). The most frequently reported Grade  $\geq 3$  treatment-related TEAE in patients with dMMR EC was anaemia (3 patients [2.9%]). All other Grade  $\geq 3$  treatment-related TEAEs were reported in 1 or 2 patients (<2%) each.

One patient (1.0%) had a Grade 4 treatment-related TEAE of gamma-glutamyl transferase increased. No patient experienced a Grade 5 treatment-related TEAE.

TEAEs leading to death are discussed in Section 8.1.2 under Deaths. None of the TEAEs leading to death were assessed as related to study treatment by Investigators.

**Table 27: Common Treatment-Emergent Adverse Events (Safety Analysis Set - ≥10% of Subjects with dMMR EC)**

Preferred Term, n (%)	dMMR EC (N=104)	
	All Grades <sup>a</sup>	Grades 3-5 <sup>a</sup>
Patients with at least 1 TEAE	97 (93.3)	48 (46.2)
Nausea	31 (29.8)	0
Diarrhoea	27 (26.0)	2 (1.9)
Fatigue	26 (25.0)	0
Asthenia	25 (24.0)	1 (1.0)
Anaemia	23 (22.1)	12 (11.5)
Constipation	21 (20.2)	1 (1.0)
Vomiting	19 (18.3)	0
Abdominal pain	17 (16.3)	6 (5.8)
Arthralgia	16 (15.4)	0
Cough	15 (14.4)	0
Decreased appetite	15 (14.4)	0
Pruritus	15 (14.4)	1 (1.0)
Urinary tract infection	14 (13.5)	2 (1.9)
Myalgia	12 (11.5)	0

Source: CSR 4010-01-001, Table 14.3.1.2a; CSR 4010-01-001, Table 14.3.1.5a

Abbreviations: CSR=Case Study Report; CTCAE=Common Terminology Criteria for Adverse Events; dMMR=mismatch repair-deficient; EC=endometrial cancer; MedDRA=Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event.

Note: Adverse events are coded using MedDRA version 20.0.

<sup>a</sup> Graded by CTCAE v4.03

The incidences of TEAEs, treatment-related TEAEs, Grade ≥3 TEAEs, and serious TEAEs, along with medical history, were assessed to determine the suspected adverse drug reactions (ADRs). ADRs for ≥10% patients with dMMR EC are presented in Table 28. AEs reported in ≥10% of patients that were considered reasonably attributable to dostarlimab (ie, ADRs) include the following:

- Diarrhoea, pruritus, and myalgia were determined to be ADRs based on the frequency of events considered related to dostarlimab by the Investigator as

compared to the overall frequency, and the low frequency in medical history compared to the frequency during the study.

- Nausea and vomiting were included as ADRs based on the high frequency of TEAEs combined with the consistent identification and similar frequencies of these events as adverse reactions for other PD-1/PD-L1 inhibitors.

There were no Grade 5 adverse drug reactions that occurred in patients with dMMR EC.

**Table 28: Adverse Reactions Occurring in ≥10% of Patients with dMMR Endometrial Cancer in GARNET**

Adverse Reaction	dMMR EC N=104	
	All Grades (%)	Grades 3-4 <sup>a</sup> (%)
Gastrointestinal Disorders		
Nausea	29.8	0
Diarrhea	26.0	1.9
Vomiting	18.3	0
Skin and Subcutaneous Tissue Disorders		
Pruritus	14.4	1.0
Musculoskeletal and Connective Tissue Disorders		
Myalgia	11.5	0

Abbreviations: CTCAE=Common Terminology Criteria for Adverse Events; dMMR=mismatch repair-deficient; EC=endometrial cancer; MedDRA=Medical Dictionary for Regulatory Activities.

Note: Adverse events are coded using MedDRA version 20.0.

<sup>a</sup> Graded by CTCAE v4.03

**The FDA’s Assessment:**

The 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 48%. The most common Grades 1-4 adverse reactions occurring in ≥20% of patients were fatigue/asthenia, nausea, diarrhea, anemia, and constipation. In addition, the incidence of any Grade 3-4 AEs was reported to be 41% in patients with dMMR EC. The most common Grade 3–4 AEs reported with an incidence ≥ 2% were anemia and transaminase elevation.

**Laboratory Findings**

**The Applicant’s Position:**

The most frequent laboratory abnormalities that worsened from baseline to Grade 3 or 4, observed in patients as shown in [Table 29](#) below.

**Table 29: Laboratory Abnormalities that Worsened from Baseline to Grade 3 or 4 Occurring in ≥1% of Patients with dMMR EC Receiving Dostarlimab in GARNET (Safety Analysis Set)**

Laboratory Test	dMMR EC N=104
	Grades 3-4 %
Chemistry	
Hyponatremia	5
Hypoalbuminemia	3
Increased alanine aminotransferase	3
Increased alkaline phosphatase	3
Increased creatinine	3
Increased aspartate aminotransferase	2
Hypokalemia	2
Hypercalcemia	2
Hematology	
Anemia	14
Lymphopenia	9
Leukopenia	3

Source: CSR 4010-01-001, Table 14.4.3a; CSR 4010-01-001, Table 14.4.6a

Abbreviations: CSR=clinical study report; dMMR=mismatch repair-deficient; EC=endometrial cancer.

### *Hematology*

Of the 104 patients with dMMR EC who received dostarlimab, 2 patients had Grade 3 decreased lymphocytes at baseline and 1 patient had Grade 3 decreased hemoglobin at baseline. No patients had a Grade 4 baseline value for any hemoglobin parameter.

Shifts to Grade 3 or 4 hematology parameters of >2 grades from baseline to maximum postbaseline value were generally infrequent. Shifts to Grade 3 hematology parameters in >1% of patients included shifts from Grade 0 (1.9% of patients), Grade 1 (2.9% of patients), and Grade 2 (9.6% of patients) for decreased hemoglobin; shifts from Grade 0 (1.9% of patients), Grade 1 (1.9% of patients), and Grade 2 (3.8% of patients) for decreased lymphocytes; and shifts from Grade 1 (1.9% of patients) for decreased WBCs. Shifts to Grade 4 hematology parameters were observed from Grade 0 (1.0% of patients) for decreased neutrophil count.

### *Blood Chemistry*

Of the 104 patients with dMMR EC who received dostarlimab, Grade 3 baseline chemistry values included decreased sodium (2 patients), decreased magnesium (1 patient), and decreased potassium (2 patients). There was 1 patient with a Grade 4 baseline chemistry value for low corrected calcium.

Shifts to Grade 3 or 4 blood chemistry parameters of >2 grades from baseline to maximum postbaseline value were generally infrequent. Shifts to Grade 3 chemistry parameters observed in >1% of patients included shifts from Grade 2 (1.9% of patients) for decreased albumin, shifts from Grade 2 (1.9% of patients) for increased ALP, shifts from Grade 0 (1.9%) for increased ALT, shifts from Grade 1 (1.9% of patients) for increased creatinine, shifts from Grade 0 (1.9% of patients) for decreased potassium, and shifts from Grade 0 (1.9% of patients) and Grade 1 (1.9% of patients) for decreased sodium. Shifts to Grade 4 chemistry parameters included shifts from Grade 0 (1.9%) for increased corrected calcium and shifts from Grade 3 (1.0%) for decreased sodium.

**The FDA's Assessment:**

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

**Vital Signs**

**The Applicant's Position:**

Vital signs were not analyzed in Study 4010-01-001, Study 4020-01-001, or Study 3000-01-002.

**The FDA's Assessment:**

The 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.

**Electrocardiograms and QT**

**The Applicant's Position:**

No dedicated QT studies were conducted for dostarlimab.

The cardiac effects of dostarlimab on QT were studied by analysis of central tendency and concentration- $\Delta$ corrected QT interval (QTc) analysis in patients with solid tumors dosed at the RTD (data cutoff date of 15 May 2019).

