STUDY DESIGN TO EVALUATE DOSTARLIMAB IN TREATMENT-NAÏVE dMMR/MSI-H LOCALLY ADVANCED RECTAL CANCER

SPONSOR BRIEFING DOCUMENT

ONCOLOGIC DRUGS ADVISORY COMMITTEE

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List of Abbreviations

Abbreviation	Definition
AE(s)	adverse event(s)
BICR	Blinded Independent Central Review
BID	twice daily
CAP	chest, abdomen, pelvis
cCR	clinical complete response
cCR12	clinical complete response for 12 months
cCR36	clinical complete response for 36 months
CRC	colorectal cancer
CRT	chemoradiotherapy
CT	computed tomography
DCR	disease control rate
DFS	disease-free survival
DFS3	disease-free survival at Year 3
dMMR	mismatch-repair deficient
DoR	duration of response
DSS	disease-specific survival
DSS5	disease-specific survival at Year 5
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
EFS3	event-free survival at Year 3
FDA	Food and Drug Administration
GSK	GlaxoSmithKline
HR	hazard ratio
iCR	incomplete response
IHC	immunohistochemistry
IQR	interquartile range
irAE(s)	Immune-related adverse event(s)
IV	Intravenous(ly)
LARC	locally advanced rectal cancer
LARS	low anterior resection syndrome
MLR	mixed lymphocyte reaction
MRI	magnetic resonance imaging
MSI-H	microsatellite-instability-high

MSKCC	Memorial Sloan Kettering Cancer Center
MSS	microsatellite stable
NCCN	National Comprehensive Cancer Network
nCR	near complete response
NOM	non-operative management
ORR	overall response rate
OS	overall survival
OS5	overall survival at Year 5
pCR	pathological complete response
PD-1	programmed cell death protein-1
PD-L1	programmed cell death protein ligand-1
PD-L2	programmed cell death protein ligand-2
PET	positron-emission tomography
PFS	progression-free survival
PGIS	Patient Global Impression of Severity
pMMR	proficient-mismatch repair
PR	partial response
PRO	patient-reported outcome
PRO-CTCAE	Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events
Q3W	once every 3 weeks
Q6W	once every 6 weeks
QLQ-C30	Quality-of-Life of Cancer Patients
QLQ-CR29	Quality-of-Life – Colorectal Specific
RO	receptor occupancy
SAEs	serious adverse event(s)
SoC	standard of care
TME	total mesorectal excision
TNM	tumor, node, metastasis
TNT	total neoadjuvant therapy
TRG	tumor regression grade
US	United States
WPAI	Work Productivity and Activity Impairment
^{18}F-FDG	^{18}F-fluorodeoxyglucose

1 EXECUTIVE SUMMARY

1.1 Introduction

Dostarlimab is an established anti-programmed cell death protein-1 (PD-1) monoclonal antibody. Dostarlimab binds with high affinity and specificity to human PD-1, blocking the binding of its ligands, programmed cell death protein ligand-1 and -2 (PD-L1/2), resulting in the enhancement of T-cell reactivity.

Dostarlimab has received accelerated approval in the United States (US) for two indications in adults with mismatch-repair deficient (dMMR) solid tumors, including:

- Endometrial cancer that has progressed on or following prior treatment with a platinum containing regimen, and
- dMMR solid tumors that have progressed on or following prior treatment with no satisfactory alternative treatment options.

Mismatch-repair deficient/microsatellite-instability-high (dMMR/MSI-H) biomarker is highly predictive of PD-1 clinical benefit regardless disease/cell of origin. Our data for dostarlimab in solid tumors with disease progression following at least 2 lines of previous therapy for recurrent or advanced disease have demonstrated deep, durable responses in dMMR/MSI-H solid tumors (N=327) including a subgroup of 105 patients with advanced metastatic dMMR/MSI-H colorectal cancer (Table 1). The overall response rate (ORR) in the subgroup of patients with dMMR/MSI-H colorectal cancer was 43% and a median duration of response (DoR) has not been reached (range: 2.8–41.5+ months) with response ongoing in 88.0% (95% confidence interval [CI]: 74–95%) of responders at 12 months. Additionally, in patients with dMMR solid tumors, the median overall survival (OS) was not reached after a median follow-up of 27.7 months suggesting deep and durable response result in improved long-term survival. This is further reinforced by the dMMR subgroup from the recently announced positive phase 3 study (RUBY) in first-line endometrial cancer showing improved progression-free survival (PFS) over standard of care.

Table 1: GARNET Trial: Dostarlimab Demonstrated Deep, Durable Response in 2L+ dMMR/MSI-H Solid Tumors

	N	ORR	Median DoR, Months (Range)	DoR Rate[1] at 12 Months (95% CI)	DoR Rate[1] at 24 Months (95% CI)
All evaluated advanced, metastatic dMMR/MSI-H tumors	327	44%	NR (1.2, 47.2+)	92% (86%, 96%)	85% (77%, 90%)
Advanced metastatic dMMR/MSI-H colorectal cancer	105	43%	NR (2.8, 41.5+)	88% (74%, 95%)	NA

1. Probability of remaining in response.
DOR=duration of response; NA=not available; NR=not reached; ORR=overall response rate.

Given the strong and durable responses in refractory metastatic dMMR/MSI-H colorectal cancer, an ongoing, Investigator-initiated Phase 2 study (N=30 planned) designed and conducted by researchers at Memorial Sloan Kettering Cancer Center (MSKCC; Study 19-288; NCT04165772) evaluated dostarlimab in treatment naïve, early stage locally advanced rectal cancer, and demonstrated strongly encouraging efficacy of dostarlimab as a neoadjuvant monotherapy in patients with treatment-naïve dMMR/MSI-H locally advanced rectal cancer (LARC). The goal of this study is to determine whether dostarlimab can replace the standard of care of trimodality treatment (chemotherapy ± radiation ± surgery). As of 05 June 2012, 14 patients have completed dostarlimab treatment and 100% of patients (14/14) had a clinical complete response (cCR). cCR in rectal cancer is defined as the absence of clinical evidence of residual tumor following neoadjuvant therapy. All 14 patients maintained cCR as of their most recent follow-up. In addition, four out of 14 patients have completed 12 months of post-treatment follow-up, and all remain in cCR. This observed response rate compares favorably with published results. The study is open and continues to accrue patients.

GlaxoSmithKline (GSK) is initiating a Phase 2 study (Study 53393) that is similar in design to the MSKCC study but multi-center and global in nature, with the intent to generate pivotal data to support accelerated approval of dostarlimab monotherapy in patients with treatment-naïve dMMR/MSI-H locally advanced rectal cancer. The primary endpoint of Study 53393 will be cCR at 12 months, similar to the MSKCC Study 19-288. The key secondary endpoints are event-free survival rate at 3 years (EFS3) and rate of sustained clinical complete response at 36 months after dostarlimab therapy (cCR36). Other secondary endpoints include rates of disease-specific and overall survival at 5 years (DSS5 and OS5, respectively), as well as safety and tolerability, among others. The goal of this study is to further determine whether dostarlimab can replace the standard of care of trimodality treatment (chemoradiotherapy [CRT] plus surgery).

dMMR/MSI-H locally advanced rectal cancer is a serious disease as almost one-third of patients will die of distant metastases despite current standard of care treatment with chemotherapy ± radiation ± surgery. The trimodal standard of care is associated with significant and lifestyle altering treatment-related morbidity and long-term sequalae including bowel, urinary, and sexual dysfunction, secondary malignancy, and infertility (additional details are provided in Section 2.6.2). While non-operative management in patients who achieve cCR following neoadjuvant therapy can avoid the morbidity of surgery, only a minority of patients achieve cCR with current therapy and those patients still require chemotherapy and radiation to do so. The pivotal Study 53393 in treatment-naïve dMMR/MSI-H locally advanced rectal cancer is designed to demonstrate that treatment with dostarlimab would result in high rates of durable cCR which would provide patients the option of non-operative management and spare them the long-term sequalae associated with chemotherapy ± radiation and surgery.

GSK is not seeking approval at this time based on the MSKCC data. As per the Federal Register Notice[1], this document is intended to outline and gain the Oncologic Drug Advisory Committee's input to our proposed study, Study 53393 including trial design, study population, clinical endpoint, and patient follow-up, and the proposed approach to evaluate the benefits and risks of dostarlimab for the planned indication. The proposed GSK data package will allow for the evaluation of the benefits and risks of dostarlimab in patients with treatment-naïve dMMR/MSI-H locally advanced rectal cancer.

Furthermore, GSK will seek Accelerated Approval, per the Food and Drug Administration (FDA) guidance titled "Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics" (May 2014), for the neoadjuvant use of dostarlimab monotherapy in patients with treatment-naïve dMMR/MSI-H locally advanced rectal cancer based on data for approximately 130 patients participating in the MSKCC (19-288, n=30) and GSK (53393, n=100) studies. This data will be used to support that dostarlimab neoadjuvant treatment in patients with dMMR/MSI-H locally advanced rectal cancer has the potential to provide a meaningful advantage over the standard of care, based on a significantly higher achieved rate of cCR that allow for non-operative management with reduced long-term adverse outcomes. dMMR/MSI-H biomarker selected patient populations have well understood pathophysiological and causal pathways that directly correlate with the relationship between the dostarlimab mechanism of action and the disruption of the disease. Additionally, cCR12 is reasonability likely to predict clinical benefit based on the published literature in the chemotherapy and immuno-oncology settings, as demonstrated by dostarlimab and other anti-PD-1 antibodies, based on radiological evidence of tumor shrinkage and the duration of response in dMMR-MSI-H solid tumors. For conversion, we plan to have a confirmatory package with longer follow-up of patients in the MSKCC (19-288) and GSK (53393) studies. To augment our knowledge, we will be initiating in 2023, a Phase 3 global, randomized controlled study in dMMR/MSI-H selected early-stage colon cancer patients.

1.2 Background

1.2.1 dMMR/MSI-H Cancers

dMMR/MSI-H cancers are caused by genetic mutations or epigenetic inactivation of MMR genes, resulting in Lynch syndrome or sporadic dMMR cancers (Gelsomino et al 2016). Solid tumor cells with defects in DNA MMR proteins develop MSI-H tumors following DNA replication and have accumulation of mutation loads in multiple genes, leading to the generation of neoantigens that stimulate the antitumor immune response. Solid tumors with dMMR/MSI-H have increased expression of PD-1 and PD-L1.

[1] The Food and Drug Administration would like to obtain the committee's input on the following, (1) the adequacy of the proposed trial(s) to evaluate the benefits and risks of dostarlimab for the proposed indication, including trial design, study population, clinical endpoint, and patient follow-up; and (2) the adequacy of the proposed data package to permit a fair evaluation in assessment of the benefits and risks of dostarlimab for the proposed indication.

Cancers with high tumor mutation burden generally have more immune cell infiltration in the tumor microenvironment and are known to be more sensitive to immune therapy than tumors with low mutation burden. Therefore, dMMR/MSI-H tumors are considered highly susceptible to checkpoint inhibitors. Status for dMMR is a well-established and predictive biomarker in colon and rectal cancer and National Comprehensive Cancer Network (NCCN) guidelines recommend testing for all patients with rectal cancer. Immune checkpoint inhibitor therapy is already approved in patients with dMMR/MSI-H metastatic colorectal cancer (CRC) in the first- and second-line settings.

In the United States, approximately 20,220 individuals are diagnosed annually with rectal cancer (SEER Explorer, 2019). Approximately 5–10% of all rectal cancers are dMMR/MSI-H. dMMR/MSI-H status varies across rectal tumor stages with the highest incidence in locally advanced rectal cancer (15–20%) (Andre et al 2015; Hutchins et al 2011; Lorenzi et al 2020; Ribic et al 2003; Venderbosch et al 2014; Zaanan et al 2018). Lynch syndrome, a hereditary cause of dMMR, confers increased lifetime risk of a spectrum of cancers, primarily colorectal and endometrial cancers. Lynch syndrome accounts for approximately 1–3% of all colorectal cancers (Moreira et al 2012). The incidence of Lynch syndrome in patients with dMMR/MSI-H locally advanced rectal cancer is not well characterized. Although only 15–20% of dMMR/MSI-H tumors are reported to be attributed to Lynch syndrome (Leclerc et al 2021), small studies in rectal cancer patient populations suggests that Lynch syndrome incidence may be higher (Cercek et al 2020; Cercek et al 2022; Wang et al 2022).

1.2.2 Treatment Effectiveness of Current Standard of Care for dMMR/MSI-H Locally Advanced Rectal Cancer

The most accepted standard of care for locally advanced rectal cancer, inclusive of dMMR tumors, is the trimodality approach of neoadjuvant chemotherapy, radiation, and surgery (Ali et al 2021; Glynne-Jones et al 2018; NCCN 2022; Oronsky et al 2020). Standard of care provides local tumor control in most patients, but almost one-third ultimately die from distant metastasis (Minsky et al 2010). Following neoadjuvant chemoradiotherapy, approximately 10–40% of patients with rectal cancer achieve cCR (Glynne-Jones et al 2018).

According to the NCCN guidelines and clinical practice guidelines provided by the American Society of Colon and Rectal Surgeons, treatment of patients with Lynch syndrome and rectal cancer should be based on standard oncologic principles as in sporadic dMMR rectal cancer, as noted above (Herzig et al 2017; NCCN 2022)

Another accepted standard of care for locally advanced rectal cancer is Total Neoadjuvant Therapy (TNT) that consists of chemoradiation and neoadjuvant chemotherapy followed by total mesorectal excision (TME) (Cercek et al 2018; Fokas et al 2022; NCCN 2022). In a meta-analysis, total neoadjuvant therapy or TNT showed superior rates of pathological complete response (pCR) compared with neoadjuvant chemoradiotherapy, and significantly higher odds of improved disease-free survival (DFS) (Kasi et al 2020) (Table 2). Furthermore, TNT compared with neoadjuvant

chemoradiotherapy has shown improved combined rates of clinical and pathologic response as well as 3-year DFS (DFS3; Table 2) (Cercek et al 2018; Conroy et al 2021; Kasi et al 2020). However, even with a CR rate of 36% for TNT, most patients would not be candidates for non-operative management. Consequently, majority of patients undergo total mesorectal excision that is associated with significant morbidities.

With the higher complete response rate associated with TNT, there is an increasing interest in organ preservation in patients with cCR. Management of patients without surgery, NOM, has been investigated in a number of prospective studies and has been demonstrated to result in comparable long-term outcomes in patients who achieve cCR regardless of whether they undergo surgery. In a meta-analysis, patients managed with NOM had no detriment in disease-free and overall survival (Section 2.2.1.3). While patients who undergo NOM have a higher rate of local recurrence then those who have surgery, the large majority of these patients can be salvaged surgically and still have favorable oncological outcomes (van der Valk et al 2018). Finally, the OPRA trial (discussed in more detail in Section 1.3 below) demonstrated that NOM following TNT results in favorable clinical outcomes, particularly in patients who achieve cCR.

