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FDA Briefing Document

IND# 157775

Drug name: dostarlimab-gxly

Applicant: GSK

Oncologic Drugs Advisory Committee Meeting

February 9, 2023

Division of Oncology 3/Office of Oncologic Diseases

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the Advisory Committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought dostarlimab.gxly IND 157775 to this Advisory Committee in order to gain the Committee's insights and opinions on some aspects of the clinical development program. As such, the background package does not include all issues relevant to the final regulatory recommendation but instead is intended to focus on issues identified by the Agency for discussion by the Advisory Committee. The FDA will not issue a final determination on the issues at hand until input from the Advisory Committee process has been considered. FDA's final determination may consider issues not discussed at the Advisory Committee meeting.

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Glossary

ACS	American Cancer Society
ADC	apparent diffusion coefficient
AE	adverse event
CAPOX	capecitabine and oxaliplatin
cCR	clinical complete response
CI	confidence interval
CRC	colorectal cancer
CT	computed tomography scan
DFS	disease-free survival
dMMR	deficient mismatch repair
DO3	Division of Oncology 3
DOR	duration of response
DRE	digital rectal examination
EFS	event-free survival
FDA	Food and Drug Administration
FOLFOX	fluorouracil, leucovorin and oxaliplatin
HIV	human immunodeficiency virus
HR	hazard ratio
ICR	independent central review
iCR	incomplete clinical response
IHC	immunohistochemistry
IV	intravenous
LARC	locally advanced rectal cancer
LR	local relapse
MRI	magnetic resonance imaging
MSI-H	microsatellite instability-high
MTD	maximum tolerated dose
NAR	neoadjuvant rectal score
nCRT	neoadjuvant chemoradiotherapy
NGS	next generation sequencing

NOM	non operative management
ODAC	Oncologic Drugs Advisory Committee
OOD	Office of Oncologic Diseases
ORR	overall response rate
OS	overall survival
pCR	pathological complete response
PCR	polymerase chain reaction
PD-1	programmed death receptor-1
PD-L1 and 2	programmed death ligand-1 and 2
PET	Positive-emission tomography scan
PFS	progression-free survival
PK	pharmacokinetics
RFS	relapse-free survival
RP2D	recommended Phase 2 dose
RT	radiotherapy
SAP	Statistical Analysis Plan
sBLA	Supplemental Biologic License Application
SEER	Surveillance, Epidemiology and End Results Program
SOC	standard of care
TMB	tumor mutational burden
TME	total mesorectal excision
TNT	total neoadjuvant therapy
W&W	Watch and Wait

1. Executive Summary

GlaxoSmithKline LLC (GSK) is developing dostarlimab-gxly (dostarlimab), a programmed death receptor-1 (PD-1)–blocking IgG4 humanized monoclonal antibody for the treatment of patients with locally advanced rectal cancer (LARC) that is mismatch-repair deficient (dMMR) or microsatellite-instability-high (MSI-H).

The proposed overall clinical development program will consist of two single-arm trials: a single-center trial that will enroll a total of 30 patients, and a proposed multi-center trial that will enroll 100 patients. Patients in both trials will receive dostarlimab 500 mg intravenously (IV) every 3 weeks for 9 cycles and will evaluate the clinical complete response rate at 12 months (cCR12) as the primary endpoint. cCR12 is a composite endpoint defined as no evidence of residual disease by endoscopy, or rectal-specific MRI and, no evidence of metastatic disease 12 months after the first post-treatment cCR assessment by Independent Central Review (ICR). GSK plans to provide the results as the clinical endpoint to support a future supplemental Biologics License Application (sBLA) for accelerated approval of dostarlimab for treatment naïve dMMR/MSI-H LARC.

In addition to cCR12, the proposed multi-center study will evaluate two key secondary endpoints: cCR at 36 months (cCR36) as assessed by ICR, and investigator-assessed event-free survival at 3 years (EFS3), defined as remaining alive and free of disease progression that precludes surgery, local recurrence, or distant recurrence. GSK plans to submit the results of cCR36 and EFS3 analyses to verify the clinical benefit of dostarlimab. Additionally, data from a randomized controlled trial of dostarlimab versus standard of care [redacted] chemotherapy for the treatment of Stage II/III dMMR/MSI-H colon cancer is proposed for inclusion as supportive confirmatory evidence in the data package to verify clinical benefit.

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Standard of care treatment of LARC consists of multimodality treatment that combines fluoropyrimidine-based chemotherapy, chemoradiotherapy or other short course radiotherapy, and surgery. Although administered with curative intent, this treatment is associated with both short- and long-term toxicities that adversely impact quality of life, leading to the growing interest in non-operative management (NOM) of this disease. Data informing a non-operative approach for treating LARC derives from small, mostly retrospective studies conducted at highly specialized centers, evaluating outcomes following variable neoadjuvant chemotherapy and chemoradiotherapy regimens. Given the limitations of these data, the unprecedented use of single arm trials in the curative-intent setting that is LARC, and the proposal for the unprecedented use of cCR as the major efficacy endpoint to support a regulatory action in oncology, the U.S. Food and Drug Administration (FDA) is convening this Oncologic Drugs Advisory Committee (ODAC) meeting to request

input from the Committee on the adequacy of the dostarlimab clinical development program to generate the data that will be the basis for a future marketing application.

The major topics for discussion at the ODAC are:

a. Adequacy and appropriateness of the proposed single-arm trials to evaluate the efficacy and safety of dostarlimab, including the long-term benefits and risks of treatment in the indicated population;
b. Adequacy of the proposed clinical endpoints (clinical complete response rate, event free survival), to characterize and verify the benefit of dostarlimab, including the proposed timing of the analyses of these endpoints;
c. Appropriateness of the study population comprising patients with Stage II/III LARC dMMR/MSI-H for a non-operative treatment approach;
d. Role of data from a study evaluating dostarlimab for the [redacted] treatment of locally advanced colon cancer to provide supportive evidence of dostarlimab's safety and effectiveness as a treatment for dMMR/MSI-H LARC; and, SEE ERRATA
e. Potential impact of the variability in care, expertise, etc., across multi-disciplinary study staff and across study sites on study conduct and ultimately, on clinical outcomes.

FDA will consider the discussion of these key topics and any (non-binding) recommendations provided by the Committee as it advises GSK on its clinical program for dMMR/MSI-H LARC.

2. Introduction

GSK submitted a pre-investigational new drug application to support the clinical development of dostarlimab monotherapy for the following proposed indication:

> "*Dostarlimab for the treatment of patients with locally advanced, treatment-naïve mismatch-repair deficient (dMMR) or microsatellite-instability-high (MSI-H) rectal cancer*."

Locally advanced rectal cancer (LARC) encompasses tumors that are Stage II (i.e., node-negative tumor that invades through the muscularis propria into peri-colorectal tissues (T3) or tumor that invades the visceral peritoneum or invades or adheres to adjacent organ or structure (T4)) and Stage III (consisting of non-metastatic, regional node-positive tumors of any size) (AJCC, 2017).

The current standard of care (SOC) for treating LARC irrespective of dMMR/MSI-H status, consists of multi-modality therapy which includes neoadjuvant chemotherapy and radiation (or short course radiation), followed by surgery and (generally in the U.S.) adjuvant chemotherapy. Due to post-operative morbidity (e.g., fecal incontinence, genitourinary dysfunction, etc.), there is growing interest in the non-

operative management (NOM) of LARC. At some institutions and in highly selected patients, a watch and wait (W&W) approach may be employed following completion of neoadjuvant chemotherapy and radiation therapy, if a complete clinical response (cCR) is observed.