The objectives of these analyses were to characterize the cardiac safety of dostarlimab, to estimate the change from baseline-corrected QT interval using Fridericia's formula (QTcF) at relevant concentrations, and to meet the guidelines of the ICH E14 Guidance for central tendency of QTcF prolongation. A mean QTcF increase of 5.741 msec (2-sided CI: 3.438, 8.043 msec) was seen at a single time point. At all other postdose time points, the mean  $\Delta$ QTcF was <5 msec and the upper 90% 2-sided CI ranged from 1.885 to 8.043 msec.

The slope of the exposure-response relationship between the change from baseline in QTcF interval and dostarlimab concentration was not significantly different from zero (0.001589 msec/ $\mu$ g/mL; 95% CI: -0.004208, 0.007386 msec/ $\mu$ g/mL; p=0.5906) and the intercept estimate was 2.406 msec (95% CI: 0.1037, 4.709 msec).

The mean  $\Delta$ QTcF increase was less than 5 msec at all scheduled post-dose timepoints with associated drug concentrations. The upper bound of the 2 sided 90% CI was less than 10 msec, below the threshold of regulatory concern per the ICH E14 Guidance.<sup>23</sup>

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 electrocardiogram (ECG) changes or QT prolongation at the recommended therapeutic dose.

The FDA's Assessment:

The FDA agrees with the Applicant's QTc assessment.

**Immunogenicity**

The Applicant's Position:

Samples from 477 out of 478 patients from Study 4010-01-001 were examined for the presence of ADAs; 1 patient sample was not viable for examination.

The incidence of treatment-emergent (treatment-induced or treatment-boosted) ADA was low and comparable to that of other anti-PD-1 antibodies.<sup>24,25</sup> The incidence of treatment-emergent ADA in subjects receiving the RTD (Part 2B) was 2.5%, with 1.3% being neutralizing antibody (NAb) positive. For all patients in Study 4010-01-001, the incidence of treatment-emergent anti-dostarlimab antibodies was similarly low (3.7%; 2.0% NAb positive). The ADA titers in patients were generally low. There is no evidence of a clinically-meaningful impact of ADA formation on any safety or efficacy measures.

The FDA's Assessment:

The FDA agrees with the Applicant's immunogenicity assessment.

**8.2.5. COA Analyses Informing Safety/Tolerability**

The Applicant's Position:

PRO is an exploratory endpoint. The European Quality of Life scale, 5 Dimensions, 5 Levels and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire were used to assess cancer-specific health-related quality of life. PRO assessments were added to the study under amendment 3, and only limited data were available at the data cutoff. In addition, because of the nonrandomized nature of the study, interpretation of the PRO data is potentially biased. Therefore, PRO data were not evaluated at this time.

The FDA's Assessment:

The completion rate for the sub-group (n = 66) who received the PRO at baseline was 100%. Over the course of treatment this steadily declined and at cycle 7 (with 42 patients eligible to complete a PRO measure) just under half of patients completed the measure.

The EORTC QLQ-C30 was used to capture the patient experience and captures important core concepts the Agency is interested in, it is, however, limited in the symptomatic adverse events captured.

For this application, we considered the PRO analyses exploratory. Because of this, our review focuses on the symptoms that were captured by the Applicant and relies only on descriptive summaries. Due to the small numbers and rapid decline in completion rates, the ability to interpret the results is limited. However, for the patients who were asked to provide responses,

we noted that there was a small decline from baseline in physical function at the first 2 assessments (6- and 3-points at cycles 2 and 3, respectively). For patients who remained on trial and completed the PRO measures, average physical functioning returned to similar pre-treatment values. Fatigue followed a similar trajectory.

With respect to the side effects captured on the EORTC QLQ-C30, during the application review the FDA requested descriptive analysis for 3 fatigue items including the amount of rest, weakness and feeling tired, as well as appetite loss, nausea, vomiting, constipation and diarrhea. All side effects, aside from diarrhea, were at their worst at cycle 2. Diarrhea was relatively uncommon but was observed to be worst at cycle 7. Aside from fatigue items, of those captured, the most commonly reported symptom was constipation.

## 8.2.6. Analysis of Submission-Specific Safety Issues

### 8.2.6.1. Immune-Related Adverse Events (irAEs)

#### The Applicant's Position:

irAEs were defined as any Grade  $\geq 2$  AEs identified by a pre-specified list of PTs.

In patients treated with dostarlimab as a single agent at the RTD, 141 patients (31.8%) reported irAEs and 94 patients (21.2%) reported treatment-related irAEs (Table 30). The most frequently reported irAEs ( $>5\%$ ) were diarrhoea (5.9%) and hypothyroidism (5.6%). Hypothyroidism (5.4%) and diarrhoea (3.6%) were also the most frequently reported irAEs for patients with dMMR EC. Median time to first onset of irAEs was 2.0 months.

Of the 141 patients with an irAE, 54 patients (38.3%) were treated with immune modulatory medications (IMMs); the majority received systemic steroids (29 of 54 patients; 11 of these patients were treated with high-dose prednisone) and/or thyroid therapy (29 of 54 patients). irAEs in 29 patients (53.7%) treated with IMMs resolved after a median time to resolution of 64.0 days. Eighty-seven patients (61.7%) were not treated with IMMs; of these, irAEs in 50 patients (57.5%) resolved after a median time to resolution of 28.0 days.

Forty-four patients (9.9%) treated with dostarlimab as a single agent at the RTD experienced a Grade  $\geq 3$  irAE. The most frequently reported Grade  $\geq 3$  irAEs were hyperglycaemia (1.4%), and diarrhoea (1.1%). Median time to first onset of Grade  $\geq 3$  irAEs was 1.5 months. Thirteen of the 44 patients (29.5%) were treated with IMMs; the majority received steroids (12 of 13 patients; 7 of these patients were treated with high-dose prednisone). Grade  $\geq 3$  irAEs in 12 patients (92.3%) resolved after treatment with IMMs with a median time to resolution of 12.5 days. Thirty-one patients (70.5%) were not treated with IMMs; of these, Grade  $\geq 3$  irAEs in 16 patients (51.6%) resolved after a median time to resolution of 30.0 days.

Serious irAEs were reported in 23 patients (5.2%); the most frequently reported event was pneumonitis (N=3, 0.7%). irAEs leading to treatment interruption were reported in 36 patients (8.1%); the most frequently reported event was diarrhoea (1.1%). irAEs leading to permanent treatment discontinuation were reported in 15 patients (3.4%); the most frequently reported events were pneumonitis and transaminases increased (0.7% each). It should be noted that

Grade 3 transaminases increased, and Grade 3 pneumonitis required permanent discontinuation of study treatment per protocol.

One irAE (gastroenteritis) resulted in death in 1 patient and was considered not treatment-related by the Investigator. TEAEs leading to death are discussed in Section [8.1.2](#) under Deaths.

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**Table 30: Overview of Adverse Events of Special Interest – irAE (≥2% Subjects) (Safety Analysis Set – Subjects Treated with Monotherapy Dostarlimab at the RTD)**

Preferred Term, n (%)	Dostarlimab Single Agent (N=444)							
	Overall	Treatment-related	≥G3	Treatment-related ≥G3	SAE	Leading to Treatment Interruption	Leading to Treatment Discontinuation	Leading to Death
Any immune-related TEAE	141 (31.8)	94 (21.2)	44 (9.9)	28 (6.3)	23 (5.2)	36 (8.1)	15 (3.4)	1 (0.2)
Diarrhoea	26 (5.9)	16 (3.6)	5 (1.1)	5 (1.1)	0	5 (1.1)	0	0
Hypothyroidism	25 (5.6)	24 (5.4)	0	0	0	2 (0.5)	0	0
Arthralgia	16 (3.6)	7 (1.6)	2 (0.5)	0	1 (0.2)	1 (0.2)	0	0
Blood creatinine increased	15 (3.4)	2 (0.5)	2 (0.5)	0	0	4 (0.9)	1 (0.2)	0
Hyperglycaemia	12 (2.7)	4 (0.9)	6 (1.4)	2 (0.5)	0	2 (0.5)	0	0
Amylase increased	10 (2.3)	7 (1.6)	4 (0.9)	2 (0.5)	0	2 (0.5)	0	0
Rash	9 (2.0)	7 (1.6)	4 (0.9)	3 (0.7)	0	2 (0.5)	0	0
Aspartate aminotransferase increased	9 (2.0)	5 (1.1)	4 (0.9)	2 (0.5)	1 (0.2)	3 (0.7)	1 (0.2)	0
Alanine aminotransferase increased	9 (2.0)	8 (1.8)	3 (0.7)	3 (0.7)	0	2 (0.5)	1 (0.2)	0

Source: Table 14.3.1.18.1

Abbreviations: G3=grade 3; irAE=immune-related adverse event; RTD=recommended therapeutic dose; SAE=serious adverse event; TEAE=treatment-emergent adverse event.