The National Cancer Institute-sponsored JANUS trial (NCT05610163) also opened in late 2022 and is exploring intensification of neoadjuvant chemotherapy as a part of TNT. Both arms of this large (N=312), multi-center cooperative group trial will use non-operative management (ClinicalTrials.gov, 2022). The primary endpoint will be cCR, further supporting that cCR is perceived as a feasible and acceptable surrogate endpoint for long-term outcomes in this disease setting in the US. Secondary endpoints will include DFS and OS at 5 years.

Table 2: Response and Disease-Free Survival Rates for Neoadjuvant Chemoradiotherapy vs Total Neoadjuvant Therapy in Patients with Locally Advanced Rectal Cancer

	Neoadjuvant Chemoradiotherapy (CRT)	Total Neoadjuvant Therapy (TNT)
Combined CR rate (pCR+cCR12)[a]	21%	36%
pCR rate, (range)[b]	14.9% (4.2%, 21.3%)	29.9% (17.2%, 38.5%)
DFS odds ratio, (95% CI)[b]	2.07 (1.20, 3.56)	
DFS3 rate[c]	69%	76%

a. Cercek et al 2018
b. Kasi et al 2020
c. Conroy et al 2021
cCR12=clinical complete response for 12 months; DFS3=disease-free survival at 3 years; pCR=pathological complete response.

1.2.3 Unmet Need for the Treatment of dMMR/MSI-H Locally Advanced Rectal Cancer

Current standard of care provides local tumor control in most patients, but almost one-third ultimately die from distant metastasis (Minsky et al 2010). However, the impact of dMMR on long-term outcomes has not been established. Responses to neoadjuvant chemotherapy are lower in patients with dMMR than pMMR colon cancers (7% vs 23%) and a higher rate of progressive disease occurs during neoadjuvant chemotherapy for rectal cancer (29% in dMMR/MSI-H patients vs 0% for pMMR/MSS patients) (Cercek et al 2020; Seligmann and Group 2020), highlighting the unmet need for dMMR/MSI-H tumors.

While the standard of care treatment is efficacious for most patients it is also highly morbid. Patients undergoing surgical resection will require temporary colostomy with 20–30% of patients requiring permanent colostomy. Colostomy is associated with a variety of complications including sexual, social, and physiological dysfunction, depression, and stoma complications (Hassan and Cima 2007). Surgical complications occur in approximately 20% of patients and can include wound dehiscence, anastomotic leak, and pelvic sepsis (Paun et al 2010; van der Valk et al 2018; Zhang et al 2022). In addition, TME has been associated with 41% of patients experiencing complications of major low anterior resection syndrome including incontinence, urgency, diarrhea, frequency and clustering of bowel movements (Croese et al 2018). Furthermore, current standard of care treatment, including radiation, results in significant adverse effects including not only bowel but also urinary and sexual dysfunction, increased risk for secondary malignancies, and infertility (Contin et al 2014; Kneist et al 2005; Kwaan et al 2017; Lange et al 2008; Sterk et al 2005). These significant adverse effects have long-term sequalae all of which negatively impact quality-of-life.

Therefore, there is a high-unmet need for an organ sparing therapy that can avoid chemoradiation and surgery. Achieving cCR with no evidence of residual disease may not only lead to the option of non-operative management but is also reasonably likely to predict other favorable outcomes when cCR is sustained for 12 months.

1.3 Scientific Rationale for cCR12 as Reasonably Predictive of Clinically Meaningful Benefit

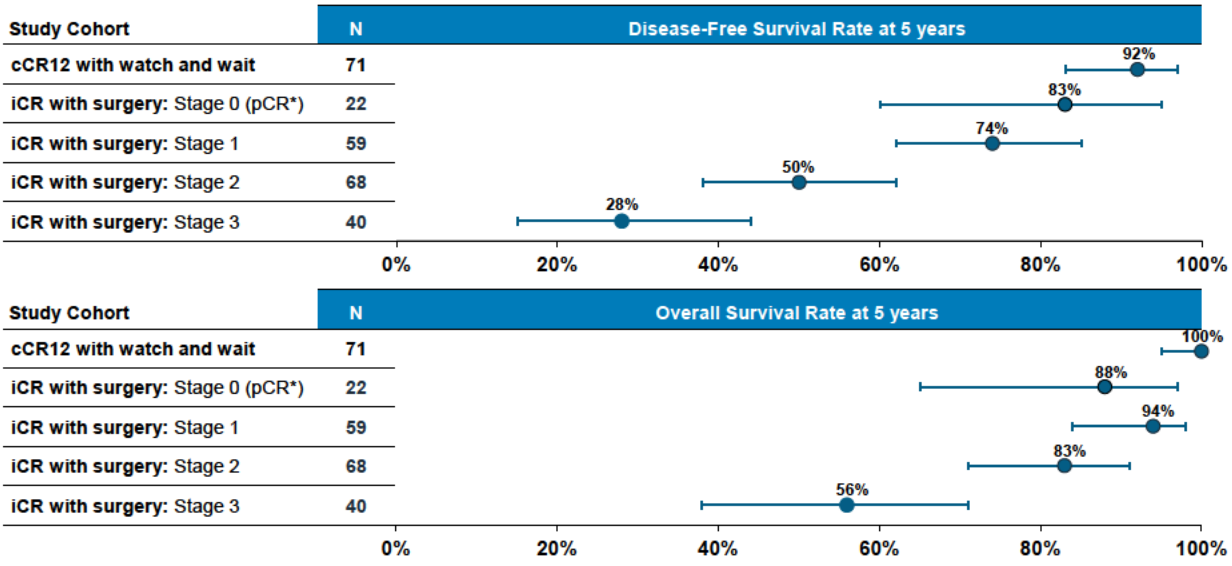
The available published data support that cCR12 is a surrogate endpoint that is reasonably likely to predict clinically meaningful benefit in the chemotherapy setting and that a higher rate of cCR is achieved with neoadjuvant immuno-oncology therapy than conventional neoadjuvant chemoradiotherapy.

cCR is defined as the absence of residual disease based on endoscopic examination, diagnostic imaging, and potentially physical examination. cCR12 is defined as cCR being maintained for 12 months after completion of treatment. Selection of cCR12 as the primary endpoint of the GSK study (53393) was based on published literature that

established this endpoint as predictive of favorable long-term outcomes in locally advanced rectal cancer.

From publications by Habr-Gama, achieving cCR after 8 weeks of completion of neoadjuvant therapy and maintaining a durable cCR for 12 months with non-operative management (N=71, Watch and Wait) resulted in improved clinical outcomes (5-year OS; 100% and 5-year DFS: 92%) compared to patients who only achieved an incomplete CR (Habr-Gama et al 2005; Habr-Gama et al 2004)(Figure 1). Patients who achieved an incomplete CR experienced relatively lower rates for both 5-year DFS and OS. Within the category of incomplete CR, the patients with lesser response to treatment (as indicated by higher stages of disease following surgery) generally experienced lower disease-free survival rates at 5 years. Overall, cCR12 was predictive of favorable long-term outcomes including DFS and OS at 5 years. Further detail is provided in Section 2.2.2.

Figure 1: Sustained cCR (cCR12) is Predictive of Long-Term Clinical Outcomes Including 5-Year Disease-Free Survival and Overall Survival



Habr-Gama et al., 2004 and 2005.
iCR=incomplete response; pCR=pathological complete response; cCR12=clinical complete response for 12 months.

Furthermore, the OPRA (Organ Preservation in Patients with Rectal Adenocarcinoma Following Total Neoadjuvant Therapy) trial has reinforced that cCR, defined as the absence of detectable tumor by clinical means after neoadjuvant therapy, is a predictor for long-term favorable outcomes. This trial evaluated the response for patients with locally advanced rectal cancer who underwent TNT, categorizing patients into 3-tiers of clinical response: cCR (n=124), near-complete CR (n=113), and incomplete CR (n=57). This study established that achievement of cCR as a clinical endpoint was a predictor of favorable outcomes for DFS and OS at 3-years with rates of 84% and 97% (Table 3). In contrast, patients achieving only near-complete CR or incomplete CR appeared to have relatively lower rates of DFS and OS at Year 3. Additionally, achieving DFS at 3 years

for patients with cCR was accompanied with higher rates of organ preservation in comparison to the other response groups. These results combined with Habr-Gama data, support that cCR to neoadjuvant therapy should predict long-term benefits in patients with locally advanced rectal cancer.

Table 3: OPRA Trial: Clinical Response is a Predictor of Disease-Free and Overall Survival

	Total Neoadjuvant Therapy (TNT) (N=294)		
	cCR[a] (n=124)	nCR[a] (n=113)	iCR (n=57)
Proportion of patients achieving CR, %	42%	38%	19%
3-year, % (95% CI)			
DFS	84 (77–92)	76 (67–86)	52 (37–72)
Organ preservation	79 (72–87)	52 (42–63)	9 (4–21)
TME-free DFS	72 (64–81)	44 (35–55)	4 (1–14)
OS	97 (93–100)	93 (87–99)	90 (79–100)

a. Patients with cCR and nCR were offered NOM.
Note: nCR is defined as near complete resolution of tumor with some ambiguous radiological or endoscopic findings.
Note: iCR is defined as any response less than an nCR or cCR.
cCR=clinical complete response; DFS=disease-free survival; iCR=incomplete response; nCR=near-complete response; NOM=non-operative management; OS=overall survival; TME=total mesorectal excision.

Finally, results from an analysis of the International Watch and Wait Database, which focused on 880 patients who attained cCR after neoadjuvant treatment and underwent non-operative management, further demonstrated the predictive value of cCR for long-term clinical outcomes (van der Valk et al 2018). The subgroup of 634 patients who achieved and sustained cCR defined as maintaining cCR at the most recent disease assessment, had a significantly higher 5-year disease-specific survival (DSS) rate of 97.3% compared to the subgroup of patients with local recurrence who failed to maintain cCR (84.0%). Further details are provided in Section 2.2.2.

GSK is planning to conduct a global Phase 2 study (Study 53393) in support of accelerated approval of dostarlimab monotherapy in patients with treatment-naïve dMMR/MSI-H locally advanced rectal cancer. The primary endpoint of Study 53393 will be cCR at 12 months because it is reasonably likely to predict long-term outcomes based on established literature. In addition, patients in the GSK study will be followed with disease assessments for 5 years and for multiple long-term outcomes, including key secondary endpoints of event-free survival rate at 3 years (EFS3) and the rate of maintenance of cCR for 36 months (cCR36). Other secondary endpoints are 5-year rates of disease-specific and overall survival (DSS5 and OS5).

1.4 Immunotherapy for the Treatment of dMMR/MSI-H Solid Tumors

Immune checkpoint inhibitor monotherapy has been demonstrated to be a highly effective treatment in dMMR/MSI-H tumors (Andre et al 2020; Diaz et al 2022; Lenz et al 2022). dMMR/MSI-H tumors have increased tumor mutation burden, increased expression of immune checkpoint inhibitors PD-1 and PD-L1, and increased tumor infiltration of CD8+ T-cells compared with microsatellite stable tumors (Dudley et al 2016; Llosa et al 2015), which renders dMMR/MSI-H tumors susceptible to checkpoint blockade.

As previously discussed, dostarlimab is approved for previously treated patients with dMMR recurrent or advanced solid tumors (Jemperli USPI, 2022). Dostarlimab demonstrated deep, durable responses in patients with advanced, metastatic dMMR/MSI-H tumors. In addition, dostarlimab has shown promising preliminary efficacy data as monotherapy in the PD-1 naïve non-small cell lung cancer (NSCLC; GARNET; additional details are provided in Appendix 6.1; PERLA Press Release – 07 December 2022, provided in Appendix 6.2) (Moreno et al 2022).

Pembrolizumab is approved for treatment of previously untreated patients with dMMR/MSI-H metastatic colorectal cancer and previously treated recurrent or metastatic dMMR/MSI-H solid tumors (Keytruda USPI, 2022). Nivolumab ± ipilimumab is indicated in dMMR/MSI-H recurrent metastatic CRC that has progressed following treatment with fluoropyrimidine, oxaliplatin, and irinotecan (Lenz et al 2022).

Recently, a Phase 3 study in first-line endometrial cancer (RUBY) of SoC chemotherapy (carboplatin-paclitaxel) plus dostarlimab compared to chemotherapy plus placebo in adult patients with primary advanced or recurrent endometrial cancer met its primary endpoint of Investigator-assessed progression-free survival (PFS). Efficacy results showed a statistically significant and clinically meaningful benefit in the prespecified dMMR/MSI-H patient subgroup and in the overall population. While the OS data were immature at the time of this analysis, a favorable trend was observed in the overall population and the dMMR/MSI-H subgroup (GSK Press Release – 2 December 2022, provided in Appendix 6.3).

In addition, Phase 1/2 studies in patients with operable Stage I-III colon cancer treated with neoadjuvant immunotherapy (nivolumab + ipilimumab) resulted in pathological complete response in 100% (32/32) of dMMR tumors and pCR was observed in 22/32 (68%) patients (Verschoor et al 2022). Similar findings were seen in another smaller study of the PD-1 inhibitor toripalimab in Chinese patients with dMMR/MSI-H locally advanced colorectal cancer (Hu et al 2022).

1.5 Overview of Dostarlimab

1.5.1 Mechanism of Action

Dostarlimab binds with high affinity and specificity to human PD-1, blocking the binding of PD-L1/2 to PD-1, resulting in the enhancement of T-cell reactivity in the presence of

T-cell receptor stimulation (Kumar et al 2021; Laken et al 2016). The functional antagonist activity of dostarlimab was confirmed in a mixed lymphocyte reaction (MLR) assay, demonstrating enhanced activation of T cells.

1.5.2 Planned Indication

The planned indication of dostarlimab following Study 53393 will be as monotherapy for patients with treatment-naïve dMMR/MSI-H locally advanced rectal cancer.

The recommended dose is anticipated to be 500 mg once every 3 weeks (Q3W) for 6 months, administered as a 30-minute intravenous (IV) infusion.