There are no FDA approved agents for the treatment of LARC as an alternative to the above-described SOC. GSK is developing dostarlimab as a replacement of current SOC for patients who experience a cCR.

3. Background

3.1. Epidemiology of Rectal Cancer

Data characterizing the epidemiology of rectal cancer (including dMMR/MSI-H disease) as a separate entity from colon cancer are limited due to historic data collection, reporting, and coding practices used across large epidemiological databases which tend to combine these diseases based on anatomic relatedness and similarities in treatments in the advanced/metastatic setting. The American Cancer Society (ACS) report estimates that 44,850 new cases of rectal cancer were diagnosed in 2022 (American Cancer Society, 2022); SEE ERRATA Women comprise 59% of rectal cancer cases and the median age at diagnosis is 63 years (Colorectal Cancer Facts and Figures 2020-2022, 2022). Rectal cancer rates from 2014 to 2018 declined by approximately 2% per year in individuals aged 50 years and older but have increased by 1.5% per year in individuals younger than 50 years of age (Siegel R, 2017). The reasons for the increasing incidence in young adults are unknown.

In cases of rectal cancer for whom information on disease stage is available, approximately 72% have localized or regional disease (SEER). Distribution of cases across race and ethnicity categories is as follows: Non-Hispanic Whites 66%, Non-Hispanic Blacks 11%, Non-Hispanic Asian/Pacific Islanders 8%, American Indian/Alaskan 0.8% and Hispanic of any race 15%.

The 5-year estimated survival rate is 68%, ranging from approximately 90% in patients with localized disease to 17% in patients with metastatic disease (SEER database). Although the risk of death from rectal cancer has been decreasing steadily, a precise estimation of the rate of mortality is limited by the large number of deaths from rectal cancer that are misclassified as colon cancer (Siegel R, 2022).

3.2. Current treatment of LARC

Standard of care treatment of LARC

The current standard of care for the treatment of LARC consists of multimodality treatment. Several sequencing strategies have been evaluated and continue to evolve but the following two strategies are used predominantly:

- "Standard" neoadjuvant therapy
    - neoadjuvant chemoradiotherapy (nCRT) consisting of a "long course" of radiotherapy (45-56 Gy over approximately 5-6 weeks) with concomitant administration of fluoropyrimidine-based chemotherapy, followed by total mesorectal excision (TME) and, generally, postoperative adjuvant chemotherapy; or
    - "short-course" radiotherapy (RT) administered alone (25 Gy over 1 week), followed by TME and, in some cases, postoperative adjuvant chemotherapy.
- Total neoadjuvant therapy (TNT):
    - fluoropyrimidine- and oxaliplatin-based chemotherapy for 12-16 weeks followed by nCRT or short course radiotherapy followed by surgery, or,
    - nCRT or short course radiotherapy followed by fluoropyrimidine- and oxaliplatin-based chemotherapy for 12-16 weeks, followed by surgery.

Treatment with the SOC approach is associated with a 5% to 10% local recurrence rate, and approximately 20-30% rate of distant metastasis recurrence, which constitutes the leading cause of death (Schmoll H,2013; Rahbari N, 2013; Ludmir E, 2017). Two randomized trials, PRODIGE 23 (Conroy T, 2021) and RAPIDO (Bahadoer R, 2021) compared the TNT approach to the standard neoadjuvant therapy approach.

PRODIGE-23 randomized patients to the TNT group (using a FOLFIRINOX chemotherapy regimen followed by chemoradiotherapy) followed by TME or the standard chemoradiotherapy group followed by TME. The 3-year disease-free survival (DFS3) rates were 76% (95% confidence interval [CI] 69, 81) in the TNT group compared to 69% (95% CI 62, 74) in the standard neoadjuvant therapy group (hazard ratio [HR] 0.69, 95% CI 0.49, 0.97; p=0.034). The RAPIDO trial randomized patients to short course radiotherapy followed by six cycles of CAPOX followed by TME or the standard chemoradiotherapy group followed by TME with or without adjuvant therapy. The disease-related treatment failure (defined as first occurrence of locoregional failure, distant metastasis, a new primary colorectal tumor, or treatment-related death) at 3 years was 23.7% (95% CI 19.8, 27.6) in the TNT group versus 30.4% (95% CI 26.1, 34.6) in the standard neoadjuvant therapy group (HR 0.75, 95% CI 0.60, 0.95; p=0.019). The survival rates at 3 years in the TNT arms of PRODIGE- 23 and RAPIDO were 90.8% and 89.1%, respectively compared to 87.7% and 88.8% in the standard

neoadjuvant therapy arms respectively; in a metanalysis of both trials (Kasi A, 2020), the pCR rates in the TNT groups were 27.8% and 28%, respectively, compared with pCR rates of 14.9 and 12.1% in the standard neoadjuvant therapy groups, respectively.

Although at the patient level a response appears to predict better outcomes, and, the absence of a response may be associated with increased risk of shorter disease-free survival (Karagkounis G, 2019), there is limited evidence from large randomized controlled studies that characterize the relationship between pCR and long-term outcomes such as disease-free survival (DFS) or overall survival (OS). In a pooled analysis of survival outcomes, 87.6% of patients with a pCR following treatment with preoperative chemoradiotherapy remained free of distant metastasis compared with 76.4% of patients without a pCR (Maas M, 2010). In the preoperative chemotherapy arm of the CAO/ARO/AIO-94 study (Rodel C, 2005), 86% of patients with a pCR were free of disease at 5 years, compared with 63% of patients who had an incomplete pathological response.

While both standard approaches to treating LARC lead to improved outcomes, treatment with chemotherapy, radiotherapy, and surgery can adversely impact the quality of patients' survivorship. The rates of long-term treatment-related complications are difficult to estimate due to differences across studies on factors such as the chemotherapy regimen used, radiotherapy protocol, surgical approach, anatomic location of the primary tumor, and need for diverting colostomy or ileostomy (transient or permanent). Following radiotherapy and surgery, 19-52% of patients experience low anterior resection syndrome which is characterized by incontinence (to feces and flatus), urgency, diarrhea, bowel movement frequency and clustering (either a pattern of urgency and incontinence, or alternately, obstructed defecation) (Croese A, 2018). Sexual and urinary dysfunction can occur in as high as 79% (Saito S, 2016; Pietrangeli A, 2009) and 35% (Lange M, 2008) of patients, respectively. In addition, in a cohort of more than 20,000 women with rectal cancer treated with radiotherapy, there was an up to 3-fold increase in risk of secondary gynecological cancers when compared with women who did not receive radiotherapy (Guan X, 2021).

Non-operative "Watch and Wait" Approach

Given the toxicities and treatment-related sequalae of SOC treatment of LARC, and the above-described data which suggest that individuals with pathological complete response to neoadjuvant treatment appear to have better outcomes, there has been growing interest in non-operative management (NOM) approaches for patients with LARC. cCR (defined as no evidence of disease by digital rectal examination, endoscopic examination, and imaging assessment) following neoadjuvant chemotherapy and radiotherapy has been used to identify patients who may be candidates to receive immediate surgery following completion of neoadjuvant therapy versus those for whom surgery may be deferred or omitted entirely; this latter approach has been referred to as the W&W approach.