## Infusion-Related Reactions

### The Applicant's Position:

No infusion-related reactions were reported in subjects with dMMR EC.

In patients treated with dostarlimab as a single agent at the RTD, 6 patients (1.4%) reported infusion-related TEAEs, as presented in [Table 31](#). These infusion-related reaction TEAEs were reported as infusion-related reaction (1.1%) and hypersensitivity (0.2%). For 3 patients, the first infusion-related TEAE occurred on the day of the first administration of dostarlimab. The other 3 patients had the first infusion-related TEAE on the day of the second administration of dostarlimab. There were no delayed infusion-related TEAEs; all TEAEs were reported on the day of an administration of dostarlimab.

A Grade  $\geq 3$  infusion-related reaction was reported in 1 patient (0.2%), infusion-related reactions leading to treatment interruption were reported in 3 patients (0.7%), and infusion-related reactions leading to permanent discontinuation of study drug were reported in 2 patients (0.5%). Two of the 3 patients with infusion-related reactions leading to treatment interruption later had study drug permanently discontinued as a result of the event.

No infusion-related reaction SAEs or infusion-related reaction TEAEs leading to death were reported.

Of the 6 patients treated with dostarlimab as a single agent at the RTD who experienced an infusion-related reaction, 1 patient (16.7%) was treated with IMM (steroids; Grade  $\geq 3$  infusion related reaction). The event resolved after 1.0 day.

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**Table 31: Overview of AESIs – Infusion-related Reactions (Safety Analysis Set – Subjects Treated with Dostarlimab at the RTD)**

Preferred Term/Treatment, n (%)	Overall	≥G3	SAE	Leading to Dostarlimab Infusion Interruption	Leading to Dostarlimab Infusion Discontinuation	Leading to Death
Any infusion-related reaction TEAE						
Dostarlimab single agent (N=444)	6 (1.4)	1 (0.2)	0	3 (0.7)	2 (0.5)	0
Dostarlimab + niraparib (N=35) <sup>a</sup>	1 (2.9)	0	0	0	0	0
Dostarlimab + TSR-022 (N=220) <sup>bc</sup>	2 (0.9)	0	0	2 (0.9)	0	0
Dostarlimab + chemotherapy agents (N=20) <sup>d</sup>	0	0	0	0	0	0
Infusion related reaction						
Dostarlimab single agent (N=444)	5 (1.1)	1 (0.2)	0	2 (0.5)	1 (0.2)	0
Dostarlimab + niraparib (N=35) <sup>a</sup>	1 (2.9)	0	0	0	0	0
Dostarlimab + TSR-022 (N=220) <sup>bc</sup>	2 (0.9)	0	0	2 (0.9)	0	0
Dostarlimab + chemotherapy agents (N=20) <sup>d</sup>	0	0	0	0	0	0

Source: Table 14.3.1.20.1

Abbreviations: AESI=adverse event of special interest; G3=grade 3; RTD=recommended therapeutic dose; SAE=serious adverse event; TEAE=treatment-emergent adverse event.

<sup>a</sup> Thirteen patients have received combination therapy of dostarlimab + niraparib + bevacizumab.

<sup>b</sup> Includes 11 patients who were treated with combination of dostarlimab, TSR 022, and TSR 033. Four patients who crossed over from TSR 022 monotherapy to dostarlimab + TSR 022 are excluded.

<sup>c</sup> Relationship was assessed based on combination of dostarlimab and TSR 022, not dostarlimab alone. Discontinuation of both drugs at the same time is required.

<sup>d</sup> Six patients have received combination therapy of dostarlimab + carboplatin paclitaxel + bevacizumab.

The FDA's Assessment:

FDA conducted its own analysis of immune-mediated adverse events in the dMMR endometrial cancer population (n=104), and in the single agent dostarlimab safety database (n=444). The FDA analysis is presented in Table 32. In the individual sections of product labeling (within Section 5), descriptions of incidence and severity are described for each of the categories of immune-mediated adverse events in the larger safety database of 444 patient treated with dostarlimab,

Immune mediated adverse events (irAEs) occurred in 33% of patients with dMMR endometrial cancer treated on cohort A1 and in 39% of patients in the n=444 overall safety population. The majority of irAEs, regardless of organ involved, were Grade 1 or 2 in severity. Concomitant medications (which may have included corticosteroids) were administered in 25% of cases of immune-mediated adverse events overall. Most events presented in Table 32 are consistent with what is described in labeling, with a few exceptions.

FDA agrees with the Applicant that there was one death due to an immune-mediated event of colitis; this event is discussed in section 8.2.4 of this review. It was determined that there were confounding factors surrounding the case, which made attribution difficult, and the event was ultimately not described as a study-treatment related adverse event leading to death in the product labeling. As noted in Section 8.2.4, there were no treatment-related adverse events leading to death in the dMMR (n=104) endometrial cohort.

FDA assessed that immune-mediated colitis or diarrhea occurred in 9 (9%) of patients in the dMMR endometrial cancer cohort and in 34/444 (8%) patients in the dostarlimab overall safety database. The Applicant, however, only reported an incidence of immune-mediated colitis in 1.4% (6/444) of patients in the product labeling of dostarlimab. After requesting additional details from the Applicant, it was determined that only 6 cases (out of n=444, for 1.4%) of documented colitis events would be described in labeling, and that events described as diarrhea would be excluded from labeling. All 6 cases of colitis were of grade 2 or 3 in severity. One of the 6 patients was treated with corticosteroids for colitis, and although there were no discontinuations due to colitis, only 3 of 6 events had resolved by the time of data cutoff. It is also notable that it is possible that some cases of diarrhea may have been events of immune-mediated colitis that were not formally diagnosed, so the true incidence of immune-mediated colitis may have been higher. The incidence of immune-mediated colitis with dostarlimab is similar to those reported with other approved Anti-PD1 agents.

FDA assessed that immune-mediated pneumonitis occurred in 2 patients (2%) in the dMMR endometrial cohort and in 5 patients (1%) in the overall dostarlimab safety database. All 5 patients received steroids, 4 of 5 cases resolved, and 3 of the events resulted in permanent discontinuation of dostarlimab. The incidence of pneumonitis in the dostarlimab database (1%) is slightly lower than the incidence reported in the pembrolizumab database (3.4%) and the atezolizumab database (3%), but this may be due to the smaller size of the safety database for dostarlimab.

There were some additional discrepancies between FDA analysis and Applicant analysis of immune-mediated adverse events including the assessments of immune-mediated

hyperglycemia/ diabetes events, immune-mediated hepatitis, immune mediated nephritis and immune-mediated skin reactions. In these cases, numbers depicted in Table 32 (FDA Analysis) are higher than those described in product labeling, and the discrepancy stems from FDA’s combining of similar preferred terms, which the Applicant did not do. The numbers reported in product labeling were agreed upon through the course of labeling negotiations after further details were provided by the Applicant. Additionally, none of the discrepancies lead the review team to conclude that there is not a favorable risk-benefit profile for dostarlimab in the labeled indication.

Acknowledging the pitfalls of cross-study comparisons, the incidence rate and severity of the specific irAEs observed with dostarlimab were compared with other approved anti-PD-1/PD-L1 agents. The rates slightly varied when compared to the frequency of similar events reported for other agents (namely pembrolizumab and atezolizumab), with some events occurring with a higher frequency on dostarlimab and others occurring with similar or lower frequency on dostarlimab. It is difficult to determine what factors may account for this variability, which had no consistent trend, but it could be related to factors including underlying cancer type, overall treatment regimen, duration of therapy, disease stage, or other patient or disease characteristics that have not yet been identified. Overall, the safety profile of dostarlimab is similar to that of other approved anti-PD-1/ PD-L1 agents.