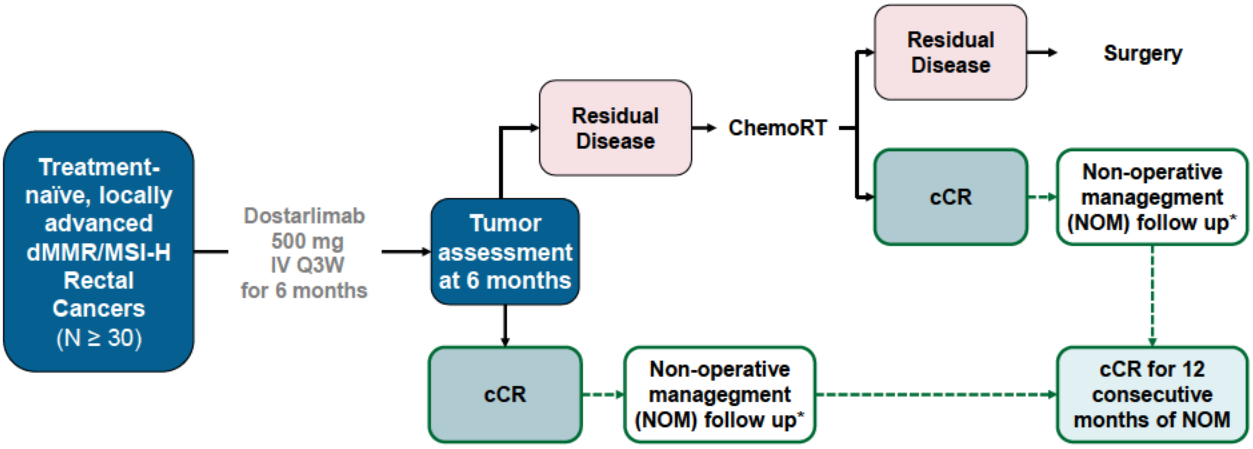
1.6 Clinical Development Program of Dostarlimab Supporting Treatment of dMMR/MSI-H Locally Advanced Rectal Cancer

1.6.1 Investigator-Initiated MSKCC Study 19-288 (NCT04165772): Study Design

The safety and effectiveness of dostarlimab 500 mg Q3W for 9 cycles (6 months) is being evaluated in an on-going, Investigator-initiated, open-label, single-institution, single-arm, prospective Phase 2 study conducted by the MSKCC in patients with treatment naïve dMMR/MSI-H locally advanced rectal cancer (Study 19-288; NCT04165772; Figure 2). Key enrollment criteria for MSKCC Study 19-288, include patients ≥ 18 years of age with histologically confirmed rectal cancer, clinical Stage II or III (T3–4, N0 or T any, N+) disease, a dMMR/MSI-H status confirmed by next generation sequencing, polymerase chain reaction, or immunohistochemistry (IHC). Patients are ineligible if they have presence of metastatic or recurrent disease. A full list of eligibility criteria is provided in Appendix 6.4.1.

cCR12 was selected as a co-primary efficacy endpoint as this endpoint has been demonstrated as highly predictive of long-term clinical outcomes including 5-year OS and DFS (additional details are provided in Sections 1.3 and 2.2). The other co-primary endpoint of the study is ORR to neoadjuvant dostarlimab therapy with or without chemoradiotherapy.

Figure 2: Ongoing MSKCC Study 19-288: Study Design

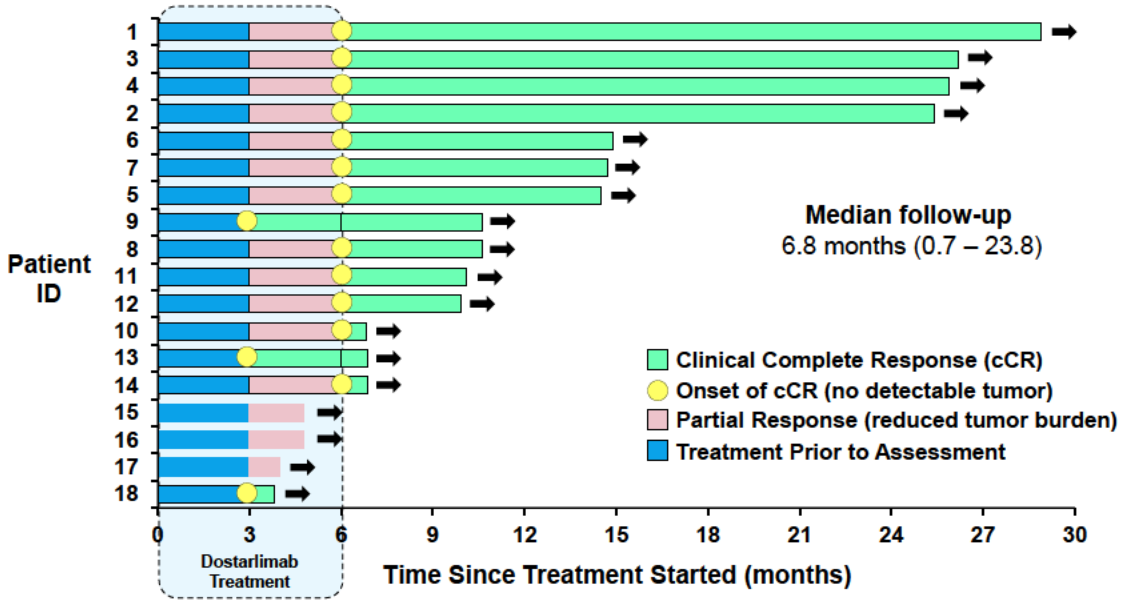


*Tumor assessments included digital rectal exam, CT CAP, rectal MRI, endoscopy, and biopsy [when applicable].
Note: cCR is defined as no evidence of residual disease by digital rectal exam, endoscopy, or rectal-specific MRI and no evidence of metastatic disease.
cCR=clinical complete response; chemoRT=chemoradiotherapy; CT CAP=staging computed tomography scans of the chest, abdomen, pelvis; IV=intravenously; dMMR=mismatch repair deficient; MRI=magnetic resonance imaging; MSI-H=microsatellite-instability-high; NOM=non-operative management; Q3W=once every 3 weeks.

1.6.2 Investigator-Initiated MSKCC Study 19-288 (NCT04165772): Results

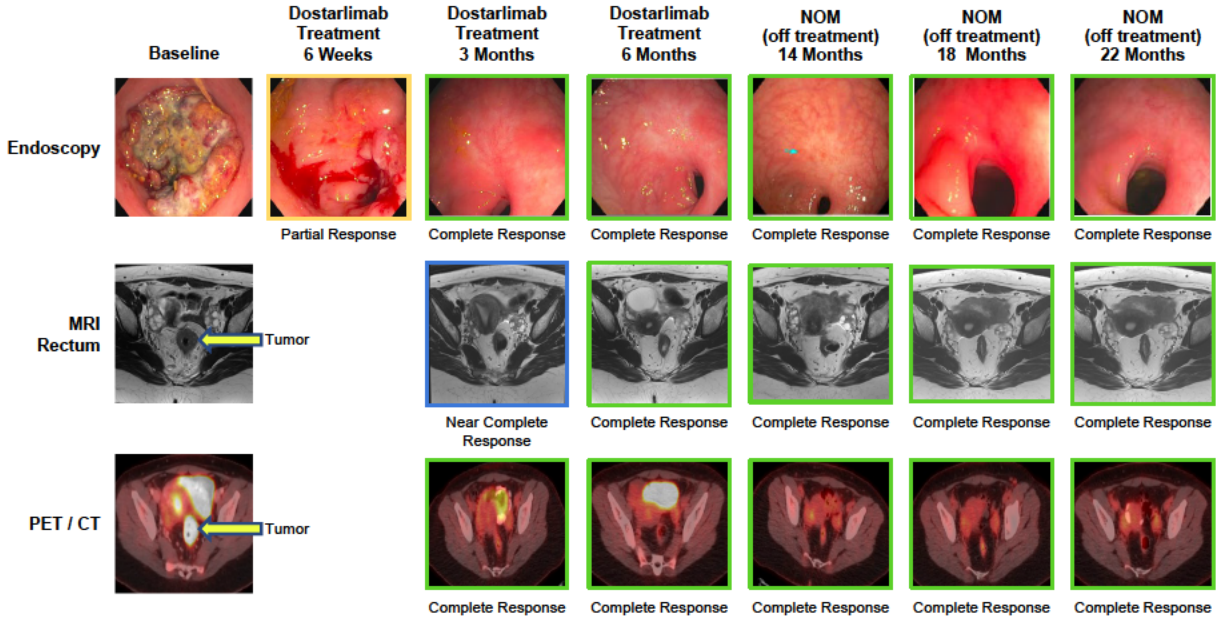
As of 05 June 2022, 14 patients have completed treatment and 100% of patients (14/14) have a cCR. In the protocol, cCR was defined as the absence of clinical evidence of residual tumor following neoadjuvant therapy as assessed by physical examination, endoscopic evaluation, rectal magnetic resonance imaging (MRI), and computed tomography (CT) of chest/abdomen/pelvis. Positron-emission tomography (PET) was performed. With a median follow-up of 6.8 months, all 14 patients maintained cCR (Figure 3). Baseline and serial imaging studies are provided for Patient 2 (Figure 4). Serial endoscopic examinations, MRI studies, and PET/CT scans of this patient, demonstrated CR at 3 months by endoscopic exam and a near complete response on MRI with dostarlimab treatment. In addition, 4 out of the 14 patients, including Patient 2 featured below, have completed 12 months of post-treatment follow up and all remain in cCR, thus achieving cCR12. No disease progression or recurrence has occurred thus far. Importantly, patients were spared from significant adverse effects and complications associated with current standard of care treatment. Additionally, there have been no adverse events (AEs) of Grade ≥ 3. No new safety signals were observed, and the safety profile aligned with other checkpoint inhibitors. The MSKCC study is currently ongoing.

Figure 3: Ongoing MSKCC Study 19-288: Duration of Response (All Enrolled Patients)



Note: cCR12 (6 months of dostarlimab treatment+12 months of maintained cCR=18 months since initiation of treatment).
MSKCC=Memorial Sloan Kettering Cancer Center.

Figure 4: Ongoing MSKCC Study 19-288: Baseline and Serial Endoscopic Examinations, MRI Studies, and PET/CT Scans (Patient 2)



CT=computed tomography; MRI=magnetic resonance imaging; MSKCC=Memorial Sloan Kettering Cancer Center; NOM=non-operative management; PET=positron-emission tomography.

GSK believes that this encouraging preliminary data from Study 19-288 merit additional study in a larger multicenter clinical trial to generate pivotal data that may potentially support registration.

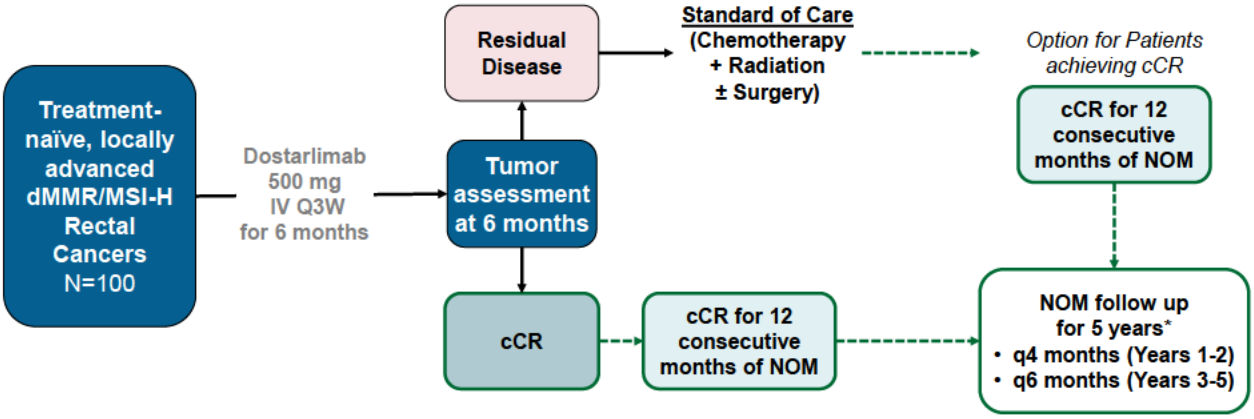
1.6.3 Planned Study 53393

This is an open-label, global, multi-site, single-arm, Phase 2 study (Study 53393) designed to further investigate the efficacy and safety of dostarlimab as monotherapy for treatment-naïve patients with dMMR/MSI-H locally advanced rectal cancer in the same patient population as MSKCC Study 19-288 (Figure 5). Patient eligibility criteria are similar between both studies. Key eligibility criteria include histologically confirmed rectal cancer, clinical Stage II or III (T3–4, N0 or T any, N+), and dMMR/MSI-H confirmed status. The Ventana MMR RxDx Panel is an FDA approved test that will be used for determination of dMMR status, as assessed by loss of proteins involved in mismatch repair (P200019, P210001). Full eligibility criteria for Study 53393 are provided in Appendix 6.4.2.

Patients achieving cCR after 6 months of initiation of dostarlimab therapy will begin non-operative management and will be followed for up to 5 years. For patients who undergo non-operative management, disease assessments will be performed more frequently than standard clinical surveillance, with evaluations every 4 months for 2 years and then every 6 months in Years 3–5.

There are key factors in the single-arm, open-label design for Study 53393. A study exclusively enrolling patients with dMMR/MSI-H locally advanced rectal cancer, a rare tumor with a limited number of confirmed patients. The results of the MSKCC Study 19-288 were listed in New England Journal of Medicine as a top 10 notable article of 2022 with wide dissemination and awareness. These unprecedented results and the potential for off-label use resulting from commercial availability of dostarlimab may result in challenges in recruitment and retention in the control arm of a randomized study. Even if a control arm with neoadjuvant chemoradiation had been implemented, an imbalance of the toxicity profiles would have likely led to a high drop-out rate in the control arm thereby necessitating an open-label design. A single arm study was validated as the optimal design in consultation with over 30 global experts in rectal cancer who provided feedback on the design of Study 53393.

Figure 5: Study 53393: Study Design



*Disease assessments (digital rectal exam, CT CAP, rectal MRI, endoscopy, biopsy [when applicable]) by Blinded Independent Central Review.
cCR=clinical complete response; CT CAP=staging computed tomography scans of the chest, abdomen, and pelvis; dMMR=mismatch repair deficient; IV=intravenously; LARC=locally advanced rectal cancer; MRI=magnetic resonance imaging; MSI-H=microsatellite-instability-high; NOM=non-operative management; Q3W=every 3 weeks; QnM=event n months.

The primary endpoint of the study is cCR12, defined as achieving and maintaining cCR for a period of 12 months after completion of dostarlimab therapy and initiation of non-operative management, as assessed by Blinded Independent Central Review (BICR). BICR will occur at each assessment of cCR following the end of treatment.

Key secondary efficacy endpoints are cCR36 (rate of cCR for 36 months after completion of dostarlimab treatment) as assessed by BICR and event-free survival at Year 3 (EFS3) by Investigator assessment.

Additional secondary efficacy endpoints include:

- EFS by Investigator assessment,
- cCR12 by Investigator assessment,
- ORR (partial response [PR] + near complete response [nCR] + cCR) by BICR and Investigator assessment,
- Proportion of patients undergoing total mesorectal excision at any time up to 3 years,
- Disease-specific survival at Year 5 (DSS5), and
- OS at Year 5 (OS5).

The safety and tolerability of dostarlimab in treatment-naïve patients with dMMR/MSI-H locally advanced rectal cancer will also be assessed by the frequency and severity of AEs, serious AEs (SAEs), immune-related AEs (irAEs), and AEs leading to death or discontinuation of study drug.