Similar to pCR, there is limited evidence from randomized controlled studies that characterize the relationship between cCR and long-term outcomes. The evidence supporting the W&W approach derives from non-randomized, mostly retrospective studies (see Table). Heterogeneity across studies (e.g., due to differences in the chemoradiation and chemotherapy regimens used, schedule of assessments, definitions of cCR, imaging protocols, follow up protocols, etc.) limit the interpretation of data from these studies. Available data from small series using variable chemotherapy and radiotherapy regimens and protocols demonstrate cCR rates ranging from 10%-78% (Appelt AL, 2015; Maas M, 2011). In a case series which included 880 patients who underwent W&W after an observed cCR in the International Watch and Wait Database, the 2-year cumulative incidence of local regrowth was 25% with 64% and 88% of local relapses occurring by year 1 and year 2 following initiation of W&W, respectively (van der Walk MJM, 2018).

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The 5-year overall survival rate in the van der Walk MJM et al series was 85%. This is in contrast to one of the first published series of the patients who had cCR (Habr-Gama A, 2004), which demonstrated a 5-year overall survival rate of 100%; however, those results were not replicated in other studies. Since then, data from retrospective pooled analyses and some prospective trials suggest that NOM may result in comparable outcomes to surgical management in appropriately selected patients, though selection criteria are variable, potentially subject to selection bias, and in some cases, not clearly described in these publications (Dossa F, 2017; Sammour T, 2017; Kong JC, 2017; van der Valk MJM, 2018). Individual studies included in the Sammour systematic review are summarized in Table 2 in the Appendices section.

In a retrospective cohort analysis of 113 patients treated at MSKCC with cCR following chemoradiation (45 to 54 Gy given in 25 to 28 fractions, with concurrent, continuous infusion of fluorouracil or oral capecitabine) and chemotherapy (FOLFOX x 8 cycles as induction or consolidation therapy) and who were managed following a W&W approach, 19.5% experienced a local relapse, 80.5% had a sustained cCR (undefined), 81% avoided resection of the rectum, and 17.7% required TME for management of relapse (JJ Smith, 2019). The 5-year OS in this cohort was 73% (95% CI, 60%-89%).

The Organ Preservation for Rectal Adenocarcinoma (OPRA) Trial (Garcia Aguilar J, 2022) was a randomized, non-blinded, multicenter study in adult patients with LARC to evaluate two different sequences of TNT. The primary endpoint was DFS, defined as the interval from random assignment to the first occurrence of locoregional failure (either an unresectable rectal primary tumor following protocol neoadjuvant treatment, an R2 resection for the rectal primary tumor, or recurrence in the primary tumor bed after an R0-R1 resection), distant metastasis, a new invasive colorectal primary cancer, or death from any cause. Tumor regrowth in the rectal wall or in regional lymph nodes after a cCR or near complete response and a period of W&W was not considered a locoregional failure in this study if it was followed by an R0-R1 resection. Patients were randomized to receive induction chemotherapy (FOLFOX or CAPOX) followed by CRT (INCT-CRT group) or, CRT followed by consolidation chemotherapy (FOLFOX or

CAPOX) (CRT-CNCT group). Patients were restaged within 8 (±4) weeks after TNT. Patients with an incomplete clinical response (defined as “visible tumor on endoscopy, or palpable nodules on examination, MRI-T2W with no scar or more intermediate than dark and/or no regression in lymph nodes, and MRI-DW with insignificant regression of signal and/or obvious los signal on ADC map (Smith JJ 2015)”) were recommended to undergo TME. Patients who had a cCR or near-complete response were offered participation in a W&W protocol; the protocol included disease assessments with digital rectal examination (DRE) and flexible sigmoidoscopy every 4 months for the first 2 years from the time of assessment of complete or near-complete clinical response, and every 6 months for 3 years after that. Rectal MRI was to be performed every 6 months for the first 2 years and yearly for 3 years after that.

Patients were followed for a median of 3 years. The DFS3 was 76% (95% CI 69, 84) for the INCT-CRT group and 76% (95% CI 69, 83) in the CRT-CNCT group. The rates of local recurrence-free survival was 94% in both arms and distant metastasis-free survival was 84% and 82% in the INCT-CRT and CRT-CNCT groups, respectively. TME was recommended to 26% and 28% of patients in the INCT-CRT and CRT-CNCT groups, respectively. Of the 225 patients who received NOM, 42/105 (40%) in the INCT-CRT group and 33/120 (27%) in the CRT-CNCT group developed tumor regrowth during follow-up. All patients diagnosed with tumor regrowth (42 and 33 patients in the INCT-CRT and CRT-CNCT arms, respectively) were recommended for TME. The proportion of patients who actually preserved the rectum (TME-free survival) at 3 years was 53% (95% CI 45, 62) in the CRT-CNCT group and 41% (95% CI 33, 50) in the INCT-CRT group.

Association between treatment center and outcomes

Irrespective of treatment strategy that is used, studies have shown that high volume centers with surgical expertise and specialization in the treatment of LARC are associated with higher rates of sphincter preservation, decreased rates of postoperative morbidity and mortality, lower rates of local recurrence, and improved survival compared to lower-volume centers. (Charlton M, 2016; Etzione D, 2014; Gietelink L, 2017; Lorimer P, 2017; Yeo HL, 2017; Gao X, 2021). For patients who undergo a W&W strategy, intensive follow-up to facilitate early recognition of local or systemic recurrences and to increase the chances of a successful salvage treatment is needed. It is recommended that a multidisciplinary team be involved in the care of patients with LARC (NCCN Guidelines, Rectal Cancer V3; Fokas E, 2021), particularly when implementing the W&W strategy, as patients with LARC may represent a heterogenous group with respect to risk of recurrence. For example, patients with cT2 disease who achieve a cCR after extended chemoradiation and who are managed nonoperatively are less likely to develop early tumor regrowth when compared with those with cT3/4 disease (Habr Gama 2017), raising questions regarding whether the overall assessment of the potential risks and benefits of a NOM approach in patients

with LARC would differ significantly based on tumor size or depth of penetration. Prospective studies with contemporary neoadjuvant strategies are needed to provide guidelines for selecting patients who are good candidates for NOM and for monitoring patients for recurrence, that can be followed across centers with variable experience with the NOM approach.

3.3 Investigational studies for LARC (table- endpoints)

Table below summarizes ongoing clinical studies in the US in patients with LARC as reported on the clinicaltrials.gov website. The search (conducted on November 29, 2022) was filtered for active studies (currently enrolling, not yet recruiting, enrolling by invitation) in adult patients (>18 years of age) with locally advanced rectal cancers with no prior therapy. Studies exploring imaging, surgical techniques, novel biomarkers, or those that did not include efficacy endpoints as primary or secondary endpoints were excluded. Notwithstanding the potential limitations of the search for example due to ongoing studies not yet reported on the site, multi-cohort studies of solid tumors that may be enrolling LARC cohorts, etc., these studies illustrate the heterogeneity in contemporary studies evaluating surgery-sparing treatments for LARC, including with respect to the definition and timing of the cCR endpoint, follow up protocols, patient selection, etc., across these trials.