Finally, FDA conducted an analysis of infusion related reactions in the dostarlimab database and the results were consistent with those reported by the Applicant. Infusion related reactions occurred in 6/444 patients (1.4%); these events included both hypersensitivity and/or infusion reactions. One event was grade 3 in severity and the remaining events were of grade 1-2 in severity. There were no serious events and although all patients recovered, 2 patients discontinued therapy with dostarlimab as a result.

**Table 32 FDA Analysis Immune-Related Adverse Events**

Immune mediated AEs	Dostarlimab dMMR N=104 (%) G1-4	Dostarlimab single agent N= 444 (%) G1-4
<b>Any Immune mediated AE</b>	<b>35 (33)</b>	<b>171 (39)</b>
Immune mediated diarrhea/colitis	9 (9)	34 (8)
Immune mediated ocular	1 (1)	1 (0.2)
Immune mediated hyperthyroid	3 (3)	8 (2)
Immune mediated hypothyroid	7 (7)	25 (6)
Thyroiditis	0	2 (0.5)
Immune mediated hyperglycemia/ diabetes	1 (1)	14 (3)
Adrenal insufficiency	0	4 (1)
Immune mediated hepatitis	4 (4)	23 (5)
Immune mediated musculoskeletal	0	20 (5)
Immune mediated neurologic disorder	1 (1)	11 (2)

Immune mediated pancreatitis	4 (4)	5 (1)
Immune mediated pneumonitis	2 (2)	5 (1)
Immune mediated renal/nephritis	4 (4)	18 (4)
Immune mediated skin	4 (4)	19 (4)

### 8.2.7. Safety Analyses by Demographic Subgroups

#### The Applicant's Position:

Demographic subgroups evaluated in the RTD are presented in the following sections. No overall differences in safety or effectiveness were observed based on age (range), sex or race.

*Sex:* The incidence of TEAEs was generally similar between male and female patients treated with dostarlimab as a single agent at the RTD; however, treatment-related TEAEs and Grade  $\geq 3$  treatment-related TEAEs were reported more frequently in female patients (66.6% and 14.0%, respectively) than in male patients (54.3% and 7.4%, respectively); SAEs and treatment-related SAEs were more frequent in female patients (37.1% and 8.3%, respectively) than in male patients (25.5% and 2.1%, respectively).

*Age:* Of the 444 patients treated with dostarlimab monotherapy, 48.6% were <65 years, 39.4% were 65 to 75 years, and 11.5% were 75 years or older. Overall safety risks were not observed to be increased in older patients compared to younger patients.

The incidence of TEAEs was generally similar among patients <65 years old (N=216),  $\geq 65$  to <75 years old (N=175), and  $\geq 75$  to <85 years old (N=51). Treatment-related TEAEs, treatment-related TEAEs Grade  $\geq 3$ , treatment-related SAEs, and TEAEs leading to treatment interruption were reported slightly more frequently in the <65 (63.4%, 14.8%, 8.3%, and 25.9%, respectively) and  $\geq 65$  to <75 years old age groups (68.0%, 12.6%, 7.4%, and 19.4%, respectively) than in the  $\geq 75$  to <85 years old age group (52.9%, 3.9%, 0%, and 15.7%, respectively).

There were 2 patients treated with dostarlimab as a single agent at the RTD in the >85 years old group. In this age group, there was only 1 TEAE. Due to the small number of patients ( $\leq 20$  patients) >85 years old, a meaningful comparison based on age could not be made.

*Ethnicity/Race:* A meaningful comparison based on ethnicity and race could not be made due to the small number of subjects who were Hispanic or Latino and Asian or Black or African American, respectively.

#### The FDA's Assessment:

The 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**

#### **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.

#### **Human Reproduction and Pregnancy**

The Applicant's Position:

Dostarlimab has not been studied in pregnant or lactating women.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

#### **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 PREA requirement for pediatric evaluation was requested for the proposed indication in endometrial cancer based on pediatric studies being "impossible or highly impractical" given the extreme rarity of the condition in the pediatric population.

The FDA's Assessment:

The 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.

#### **Overdose, Drug Abuse Potential, Withdrawal, and Rebound**

The Applicant's Position:

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

The FDA's Assessment:

The FDA agrees with the Applicant's position.

### **8.2.10. Safety in the Post-Market Setting**

#### **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:

The FDA agrees with the Applicant's position.

**Expectations on Safety in the Post-Market Setting**

The Applicant's Position:

Potential safety concerns beyond the risks conveyed in the proposed labeling with associated management recommendations are not expected. Routine pharmacovigilance will be conducted to monitor for unexpected adverse events.

The FDA's Assessment:

The 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:

Patients with recurrent or advanced EC who have progressed on platinum-based chemotherapy have limited options for treatment. NCCN guidelines recommend single-agent IV chemotherapy or bevacizumab based on small, uncontrolled studies conducted in heterogeneous patient populations that provide ORR of ~7% to 13.5% (all PRs) and a median OS of 9 to 11 months. For patients with unresectable or metastatic dMMR/MSI-H EC, pembrolizumab provides an alternative treatment option. In the dataset supporting the accelerated approval of pembrolizumab in patients with metastatic or advanced dMMR/MSI-H solid tumors, based on data derived from a very limited number of patients (N=14), pembrolizumab has an ORR of 36% in patients with dMMR/MSI-H EC. The benefit of treatment with pembrolizumab in this setting is still to be confirmed, thus leaving the treatment of patients with dMMR EC as an unmet medical need.

Based on data from Study 4010-01-001, dostarlimab demonstrated an acceptable safety profile with manageable toxicities. The most frequently reported TEAEs ( $\geq 20\%$ ) in patients with dMMR EC (N=104) were nausea, diarrhoea, fatigue, asthenia, anaemia, and constipation. These common TEAEs were Grade 1 or 2 in severity in most patients for whom the TEAEs were reported with the exception of anaemia, which were generally Grade 2 or 3. The most frequently reported treatment-related TEAEs ( $\geq 10\%$ ) for patients with dMMR EC were asthenia, diarrhoea, fatigue, and nausea. Grade  $\geq 3$  TEAEs regardless of causality were reported in 46.2% of patients, and for 11.5%, the event was assessed to be treatment-related.

Treatment-emergent SAEs regardless of causality were reported in 33.7% of patients, and 9.6% of patients had treatment-related SAEs. TEAEs leading to treatment discontinuation regardless of causality were reported in 10.6% of patients, with 1.9% of patients having events assessed to be treatment-related. TEAEs were the primary cause of death in 4.8% of patients. None of the deaths were due to treatment-related TEAEs.

In patients treated with dostarlimab as a single agent at the RTD, 31.8% of patients reported irAEs, and 21.2% of patients reported treatment-related irAEs. The most frequently reported irAEs ( $\geq 5\%$  of patients) were diarrhoea (5.9%) and hypothyroidism (5.6%). Grade  $\geq 3$  irAEs were reported in 9.9% of patients, with hyperglycaemia (1.4%) and diarrhoea (1.1%) being the most frequent ( $>1.0\%$ ). One irAE of gastroenteritis, considered not related to dostarlimab by the Investigator, resulted in death in 1 patient. In general, irAEs may have been managed with IMM, including systemic steroids (such as high-dose prednisone), immune suppressants, and thyroid therapy, as well as dose interruptions and discontinuations, as needed. Six patients (1.4%) treated with dostarlimab as a single agent at the RTD reported infusion-related TEAEs, none of which were serious. Of these 6 patients, 1 patient experienced a Grade  $\geq 3$  infusion-related reaction and was treated with IMM.

Observed AEs included events that were manageable and in line with those expected in patients with recurrent or advanced EC, as well as those consistent with reported AEs for other mAbs blocking PD-1.