1.6.4 Conclusions

Locally advanced rectal cancer is a serious disease with a highly morbid current standard of care. The sub-population of patients with dMMR/MSI-H tumors have a high unmet need for less toxic and potentially more efficacious treatment. GSK is initiating a global, multi-center single-arm study (Study 53393) to confirm the encouraging efficacy results generated by a team of researchers at Memorial Sloan Kettering Cancer Center using GSK's immunotherapy, dostarlimab, as neoadjuvant treatment for patients with dMMR/MSI-H locally advanced rectal cancer. This Phase 2, multi-center, global study is designed to generate pivotal data to confirm dostarlimab's efficacy and safety while sparing patients from the long-term sequalae that can result from chemotherapy, radiation, and surgery in the current management of dMMR/MSI-H locally advanced rectal cancer. This study will be single-arm due to the impracticality of conducting a randomized controlled study given likely recruitment and retention issues resulting from the publishing and wide dissemination of the MSKCC study's unprecedented results and the potential for off-label use resulting from commercial availability of the product, in addition to the rare patient population. As discussed in Section 1.3, the primary endpoint of cCR12 is reasonably likely to predict survival benefit in this patient population. The study will also assess a variety of other short- and long-term efficacy outcomes to further characterize the benefit-risk profile of this therapy.

Study 53393 in combination with the MSKCC Study, will provide data on benefit-risk in ≥ 130 patients with dMMR/MSI-H locally advanced rectal cancer. The similarity in patient population as well as study design using common endpoints collected in the completed MSKCC study will enable pooled data analyses that enhance the robustness and generalizability of the reported efficacy and safety results.

2 BACKGROUND ON DMMR/MSI-H LOCALLY ADVANCED RECTAL CANCER

Summary

- dMMR/MSI-H locally advanced rectal cancer is a rare, serious disease with a high unmet need for less toxic and potentially more efficacious treatment.
- Concurrent chemoradiotherapy and chemotherapy in the neoadjuvant setting (i.e., TNT) followed by TME is an accepted SoC for locally advanced rectal cancer. Trimodality treatment provides local tumor control in most patients, but approximately 30% of patients experience distant metastasis.
- Current SoC treatment is associated with significant adverse effects for patients, including bowel, urinary, and sexual dysfunction, secondary malignancy, and infertility.
- Published literature establishes cCR12 as reasonably likely to predict favorable long-term outcomes including 5-year DFS.
- The cCR rate in patients treated with SoC is 10–40%. Patients who achieve cCR and are managed with NOM have comparable clinical outcome as patients who achieve cCR and were managed surgically.
- The durability of responses observed with immunotherapy indicates that achievement of cCR12 following immunotherapy is reasonably likely to predict long-term clinical benefit.
- A treatment that effectively treats dMMR/MSI-H locally advanced rectal cancer and preserves patient function and quality-of-life would have a profound impact on the patients diagnosed with this serious disease.

2.1 Overview of dMMR/MSI-H Locally Advanced Rectal Cancer

In the US, approximately 20,220 individuals are diagnosed annually with rectal cancer (SEER Explorer, 2019). Approximately 5–10% of all rectal cancers are dMMR/MSI-H (Alex et al 2017; Cercek et al 2020). dMMR/MSI-H status varies across rectal tumor stages with the highest incidence in Stage II tumors and decreases with increasing stage (15%–20%, 10%, and 5% in Stage II, III, and IV, respectively) (Andre et al 2015; Hutchins et al 2011; Lorenzi et al 2020; Ribic et al 2003; Venderbosch et al 2014; Zaanan et al 2018). The prevalence of Lynch syndrome in patients with dMMR rectal cancer remains to be fully elucidated. However, clinical studies with small sample sizes have identified greater than half of all dMMR rectal cancers are attributed to Lynch syndrome (Alex et al 2017; Cercek et al 2020; Cercek et al 2022; Wang et al 2022).

2.1.1 Locally Advanced Rectal Cancer Staging

Rectal cancer is commonly staged using the tumor, node, metastasis (TNM) system, where T, N, and M scores are combined and correspond to Stage 0 through Stage IV (NCCN 2022). Stage 0 is the earliest stage with no growth beyond the inner layer of the rectum. The term locally advanced rectal cancer refers to T3 and T4 tumors and/or those involving locoregional lymph nodes and encompasses all Stage II/III cancers. Stage IV indicates the cancer has spread to areas far from the rectum (Ali et al 2021; Glynne-Jones et al 2017; Glynne-Jones et al 2018; NCCN 2022; Oronsky et al 2020).

2.1.1.1 dMMR/MSI-H Diagnosis

NCCN guidelines recommend dMMR/MSI-H testing for all patients with a personal history of rectal cancer (NCCN 2022). Rectal cancers are then categorized into 2 distinct groups: dMMR/MSI-H tumors that have a higher overall mutation burden and pMMR tumors that have a lower mutation burden (Cancer Genome Atlas Network, 2012).

Lynch syndrome is a hereditary cause of dMMR characterized by a germline mutation in one of the DNA MMR genes (MLH1, MSH2, MSH6 and PMS2) or by an EPCAM gene deletion resulting in MSH2 silencing (Ligtenberg et al 2013). Lynch syndrome confers increased lifetime risk of a spectrum of cancers, primarily colorectal and endometrial cancers. Lynch syndrome accounts for approximately 1–3% of all colorectal cancers (Moreira et al 2012). The incidence of Lynch syndrome in patients with dMMR/MSI-H locally advanced rectal cancers is not well characterized. Although only 15–20% of dMMR/MSI tumors are reported to be attributed to Lynch syndrome (Leclerc et al 2021), small studies in rectal cancer patient populations suggests that Lynch syndrome incidence may be higher (Cercek et al 2020; Cercek et al 2022; Wang et al 2022).

dMMR/MSI-H tumors have increased expression of immune checkpoint inhibitors PD-1 and PD-L1, and increased tumor infiltration of CD8+ T-cells compared with microsatellite stable tumors (Dudley et al 2016; Llosa et al 2015), which renders dMMR/MSI-H tumors susceptible to checkpoint blockade.

2.2 Evidence for the Clinical Relevance of cCR and cCR12

Published literature on assessment of clinical response and outcomes following non-operative management in patients with locally advanced rectal cancer dates back nearly 20 years, starting with the seminal findings Dr. Habr-Gama and her colleagues published in 2004. Patients achieving cCR following neoadjuvant therapy have been shown to have excellent long-term outcomes, especially when that clinical response is sustained. Non-operative management has also been demonstrated to be safe, with meta-analyses demonstrating no significant differences in OS or DFS rates between patients managed with NOM and those managed operatively.

One of the main challenges to implementation of a NOM protocol at a multi-institutional level is the development of uniform and reproducible criteria for tumor response. To that

end, the OPRA consortium organized a multidisciplinary videoconference on 26 January 2014 aimed at developing a consensus on the clinical criteria of tumor response. The participants—colorectal surgeons, medical oncologists, radiation oncologists, pathologists and radiologists—elaborated a three-tiered assessment of response/regression schema to differentiate between patients with a cCR who are therefore candidates for NOM, from those without a cCR who are candidates for TME. This regression schema was further discussed at the American Society of Colon and Rectal Surgeons Scientific Meeting in Hollywood, Florida in May 2014, and finalized at the 2014 American College of Surgeons Clinical Congress in October 2014 (Smith et al 2015).

2.2.1 Evidence for cCR

2.2.1.1 Improved Clinical Outcomes in Patients with cCR and Near-Complete Response (nCR) or Incomplete Response (iCR)

As discussed in Section 1.3, in the OPRA trial (N=294), a 3-tier schema was utilized to stratify clinical response. Patients with cCR and nCR (defined as the presence of near complete resolution of tumor with some ambiguous radiological or endoscopic findings) were considered for non-operative management while patients with iCR (defined as any response less than a near complete or clinical complete response) were recommended for total mesorectal excision. In this study, the degree of clinical response was a predictor of 3-year DFS (Table 3) (Thompson et al 2021). Patients with cCR had higher rates of organ preservation and improved DFS after 3 years compared with those with iCR. The median duration of follow-up was 2.36 years. This study demonstrates that the 3-tier clinical response assessment has prognostic implications for 3-year DFS in patients with locally advanced rectal cancer who underwent total neoadjuvant therapy. These results also suggest that organ preservation is achievable in patients with a stringently defined cCR following total neoadjuvant therapy, without an apparent detriment in 3-year OS.

2.2.1.2 Comparable Clinical Outcomes Between Patients with cCR + Non-Operative Management and Patients with cCR + Radical Surgery

There have been studies demonstrating that once cCR is achieved, whether patients are managed by non-operative management or radical surgery, long-term clinical outcomes are not significantly different. Three studies compared patients with cCR who had Watch and Wait vs patients with cCR who had radical surgery. In each study, both groups had predominantly T3 tumors (Ayloor Seshadri et al 2013; Lai et al 2016; Li et al 2015). Two studies reported the 5-year OS. In these two groups, there were no significant differences in the risk of local recurrence, overall distant metastasis, and OS (pooled hazard ratio [HR]: 3.91, 95% CI: 0.57–26.72) (Dossa et al 2017).

2.2.1.3 *Comparable Survival Outcomes Between Patients with cCR Followed by Non-Operative Management and Patients Who Received Surgery*

Two meta-analyses (Kong et al 2017; Sammour et al 2017) compared the clinical outcomes of patients with cCR after neoadjuvant therapy who underwent NOM vs patients who had surgery after neoadjuvant therapy. The meta-analysis by Sammour included eight studies that reported data for an adequately controlled proctectomy group. For surgical group comparison, among the eight studies, four used a post-surgical pCR group, two used cCR tumors undergoing surgery and one used both. The meta-analysis by Kong included patients who underwent surgery regardless of response. About one fifth of patients managed with non-operative management had local regrowth; but salvage surgery was possible and undertaken in 83.8–93.2% patients. In both meta-analyses, there were no significant differences in OS and DFS rates between patients managed with NOM and patients managed operatively (Table 4).

Table 4: Sammour[a]: Survival and Disease-Free Rates in Patients Treated with Neoadjuvant Therapy and Either Managed Non-Operatively or with Surgery

	Neoadjuvant Chemoradiation ± Surgery (N=920)
NOM after cCR, n	575
OS, %	91.7%
DFS, %	82.7%
Pooled regrowth rate, %	21.3%
Surgery, n	345
OS, %	92.4%
DFS, %	87.5%
Local recurrence rate, %	8.4%

a. (Sammour et al 2017)
cCR=clinical complete response; DFS=disease-free survival; NOM=non-operative management; OS=overall survival.

2.2.2 Evidence for cCR12

As discussed in Section 1.3, sustained cCR, defined as maintaining cCR for a period of time after the end of neoadjuvant treatment, was determined to be highly predictive of high rates of long-term clinical outcomes including 5-Year DFS and OS (Table 5).

Patients who achieved cCR12, defined as achieving complete response after 8 weeks of completion of neoadjuvant therapy and maintained that response for 12 months, were considered clinical Stage 0 (Stage C0) (Habr-Gama et al 2005; Habr-Gama et al 2004). The correlation between final stage and survival were evaluated in 260 patients. During the follow-up period, among the 260 patients, 71 patients with cCR12 were managed by observation alone (Stage C0). The remaining patients with iCR were divided into 4 groups based on pathologic response defined after surgery: 22 patients with pathologic

complete response (pT0), 59 patients with pathologic stage I, 68 pathological stage II, and 40 pathological stage III. Across the four groups, there was no statistically significant difference in pre-treatment characteristics in terms of age, gender, pre-treatment tumor size, distance from anal verge, and disease stage. Recurrence and cancer related mortality rates showed no statistical difference between clinical stage 0 and pathological stage 0 (7% in Stage C0 vs 13.6% in Stage P0, p=0.2). Patients with clinical Stage 0 showed numerically higher 5-year OS and 5-year DFS rates (Table 5). Therefore, cCR12 responses from neoadjuvant therapy are predictive of long-term outcomes.

Table 5: Habr-Gama[a]: Long-term Clinical Outcomes in Patients with cCR12 vs iCR

	cCR12 with Watch and Wait (N=71)	iCR with Surgery			
		Pathologic Stage 0 (pCR) (N=22)	Pathologic Stage 1 (N=59)	Pathologic Stage 2 (N=68)	Pathologic Stage 3 (N=40)
5-year DFS (%)	92	83	74	50	28
5-year OS (%)	100	88	94	83	56

a. Habr-Gama, 2004 and Habr-Gama, 2005.
cCR12=clinical complete response at 12 months; DFS=disease-free survival; iCR=incomplete response; pCR=pathological complete response; OS=overall survival.

Results from an analysis of the International Watch and Wait Database, which focused on 880 patients with a cCR after neoadjuvant treatment who were managed by Watch and Wait further demonstrated the effectiveness of cCR plus non-operative management (van der Valk et al 2018). The median follow-up time was 3.4 (interquartile range [IQR]: 1.8–5.5) years. As shown in Table 6, the subgroup of patients who achieved and sustained cCR (n=634), defined as maintaining cCR at the most recent disease assessment, had a significantly higher 5-year DSS rate (97.3% vs 84%) and 5-year OS rate compared to the subgroup of patients (n=213) with local recurrence who failed to maintain cCR (87.9% vs 75.4%). The majority of the local recurrences were diagnosed within the first 12 months after the decision for a non-operative management approach (136/213, 63.8%). This indicates that a sustained cCR is associated with more favorable long-term outcomes and is consistent with the findings from Habr-Gama studies.

Table 6: International Watch and Wait Database: Long-Term Clinical Outcomes in Rectal Cancer Patients Who Achieved cCR after Neoadjuvant Chemoradiation and Underwent Non-Operative Management

	Patients Attaining cCR		
	All (N=880)	Local Recurrence (N=213)	Sustained cCR (N=634)
Median follow-up time, year (IQR)	3.4 (1.5–5.5)	NA	NA
5-year DSS, % (95% CI)	93.8 (90.8–95.8)	84.0 (75.0–89.9)	97.3 (94.5–98.7)
5-year OS, % (95% CI)	84.6 (80.8–87.6)	75.4 (66.2–82.4)	87.9 (83.8–91.0)
Metastatic disease, n (%)	71 (8.1)	38 (17.8)	33 (4.9)

IQR=Interquartile range; cCR=clinical complete response; DSS=disease-specific survival; NA=not available; OS=overall survival.

2.3 Improved Durable Response with Immunotherapy Compared to Chemotherapy in dMMR Metastatic Tumors

The durability of overall response that is observed with immunotherapy indicates that achievement of cCR12 in studies with immunotherapy would be reasonably likely to predict long-term clinical benefit.

While chemotherapy takes effect only when the drugs remain in the body, immunotherapy can potentially provide long-term protection against tumor cells after discontinuation for more than 5 half-lives due to the immune memory (Caserta and Pera 2021; Mondino and Manzo 2020). Anti-PD-1 antibody monotherapy has been approved by the FDA for the treatment of various tumor types under metastatic settings based on results from adequate, well-controlled, phase 3 clinical trials comparing the effectiveness of anti-PD-1 monotherapy to that of chemotherapy. Among these five phase 3 studies, KEYNOTE-177 compared pembrolizumab monotherapy with chemotherapy in patients with metastatic dMMR/MSI-H colorectal cancer in the first-line setting. The remaining four phase 3 clinical studies compared anti-PD-1 monotherapy with chemotherapy in all comers, regardless of MMR status.

As summarized in Table 7, monotherapy with anti-PD-1 antibodies showed variable response rates, but importantly the DoR was consistently prolonged compared to the DoR of chemotherapy (Burtness et al 2019; Diaz et al 2022; Herbst et al 2016; Kato et al 2019; Reck et al 2019).