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Table 1: Ongoing studies for LARC (adapted from www.clinicaltrials.gov)

Title	Population	Design and Intervention	N	Primary Endpoint	Secondary Endpoints
Selective Treatment with Magnetic Resonance Image Guided Pelvic Adaptive Radiation Therapy Combined With Total Neoadjuvant Chemotherapy for the Conservative Management of Locally Advanced Rectal Cancer (SMART TNT)	LARC	Open-label, sequential assignment study. Patients treated with TNT (FOLFOX or CAPOX+ LCRT) who do not achieve a cCR have MRI-guided accelerated RT boost to primary tumor (dose escalation of boost)	25	Toxicity	acute and long-term toxicity, rate of local control, rate of distant metastases, DFS2, OS2
Neoadjuvant FOLFOX Therapy With Short Course Radiation and Active Surveillance in Locally Advanced Rectal Cancer: A Phase II Study	LARC	Open-label, single arm study. Patients are treated with FOLFOX + SCRT; patients with cCR are followed with NOM.	40	cCR (defined as digital rectal exam with normal appearing mucosa and sigmoidoscopy/proctoscopy with scarring but no nodularity or ulcerations)	OS5y
Phase I Trial of Ultra-fractionated Adaptive Radiotherapy, Chemotherapy and Selective Omission of Surgery for Locally Advanced Rectal Cancer	LARC	Open-label, dose escalation study of hypofractionated radiotherapy. Patients receive chemotherapy with FOLFOX/CAPOX	27	determine MTD of hypofractionated RT	cCR and nCR rate (assessed at 4-8 weeks after completion of chemotherapy & radiation & based on endoscopy and MRI), organ preservation-1y, locoregional recurrence, DFS1, rate of R0, rate of distant failure
Phase I Study of Epacadostat (INCB024360) Added to Preoperative Chemoradiation in Patients With Locally Advanced Rectal Cancer	LARC	Open-label, dose-escalation and expansion study. This is an add-on trial of epacadostat to SOC chemoradiotherapy.	39	determine RP2D of epacadostat	NAR score, pCR, PFS, cCR at Week 25 (no clinical evidence of tumor as assessed by radiographic, endoscopic, and physical examinations after completion of planned protocol therapy).
A Phase 1b/2 Trial of Preoperative Niraparib, Dostarlimab, and Hypofractionated Radiotherapy for the Treatment of Locally-advanced Rectal Cancers (Desc)	LARC	open-label, sequential assignment Niraparib, SCRT, dostarlimab	38	determine RP2D of niraparib, pCR, cCR Week8	OS1
A Phase II Multicenter Randomized Trial Evaluating 3-year Disease Free Survival in	LARC	Open-label, randomized, 2-arm study of induction neoadjuvant	358	DFS3	Major adverse events

Patients With Locally Advanced Rectal Cancer Treated With Chemoradiation Plus Induction or Consolidation Chemotherapy and Total Mesorectal Excision or Non-operative Management		FOLFOXCAPOX), radiotherapy, and surgery or NOM vs. chemoRT, surgery & adjuvant chemotherapy.			
Organ Preservation for Patients With Locally Advanced Rectal Adenocarcinoma: Evaluating the Efficacy of Short Course Radiation Therapy Followed by FOLFOX or CapeOX	LARC	Open-label, single arm study of SCRT, FOLFOX/CAPOX, surgery or NOM	25	cCR (not defined)	RFS1, PFS1, acute-late toxicities
INNATE: Immunotherapy During Neoadjuvant Therapy for Rectal Cancer, a Phase II Randomized Multi-center Trial With and Without APX005M, an Anti-CD40 Agonist	LARC (high risk, defined as Stage III or Stage II with at ≥ 1 high-risk features: -Distal (<1cm from anal ring) -cT4 or within 3mm of mesorectal fascia -Not candidate for sphincter preservation -Extramural venous invasion).	Open-label, randomized, 2 arm study comparing SCRT/FOLFOX ± APX005M.	58	pCR	OS3, toxicity, DFS3, immune response (tissue)
A Phase II Clinical Trial Platform of Sensitization Utilizing Total Neoadjuvant Therapy (TNT) in Rectal Cancer	LARC (high risk & not candidate for organ preservation, defined as a tumor with a distal location =< 5 cm from the anal verge; any N Bulky; any cT4 or evidence that the tumor is within 3 mm of the mesorectal fascia; high risk for metastatic disease with ≥4 regional nodes (cN2)) & not a candidate for sphincter-sparing surgical resection prior to neoadjuvant	Open-label, randomized, 3-arm study comparing SOC with FOLFOX, RT, capecitabine vs.an add-on veliparib arm (Arm 2) or add-on pembrolizumab arm (Arm 3)	362	NAR	OS3, DFS3, pCR, rate of sphincter preservation

	therapy (as planned by the primary surgeon)				
A Phase II/III Trial of Neoadjuvant FOLFOX With Selective Use of Combined Modality Chemoradiation Versus Preoperative Combined Modality Chemoradiation for Locally Advanced Rectal Cancer Patients Undergoing Low Anterior Resection With Total Mesorectal Excision (PROSPECT)	LARC	Open-label, randomized, 2 arm study comparing two SOC strategies	1194	R0 resection rate, DFS, local recurrence	pCR, OS, AE, rate of postoperative RT
Phase II Study of TGFβ Type I Receptor Inhibitor LY2157299 With Neoadjuvant Chemoradiation in Patients With Locally Advanced Rectal Adenocarcinoma	LARC and Metastatic to undergo surgery	Open-label, single arm study of the addition of galunisertib to SOC.	50	pCR, immunoscore changes, biomarkers	
MRI Guided Adaptive Radiation for Locally Advanced Rectal Adenocarcinoma to Enhance Complete Response	LARC	Open-label, single arm, feasibility study of capecitabine +LCRT and FOLFOX exploring an adaptive (MRI-based) radiotherapy dose based on daily tumor changes.	20	feasibility	cCR 6 months (absence of clinically detectable tumor after treatment), pCR, DFS5
A Phase II Study of Neoadjuvant Nivolumab Plus Ipilimumab and Short-Course Radiation in MSI-H/dMMR Locally Advanced Rectal Adenocarcinoma	MSI-H/dMMR LARC	Open-label, single arm study of nivolumab and ipilimumab and SCRT	31	pCR	sphincter preservation, DFS5, OS, safety
A Phase 1 Study of IPdR in Combination With Capecitabine and Radiotherapy in Rectal Cancer	LARC	Open-label, single arm, dose-finding study of ropidoxuridine in combination with capecitabine and LCRT, followed by surgery	30	determine MTD of ropidoxuridine (radiosensitizer)	PK, uptake by tumor cells, pCR, NAR
Randomized Multicentre Phase III Study of Short Course Radiation Therapy Followed by Prolonged Pre-operative Chemotherapy and Surgery in Primary High Risk Rectal Cancer Compared to Standard Chemoradiotherapy and Surgery and Optional Adjuvant (RAPIDO) Chemotherapy.	LARC	Open-label, randomized, 2-arm study comparing 2 SOC strategies	920	disease-related treatment failure 3y	OS, Circumferential radio margin negative rate, pCR rate, toxicity, surgical complications
Timing of Rectal Cancer Response to Chemoradiation	LARC	Non-randomized, open-label, 4-arm parallel assignments. Cohort 1: standard surgical resection after completion of chemoRT. Cohort 2, 3, and 4 vary in the number of courses of chemotherapy administered before surgery.	248	pCR, rate surgical difficulty and complications for different intervals from chemoRT to surgery	

3.4. MSI-H/dMMR LARC

Mismatch repair deficiency (dMMR) typically results from a somatic or germline mutation in one of four genes (MLH1, MSH2, MSH6, or PMS2) that code for proteins that repair mismatches or certain insertion/deletion errors during DNA replication or recombination, or through methylation of the MLH1 promoter. Mutations in these genes lead to the accumulation of errors in short repetitive sequences in DNA called microsatellites. MSI-H/dMMR cancers are characterized by high mutation burden which is associated with an increased probability of expressing neoantigens, which can serve as targets for the immune system, increasing their susceptibility to drugs that promote immune mediated anti-tumor activity. Currently, FDA has approved 4 immune checkpoint inhibitors for dMMR/MSI-H solid tumor indications: pembrolizumab (Keytruda USPI), nivolumab (Opdivo USPI) as a single agent or in combination with ipilimumab (Yervoy USPI), and dostarlimab (Jemperli USPI).