The FDA's Assessment:

The FDA agrees that dostarlimab demonstrated an acceptable safety profile with manageable toxicities based on data from 104 patients with dMMR endometrial cancer and from a larger safety database of 444 patients with advanced solid tumors treated with dostarlimab monotherapy on Study 4010-01-001 (GARNET). An FDA safety overview, summarizing key adverse reaction categories in both the 104 dMMR endometrial cancer patients and the 444 patients from the safety database is shown in Table 33. Overall, the safety profile of dostarlimab in the dMMR cohort A1 from Study 4010-01-001 was consistent with the safety profile in the larger safety database for dostarlimab.

**Table 33 FDA Safety Overview for Integrated Safety**

	dMMR EC n=104 (%)	Safety database N=444 (%)
Treatment emergent AEs (G1-4)	97 (93)	428 (96)
Treatment emergent AEs (G 3-4)	48 (46)	207 (46)
TEAEs leading to discontinuation	5 (6)	33 (7)
TEAEs leading to treatment interruption	24 (23)	101 (23)
Serious TEAEs	35 (34)	166 (37)
TEAEs with outcome of death	5 (5)	16 (4)
Immune-mediated TEAE	35 (33)	171 (39)

### 8.3. Statistical Issues

#### The FDA's Assessment:

Study GARNET is an open-label, single-arm, non-randomized 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) was conducted to evaluate the single-arm trial results. The efficacy evaluation was based on the magnitude of ORR and adequate duration of response. The PFS and OS results from a nonrandomized single-arm study without comparators are not interpretable.

There are no major statistical issues identified in this application.

### 8.4. Conclusions and Recommendations

#### The FDA's Assessment:

Patients with recurrent or advanced dMMR endometrial cancer that has progressed following a platinum-containing systemic therapy have a serious and life-threatening disease for which there are currently no therapies with regular FDA approval for this indication. The review team concludes that an ORR of 42.3% with a median DoR not reached at the time of data cutoff and the majority of responses durable for at least six months, is of sufficient magnitude to serve as evidence that is reasonably likely to predict clinical benefit over available therapies in support of accelerated approval. The safety of dostarlimab-gxly is acceptable for this patient population. The clinical and statistical reviewers agree that dostarlimab-gxly has a favorable risk-benefit profile in the indicated population and agree with accelerated approval for this BLA with a post-marketing requirement that the Applicant provide additional clinical trial results to confirm direct clinical benefit.

X

X

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Hui Zhang, PhD  
Primary Statistical Reviewer

Erik Bloomquist, PhD  
Statistical Team Leader

X

X

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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 for endometrial cancer under PREA.

### The FDA's Assessment:

The 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.

**11. LABELING RECOMMENDATIONS****Table 34: Prescription Drug Labeling: Summary of Significant Labeling Changes (High Level Changes and Not Direct Quotations)**

Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
Indications and Usage	(b) (4)	<p>FDA revised this to:</p> <p>JEMPERLI is indicated for the treatment of adult patients with mismatch repair deficient (dMMR) recurrent or advanced endometrial cancer (EC), as determined by an FDA-approved test, that has progressed on or following prior treatment with a platinum-containing regimen [see Dosage and Administration (2.1)].</p> <p>This indication is approved under accelerated approval based on tumor response rate and durability of response [see Clinical Studies (14)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).</p>
Dosage and Administration	(b) (4)	<ul style="list-style-type: none"> <li>FDA revised the patient Selection to:</li> </ul> <p>Mismatch Repair Deficient (dMMR)Advanced Endometrial Cancer</p> <p>Select patients with recurrent or advanced endometrial cancer (EC) that has progressed on or following prior treatment with a platinum-containing regimen for treatment with JEMPERLI based on the presence of dMMR in tumor</p>

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Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
	<p><u>Preparation</u></p> <ul style="list-style-type: none"> <li>▪ Visually inspect the solution for particulate matter and discoloration. The solution is clear to slightly opalescent, colorless to yellow. Discard the vial if visible particles are observed.</li> <li>▪ Do not shake.</li> <li>▪ For the 500-mg dose, withdraw 10 mL of TRADENAME from a vial (b) (4) an intravenous (IV) bag containing 0.9% Sodium Chloride (b) (4) USP or 5% Dextrose (b) (4) Injection, USP to a final concentration between 2 mg/mL to 10 mg/mL.</li> <li>▪ For the 1,000-mg dose, withdraw 10 mL from each of two vials (withdraw 20 mL total) and dilute into an IV bag containing 0.9% Sodium Chloride (b) (4) USP or 5% Dextrose (b) (4) Injection, USP to a final concentration between (b) (4) mg/mL to 10 mg/mL.</li> <li>▪ Mix diluted solution by gentle inversion. Do not shake.</li> <li>▪ Discard any unused portion left in the vial.</li> </ul> <p><u>Storage of Infusion Solution</u></p> <p>Store in the original carton until time of preparation in order to protect from light. The prepared dose may be stored either:</p> <ul style="list-style-type: none"> <li>▪ At room temperature for no more than 6 hours from the time of preparation until the end of infusion.</li> <li>▪ Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from time of preparation until end of infusion. If refrigerated, allow the diluted solution to come to room temperature prior to administration.</li> </ul> <p>Discard after 6 hours at room temperature or after 24 hours under refrigeration. Do not freeze.</p> <p><u>Administration</u></p> <p>Administer infusion solution (b) (4) intravenously over 30 minutes through an IV line (b) (4)</p> <p>TRADENAME must not be administered as an intravenous push or bolus injection. Do not co-administer other drugs through the same infusion line.</p>	<p>specimens [see Clinical Studies (14)]. Information on FDA-approved tests for the detection of dMMR status is available at <a href="http://www.fda.gov/CompanionDiagnostics">http://www.fda.gov/CompanionDiagnostics</a>.</p> <p>(b) (4)</p> <p>The recommended dosage of JEMPERLI is:</p> <p>Dose 1 through Dose 4: 500 mg every 3 weeks</p> <p>Subsequent dosing beginning 3 weeks after Dose 4 (Dose 5 onwards): 1,000 mg every 6 weeks</p> <p>Administer JEMPERLI as an intravenous infusion over 30 minutes. Treat patients until disease progression or unacceptable toxicity.</p> <p>(b) (4)</p>

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Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
		<p style="text-align: right;">(b) (4)</p> <div style="background-color: #cccccc; height: 100px; width: 100%;"></div> <ul style="list-style-type: none"> <li>FDA revised the Preparation section to the following:            For the 500-mg dose, withdraw 10 mL of JEMPERLI from a vial using a disposable sterile syringe made of polypropylene and dilute into an intravenous infusion bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to a final concentration between 2 to 10 mg/mL (maximum 250 mL). JEMPERLI is compatible with an infusion bag made of polyolefine, ethylene vinyl acetate, or polyvinyl chloride with DEHP.</li> </ul> <p>For the 1,000-mg dose, withdraw 10 mL from each of 2 vials (withdraw 20 mL total) and dilute into an intravenous bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to a final concentration between 4 to 10 mg/mL (maximum 250 mL).</p>
Dosage Forms and Strengths	Injection: 500 mg/10 mL (50 mg/mL) clear to slightly opalescent colorless to yellow solution (b) (4)	FDA agrees
Contraindications	None.	FDA agrees

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Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
Warnings and Precautions	<p>(b) (4)</p> <p><b>Immune-Mediated Adverse Reactions</b> Immune-mediated adverse reactions, which may be severe or fatal, can occur (b) (4) (b) (4) While immune-mediated adverse reactions usually (b) (4) (b) (4)</p> <p>Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor for symptoms and signs (b) (4) (b) (4)</p> <p><b>Infusion-Related Reactions</b> (b) (4)</p> <p><b>Embryo-Fetal Toxicity</b> (b) (4) (b) (4) Advise females of reproductive potential to use effective contraception during treatment with TRADENAME and fo (b) (4) onths after the last dose.</p>	<p>(b) (4)</p> <p>WARNINGS AND PRECAUTIONS section and the Immune-mediated Adverse Reactions subsections to simplify the labels by recognizing the common pathophysiology underlying all immune-mediated adverse reactions (IMARs) and replacing redundant text included for each type of IMARs with general text applying to all IMARs, to increase safety by applying experience with rare but serious IMARs from one PD1/L1 antibody block drug to all of these drugs, and to increase readability by utilizing a consistent set of data and format for all IMARs across all the labels.</p> <p>Therefore, the FDA revised the WARNINGS AND PRECAUTIONS section of the dostarlimab PI to reflect the most current harmonized labeling available for these products. For details, please see the approved Full Prescribing Information.</p>
Adverse Reactions	<p>The following clinically significant adverse reactions are described elsewhere in the labeling.</p> <ul style="list-style-type: none"> <li>▪ Immune-mediated adverse reactions [see Warnings and Precautions (5.1)]</li> <li>▪ Infusion-related reactions [see Warnings and Precautions (5.2)]</li> </ul>	<p>FDA revised the order, made additions and revisions to section 6 based on the OOD Adverse Reactions</p>