Table 7: Response and Duration of Response for Immunotherapy vs Chemotherapy in Various Tumor Types and Lines of Treatment

Immunotherapy	Line of Treatment and Disease Setting	Anti-PD-1 Monotherapy		Chemotherapy	
		ORR (95% CI)	Median DoR of ORR, Months, (Range)	ORR (95% CI)	Median DoR of ORR, Months, (Range)
Pembrolizumab[1]	Untreated unresectable or metastatic dMMR/MSI-H CRC	44% (35.8, 52.0)	NR (2.3+, 41.4+)	33% (25.8, 41.1)	10.6 (2.8-37.5)
Pembrolizumab[2]	Previously untreated metastatic NSCLC	45% (37, 53)	NR (1.9+, 14.5+)	28% (21, 36)	6.3 (2.1+, 12.6+)
Pembrolizumab[3]	Previously untreated recurrent or metastatic HNSCC (CPS ≥ 1)	19% (14.5, 24.4)	20.9 (1.5+, 34.8+)	35% (29.1, 41.1)	4.5 (1.2+, 28.6+)
Pembrolizumab[3]	Previously untreated recurrent or metastatic HNSCC (CPS ≥ 20)	23% (16.4, 31.4)	20.9 (2.7, 34.8+)	36% (27.6, 45.3)	4.2 (1.2+, 22.3+)
Pembrolizumab[4]	Previously treated metastatic NSCLC following platinum-containing chemotherapy	30% (23, 39)	NR (0.7+, 16.8+)	8% (4, 13)	8.1 (2.1+, 8.8+)
Nivolumab[5]	Previously treated unresectable recurrent or metastatic ESCC following platinum- and fluoropyrimidine-containing chemotherapy	33% (13.7, 26.0)	6.9 (5.4, 11.1)	34% (15.4, 28.8)	3.9 (2.8, 4.2)

1. KEYNOTE-17.
2. KEYNOTE-024.
3. KEYNOTE-048.
4. KEYNOTE-010. (Herbst et al 2016)
5. ATTRACTION-3.

Note: '+' indicates ongoing duration of response.

CPS=combined positive score; CRC=colorectal cancer; dMMR=mismatch repair deficient; DoR=duration of response; ESCC=esophageal squamous cell carcinoma; HNSCC=head and neck squamous cell carcinoma; MSI-H=microsatellite-instability-high; NR=not reached; NSCLC=non-small cell lung cancer; ORR=objective response rate.

2.4 Checkpoint Inhibitors in dMMR/MSI-H Solid Tumors

dMMR/MSI-H tumors have increased tumor mutation burden, increased expression of immune checkpoint inhibitors PD-1 and PD-L1, and increased tumor infiltration of CD8+ T-cells compared with microsatellite stable tumors (Dudley et al 2016; Llosa et al 2015), which renders dMMR/MSI-H tumors susceptible to checkpoint blockade. Evidence from clinical studies suggest that the efficacy of immune checkpoint inhibitor therapy in dMMR/MSI-H cancers is independent of the existence of Lynch syndrome (Overman et al 2018; Overman et al 2017; Sclafani 2017). To date, a number of immune checkpoint inhibitors, including dostarlimab have been approved for the treatment of patients with dMMR/MSI-H solid tumors, including patients with Lynch syndrome.

2.4.1 Dostarlimab

Dostarlimab is approved for treatment of previously treated adult patients with dMMR recurrent or advanced solid tumors. In a total of 327 patients, ORR was 42.3% and median DoR was not reached (range: 1.2+ to 47.2+) with a DoR rate at 24 months of 85% (95% CI: 77–90%). A subset of patients with colorectal cancer (n=105) had a confirmed ORR of 43% and median DoR was not reached (range: 2.8 to 41.5+) with a DoR rate at 12 months of 88% (95% CI: 74–95%).

Dostarlimab has shown promising results in an adequate, well-controlled phase 3 study (RUBY) comparing standard of care chemotherapy (carboplatin-paclitaxel) plus dostarlimab to chemotherapy plus placebo in adult patients with primary advanced or recurrent endometrial cancer that is either dMMR or pMMR. This study is powered for the dMMR subgroup as well as the overall population. At the time of this ODAC meeting, topline data showed the study met its primary endpoint of Investigator-assessed PFS. Efficacy results showed a statistically significant and clinically meaningful benefit in the prespecified dMMR/MSI-H patient subgroup and in the overall population. While the OS data were immature at the time of this analysis, a favorable trend was observed in the overall population and the dMMR/MSI-H subgroup.

Dostarlimab monotherapy has also shown promising preliminary efficacy data in patients with recurrent advanced NSCLC (Appendix 6.1).

2.4.2 Other Immune Checkpoint Inhibitors

Immune checkpoint inhibitor monotherapy has been approved for the treatment of dMMR/MSI-H metastatic colorectal cancer based on data from clinical trials demonstrating a high rate of durable clinical response (Keytruda USPI, 2022)(Andre et al 2015; Diaz et al 2022; Lenz et al 2022). Pembrolizumab is approved for treatment of previously untreated patients with dMMR/MSI-H metastatic colorectal cancer and previously treated recurrent or metastatic dMMR/MSI-H solid tumors. Pembrolizumab

demonstrated improvements in ORR and PFS and a trend toward improved OS vs fluoropyrimidine-based chemotherapy in dMMR/MSI-H metastatic colorectal cancer (Diaz et al 2022) and demonstrated an ORR of 36% in previously treated metastatic dMMR/MSI-H colorectal cancer (Keytruda USPI, 2022). Nivolumab ± ipilimumab is indicated in dMMR/MSI-H recurrent metastatic colorectal cancer that has progressed following treatment with fluoropyrimidine, oxaliplatin, and irinotecan (nivolumab, ORR: 32%; nivolumab + ipilimumab, ORR: 69%, disease control rate [DCR] 84%) (Opdivo USPI, 2022; (Lenz et al 2022). Median PFS and OS were not reached after 24.2 months of follow-up and the 24-month rates of PFS and OS were 74% and 79%, respectively (Lenz et al 2022).

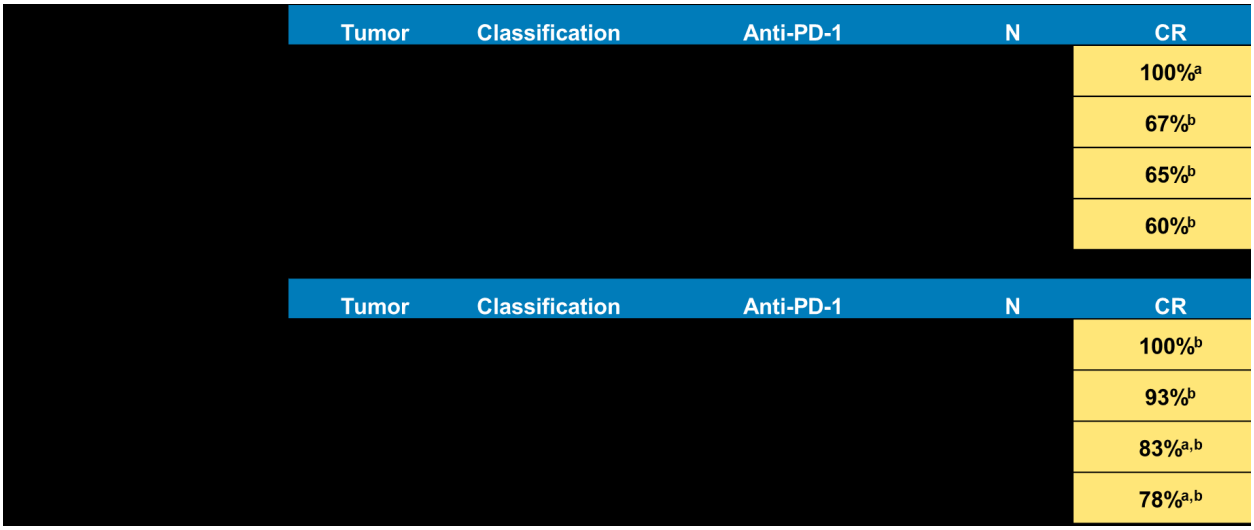
2.5 Neoadjuvant Immunotherapy in dMMR/MSI-H Locally Advanced Colon and Rectal Cancers

Patients with treatment naïve, early to middle stage dMMR/MSI-H colon and rectal tumors have relatively intact immune systems compared with patients who have had multi-line treatments. Patients with treatment naïve, early to middle stage dMMR/MSI-H colon and rectal tumors also have less tumor burden compared to patients with metastatic disease (Gonzalez et al 2018). In addition, many new tumor antigens before operation can increase the activity of anti-tumor immune T cells. Therefore, earlier application of immunotherapy in dMMR/MSI-H colon and rectal tumors could theoretically achieve a better anti-tumor response.

In line with this hypothesis, findings from a number of published prospective and retrospective clinical studies revealed substantial anti-tumor response with neoadjuvant immunotherapy in patients with early stage dMMR/MSI-H colon and rectal cancers. Figure 6 summarizes the response rate from 8 studies evaluating neoadjuvant immunotherapy in dMMR/MSI-H colon or rectal cancers. Reported percentages of Lynch syndrome in dMMR rectal cancer and dMMR colorectal cancer was 57–63.2% and 33%, respectively. As shown in Figure 6, the complete response rate, including cCR and pCR for the Cercek 2022 study, was 100%, with the remaining studies ranging from 60–67%. Where major pathological response rate was reported, the response rate range was 86–100%.

Among these studies, the retrospective Wang 2022 study was conducted in 29 patients with dMMR/MSI-H rectal cancer who received neoadjuvant anti-PD-1 immunotherapy, 19 patients with Stage I–III (Stage I, n=1; 4 Stage II, n=4; Stage III, n=14) treated with PD-1 inhibitor therapy (16 patients) or with PD-1 inhibitor therapy after failure of neoadjuvant chemotherapy/CRT (3 patients), either alone (11 patients) or in combination with other therapies, all 19 patients achieved cCR and were managed non-operatively. The anti-PD-1 agents used included pembrolizumab (7/19), sintilimab (7/19), toripalimab (2/19), camrelizumab (2/19) and nivolumab (1/19). The median treatment duration of anti-PD-1 antibody was 6.4 months (range: 1.2–26.6 months). Two-year rates of local recurrence-free survival, distant metastasis-free survival, DFS, and OS were all 100% (Wang et al 2022).

Figure 6: Response Rates of Neoadjuvant Immunotherapy in dMMR/MSI-H Colorectal Tumors



a. Clinical complete response assessment.
b. Pathological complete response assessment.
Note: Clinical complete response assessment based on accepted evaluation method for corresponding tumor type.
CR=complete response: CRC=colorectal cancer; PD-1=programmed cell death protein-1.

These dMMR/MSI-high tumors show consistent susceptibility to anti-PD-1 therapy – providing further confidence in the ability of dostarlimab to attain a high CR response.

2.6 Patient Unmet Medical Need

2.6.1 Risk for Distant Metastasis

The intense trimodality treatment of standard of care provides local tumor control in most patients, but almost one-third of patients ultimately die from distant metastasis (Minsky et al 2010). In patients with locally advanced rectal cancer, treated with the total neoadjuvant therapy approach, distant metastasis rates are slightly lower (TNT:17–20% vs neoadjuvant CRT: 20–40%) (Zwart et al 2022).

2.6.2 Treatment-Related Morbidity

Unfortunately, current standard of care therapy for locally advanced rectal cancer results in significant morbidity for patients, including bowel, urinary, and sexual dysfunction, secondary malignancy, and infertility (Contin et al 2014; Kneist et al 2005; Kwaan et al 2017; Lange et al 2008; Sterk et al 2005).

- Bowel dysfunction: All patients undergoing total mesorectal excision require temporary colostomy, with 20–30% of patients requiring abdominoperineal resection that ultimately results in permanent colostomy (Hassan and Cima 2007).
- Urinary dysfunction: Pelvic radiation and total mesorectal excision have been reported to be associated with urinary dysfunction in 35%–51% of patients (Chill

et al 2021; Contin et al 2014). Patients experience decreased urinary flow rates, leaking, urinary retention, and incontinence (Contin et al 2014; Kneist et al 2005; Kwaan et al 2017; Lange et al 2008; Sterk et al 2005).

- Sexual dysfunction: Both men and women are less likely to be sexually active (50% and 32%, respectively, vs 91% and 61% before treatment; p<0.004) and 29% of women and 45% of men reported that treatment "made their sexual lives worse" (Hendren et al 2005).
- Secondary malignancy: The cumulative incidence of secondary gynecologic malignant neoplasms is reported to increase by 3-fold in women who received neoadjuvant radiotherapy for rectal cancer compared with patients who did not (4.53% vs 1.53%) (Guan et al 2021).

Moreover, this approach results in surgical complications including dehiscence, anastomotic leak, and pelvis sepsis in approximately 20% of patients (Paun et al 2010; van der Valk et al 2018; Zhang et al 2022).

2.6.3 Impact on Patient Quality-of-Life and Function

Significant morbidity associated with standard of care for locally advanced rectal cancer results in substantially impaired quality-of-life and function (Contin et al 2014; Kneist et al 2005; Kwaan et al 2017; Lange et al 2008; Sterk et al 2005). Symptoms of urinary dysfunction include decreased urinary flow rates, leaking, urinary retention, and incontinence, all of which negatively affect quality of life (Chill et al 2021; Contin et al 2014). Colostomy is associated with a variety of complications including sexual, social, and physiological dysfunction; depression; and stoma complications such as parastomal hernia, ischemia/necrosis, stoma blockage, etc. (Hassan and Cima 2007).

In summary, dMMR/MSI-H locally advanced rectal cancer is a rare, serious disease for which there is non-satisfactory treatment. Current standard of care is associated with serious adverse effects and complications which negatively impact patient quality-of-life and function, highlighting the significant unmet need in this patient population. New treatment options with different mechanisms of action specifically effective for patients with dMMR/MSI-H locally advanced rectal cancer is needed to improve cCR12 and the opportunity for non-operative management to help reduce the risk of long-term adverse effects.

3 ONGOING MSKCC STUDY 19-288 DESIGN AND INTERIM RESULTS

Summary

- MSKCC Study 19-288 is an ongoing, open-label, single center, single-arm, prospective Phase 2 study to assess the efficacy and safety of dostarlimab as neoadjuvant treatment in treatment-naïve patients with dMMR/MSI-H locally advanced rectal cancer.
- The study was listed in New England Journal of Medicine as a top 10 notable article of 2022 with wide dissemination and awareness. These unprecedented results and the potential for off-label use resulting from commercial availability of dostarlimab may result in challenges in recruitment and retention in the control arm of a randomized study.
- Dostarlimab 500 mg is administered Q3W IV for up to 9 cycles (6 months).
- Patients with treatment naïve dMMR/MSI-H locally advanced rectal cancer completing dostarlimab treatment (14/14) achieved cCR.
    - Patients evaluable (4/4; 100%) for a 12-month evaluation achieved a sustained cCR12.
- The preliminary efficacy data of the MSKCC Study 19-288 merit additional patient follow-up to confirm results and demonstrate prolonged response and patient benefit.