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For patients with Stage 1-2 disease, the prevalence rate is approximately 20% (range 10%–32%), while for patients with Stage 3-4 disease, the prevalence rate is approximately 9% (range 3–16%). (Lorenzi M, 2020).

The data describing the demographic characteristics of patients with dMMR/MSI-H rectal cancer is limited. In two single-institution series each comprising less than 100 patients with LARC, the median age of patients with dMMR/MSI-H rectal cancer was 39- 41 years old (range 23-83), (Cercek A, 2020; de Rosa N 2016); men and women comprise 52%- 68% and 32%- 48% of patients, respectively. The racial and ethnic distribution among patients was as follows: White (78-82%), Black (2-5%), Asian (6.5-10%), and Hispanic ethnicity (6%). However, these results should be interpreted with caution given the historical underrepresentation of racial and ethnic minorities in clinical trials. Furthermore, based on the trial conducted at a single, large academic center, study the data may not reflect the prevalence of the case distribution observed in most settings.

Treatment outcomes for patients with LARC receiving SOC chemotherapy or chemoradiotherapy in rectal cancers are limited and suggest lower overall response to treatment in patients with dMMR/MSI-H disease. In a single-institution retrospective analysis in patients with LARC who received neoadjuvant FOLFOX, 6 of 21 patients (29%) with dMMR LARC had disease progression compared with no cases of disease progression among the 63 patients with pMMR LARC (Cercek A, 2020). However, the addition of radiotherapy appears to increase response with another single-institution

retrospective analysis showing a pCR of 27.6% among 62 patients with dMMR LARC who received multimodality treatment, fluoropyrimidine-based nCRT (de Rosa N, 2016).

In the neoadjuvant treatment setting for colon or rectal cancer, no data from randomized controlled trials are available. In the NICHE study, 40 patients with 21 dMMR and 20 dMMR colon cancer tumors (1 patient had tumors that were dMMR and pMMR) received neoadjuvant therapy with a single dose of ipilimumab and two doses of nivolumab before surgery. All evaluable patients with dMMR tumors (n: 20) experienced pathological responses, and 12/20 patients (60%) experienced complete pathological response (pCR) (9/12 patients had Stage 3 disease) (Chalabi M, 2020). In the subsequent NICHE-2 study, a total of 112 patients with dMMR colon cancer who received one dose of ipilimumab and two doses of nivolumab and underwent surgery ≤6 weeks later, the pCR rate was 67% in 107 efficacy evaluable patients; most (89%) patients had Stage 3 disease (Chalabi M et al; 2022 ESMO). For LARC, an interim analysis of a single-institution study of neoadjuvant dostarlimab monotherapy has demonstrated a cCR rate of 100% among the initial 12 patients enrolled (see Section 4.3). Data from subgroup analyses of other studies and case reports also show activity of immune checkpoint inhibitors in the neoadjuvant setting but the number of patients is limited and the response is confounded by the concurrent use of chemotherapy and radiation therapy.

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4. Dostarlimab CDP

4.1. Product Information

Dostarlimab-gxly is a programmed death receptor-1 (PD-1)–blocking IgG4 humanized monoclonal antibody. 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 binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response (Dostarlimab USPI).

4.2 Regulatory History

On August 17, 2021, FDA granted accelerated approval to dostarlimab (Jemperli) for the treatment of adult patients with dMMR recurrent or advanced solid tumors, as determined by an FDA-approved test, that have progressed on or following prior treatment and who have no satisfactory alternative treatment options. Accelerated

approval was based on tumor response rate and durability of response. As a condition of continued approval, FDA required and GSK agreed to conduct a clinical trial evaluating ORR and duration of response (DOR) to verify and describe the clinical benefit of Jemperli in patients with dMMR, recurrent or advanced solid tumors, including at least 300 patients across all tumor types, and including a sufficient number of patients and representation of tumor types (other than endometrial and gastrointestinal tumors).

On April 22, 2021, FDA granted accelerated approval to Jemperli for the treatment of adult patients with 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. Accelerated approval was based on tumor response rate and durability of response. As a condition of continued approval, FDA required, and GSK agreed to submit the results of a clinical trial evaluating overall response rate and duration of response in patients with dMMR recurrent or advanced endometrial cancer that has progressed on or following prior treatment with a platinum-containing regimen.

The investigation of dostarlimab in patients with LARC was initiated with Study 19-288, a single-institution, investigator-initiated trial. Study 19-288 was initiated under IND 146194. Refer to Section 4.3 for a description of clinical investigations of dostarlimab in patients with LARC.

On September 19, 2022, FDA and GSK held a Type B meeting to discuss the development of dostarlimab for the proposed indication:

> *dostarlimab as a single agent for the treatment of patients with locally advanced, treatment-naïve dMMR/MSI-H rectal cancer.*

FDA expressed concerns regarding some elements of the proposed strategy to support accelerated approval and to subsequently verify clinical benefit. These include the adequacy of a) data derived from a small cohort of patients from two single-arm trials (with one from a single center providing a significant number of patients) to support approval, b) the proposed and unprecedented use of cCR12 as an endpoint for accelerated approval, and c) the data package proposed to verify clinical benefit, including the role of a proposed study in patients with colon cancer. As such, FDA considered venues that may provide the perspectives of external stakeholders regarding clinical trial designs to assess treatment effects in patients with locally advanced rectal cancer, including potentially convening an Oncologic Drugs Advisory Committee meeting. FDA requested that a multicenter study designed to assess the risks and benefit of dostarlimab for the treatment of dMMR/MSI-H LARC be sized to provide (1) confidence around the point estimate to ensure that the MSKCC experience is generalizable, (2) confidence that the use of an untested endpoint in this clinical setting (cCR12) could adequately characterize the benefits and risks of treatment, and (3) that the long-term oncologic outcomes of an approach that withholds surgery from most patients will be acceptable.

On January 19, 2023, FDA and GSK held a Type B meeting to discuss Study 219606, a proposed randomized controlled perioperative study in patients with locally advanced Stage II/III dMMR/MSI-H colon cancer comparing dostarlimab versus SOC chemotherapy.

4.3. Clinical studies/Proposed clinical investigations in LARC

Study 19-288

Study 19-288 is an ongoing single institution, single-arm, 2-cohort prospective study of neoadjuvant dostarlimab being conducted at the Memorial Sloan Kettering Cancer Center (MSKCC; Cercek A, 2022). Cohort 1 enrolled adult patients with dMMR / MSI-H LARC and no prior surgery, radiotherapy, or systemic therapy. dMMR/MSI-H status was determined by immunohistochemistry (IHC), polymerase chain reaction (PCR), or next generation sequencing (NGS) testing. Patients with HIV, active Hepatitis B or C were excluded. The co-primary endpoints were ORR and cCR at 12 months (cCR12) after completion of dostarlimab. cCR is defined as no evidence of residual disease by endoscopy (e.g., colonoscopy or flexible sigmoidoscopy), digital rectal exam, or rectal-specific MRI and no evidence of metastatic disease. Biopsies were planned to be obtained in the presence of viable tumor tissue. Images and endoscopies will be submitted for independent central review.

Patients received dostarlimab 500 mg IV every 3 weeks (Q3W) for 9 cycles. After 9 cycles of dostarlimab,

- patients with a cCR proceed with non-operative management (NOM)
- patients with a non-cCR go on to receive standard TNT with concurrent chemoradiation (capecitabine) followed by FOLFOX.
    - patients who after TNT achieve a cCR, proceed to NOM.
    - patients who after TNT do not achieve a cCR, undergo TME.