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Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
	<p><b>Clinical Trial Experience</b></p> <p>Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.</p> <p>The data described in Warnings and Precautions (b) (4)</p> <p>[Redacted]</p> <p>dMMR Endometrial Cancer (b) (4)</p> <p>[Redacted]</p> <p><b>Immunogenicity</b></p> <p>As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to dostarlimab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.</p> <p>[Redacted] (b) (4)</p>	<p>Section Best Labeling Practices for all drug products.</p> <p>Section 6 was revised to:</p> <p>Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.</p> <p>The pooled safety population described in WARNINGS AND PRECAUTIONS reflects exposure to JEMPERLI in 444 patients with advanced or recurrent solid tumors in the open label, multicohort GARNET study including 268 patients with EC and 176 patients with other solid tumors. JEMPERLI as a single agent was administered intravenously at doses of 500 mg every 3 weeks for 4 doses followed by 1,000 mg every 6 weeks until disease progression or unacceptable toxicity. Among the 444 patients, 38% were exposed for &gt;6 months and 12% were exposed for &gt;1 year.</p> <p>Mismatch Repair Deficient (dMMR) Endometrial Cancer</p> <p>The safety of JEMPERLI was evaluated in the GARNET trial in 104 patients with advanced or recurrent dMMR EC who received at least one dose of JEMPERLI [see Clinical Studies (14)]. Patients received JEMPERLI 500 mg every 3 weeks for 4 doses followed by 1,000 mg every 6</p>

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Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
	<div style="background-color: #cccccc; height: 40px; width: 100%;"></div> <div style="text-align: right; font-size: small;">(b) (4)</div>	<p>weeks as an intravenous infusion until disease progression or unacceptable toxicity. Among patients receiving JEMPERLI, 47% were exposed for 6 months or longer and 20% were exposed for &gt;1 year.</p> <p>Serious adverse reactions occurred in 34% of patients receiving JEMPERLI. Serious adverse reactions in &gt;2% of patients included sepsis (2.9%), acute kidney injury (2.9%), urinary tract infection (2.9%), abdominal pain (2.9%), and pyrexia (2.9%).</p> <p>JEMPERLI was permanently discontinued due to adverse reactions in 5 (4.8%) patients, including transaminases increased, sepsis, bronchitis, and pneumonitis. Dosage interruptions due to an adverse reaction occurred in 23% of patients who received JEMPERLI. Adverse reactions that required dosage interruption in ≥1% of patients who received JEMPERLI were anemia, diarrhea, increased lipase, and pyrexia.</p> <p>The most common adverse reactions (≥20%) were fatigue/asthenia, nausea, diarrhea, anemia, and constipation. The most common Grade 3 or 4 adverse reactions (≥2%) were anemia and transaminases increased.</p> <p>6.2 Immunogenicity</p> <p>As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly</p>

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Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
		<p>dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to dostarlimab-gxly in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.</p> <p>The immunogenicity of dostarlimab was evaluated in the GARNET study. The treatment emergent anti-drug antibodies (ADAs) against dostarlimab-gxly were detected in 2.5% of 315 patients treated with dostarlimab-gxly at the recommended therapeutic dose. Neutralizing antibodies were detected in 1.3% of patients. Because of the small number of patients who developed ADAs, the impact of immunogenicity on the efficacy and safety of dostarlimab-gxly is inconclusive.</p>
Use in Specific Populations	<p><b>Pregnancy</b> <u>Risk Summary</u></p> <p>Based on its mechanism of action, TRADENAME can cause fetal harm when administered to a pregnant woman. There are no available data on the use of dostarlimab in pregnant women. Animal studies have demonstrated that inhibition of the PD-(L)1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death (see Data). Human IgG4 immunoglobulins (IgG4) are known to cross the placental barrier; therefore, (b) (4)</p>	<p>FDA revised the following Section 8 subsections to:</p> <p>8.1 Pregnancy Data Animal Data: Animal reproduction studies have not been conducted</p>

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Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
	<p>dostarlimab has the potential to be transmitted from the mother to the developing fetus. Advise women of the potential risk to a fetus.</p> <p>In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.</p> <p><u>Data – Animal Data</u></p> <p>Animal reproduction studies have not been conducted with TRADENAME to evaluate its effect on reproduction and fetal development. A central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. In murine models of pregnancy, blockade of PD-L1 signaling has been shown to disrupt tolerance to the fetus and to result in an increase in fetal loss. (b) (4)</p> <p><b>Lactation – Risk Summary</b></p> <p>There is no information regarding the presence of dostarlimab in human milk, or its effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment and for at least (b) (4) months after the last dose of TRADENAME.</p> <p><b>Females and Males of Reproductive Potential</b></p> <p><u>Pregnancy Testing</u></p> <p>Verify pregnancy status in females of reproductive potential prior to initiating TRADENAME.</p> <p><u>Contraception – Females</u></p> <p>(b) (4)</p> <p><b>Pediatric Use</b></p> <p>The safety and efficacy of TRADENAME have not been established in pediatric patients.</p> <p><b>Geriatric Use</b></p> <p>Of the 444 patients treated with dostarlimab (b) (4) 49% were (b) (4) 65 years, 39% were 65-75 years, and 12% were 75 years or older. (b) (4)</p>	<p>with JEMPERLI to evaluate its effect on reproduction and fetal development. A central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. In murine models of pregnancy, blockade of PD-L1 signaling has been shown to disrupt tolerance to the fetus and to result in an increase in fetal loss; therefore, potential risks of administering JEMPERLI during pregnancy include increased rates of abortion or stillbirth. As reported in the literature, there were no malformations related to the blockade of PD-1/PD-L1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in PD-1 and PD-L1 knockout mice. Based on its mechanism of action, fetal exposure to dostarlimab-gxly may increase the risk of developing immune-mediated disorders or altering the normal immune response.</p> <p>8.3 Females and Males of Reproductive Potential</p> <p>JEMPERLI can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations (8.1)].</p> <p><b>Pregnancy Testing</b></p> <p>Verify pregnancy status in females of reproductive potential prior to initiating JEMPERLI [see Use in Specific Populations (8.1)].</p>

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Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
		<p>Contraception</p> <p>Females: Advise females of reproductive potential to use effective contraception during treatment with JEMPERLI and for 4 months after the last dose.</p> <p>8.5 Geriatric Use</p> <p>Of the 444 patients treated with JEMPERLI, 49% were younger than 65 years, 39% were aged 65 through 75 years, and 12% were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.</p>
Description	<p>(b) (4)</p> <p>essentially free from visible particles, supplied as single-dose vials.</p> <p>Each vial contains 500 mg of TRADENAME in 10 mL of solution. Each 1 mL of solution contains 50 mg of dostarlimab, citric acid monohydrate (0.48 mg), L-arginine hydrochloride (21.07 mg), polysorbate 80 (0.2 mg), sodium chloride (1.81 mg), trisodium citrate dihydrate (6.68 mg), and Water for Injection.</p> <p>(b) (4)</p>	<p>FDA revised section 11 to add the cell line, and the dosage form has been added per 21 CFR 201.57(c)(12):</p> <p>11 DESCRIPTION</p> <p>Dostarlimab-gxly is a programmed death receptor-1 (PD-1)-blocking IgG4 humanized monoclonal antibody. Dostarlimab-gxly is produced in Chinese hamster ovary cells and has a calculated molecular weight of about 144 kDa.</p> <p>JEMPERLI (dostarlimab-gxly) injection is a sterile, clear to slightly opalescent, colorless to yellow solution essentially free from visible particles. It is supplied as single-dose vials.</p> <p>Each vial contains 500 mg of JEMPERLI in 10 mL of solution. Each</p>