3.1 Study Design

MSKCC Study 19-288 (NCT04165772) is an ongoing, open-label, single center, single-arm, 2-cohort prospective Phase 2 study to assess the efficacy and safety of dostarlimab as neoadjuvant treatment in patients with locally advanced dMMR/MSI-H solid tumors Cohort 1 includes patients with treatment naïve dMMR/MSI-H locally advanced rectal cancer.

Dostarlimab 500 mg is administered Q3W IV for up to 9 cycles (6 months). Disease assessments, including endoscopic and digital rectal examinations, T2-weighted and diffusion-weighted MRI of the rectum, ^{18}F-fluorodeoxyglucose (^{18}F-FDG)–positron-emission tomography (PET), and computed tomography scans of the chest, abdomen, and pelvis (CT CAP) are conducted at baseline (before treatment) and at 6 weeks, 3 months, and 6 months after start of treatment, at which point tumor response is determined (Smith et al 2012). Patients who achieve a cCR after completion of dostarlimab therapy receive no further treatment and proceed with non-operative management. Patients with any response less than cCR receive standard total neoadjuvant therapy (concurrent chemoradiotherapy with capecitabine at standard doses followed by FOLFOX to complete a total of 6-months of treatment). Patients who

achieve cCR after standard TNT proceed with non-operative management. Any patients not achieving cCR are assigned to undergo surgery.

For patients who transition to non-operative management, disease assessments are performed more frequently than standard clinical surveillance, with evaluations every 4 months for 2 years and then every 6 months in Years 3–5. Increased surveillance includes imaging, endoscopic assessments, and blood tests. During each endoscopy, tumor biopsies are performed if there is residual disease. Unscheduled disease assessments will be performed if clinical signs suggest disease progression.

3.1.1 Key Enrollment Criteria

Key enrollment criteria for MSKCC Study 19-288, Cohort 1 includes:

- ≥ 18 years of age,
- Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1,
- Histologically confirmed rectal cancer,
- Clinical Stage II or III (T3–4, N0 or T any, N+), and
- dMMR/MSI-H status confirmed by next generation sequencing, polymerase chain reaction, or immunohistochemistry.

Patients are ineligible if they have presence of metastatic or recurrent disease.

A full list of eligibility criteria is provided in Appendix 6.4.1.

3.1.2 Endpoint Selection

3.1.2.1 Co-Primary Endpoint – Overall Response Rate

A co-primary endpoint of the study is ORR to neoadjuvant dostarlimab therapy with or without chemoradiotherapy. Overall response is determined from T2-weighted and diffusion-weighted MRI of the rectum, PET/CT, endoscopic visualization, and digital rectal examination. Overall response is defined as progressive disease, stable disease, partial response, near-complete response, or complete response.

3.1.2.2 Co-Primary Endpoint – cCR12 or Pathological Complete Response

The other co-primary endpoint is sustained cCR 12 months after completion of dostarlimab therapy without undergoing surgical resection or pCR in patients who undergo surgery after completion of dostarlimab therapy with or without chemoradiotherapy. cCR is defined as the absence of residual disease on digital and endoscopic rectal examination, as well as the absence of residual disease on rectal MRI, with no restricted diffusion on T2-weighted imaging and pCR is defined as the absence of residual cancer cells on the histologic examination of surgical specimens.

3.1.2.2.1 Long-Term Monitoring in Patients Attaining cCR

Patients with cCR after 6 months of dostarlimab treatment continue with non-operative follow-up. Patients will be followed for up to 5 years. Assessments include imaging, endoscopy, surgical assessments, biopsies, and blood tests.

3.1.3 Dose Selection

The dosing regimen used in this study was dostarlimab 500 mg IV Q3W for 6 months. Based on dose-escalation and a fixed-dose study this regimen was determined to be safe and tolerable as well as adequately efficacious for the treatment of patients with treatment-naïve dMMR/MSI-H locally advanced rectal cancer (additional details are provided in Appendix 6.5).

3.1.4 Determination of Sample Size

The ongoing MSKCC Study 19-288 has a Simon's 2-stage minimax design based on cCR12. In the first stage, 15 patients were enrolled. If ≤ 4 responders were observed in the first 15 patients, the study would have been stopped for futility. If 13 or more of the first 15 patients have cCR12, the study will stop for efficacy. In addition, if 13 or more CRs are observed out of 30, the Investigators will declare the study a success. Therefore, the Investigators would enroll up to 30 patients. Additional details are provided in Appendix 6.6.

Once the first stage futility decision point passed, rather than waiting for the full 15 patients to be evaluable for cCR12, the Investigators decided to continue with the second stage of enrollment (up to a total of 30 patients) due to the overwhelming evidence of benefit.

3.2 Patient Baseline Demographics and Disease Characteristics

As of January 2022, a total of 16 patients were enrolled and treated. Ten (62%) were women. The median age is 54 years (26–78), consistent with the findings in reported clinical studies that dMMR rectal cancer is generally diagnosed at a younger age than pMMR rectal cancer (mean age at diagnosis: 63 years). Of the 16 patients, 15 have clinical stage III disease and 1 has clinical stage II disease. As expected, the pre-treatment tumor mutational burden was high (mean, 60.0; range: 36–100 mut/mb) in 14 patients for whom mutational analysis was performed, eight of the 14 patients (57.1%) had pathologic genomic alterations that were associated with Lynch syndrome (Cercek et al 2022).

Table 8: Ongoing MSKCC Study 19-288: Baseline Demographics and Disease Characteristics

Characteristic	Dostarlimab 500 mg Q3W (N=16)
Age (years), median (range)	54 (26–78)
Female, n (%)	10 (62)
Race, n (%)	
White Non-Hispanic	11 (69)
Asian	3 (19)
Black	2 (12)
Hispanic	1 (6)
Tumor stage, n (%)	
T1 or T2	4 (25)
T3	9 (56)
T4	3 (19)
Nodal status, n (%)	
Positive	15 (94)
Negative	1 (6)
Median distance of tumor from anal verge, cm (range)	5 (0.9–8.9)

MSKCC=Memorial Sloan Kettering Cancer Center; Q3W=once every 3 weeks.

3.3 Efficacy Results

3.3.1 Co-Primary Endpoint – Overall Response Rate

Ongoing MSKCC Study 19-288 met its co-primary efficacy endpoint, ORR (PR + nCR + CR) to neoadjuvant dostarlimab monotherapy with or without chemoradiotherapy. The percentage of patients with a cCR is 100% in 14 consecutive patients who completed 6 months of dostarlimab treatment (Table 9). No difference in response is observed between patients with or without Lynch syndrome.

Table 9: Ongoing MSKCC Study 19-288: Co-Primary Endpoint – Individual Responses for Patients Who Completed 6 Months of Dostarlimab[a]

Age	Stage T	Stage N	FU (months)	Digital Rectal Exam Response	Endoscopic Best Response	Rectal MRI Best Response	Overall Response
38	T4	N+	23.8	CR	CR	CR	cCR
30	T3	N+	20.5	CR	CR	CR	cCR
61	T1/2	N+	20.6	CR	CR	CR	cCR
28	T4	N+	20.5	CR	CR	CR	cCR
53	T1/2	N+	9.1	CR	CR	CR	cCR
77	T1/2	N+	11.0	CR	CR	CR	cCR
77	T1/2	N+	8.7	CR	CR	CR	cCR
55	T3	N+	5.0	CR	CR	CR	cCR
68	T3	N+	4.9	CR	CR	CR	cCR
78	T3	N-	1.7	CR	CR	CR	cCR
55	T3	N+	4.7	CR	CR	CR	cCR
27	T3	N+	4.4	CR	CR	CR	cCR
26	T3	N+	0.8	CR	CR	CR	cCR
43	T3	N+	0.7	CR	CR	CR	cCR

a. Disease assessments including endoscopic and digital rectal examinations, T2-weighted and diffusion-weighted MRI of the rectum, ^{18}F-fluorodeoxyglucose (^{18}F-FDG)–positron-emission tomography (PET), and computed tomography scans of the chest, abdomen, and pelvis (CT CAP) were conducted at baseline (before treatment) and at 6 weeks, 3 months, and 6 months after start of treatment, at which point tumor response was determined (Smith et al 2012).
cCR=clinical complete response; CR=complete response; FU=follow-up; MRI=magnetic resonance imaging; MSKCC=Memorial Sloan Kettering Cancer Center.

3.3.2 Co-Primary Efficacy Results – Preliminary cCR12

As of 05 June 2022, all patients eligible for 12-month evaluation (n=4), including Patient 2, have achieved a sustained cCR (Figure 3; Figure 4). pCR was not evaluable as no patients underwent surgical resection.

3.3.3 Duration of Response

No disease progression or recurrence has occurred with a median follow-up of 6.8 months (Figure 3). Three cCRs occurred before the end of dostarlimab treatment and 12 occurred after 6 months of dostarlimab treatment.

3.4 Safety Results

As of January 2022, adverse events of any grade occurred in 12 patients (75%; Table 10). No AEs of Grade ≥ 3 were reported; all AEs were Grade 1 or 2. The most common AEs in patients treated with dostarlimab included rash or dermatitis (31%), pruritus (25%), fatigue (25%), and nausea (19%). Hypothyroidism occurred in 1 patient (6%).

Table 10: Ongoing MSKCC Study 19-288: Summary of Adverse Events Occurring in ≥ 2 Patients Treated with Dostarlimab

Preferred Term	AEs* N=16 n (%)
Patients with any AE	12 (75)
Rash/dermatitis[a]	5 (31)
Pruritus	4 (25)
Fatigue	4 (25)
Nausea	3 (19)
Diarrhea	2 (13)
Fever	2 (13)
Dry eye	2 (13)

* All AEs were Grade 1 or 2.
a. Includes maculopapular, papulopustular, dermatographism, dermatitis, and skin hyperpigmentation.
AEs=adverse events; MSKCC=Memorial Sloan Kettering Cancer Center.

3.5 Interim Study Conclusions

In this Investigator-initiated study, dostarlimab demonstrated clinical efficacy in treatment-naïve patients with dMMR/MSI-H locally advanced rectal cancer. The co-primary efficacy endpoints were met, 100% of patients who received 6 months of dostarlimab treatment achieved cCR. In addition, there was no evidence of disease progression or recurrence in any patient during or after dostarlimab treatment with up to 12 months of follow-up. None of the patients required chemotherapy, radiation, or surgery demonstrating that dostarlimab provided meaningful clinical benefit in this patient population. In addition, there have been no AEs of ≥ Grade 3; all AEs were Grade 1 or 2. The substantial efficacy results of this small single-institution study require confirmation in a larger, global, multi-institutional study, to help demonstrate the clinical benefits of neoadjuvant dostarlimab for patients with dMMR/MSI-H locally advanced rectal cancer.

4 PLANNED STUDY 53393

Summary

- Study 53393 is an open-label, global, multi-site, single-arm, Phase 2 study, which will generate data to confirm the efficacy, safety, and tolerability of dostarlimab as monotherapy treatment for treatment-naïve patients with dMMR/MSI-H locally advanced rectal cancer.
  - Conducted at 46 sites worldwide with a planned enrollment of 100 patients.
  - Over 30 key opinion leaders from around the world who specialize in rectal cancer research and treatment have reviewed and commented on the protocol for Study 53393.
  - Study will begin enrollment by April 2023.
- The primary objective of Study 53393 is to estimate the efficacy of dostarlimab by measuring the rate of sustained cCR (12 months after dostarlimab treatment) based on Blinded Independent Central Review.
  - cCR12 is chosen as the primary efficacy endpoint in this study due to its association with long-term beneficial clinical outcomes.
  - The avoidance of chemoradiotherapy and potentially surgery, coupled with a prolonged positive long-term outcome would fulfill an unmet need and represent a clear clinically meaningful benefit for patients.
- This Phase 2 study together with the MSKCC results will provide data from approximately 130 patients with treatment-naïve dMMR/MSI-H locally advanced rectal cancer.
- Implementation of a similar study design and common endpoints to MSKCC Study 19-288 will allow for a robust evaluation of dostarlimab benefit-risk.

4.1 Expert Consultation for Clinical Design Elements

Study 53393 is designed to closely match the ongoing Study 19-288 currently underway at MSKCC along with augmentations that enhance objectivity and reproducibility to generate pivotal data sufficient to support accelerated approval. Over 30 key opinion leaders from around the world who specialize in rectal cancer research and treatment have reviewed and provided feedback on the design for Study 53393. The study sites have received the protocol and will begin enrollment by April 2023.

4.2 Study Design

Study 53393 is an open-label, global, multi-site, single-arm, Phase 2 study of dostarlimab monotherapy in patients with treatment-naive dMMR/MSI-H locally

advanced rectal cancer (Figure 5). The primary objective of Study 53393, similar to MSKCC Study 19-288, is to estimate the efficacy of dostarlimab by measuring the rate of sustained cCR (12 months after completion of dostarlimab treatment) in treatment naïve patients with dMMR/MSI-H locally advanced rectal cancer.

The study will comprise of a pre-screening period for patients who do not have previous determination of dMMR/MSI-H status, a screening period for all patients to assess eligibility, followed by the treatment period during which all patients will receive dostarlimab 500 mg IV Q3W for up to 9 cycles. During treatment, patients will undergo disease assessments at 6 weeks (endoscopy only) and 12 weeks (endoscopy and rectal MRI) to assess for response.

Following treatment, patients will undergo post-intervention disease assessment, including endoscopy, rectal MRI, and CT CAP. If the patient meets criteria for cCR, defined as the absence of clinical evidence of residual tumor following neoadjuvant therapy, they will begin non-operative management. Non-operative management will consist of watchful waiting with regular assessments for recurrent disease. For patients who undergo non-operative management, disease assessments will be performed more frequently than standard clinical surveillance, with evaluations every 4 months for 2 years and then every 6 months in Years 3–5. Increased surveillance will include imaging, endoscopic assessments, and blood tests. During each endoscopy, tumor biopsies will be performed if there is residual disease. Unscheduled disease assessments will be performed if clinical signs suggest disease progression.

4.2.1 Single-Arm Justification

An open-label, single-arm design for Study 53393 is supported by the following 2 main factors:

1. **The planned enrollment of patients with dMMR/MSI-H locally advanced rectal cancer who respond to dostarlimab treatment.** Patients and health-care professionals will be aware of the results of the MSKCC Phase 2 Study (Cercek et al 2022) and may therefore be hesitant to enroll patients into a study randomizing between immunotherapy and standard of care chemotherapy when the experimental arm has reported a 100% (14/14 patients) cCR rate, a more than 3-fold difference compared with the reported rate of cCR with standard of care treatment. Thus far in follow-up, none of the patients in the MSKCC Study have needed chemotherapy, radiation, or surgery; therefore, avoiding long, debilitating, and permanent lifestyle changes. In addition, there is potential for off-label use of this commercially available product that could impact recruitment and retention. These concerns are supported by feedback from a large, diverse (academia and community), and global group of treating physicians, who were generally aligned that a randomized study would likely not be feasible. Finally, by virtue of the very different natures of the treatments in the control and experimental arms, a randomized study would need to be open-label resulting in a high drop-out rate in patients randomized to the control arm.