Endoscopy (with biopsies) and digital rectal exam, MRI of the rectum, PET-CT, and CT of the chest/abdomen/pelvis were performed at Week 6 and Month 3 to assess disease burden. After assessment of response, patients undergoing NOM (i.e., those with a cCR) are assessed with endoscopy, digital rectal exam, MRI of rectum, PET-CT, and CT of the chest/abdomen/pelvis every 4 months for 2 years and then every 6 months for an additional 3 years.

The target enrollment in Cohort 1 is 30 patients. Study 19-288 has a Simon's two-stage minimax design; the planned sample size for Stage 1 was 15 patients. The results of an interim analysis based on the first 12 consecutively enrolled patients who completed treatment with 9 cycles of dostarlimab out of a total of 16 patients who had been accrued, have been presented and published (ASCO 2022 annual meeting; Cercek A,

2022). The median follow-up at the time of reporting for the 12 patients was 12 months (range, 6 to 25).

Among enrolled patients, the median age was 54 years (range, 26 to 78); a total of 10 patients (62%) were women and 6 (48%) were men. Eleven (69%) patients were White, 3 (19%) patients were Asian, and 2 (12%) patients were Black. Most patients (n=12, 75%) had an ECOG performance status of 0 and 4 patients (25%) had a PS of 1. Fifteen (94%) patients had clinical Stage III disease; tumor stage was T1/2 in 4 (25%) patients, T3 in 9 (56%) patients), and T4 in 3 (19%) patients. For the 14 patients with available information, 8 (57%) have a germline mutation associated with Lynch syndrome, no patient had a BRAF V600E mutation, and all patients had a tumor mutation burden (TMB)-high status (defined as ≥ 10 mut/Mb), with a mean TMB of 67.19 (range 37.9, 103 mut/Mb).

All 12 evaluable patients had a reported cCR; of these, only 4 patients have been followed for 12 months or longer. During the follow-up period, no patients have received chemoradiotherapy or surgical resection and all patients were alive and free of disease at data cut off.

(b) (4)

Proposed Study

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GSK proposes to conduct a global, multicenter, single arm, open-label, non-randomized study that will enroll approximately 100 patients who have pathologically confirmed, previously untreated LARC that is dMMR/MSI-H as assessed by local testing. The study design is shown below in Figure 1.

Figure 1. Study [redacted] Study Design

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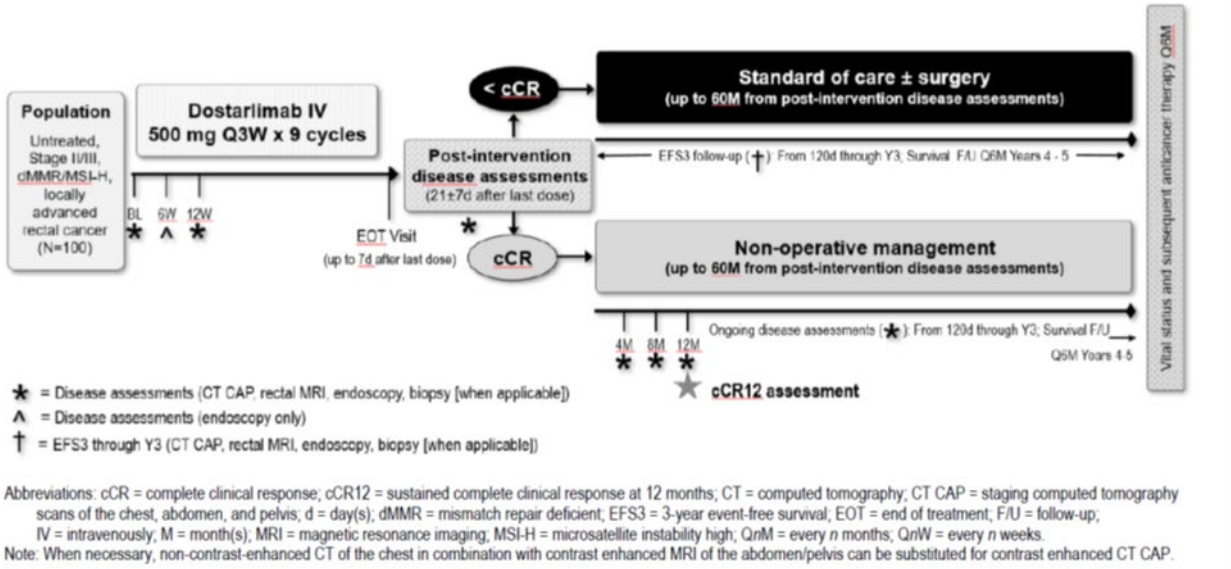

Abbreviations: cCR = complete clinical response; cCR12 = sustained complete clinical response at 12 months; CT = computed tomography; CT CAP = staging computed tomography scans of the chest, abdomen, and pelvis; d = day(s); dMMR = mismatch repair deficient; EFS3 = 3-year event-free survival; EOT = end of treatment; F/U = follow-up; IV = intravenously; M = month(s); MRI = magnetic resonance imaging; MSI-H = microsatellite instability high; Q*n*M = every *n* months; Q*n*W = every *n* weeks.
Note: When necessary, non-contrast-enhanced CT of the chest in combination with contrast enhanced MRI of the abdomen/pelvis can be substituted for contrast enhanced CT CAP.

Source: clinical study protocol

The primary endpoint is clinical complete response at 12 months (cCR12) as assessed by Independent Central Review (ICR). Two key secondary endpoints are cCR36 as assessed by ICR (defined as maintenance of cCR for 36 months), and event-free survival at 3 years (EFS3) by investigator assessment, defined as remaining alive and free of the following: disease progression precluding surgery, local recurrence, and distant recurrence.

Patients will receive dostarlimab 500 mg IV Q3W for a total of 9 cycles. During dostarlimab administration, endoscopic examination will be conducted at Week 6 (after 2 cycles of dostarlimab), Week 12 (after 4 cycles of dostarlimab), and at the end of dostarlimab treatment. Rectal MRI and CT scans will be assessed at Week 12 and at the end of dostarlimab treatment. Biopsies will be taken endoscopically at all time points where residual tumor tissue is still visible and amenable to biopsy. Biopsy tissue will be sent to GSK.

Following completion of treatment with dostarlimab, patients will undergo assessments with endoscopy, rectal MRI, and CT to determine clinical response. Subsequent treatment decisions will be made based upon the investigator's assessment of clinical response, which include digital rectal examination.

- If the participant meets criteria for cCR, they will begin the non-operative management (NOM) period.
- For participants with near CR (nCR) or incomplete CR (iCR) at the time of assessment, if the participant and investigator agree to a delay in implementing standard of care (SOC) treatment (chemotherapy, chemoradiotherapy ± surgery), a second assessment will be performed at least 4 weeks and no longer than 8 weeks after the first one. If cCR is achieved on this assessment, the participant

may enter the NOM Period instead of the SOC Period. If the participant has any response less than a cCR at the second assessment, or if they do not undergo the second assessment, they will proceed to SOC therapy. The specific SOC therapy used will be at the investigator's discretion.

NOM will consist of watchful waiting with regular assessments for recurrent disease as follows:

- Years 1-2: endoscopy, rectal MRI, and staging CT every 4 months.
- Years 3-5: endoscopy, rectal MRI, and staging CT every 6 months.

After the 60-month assessments in either the NOM Period or the SOC Period, participants will be contacted every 6 months for assessment of vital status and any subsequent anticancer therapy until death, withdrawal of consent or the closure of the study.