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Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
		<p>mL of solution contains 50 mg of dostarlimab-gxly, citric acid monohydrate (0.48 mg), L-arginine hydrochloride (21.07 mg), polysorbate 80 (0.2 mg), sodium chloride (1.81 mg), trisodium citrate dihydrate (6.68 mg), and Water for Injection, USP.</p>
Clinical Pharmacology	<p><b>Mechanism of Action</b></p> <p>Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Dostarlimab is a humanized mAb of the immunoglobulin G4 (IgG4) isotype that binds to PD-1, (b) (4). In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.</p> <p><b>Pharmacodynamics</b></p> <p>(b) (4)</p> <p><b>Pharmacokinetics</b></p> <p>(b) (4)</p>	<p>FDA revised the following Section 12 subsections to:</p> <p>12.2 Pharmacodynamics</p> <p>Dostarlimab-gxly exposure-response relationships have not been fully characterized. Dostarlimab-gxly provides sustained target engagement as measured by PD-1 binding and stimulation of IL-2 production throughout the dosing interval at the recommended dose.</p> <p>12.3 Pharmacokinetics</p> <p>The pharmacokinetics of dostarlimab-gxly were evaluated in patients with various solid tumors, including 150 patients with EC. Mean C<sub>max</sub>, AUC<sub>0-inf</sub>, and AUC<sub>0-tau</sub> increased proportionally over the dose range of 1.0 to 10 mg/kg. The Cycle 1 mean (coefficient of variation [%CV]) C<sub>max</sub> and AUC<sub>0-tau</sub> of dostarlimab-gxly are 171 mcg/mL (20%) and 35,730 mcg*h/mL (20%) at the dose of 500 mg once every 3 weeks and 309 mcg/mL (31%) and 95,820 mcg*h/mL (29%) at the dose of 1,000 mg every 6 weeks, respectively.</p> <p>Distribution</p>

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Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
	(b) (4)	<p>The mean (%CV) volume of distribution of dostarlimab-gxly at steady state is 5.3 L (12%).</p> <p>Elimination</p> <p>The mean terminal elimination half-life of dostarlimab-gxly is 25.4 days and its mean (%CV) clearance is 0.007 L/h (31%) at steady state.</p> <p>Metabolism: Dostarlimab-gxly is expected to be metabolized into small peptides and amino acids by catabolic pathways.</p> <p>Specific Populations</p> <p>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 (CLCR mL/min) (normal: CLCR ≥90 mL/min, n = 173; mild: CLCR = 60-89 mL/min, n = 210; moderate: CLCR = 30-59 mL/min, n = 90; severe: CLCR = 15-29 mL/min, n = 3; and end-stage renal disease: CLCR &lt;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 &gt;ULN to 1.5 ULN or AST &gt;ULN, n = 48; and moderate: TB &gt;1.5-3 ULN, any AST, n = 4).</p>
Nonclinical Toxicology	Carcinogenesis, Mutagenesis, Impairment of Fertility	FDA agrees

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Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
	<p>No studies have been performed to assess the potential of dostarlimab for carcinogenicity or genotoxicity.</p> <p>Fertility studies have not been conducted with dostarlimab. In 1-month and 3-month repeat-dose toxicology studies in monkeys, there were no notable effects in the male and female reproductive organs; however, many animals in these studies were not sexually mature.</p> <p><b>Animal Toxicology and/or Pharmacology</b></p> <p>In animal models, inhibition of PD-L1/PD-1 signaling increased the severity of some infections and enhanced inflammatory responses. M. tuberculosis–infected PD-1 knockout mice exhibit markedly decreased survival compared with wild-type controls, which correlated with increased bacterial proliferation and inflammatory responses in these animals. PD-L1 and PD-1 knockout mice and mice receiving PD-L1 blocking antibody have also shown decreased survival following infection with lymphocytic choriomeningitis virus.</p>	

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Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
Clinical Studies	(b) (4)	<p>FDA revised the text in section 14 for clarity, added the name of the companion diagnostic (CDx) device, and revised all percentages throughout the section to the nearest whole number. The text was revised to:</p> <p>The efficacy of JEMPERLI was evaluated in the GARNET study (NCT02715284), a multicenter, multicohort, open-label study conducted in patients with advanced solid tumors. The efficacy population consisted of a cohort of 71 patients with mismatch repair deficient (dMMR) recurrent or advanced EC who had progressed on or after treatment with a platinum-containing regimen. Patients with prior treatment with PD 1/PD L1–blocking antibodies or other immune checkpoint inhibitor therapy and patients with autoimmune disease that required systemic therapy with immunosuppressant agents within 2 years were excluded from the study. Patients received JEMPERLI 500 mg intravenously every 3 weeks for 4 doses followed by 1,000 mg intravenously every 6 weeks. Treatment continued until disease progression or unacceptable toxicity. The major efficacy outcome measures were Overall Response Rate (ORR) and Duration of Response (DOR) as assessed by blinded independent central review (BICR) according to the Response Evaluation</p>

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Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
		<p>Criteria in Solid Tumors (RECIST) v 1.1.</p> <p>The baseline characteristics were: median age 64 years (49% aged 65 years or older); 82% White, 3% Asian, 1% Black; and Eastern Cooperative Oncology Group Performance Status 0 (32%) or 1 (68%).</p> <p>At time of study entry, 66% of the patients with dMMR EC had International Federation of Gynecology and Obstetrics (FIGO) Stage IV disease. The most common histology seen was endometrioid carcinoma type 1 (70%), followed by serous (6%) and mixed and undifferentiated (2.8% each).</p> <p>All patients with dMMR EC had received prior anticancer treatment, with 90% of patients receiving prior anticancer surgery and 79% receiving prior anticancer radiotherapy. Approximately 40% had 2 lines or more of prior anticancer treatment. Approximately 11% of patients had received 3 regimens and 4% had received 4 or more prior regimens.</p> <p>The dMMR tumor status was retrospectively confirmed using the VENTANA MMR RxDx Panel assay.</p> <p>Also, FDA revised Table 4 Efficacy results based on Day 90 updated data submitted to the BLA, and added the following footnote to Table 4:</p>

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Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
		Kaplan-Meier estimate. Among responders, the median follow-up for DOR, measured from the date of first response, was 14.1 months.
How Supplied/Storage and Handling	TRADENAME injection (clear to slightly opalescent, colorless to yellow solution): Carton containing one 500 mg/10 mL (50 mg/mL), single-dose vial (NDC 0173-0898-03). Refrigerate at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze or shake.	FDA agrees
Patient Counseling Information	<p>Advise the patient to read the FDA-approved patient labeling (Medication Guide).</p> <p><u>Immune-Mediated Adverse Reactions</u></p> <p>Inform patients of the risk of immune-mediated adverse reactions that may be severe or fatal, may occur after discontinuation of treatment, and may require corticosteroid or other treatment and interruption or discontinuation of TRADENAME.</p> <p><u>Infusion-Related Reactions</u></p> <p>Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion-related reactions.</p> <p><u>Embryo-Fetal Toxicity</u></p> <ul style="list-style-type: none"> <li>▪ Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy.</li> <li>▪ Advise females of reproductive potential to use effective contraception during treatment with TRADENAME and for (b) (4) months after the last dose.</li> </ul> <p><u>Lactation</u></p> <p>Advise women not to breastfeed during treatment with TRADENAME and for (b) (4) months after the (b) (4) dose.</p> <p>(b) (4)</p>	<p>FDA removed the (b) (4)</p> <p>(b) (4)</p>

Abbreviations: ADA=anti-drug antibody; BICR= blinded independent central review; CV%=coefficient of variation percentage; dMMR=mismatch repair-deficient; EC=endometrial cancer; DOR=duration of response; ECL=electrochemiluminescence; ECOG=European Cooperative Oncology Group; FIGO=International Federation of Gynecology and Obstetrics; HIV=human immunodeficiency virus; IHC=immunohistochemistry; mAb=monoclonal antibody; ORR=objective response rate; PD-1=programmed cell death protein 1; PD-L1=programmed cell death protein ligand 1; PD-L2=programmed death ligand-2; PK=pharmacokinetic(s); t<sub>1/2</sub>=half life; USP=United States Pharmacopeia.