2. **The planned enrollment of patients with a low prevalence tumor (dMMR/MSI-H locally advanced rectal cancer) with limited number of confirmed patients.** dMMR rectal cancer is a rare tumor with limited number of histologically confirmed patients.

4.2.2 Key Enrollment Criteria

A total of 100 participants in the study will be enrolled at 46 clinical sites worldwide with key centers in the US, Europe, and the rest of the world. Key enrollment criteria for Study 53393 include:

- ≥ 18 years of age,
- ECOG performance status ≤ 1,
- Histologically confirmed rectal cancer,
- Clinical Stage II or III (T3–4, N0 or T any, N+), and
- dMMR/MSI-H status confirmed by next generation sequencing, polymerase chain reaction, or IHC.

Pre-screening for patients who do not have a previous determination of dMMR/MSI-H status will be conducted using the Ventana MMR RxDx Panel from Roche Tissue Diagnostics, which is approved for selection of patients with solid tumors for treatment with dostarlimab (P210001). Patients will be ineligible if they have presence of metastatic or recurrent disease, a tumor that is obstructing or otherwise requires emergent surgery, are immunocompromised or those taking immunosuppressive therapies, active autoimmune disease requiring treatment within 2 years, experienced previous severe immune-related AEs, a history of pneumonitis or interstitial lung disease, or patients who are unable to undergo MRI or endoscopy.

A full list of eligibility criteria is provided in Appendix 6.4.2.

4.2.3 Endpoint Selection and Rationale

The primary efficacy endpoint is the rate of cCR for 12 months after completion of dostarlimab treatment. cCR in rectal cancer is defined as the absence of clinical evidence of residual tumor following neoadjuvant therapy and is assessed with a multi-modality assessment that involves endoscopic evaluation and axial imaging. Sustained cCR12 was chosen as the primary efficacy endpoint in this study and MSKCC Study 19-288 as it is predictive of DFS and OS. In addition, there is potential for a clinically meaningful survival benefit without the patient sustaining adverse effects associated with SoC treatment. The primary endpoint will be evaluated by BICR to maintain objectivity of the results.

Key secondary efficacy endpoints are cCR36 by BICR and EFS3 by Investigator assessment, defined as remaining alive and free of (1) disease progression precluding surgery, (2) local recurrence, and (3) distant recurrence at 3 years. These endpoints were chosen because 3-year DFS is a generally accepted surrogate endpoint for

survival in this disease setting. EFS is similar to DFS but is more applicable to a neoadjuvant study. Use of EFS is consistent with FDA Guidance on Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics.

Additional secondary efficacy endpoints include:

- EFS by Investigator,
- cCR12 by Investigator,
- ORR (PR + nCR + cCR) by BICR and Investigator,
- Proportion of patients undergoing TME at any time up to 3 years,
- DSS5, and
- OS5.

Exploratory endpoints include EFS at Year 5 (EFS5) by BICR and evaluation of disease- and treatment-related symptoms and impact on function and health-related quality-of-life include the following patient-related outcomes (PROs): Quality-of-Life of Cancer Patients (QLQ-C30), Quality-of-Life – Colorectal Specific (QLQ-CR29), Patient-Reported Outcomes version of the Common Terminology Criteria for AEs (PRO-CTCAE), Patient Global Impression of Severity (PGIS), Patient Global Impression of Change (PGIC), overall impact of treatment toxicity (FACT-GP5), and Work Productivity and Activity Impairment (WPAI).

The safety and tolerability of dostarlimab in treatment-naïve patients with dMMR/MSI-H locally advanced rectal cancer will also be assessed by the frequency and severity of AEs, SAEs, irAEs, and AEs leading to death or discontinuation of study drug. During the treatment period, patients will undergo safety assessments at each infusion. Post-treatment safety assessments will occur at end-of-treatment visit and at 30-day, 90-day, and 5-year follow-up.

4.2.3.1.1 Long-Term Monitoring in Patients Attaining cCR12

For patients who attain sustained cCR (cCR12) disease assessments including endoscopy, rectal MRI, and staging CT CAP will be performed more frequently than standard clinical practice, with evaluations every 4 months for 2 years and then every 6 months in Years 3–5.

4.2.4 Determination of Sample Size

A sample size of 100 patients is expected to provide a Clopper-Pearson exact binomial 2-sided 95% CI with a lower confidence limit that is within approximately 10% of the observed cCR12 rate at the time of the primary analyses.

4.3 Management of Potential Disease Progression

4.3.1 Treatment Plans and Patient Assessments

During the treatment period, patients will undergo disease assessments at 6 weeks and 12 weeks from the start of therapy (including CT CAP and endoscopy at both time points and rectal MRI at 12 weeks). If the patient at any point has evidence of disease progression, they will be transitioned to standard of care therapy, which will be selected at the Investigator's discretion. Details of the selected subsequent anticancer therapy, response, and survival outcomes of these patients will be collected.

Following completion of the treatment period, patients will undergo the post-intervention disease assessment, including endoscopy, rectal MRI, and CT CAP. If the patient has any response less than a cCR, they will proceed to standard of care therapy. The specific standard of care therapy used will be at the Investigator's discretion.

If a patient develops evidence of recurrent disease at any point during non-operative management, they will be evaluated for salvage therapy by their local care team. The choice of salvage therapy will be at the discretion of the treating medical team. Information on the salvage therapy selected and key clinical outcomes will be collected for the final analysis.

4.4 Summary of Clinical Design

Study 53393 is an open-label, global, multi-site, single-arm, Phase 2 study similarly designed to the MSKCC Study 19-288 but with additional data in a larger patient population to confirm the efficacy, safety, and tolerability of dostarlimab monotherapy for patients with treatment-naïve dMMR/MSI-H locally advanced rectal cancer. Study 53393 is designed to assess whether using single-agent dostarlimab can deliver persistent long-term complete responses, while also sparing patients from the debilitating adverse effects typically associated with standard treatment. This study design will allow for an efficient evaluation that could lead to more patients with this rare tumor gaining urgent access to dostarlimab.

This Phase 2 study together with the MSKCC results will provide data from approximately 130 patients with treatment-naïve dMMR/MSI-H locally advanced rectal cancer needed for the benefit-risk assessment of dostarlimab in this patient population. The pooled data will be used to support accelerated approval followed by a large, randomized study to fulfill regulatory requirements. A concurrent, separate, large, randomized Phase 3 study in a dMMR/MSI-H selected neoadjuvant setting will be part of a conversion package following accelerated approval.

Overall, this document provides rationale demonstrating that the neoadjuvant use of dostarlimab monotherapy in patients with treatment-naïve dMMR/MSI-H locally advanced rectal cancer, a serious condition, has the potential to provide a meaningful advantage over the standard of care based on a significantly higher achieved rate of cCR as compared to chemotherapy, allowing for non-operative management and a

reduction in the adverse outcomes observed with chemoradiotherapy and surgery. dMMR-MSI-H biomarker selected patient populations have a well understood pathophysiological and causals pathways that directly correlate with the relationship between the dostarlimab mechanism of action and the disruption of the disease. Furthermore, cCR12 is a surrogate endpoint that is reasonability likely to predict clinical benefit based on the published literature in the chemotherapy and immune-oncology settings, as demonstrated by dostarlimab and other anti-PD-1 antibodies, based on radiological evidence of tumor shrinkage (response rate) in dMMR-MSI-H solid tumors.

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6 APPENDICES

6.1 Dostarlimab Monotherapy Treatment in Patients with Metastatic Non-Small Cell Lung Cancer (PERLA; Study 213403)

Jemperli (dostarlimab)

IND 150997

Study 213403 (PERLA)

Metastatic Non-Squamous Non-Small Cell Lung Cancer

Executive Summary

FDA Division of Oncology 2

19 December 2022

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Term	Definition
AE	Adverse Event
ALK	Anaplastic lymphoma kinase
BICR	Blinded Independent Central Review
BLA	Biologics License Application
CI	Confidence Interval
CR	Complete Response
DCO	Data Cutoff Date
dMMR	Deficient Mismatch Repair
ECOG	Eastern Cooperative Oncology Group
EGFR	Estimated glomerular filtration rate
EU	European Union
FDA	Food and Drug Administration
HR	Hazard Ratio
IgG4	Immunoglobulin G4
IND	Investigational New Drug
irAE	Immune-Related Adverse Event
ITT	Intent-to-Treat
IV	Intravenous
mAB	Monoclonal Antibody
NR	Not Reached
NSCLC	Non-Small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PD-1	Programmed Cell Death Protein – 1
PD-L1	Programmed Death-ligand 1
PI	Prescribing Information
PFS	Progression-free Survival
PHS	Public Health Service
PR	Partial Response
Q3W	Once every 3 weeks dosing
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SEER	Surveillance, Epidemiology, and End Results
SmPC	Summary of Product Characteristics
TEAE	Treatment-Emergent Adverse Event
TPS	Tumor Proportion Score
TRAE	Treatment Related Adverse Event
TTD	Time to Deterioration
US	United States of America

1. EXECUTIVE SUMMARY

Patients with metastatic NSCLC have a poor prognosis and limited first line treatment options. There remains an unmet need for effective therapies in order to delay progression of the disease and prolong survival. Patients with advanced NSCLC (Stage IIIB/IV) have a dismal prognosis with an estimated 5 year OS rate of <5% [NCI SEER NSCLC 2018]. Other factors that impact overall prognosis of NSCLC include tumor histology and targetable genomic aberrations. While earlier stages, non-squamous histology and presence of a sensitizing EGFR, ALK, ROS 1, or BRAF V600E mutation are associated with better prognosis, advanced stages and absence of targetable genomic aberrations are known to be associated with a worse prognosis [Lam 2019; Sands , 2020].

Until recently, the management of recurrent/advanced NSCLC without targetable oncogene drivers included platinum-based doublet chemotherapy, maintenance chemotherapy, and anti-angiogenic agents in combination with chemotherapy [Santarpia, 2017;]. Clinical benefit of immune checkpoint inhibitors in combination with chemotherapy has been demonstrated in multiple tumor types and may work synergistically by leveraging the rapid onset of chemotherapy. In patients with NSCLC, a new class of immunotherapies have moved to the frontline setting after the approval of pembrolizumab as the first-line monotherapy approach for patients with NSCLC whose tumors demonstrate high expression of PD-L1 (TPS ≥50%) [Reck, 2016; Spiess, 2016;, Herzberg, 2017; KEYTRUDA prescribing information(PI) 2022 and KEYTRUDA Summary of Product Characteristics (SmPC) 2022]. Further studies have shown that the addition of pembrolizumab to standard platinum-based chemotherapy resulted in significantly longer OS and PFS than chemotherapy alone in patients with previously untreated metastatic non-squamous NSCLC (without EGFR or ALK mutations) and squamous NSCLC [Gandhi,. 2018], leading to approval of the combination as first-line treatment in both indications in the US and EU [Spiess,. 2016; Paz-Ares, 2018; KEYTRUDA PI and KEYTRUDA SmPC 2022].

Dostarlimab is a PD-1 inhibitor, that has shown promising preliminary efficacy data in monotherapy in the recurrent/advanced NSCLC cohort of the ongoing Phase 1/2 dose escalation and cohort expansion study (Study 4010-01-001 [GARNET; GSK Study 213346]). This study enrolled a total of 67 NSCLC patients and observed an ORR of 26.9% including 2 complete and 16 partial responses [Moreno, 2022], which is comparable to the reported efficacy of other PD-1 inhibitors in this setting. In the lung cohort of the GARNET study activity was observed across all PD-L1 TPS categories, and encouraging activity was observed despite the fact that vast majority (90%) of participants with available PD-L1 status had a TPS <50%. Indirect comparison of the preliminary efficacy and safety profile of dostarlimab monotherapy from the GARNET study and the data of pembrolizumab monotherapy in second-line NSCLC [Herbst, 2016] indicated that the two PD-1 inhibitors may produce similar anti-tumor activity with comparable safety profiles.

PERLA (Study 213403) is an ongoing, global, randomized, double-blind, phase 2 study designed to provide a direct comparison of the efficacy, safety, and tolerability of dostarlimab versus pembrolizumab, both in combination with pemetrexed and platinum

chemotherapy in subjects with metastatic non-squamous NSCLC and no mutations for which approved targeted therapies are available.

This report summarizes the topline data from PERLA as of the primary analysis with DCO of 4 August 2022. There were 243 participants randomized with the last randomization occurring in March 2022. The primary endpoint of the study was the confirmed ORR evaluated using RECIST v1.1 based on BICR. Secondary endpoints were PFS by investigator assessment per RECIST v1.1 and OS.

At the primary analysis, dostarlimab in combination with pemetrexed and platinum chemotherapy demonstrated similar clinical benefit in terms of ORR and PFS as pembrolizumab in combination with pemetrexed and platinum chemotherapy. Consistent similarity was also observed in the exploratory analysis by PD-L1 expression subgroups. Additionally, a numerical trend was observed in ORR and PFS favoring dostarlimab in the PD-L1 TPS positive subgroups. A summary of the ORR and PFS results for overall population are presented in Table 1.

Table 1 Efficacy Summary of confirmed ORR per BICR and PFS per Investigator Assessment in ITT population

		Dostarlimab + CT (N=121)	Pembrolizumab + CT (N=122)
ORR, % (80% CI)		46 (37.2 – 55.6)	37 (28.3 – 46.1)
mPFS	months (95% CI)	8.8 (6.7–10.4)	6.7 (4.9–7.1)
	HR (95% CI)	0.70 (0.50–0.98)	

BICR, blinded independent central review; CI, confidence interval; ITT, intention-to-treat; ORR, overall response rate; PD-L1, programmed cell death ligand-1; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TPS, tumor proportion score.

Overall, the safety profile was similar between the two groups and consistent with the established safety profiles for each individual agent.

In this first global randomized study to directly compare PD-1 inhibitors in the same indication, dostarlimab plus chemotherapy showed similar efficacy to pembrolizumab plus chemotherapy in metastatic non-squamous NSCLC in the first line setting. Therefore, GSK considers that the findings from the PERLA trial support the use of dostarlimab as a combination partner for future development of novel cancer therapies.

2. BACKGROUND INFORMATION ON THE PRODUCT

Product Name and Application Number

JEMPERLI (also referred to as dostarlimab, dostarlimab-gxly, TSR-042 and GSK4057190A). Application number: IND 150997

Chemical Name, Established Name and/or Structure

Dostarlimab is an anti-PD-1 IgG4 humanized monoclonal antibody derived from a stable Chinese hamster ovary cell line. The protein consists of 2 heavy chains and 2 light chains with a single N-linked glycosylation on each heavy chain.

Mode of Action, Pharmacological Classification

Dostarlimab is a humanized IgG4 isotype PD-1 blocking mAb. Dostarlimab binds with high affinity and specificity to human PD-1, inhibiting the binding of programmed cell death PD-L1/2 to PD-1 and resulting in the enhancement of T-cell reactivity in the presence, but not the absence, of T-cell receptor stimulation [Laken, 2016; Kumar, 2021]. The functional antagonist activity of dostarlimab was confirmed in a MLR assay, demonstrating enhanced activation of T cells.