If a participant develops evidence of recurrent disease at any point during the NOM Period, they will be evaluated for salvage therapy by their local care team and will transition to the SOC Period. The choice of salvage therapy will be at the discretion of the treating medical team but information will be collected and key clinical outcomes will be collected for the final analysis. Follow-up for disease-related and survival outcomes will continue until death, withdrawal of consent, or study termination by the sponsor. cCR12 is defined as no evidence of residual disease by endoscopy, or rectal-specific MRI and no evidence of metastatic disease 12 months after the first post-treatment (nine 3-week cycles) cCR assessment by Independent Central Review (ICR). Digital rectal exam is only relevant to cCR12 assessed by the investigator and will not be included in the assessment of cCR12 per ICR.

The study will have 4 planned analyses:

1. The primary analyses of cCR12 as assessed by ICR will be performed after all enrolled participants (N=100) have the opportunity for 12 months of follow-up from the first disease assessment after the last dose of study intervention that demonstrates cCR by ICR.
2. The primary analyses of EFS3 as assessed by investigator assessment will be performed after all enrolled participants (N=100) have the opportunity for at least 3 years of follow-up from the first dose of study intervention.
3. The primary analyses of cCR36 as assessed by ICR will be performed after all enrolled participants (N=100) have the opportunity for 36 months of follow-up from the first disease assessment after the last dose of study intervention that demonstrates cCR by ICR.
4. The primary analyses of disease specific survival at 5 years and overall survival at 5 years will be performed after all enrolled participants (N=100) have the opportunity for at least 5 years of follow-up from the first dose of study intervention.

Proposed data package for future BLA submission for Accelerated Approval

Study	Design/population	Number of patients	Endpoints
19-288 Cohort 1	Open-label, single-institution, single-arm study in patients with dMMR/MSI-H LARC and no prior therapy	30	Primary Endpoints: •ORR •cCR12
[redacted]	Open-label, multicenter, single-arm study in patients with dMMR/MSI-H LARC and no prior therapy	100	Primary endpoint: •cCR12 by ICR Key Secondary Endpoints: •cCR36 by ICR •EFS3 by investigator assessment Other secondary endpoints: EFS (investigator), •cCR12 and cCR36 by investigator assessment, •ORR by ICR and investigator, TME at 3 years, •disease-specific survival (DSS), DSS-5 years, •OS, •OS-5 years
219606	Perioperative, randomized controlled study in patients with dMMR/MSI-H locally advanced colon cancer comparing dostarlimab vs. SOC with chemotherapy	711	Primary endpoint: •EFS by ICR Secondary endpoints: •EFS2 per ICR •EFS3 per ICR •pCR •OS

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5. FDA Issues for the ODAC

GSK is investigating dostarlimab for the treatment of MSI-H/dMMR LARC. The proposed clinical development program to support a future supplemental BLA for this indication includes 2 single-arm studies evaluating dostarlimab monotherapy in patients with Stage II/III rectal cancer, with cCR12 as the primary endpoint; following an accelerated approval, GSK plans to submit the results of analyses of cCR36 and EFS36 as secondary endpoints to verify clinical benefit, along with data from a randomized controlled trial in locally advanced MSI-H/dMMR colon cancer as supportive evidence. The FDA is convening this Oncologic Drugs Advisory Committee (ODAC) meeting to request the input of the Committee on the adequacy of the key elements of the dostarlimab clinical development program due to the unprecedented use of cCR as the major endpoint to support an approval in oncology, the trial designs that serve as the basis of a future application, and the limitations of data to inform the implementation of the proposed NOM strategy.

The major topics for discussion at the ODAC are described below.

a. **Discuss the adequacy and appropriateness of proposed single-arm trials to evaluate the efficacy and safety of dostarlimab, including the long-term benefits and risks of treatment in the indicated population.** GSK proposes two single-arm trials to support the safety and efficacy evaluation of dostarlimab for the treatment of LARC. FDA has generally required randomized trials to characterize a drug's safety and effectiveness in the curative setting. GSK states that conduct of a randomized trial in patients with MSI-H/dMMR LARC is infeasible. GSK has cited the rarity of the disease, and the high cCR observed in the available preliminary data (100%) leading to lack of interest in a trial comparing a drug with these preliminary effects with SOC treatment as the reasons why a randomized trial cannot be conducted. Dostarlimab, a member of the PD-1 class, is an approved agent with an extensively characterized safety profile, albeit not specifically in LARC. However, the benefits and risks of treatment with this agent may not be fully evaluable in comparison to available curative treatment with the proposed study designs; while a durable cCR of 100% could be considered clinically meaningful, especially if cure occurs without the need for salvage therapy, interpreting the results without a concurrent control may increase the uncertainty with respect to the effect of withholding standard treatment including surgery on long-term oncological outcomes.

b. **Discuss the adequacy of the proposed clinical endpoints (i.e., clinical complete response rate, event free survival), to characterize and verify the benefit of dostarlimab, including the proposed timing of analyses of these.** GSK proposes an interim assessment of cCR at 12 months (cCR12) as assessed by independent central review (ICR) to serve as an intermediate clinical endpoint reasonably likely to predict the clinical benefit of dostarlimab for a future marketing application seeking accelerated approval. cCR12 is a composite endpoint defined as no evidence of residual disease by endoscopy, or rectal-specific MRI and no evidence of metastatic disease after 6 months of dostarlimab therapy, as assessed at 12 months by an ICR. Response rate has been used extensively to support approval in oncology because this endpoint represents drug activity given that malignant tumors do not typically shrink on their own. Response rate has typically been used with standard, accepted criteria for assessing this endpoint in clinical trials (e.g., RECIST) designed with the intent to support regulatory decision-making, including modifications of standard criteria in specific settings. There has been growing interest in using other tumor-based endpoints to support approval in the early, non-metastatic, curative settings (e.g., pathological complete response rate [pCR]) but this has proven challenging due to the unclear relationship between these new endpoints and endpoints denoting clinical benefit such as overall survival or disease-free survival.

There are no evidence-based guidelines to guide use of cCR as an endpoint in clinical practice or for use in clinical trials. The use of cCR in LARC clinical decision-making is based on small, mostly retrospective, uncontrolled studies that vary in design and other important factors (e.g., chemotherapy regimen used, radiotherapy protocol, monitoring protocol for assessment of cCR, method of assessing clinical cCR, patient selection, etc.,) thus limiting the interpretability of findings. These challenges introduce uncertainty with respect to the magnitude, durability, and method of assessment of cCR, to predict clinical benefit. While the preliminary data indicate a cCR rate of 100% at a single site, it is unclear whether these results will be replicable across more sites (with potentially variable local expertise and experience with NOM), and if not, what magnitude of cCR rate would provide a favorable benefit:risk assessment in the context of available curative-intent treatment, the known toxicities of dostarlimab, and an unclear rate of relapse.