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 (REMS)**

### The FDA's Assessment:

No REMS is recommended for dostarlimab.

### **13. POSTMARKETING REQUIREMENTS AND COMMITMENT**

#### The FDA's Assessment:

The following Postmarketing requirements were agreed upon by FDA and the Applicant.

#### **Postmarketing Requirements (PMRs)**

3909-1 Submit the final report and datasets from a clinical trial evaluating overall response rate, and duration of response, to verify and describe the clinical benefit of dostarlimab in patients with mismatch repair deficient (dMMR), recurrent or advanced endometrial cancer (EC) that has progressed on or following prior treatment with a platinum containing regimen, in a sufficient number of patients. In order to characterize response rate and duration of response, patients will be followed for at least 12 months from the onset of response.

Alternatively, submit the final report and datasets from a randomized, phase 3 clinical trial that verifies and describes the clinical benefit of dostarlimab in patients with recurrent or primary advanced endometrial cancer. Patients should be randomized to receive chemotherapy with or without dostarlimab. The primary endpoint should be progression free survival, with secondary endpoints that include overall survival and objective response rate.

Final Protocol Submission: 12/2015

Study/Trial Completion: 12/2021

Final Report Submission: 07/2022

**14. DIVISION DIRECTOR (DHOT) (NME ONLY)**

**X**

\_\_\_\_\_  
John Leighton, PhD

**15. DIVISION DIRECTOR (OCP)**

X

Nam Atiqur Rahman, PhD

**16. DIVISION DIRECTOR (OB)**

X

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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

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Julia Beaver, MD

## 19. APPENDICES

### 19.1. References

#### The Applicant'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. Of the 1152 total Clinical Investigators, certification of due diligence was provided for 206 (~18%) Investigators. Four clinical Investigators (less than 1%) had financial information to disclose.

### The FDA's Assessment:

The FDA agrees with the Applicant's assessment.

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

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>1152</u>		
Number of investigators who are Applicant employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>4</u>		
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: <u>0</u> Significant payments of other sorts: <u>4</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in study: <u>0</u> Applicant of covered study: <u>TESARO/GlaxoSmithKline</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>206</u>		
Is an attachment provided with the reason:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (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:

None.

**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: 6.0	<b>Select one:</b> <input checked="" type="checkbox"/> Authored <input type="checkbox"/> Approved
	<b>Signature:</b> Safaa Burns -S <small>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: 2021.04.15 15:39:19 -04'00'</small>			
Clinical Pharmacology (TL)	Nam Atiqur Rahman, PhD	OCP	Sections: 6.0	<b>Select one:</b> <input type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
	<b>Signature:</b> Nam A. Rahman -S <small>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: 2021.04.19 07:41:19 -04'00'</small>			
Pharmacometrics	Fang Li, PhD	OCP/DPM	Sections: 6.0	<b>Select one:</b> <input checked="" type="checkbox"/> Authored <input type="checkbox"/> Approved
	<b>Signature:</b> Fang Li -S <small>Digitally signed by Fang Li -S            DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Fang Li -S, 0.9.2342.19200300.100.1.1=1300430137            Date: 2021.04.15 15:58:00 -04'00'</small>			
Pharmacometrics (TL)	Jerry (Jingyu) Yu, PhD	OCP/DPM	Sections: 6.0	<b>Select one:</b> <input type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
	<b>Signature:</b> Jingyu Yu -S <small>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: 2021.04.15 15:54:08 -04'00'</small>			
Pharm/Tox	Wimolnut Manheng, PhD	OOD/DHOT	Sections: 5	<b>Select one:</b> <input checked="" type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
	<b>Signature: Signed on behalf of Wimolnut Manheng</b> Tiffany K. Ricks -S <small>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: 2021.04.15 14:48:57 -04'00'</small>			
Pharm/Tox (TL)	Tiffany Ricks, PhD	OOD/DHOT	Sections: 5	<b>Select one:</b> <input checked="" type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Biometrics Reviewer	Hui Zhang, PhD	OB/DBV	Sections: 8.1, 8.3	<b>Select one:</b> <input checked="" type="checkbox"/> Authored <input type="checkbox"/> Approved
	<b>Signature:</b> Hui Zhang -S <small>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: 2021.04.15 14:25:15 -04'00'</small>			
Biometrics (TL)	Erik Bloomquist, PhD	OB/DBV	Sections: 8.1, 8.3	<b>Select one:</b> <input checked="" type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
	<b>Signature:</b> Erik W. Bloomquist -S <small>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: 2021.04.15 19:42:25 -04'00'</small>			
Clinical Reviewer	Sakar Wahby, PharmD	OOD/DO1	Sections: 2,3,4,7,8,9,10,11,12,13, and 19.	<b>Select one:</b> <input checked="" type="checkbox"/> Authored <input type="checkbox"/> Approved
	<b>Signature:</b> Sakar M. Wahby -S <small>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: 2021.04.15 16:42:55 -04'00'</small>			
Clinical Reviewer (TL)	Gwynn Ison, MD	OOD/DO1	Section: 1 (authored) All other Sections (approved)	<b>Select one:</b> <input checked="" type="checkbox"/> Authored <input type="checkbox"/> Approved
	<b>Signature:</b> Gwynn Ison -S <small>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: 2021.04.15 14:10:59 -04'00'</small>			
Associate Director for Labeling	Ann Marie Trentacosti, MD	OOD	Sections: Section 11	<b>Select one:</b> <input type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
	<b>Signature: Signed on behalf of Ann Marie Trentacosti</b> William F. Pierce -S5 <small>Digitally signed by William F. Pierce S5            DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300235575            cn=William F. Pierce S5            Date: 2021.04.15 14:14:50 -04'00'</small>			

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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Cross-Disciplinary Team Leader (CDTL)	Gwynn Ison, MD	OOD/DO1	Sections: 1 (authored); all other sections (approved)	<b>Select one:</b> <input checked="" type="checkbox"/> Authored
				<input checked="" type="checkbox"/> Approved
<b>Signature:</b> <b>Gwynn Ison -S</b> <small>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: 2021.04.16 09:10:14 -04'00'</small>				
Division Director (DHOT)	John Leighton, PhD	OOD/DHOT	Sections: 5	<b>Select one:</b> <input type="checkbox"/> Authored
				<input checked="" type="checkbox"/> Approved
<b>Signature:</b> <b>John K. Leighton -S</b> <small>Digitally signed by John K. Leighton -S            DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,            ou=People, 0.9.2342.19200300.100.1.1=1300065260            cn=John K. Leighton -S            Date: 2021.04.15 17:02:23 -04'00'</small>				
Division Director (OCP)	Nam Atiqur Rahman, PhD	OCP	Sections: 6.0	<b>Select one:</b> <input type="checkbox"/> Authored
				<input checked="" type="checkbox"/> Approved
<b>Signature:</b> <b>Nam A. Rahman -S</b> <small>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: 2021.04.19 07:42:29 -04'00'</small>				
Division Director OB (Acting)	Shenghui Tang, PhD	OB/DBV	Sections: 8.1, 8.3	<b>Select one:</b> <input type="checkbox"/> Authored
				<input checked="" type="checkbox"/> Approved
<b>Signature:</b> <b>Shenghui Tang -S</b> <small>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: 2021.04.15 14:17:27 -04'00'</small>				
Director	Laleh Amiri-Kordestani, MD	OOD/DO1	Sections: All	<b>Select one:</b> <input type="checkbox"/> Authored
				<input checked="" type="checkbox"/> Approved
<b>Signature:</b> <b>Laleh Amiri-kordestani -S</b> <small>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: 2021.04.15 16:22:58 -04'00'</small>				

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04/22/2021 10:15:30 AM  
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