GSK proposes to use cCR36 as assessed by the investigator and event-free survival at 36 months as assessed by ICR to verify the clinical benefit of dostarlimab if accelerated approval is granted. Time-to-event endpoints are challenging to interpret in single-arm trials and, given the heterogeneity of the data describing relapse in LARC, comparison to historical control may be challenging.

c. **Discuss the study population comprising patients with Stage II/III LARC dMMR/MSI-H for a non-operative treatment approach.** Patients with stage II/III LARC are typically treated with SOC neoadjuvant/adjuvant strategies consisting of chemotherapy, chemoradiation, and surgery. However, the presence of lymph nodes and/or large tumors typically signals a higher risk of recurrence. There are no consensus guidelines with respect to whether institutions that currently offer the W&W approach in unselected patients (i.e., with respect to dMMR/MSI-H) consider these or other factors in determining whether a patient may be a candidate for NOM. An additional consideration is patients with Lynch syndrome who have an increased lifetime risk of developing other cancers, including colon cancers. Therefore, it is unclear whether a prespecified number of patients at higher risk of recurrence (i.e., cT4, node-positive disease) is needed for a study that evaluates a treatment to replace SOC to adequately characterize treatment effects across the LARC population.

d. **Discuss the role of data from a study evaluating dostarlimab in the [redacted] treatment of locally advanced colon cancer, to provide supportive evidence of dostarlimab's role for the treatment LARC.** GSK is proposing to submit the results of a planned randomized controlled trial of dostarlimab for the [redacted] treatment of Stage II/III colon cancer, as supportive evidence to verify clinical benefit. While colon and rectal cancer are treated similarly in the

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metastatic setting, treatment in the early setting differs. Therefore, the role of the proposed randomized trial in colon cancer is unclear.

e. **Discuss the potential impact of the variability in care, expertise, etc., across multi-disciplinary study staff and across study sites on study conduct and ultimately on outcomes**. The results of the preliminary evaluation of dostarlimab in dMMR/MSI-H LARC indicate high cCR rate. These results are based on a single-institution trial conducted in a high-volume center with the expertise to provide NOM as a treatment option to patients. Studies show that high volume centers with surgical expertise and specialization in the treatment of LARC are associated with higher rates of sphincter preservation, decreased rates of postoperative morbidity and mortality, lower rates of local recurrence, and improved survival compared to lower-volume centers. For patients who undergo a W&W strategy, intensive follow-up to facilitate early recognition of local or systemic recurrences and increase the chances of a successful salvage treatment is needed. It is recommended that a multidisciplinary team be involved in the care of patients with LARC, particularly when implementing the W&W strategy, as patients with LARC may represent a heterogenous group with respect to risk of recurrence.

6. Summary

GSK is investigating dostarlimab in patients with MSI-H/dMMR LARC in single-arm trials. The sponsor plans to pursue the Accelerated approval pathway with cCR12 as the primary efficacy endpoint. The sponsor plans to provide analyses of cCR36 and EFS3 from a single-arm trial, as confirmatory evidence of dostarlimab's clinical benefit; data from a randomized controlled trial evaluating [redacted] dostarlimab in Stage II/III colon cancer is proposed as supportive.

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The current standard of care treatment of LARC consists of curative-intent multi-modality treatment consisting of neoadjuvant chemoradiotherapy, followed by surgical resection of tumor and adjuvant chemotherapy. In recent years, total neoadjuvant approaches have also been used, resulting in upfront treatment intensification of chemotherapy and radiotherapy prior to surgery. The associated treatment-related toxicities and impact on quality of like have led to growing interest in non-operative management in patients with a clinical complete response (cCR) after neoadjuvant therapy. However, this approach has not been widely adopted and outcomes between SOC treatment and treatment following the NOM approach have not been evaluated in randomized trials, and hence the relationship between cCR rate and outcomes of clinical benefit is unclear. There are no evidence-based criteria delineating which clinical factors to consider in determining whether a patient may be a candidate for NOM, how to assess cCR, and the appropriate follow-up needed to

facilitate prompt identification of patients with recurrent disease who may still be candidates for SOC treatment. These issues warrant public discussion to gain external input from the Oncologic Drugs Advisory Committee on a reasonable approach that will generate the evidence needed to adequately evaluate the benefits and risks of treatment with dostarlimab for the proposed indication.

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Appendices

Table 2: Summary of studies informing the W&W approach in patients with cCR (modified from Sammour T, 2017)

Study	Design	N patients	Disease	Consolidation chemo	Assessment type/schedule	Outcomes
Appelt AL	Prospective	40	T2 or T3, N0-N1 in the lower 6 cm of the rectum	None	clinical exam and endoscopies Q2M for the 1st year, Q3M the 2nd year, Q6M months the 3rd, and Q12M in the 4th and 5th year.	LR (1 year): 15.5%
Araujo RO	Retrospective prospective	42	LARC within 10 cm from the anal verge	Yes (unspecified)	Not described	LR 28%, 5y-OS 71.6%, DFS 60.9%, mean recurrence interval 23.5 months
Creavin B	Prospective	10	T3-4 or any T with nodal involvement	Yes (65%, all patients with N1)	Clinical exam at 6 weeks and Q3-6M thereafter including endoscopic assessment. CT–TAP Q6M for 3 years and pelvic MRI Q3–6M.	OS 90%, DFS 80% (1 LR, 1 distant recurrence)
Dalton R	Retrospective	6		None		DFS 100%
Habr-Gamma A	Prospective	90	resectable LARC, located no more than 7 cm from the anal verge	None	Monthly visits during the first 12 months (complete physical examination, DRE, and rigid proctoscopy), CEA	LR 31%, 14% distant metastases

					level determination (Q2-3M) and at least one pelvic MRI or CT.	
Habr-Gamma A	Prospective	22	T2-T4 or N1, no more than 7 cm from the anal verge	5FU (100%)	Visits Q1-2M with clinical and DRE in addition to rigid proctoscopy for 1 year. CEA Q2-3M for 1 year. After year 1, assessments Q3M until year 3 and Q6M thereafter. CT scans, MRI, and/or ERUS Q6M on year 1 and yearly thereafter.	cCR12 63.6%, LR 22.7%
Lai CL	Retrospective	18	Stage 2-3 up to 10 cm from the anal verge	None	Clinical exam, proctoscopy or colonoscopy, and CEA Q3M until year 3 and Q6M thereafter. CT and MRI Q6M on year 1 and annually thereafter.	LR 11.1%
Lee SY	Retrospective	8		Yes (12.5%)		DFS3 75%
Martens MH	Prospective	85	LARC	CapOx (38%, all patients with N1)	Year 1: DRE, endoscopy and MRI Q4M; CT for distal metastases Q6M. Year 2-5: DRE, endoscopy and MRI Q6M and CT scan Q12M. CEA was also assessed Q3M on	LR17.6%, 3yOS 96.6%, DFS 80.6%

					years 1-3 and Q6M thereafter	
Renehan AG	Retrospective prospective	109	LARC	Yes (6%)	DRE, MRI Q4-6M in the first 2 years. Endoscopy, CT scan of the chest, abdomen, and pelvis, and at least two CEA measurements in the first 2 years	LR 34%, 3y OS 96%
Sanchez Loria F	Retrospective	68	Stages 1-3	Yes (23%)	Not described.	LR 16% DFS5 y 76.3%, 3y OS 93.8%
Smith JD	Retrospective	32	LARC	FOLFOX, CapOX, 5FU (53%)	Follow-up at the discretion of the treating physicians, which generally entailed physical examinations and flexible sigmoidoscopies every Q3M for the first year and Q4-6M thereafter; diagnostic imaging was not standardized, but included cross-sectional imaging Q6M for the first 2 years for most patients.	LR 18.7%, 9.4% distant recurrence, 2y OS 96%
Smith RK	Retrospective	18	LARC	5FU (61%)	Rigid proctoscopy and CEA Q3M for 1 year, followed by Q6M on	Recurrence 11.1% (one local, one distant)

					years 2-3, and then annually thereafter. PET-CT or CT approximately 6 months following the initiation of surveillance and at annual intervals thereafter.	
Vaccaro	Retrospective	23	LARC	Not specified		LR 18.5%, DFS3 94.1%

LR: local relapse; OS: overall survival; DFS: disease-free survival: cCR: clinical complete response; DFS3: DFS at 3 years; DFS5: DFS at 5 years; 5FU: 5-fluorouracil; CapOx (capecitabine and oxaliplatin); FOLFOX: 5FU, oxaliplatin, leucovorin.

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