Approved Indications

JEMPERLI is a PD-1–blocking antibody indicated 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, or
- 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.

Dosage Form, Route of Administration and Dosing Regimen

Immunotherapy (dostarlimab or pembrolizumab) were administered using a 30-minute IV infusion, Q3W until disease progression, intolerable toxicity, patient/investigator's decision, death, or for a maximum of 35 cycles (approximately 24 months). Dostarlimab was supplied as a solution of 500 mg at a concentration of 50 mg/mL in a single-use 10 mL vial and administered at a dose of 500 mg. Pembrolizumab was supplied as a solution of 100 mg/4 mL (25 mg/mL) in a single-use vial and administered at a dose of 200 mg. Immunotherapy (dostarlimab or pembrolizumab) were administered prior to chemotherapy (platinum and pemetrexed) on the same day.

Pemetrexed is administered through an IV infusion Q3W, up to a maximum of 35 cycles total (approximately 24 months). Pre-treatment for pemetrexed (folic acid, vitamin B12, and glucocorticoids) is administered according to local guidelines and product label.

Platinum chemotherapy is administered through an IV infusion Q3W for the first 4 cycles only, following pemetrexed administration.

3. UNMET MEDICAL NEED FOR NSCLC

Lung cancer is the most common cause of cancer mortality globally and the second most common cancer in both men and women. About 13% of all new cancers in the US are lung cancer [Howlader, 2018]. Most recent lung and bronchus cancer incidence rates in the US from the Surveillance, Epidemiology, and End Results program estimate an

incidence rate of 54.9 per 100,000 from 2016 data [NCI SEER Lung Cancer 2020]. The average age of diagnosis is approximately 70 years old. The two major forms of lung cancer are NSCLC and small cell lung cancer. NSCLC is a heterogeneous disease that consists of adenocarcinoma, large cell carcinoma, and squamous cell carcinoma, and comprises approximately 84% of all lung cancers [Herbst, 2008]. Despite advances in early detection and standard treatment, NSCLC is often diagnosed at an advanced stage, has poor prognosis, and is the leading cause of cancer deaths worldwide [Santarpia, 2017]. In the US, the 5 year OS rate of all stages of NSCLC is approximately 19%, with advanced patients (Stage IIIB/IV) having a 5 year OS rate of <5% [NCI SEER NSCLC 2018].

Platinum-based doublet chemotherapy, maintenance chemotherapy, and anti-angiogenic agents in combination with chemotherapy have contributed to improved patient outcomes in advanced NSCLC [Santarpia,. 2017]. Until recently, for most patients with NSCLC without targetable oncogene drivers, first-line platinum-based chemotherapy was the only standard treatment approach [Santarpia, 2017]. However, recent understanding of the interactions between the immune system and tumor growth has led to the development of a new class of immunotherapies, which have now moved to the frontline setting for NSCLC treatment.

Approval of pembrolizumab monotherapy in the US and EU in 2016 and 2017, respectively, as the first-line treatment approach for patients with NSCLC whose tumors demonstrate high expression of PD-L1 (TPS ≥50%) led to a change in the lung cancer management paradigm [Reck,. 2016; Spiess, 2016; Herzberg,. 2017; KEYTRUDA PI and KEYTRUDA SmPC 2022].

Following this approval, it was shown that the addition of pembrolizumab to platinum-based chemotherapy resulted in significantly longer OS and PFS than chemotherapy alone in patients with previously untreated metastatic non-squamous NSCLC (without EGFR or ALK mutations) [Gandhi, 2018]. Similarly, in patients with previously untreated metastatic squamous NSCLC, the addition of pembrolizumab to standard carboplatin and either paclitaxel or nab-paclitaxel also resulted in significantly longer OS and PFS than chemotherapy alone. Based on these results, pembrolizumab has been approved in combination with chemotherapy as first-line treatment of patients with metastatic non-squamous (with no EGFR or ALK genomic tumor aberrations) and squamous NSCLC in the US and EU [Spiess, 2016, Paz-Ares, 2018, KEYTRUDA PI and KEYTRUDA SmPC 2022]. In the US, pembrolizumab monotherapy is also approved in previously untreated advanced or metastatic NSCLC patients with PD-L1 expression (TPS ≥1%; patients with EGFR or ALK genomic tumor aberrations should have disease progression on an approved therapy prior to receiving pembrolizumab monotherapy) [Mok, 2019].

Despite the use of immunotherapy in addition to chemotherapy, patients diagnosed with metastatic NSCLC continue to have dismal prognosis. Although PD-1 agents have demonstrated deep and durable responses in NSCLC patients, not all patients respond and further treatment strategies are needed. Therefore, expanding the treatment armamentarium while maintaining tolerability could further transform the NSCLC landscape and open pathways for new combination strategies to improve outcomes for patients.

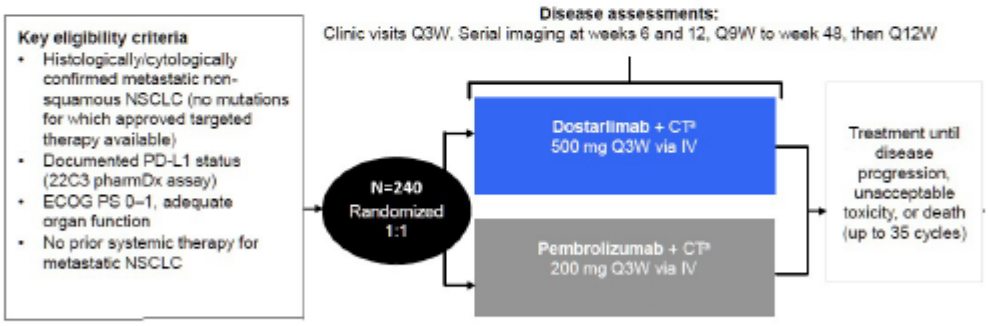
4. PERLA (STUDY 213403)

4.1. Study Design Overview

PERLA (Study 213403) is an ongoing, global, randomized, double-blind, phase 2 study. The aim of the study is to compare the efficacy and safety of dostarlimab and chemotherapy versus pembrolizumab and chemotherapy as first line treatment in adult patients (at least 18 years of age) with metastatic non-squamous NSCLC without known targetable oncogenic driver mutations. The planned sample size was 240 participants.

Key design features of PERLA are described in the following paragraphs. In addition, the study design is depicted below (Figure 1) and is described in detail in the study protocol.

Figure 1 PERLA Phase 2 Study Schema



[a]CT was pemetrexed (500 mg/m2 IV Q3W up to 35 cycles) and (carboplatin (AUC-time curve 5 mg/mL/min) or cisplatin (75 mg/m2) (IV Q3W up to 4 cycles).

AUC = area under the curve; CT = chemotherapy; ECOG PS = Eastern Cooperative Oncology Group performance status; NSCLC =non-small cell lung cancer; PD-L1 = programmed death ligand 1; QxW = every x weeks; RECIST v1.1 = Response Evaluation Criteria in Solid Tumours version 1.1.

Eligible subjects were randomized in a 1:1 ratio to the following:

- Arm 1: Subjects receive dostarlimab plus pemetrexed and platinum chemotherapy.
- Arm 2: Subjects receive pembrolizumab plus pemetrexed and platinumchemotherapy

Subjects were stratified by PD-L1 status (TPS <1% vs 1–49% vs ≥50%) and smoking status (never vs former/current). These stratification factors represent important prognostic factors for NSCLC.

Participants were required to have documented absence of a sensitizing EGFR, ALK, ROS 1, or BRAF V600E mutation or other genomic aberration for which an approved targeted therapy is available. Determination of somatic mutations was done locally and assessment at screening was only required if prior documentation was not available.

All participants had documented PD-L1 status by the 22C3 pharmDx assay (Agilent/Dako). If no prior PD-L1 result was available at the time of Screening, the participant was tested locally using the stated method, or centrally PD-L1 testing was completed prior to randomization, given that the results were needed for stratification.

The primary objective is to:

- To compare the ORR of dostarlimab vs pembrolizumab administered in combination with chemotherapy as evaluated using RECIST v1.1 based on BICR in participants with metastatic non-squamous NSCLC, without a known EGFR, ALK, ROS-1, or BRAF V600E mutation or other genomic aberration for which a targeted therapy is available, who have received no prior treatment of metastatic disease

The secondary objectives are to:

- Evaluate PFS of subjects treated with dostarlimab vs pembrolizumab administered in combination with chemotherapy as evaluated using RECIST v1.1 based on investigator assessment
- Evaluate OS of subjects treated with dostarlimab vs pembrolizumab administered in combination with chemotherapy
- Evaluate the safety of PD-1 dostarlimab vs pembrolizumab administered in combination with chemotherapy

The primary efficacy endpoint is confirmed ORR evaluated by RECIST v1.1 based on BICR and defined as proportion of subjects with a best overall response of confirmed CR or PR in the analysis population.

The secondary efficacy endpoint is PFS evaluated using RECIST v1.1 based on Investigator assessment and defined as the time from the date of randomization to the date of PD or death by any cause, whichever occurs first.

The OS is a dual secondary efficacy endpoint, defined as the time from the date of randomization to date of death due to any cause.

Safety parameters included treatment-emergent AEs (including treatment-related AEs), changes in clinical laboratory parameters (including hematology [complete blood count and coagulation], serum chemistry, urinalysis, and thyroid function), vital signs, symptom-directed physical examination findings, ECOG performance status, electrocardiogram parameters, and usage of concomitant medications.

4.2. PERLA Study Population

4.2.1. Patient Disposition

The study completed enrollment in March 2022. A total of 352 participants were screened of which 109 participants were excluded during screening and 243 were enrolled into the study with 121 and 122 participants in dostarlimab and pembrolizumab arm respectively. All results below are based on a primary analysis DCO date of 4 August 2022. Key patient disposition data is summarized in Table 2.

Table 2 Patient Disposition

	Assessed for eligibility (N=352)	
Excluded	109 (31%)	
Did not met eligibility criteria	93 (26%)	
Declined to participate	11 (3%)	
Other reasons	5 (2%)	
	Randomized	
Variable	Dostarlimab + CT	Pembrolizumab + CT
Allocated to intervention	121	122
Received allocated intervention	121	122
Lost to follow up	1	0
Discontinued intervention	66 (55%)	83 (68%)
Progressive disease	46 (38%)	47 (39%)
Adverse event	18 (15%)	28 (23%)
Withdrawal by patient	1 (<1%)	1 (<1%)
Study terminated by sponsor	1 (<1%)	1 (<1%)
Physician decision	0	5 (4%)
Other	0	1 (<1%)

4.3. Baseline Characteristics

Key baseline characteristics are summarized in Table 3. Overall, baseline characteristics were well balanced between the 2 treatment arms, with no clinically meaningful differences.

Table 3 Key Baseline Characteristics

Variable	Dostarlimab + CT (N=121)	Pembrolizumab + CT (N=122)
Sex, n (%)		
Female	36 (30)	45 (37)
Male	85 (70)	77 (63)
Age group (years), n (%)		
19–64	65 (54)	57 (47)
≥65	56 (46)	65 (53)
Metastases at baseline, n (%)		
Brain	22 (18)	15 (12)
Liver	19 (16)	14 (11)
ECOG performance status, n (%)		
0	37 (31)	50 (41)
1	84 (69)	72 (59)
PD-L1 status, n (%)		
TPS <1%	50 (41)	51 (42)
TPS 1–49%	44 (36)	44 (36)
TPS ≥50%	27 (22)	27 (22)
TPS ≥1%	71 (59)	71 (58)
Smoking status, n (%)		
Never smoked	17 (14)	17 (14)
Former/current smoker	104 (86)	105 (86)
Ethnicity, n (%)		
Hispanic or Latino	25 (21)	32 (26)
Other	90 (74)	84 (69)
Not reported	3 (2)	5 (4)
Unknown	3 (2)	1 (<1)
Race, n (%)		
White	87 (72)	84 (69)
Asian	23 (13)	21 (17)
Unknown	4 (3)	6 (5)
Multiple	3 (2)	3 (2)
Black/African American	1 (<1)	3 (2)
American Indian/Alaska Native	1 (<1)	0 (0)
Not reported	2 (2)	5 (4)
Enrollment region, n (%)		
Europe	62 (51)	65 (53)
South America	35 (29)	34 (28)
East Asia	23 (19)	21 (17)
USA	1 (<1)	2 (2)

CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; ; PD-L1, programmed cell death ligand-1.

4.4. PERLA Clinical Efficacy

4.4.1. Overall Response Rate (ORR)

At the primary analysis, the confirmed ORR based on RECIST 1.1 per BICR (in ITT population) was 46% (80% CI: 37.2%, 55.6%) in dostarlimab arm compared to 37% in pembro arm (80% CI: 28.3%, 46.1%). Complete responses were seen in 2 vs. 3 participants in dostarlimab and pembrolizumab arm respectively. Partial responses were observed in 54 vs. 42 of the participants in dostarlimab and pembrolizumab arm respectively (Table 4).

Table 4 Confirmed Responses by RECIST v1.1 based on BICR

Variable	Dostarlimab + CT (N=121)	Pembrolizumab + CT (N=122)
Complete response, n (%)	2 (2)	3 (2)
Partial response, n (%)	54 (45)	42 (34)
Stable disease, n (%)	48 (40)	52 (43)
Progressive disease, n (%)	12 (10)	11 (9)
Not evaluable, n (%)	0 (0)	1 (<1)
Not done, n (%)	5 (4)	13 (11)

BICR, blinded independent central review; CI, confidence interval; CT, chemotherapy; ORR, overall response rate; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1

Subgroup analyses by PD-L1 expression demonstrated numerically higher ORRs in the dostarlimab combination arm compared with the pembrolizumab combination arm for patients with PD-L1 TPS ≥1%.

For PD-L1 TPS thresholds of ≤1% and ≥1%, the difference in response rates between dostarlimab plus chemotherapy versus pembrolizumab plus chemotherapy was -5.31% (80% CI: -17.03, 6.42) and 19.72% (80% CI: 9.14, 30.29).

For PD-L1 TPS thresholds of 1-49% and ≥50%, the difference in response rates between dostarlimab plus chemotherapy versus pembrolizumab plus chemotherapy was 15.91% (80%CI: 2.66, 29.16) and 25.93% (80% CI: 9.88, 41.97).

A summary of ORR (BICR) by TPS expression status is shown in Table 5.

Table 5 ORRs for patients receiving dostarlimab + chemotherapy and pembrolizumab + chemotherapy evaluated by RECIST v1.1 based on BICR (ITT population)

	Dostarlimab + CT (N=121)		Pembrolizumab + CT (N=122)		Difference in Response Rate
	n/N	% (80% CI)	n/N	% (80% CI)	% (80%CI)

Overall	56/121	46 (37.2 – 55.6)	45/122	37 (28.3 – 46.1)	9.32 (1.46-17.18)
PD-L1 TPS<1%	14/50	28 (16.2–42.5)	17/51	33 (20.8–47.9)	-5.31 (-17.03-6.42)
PD-L1 TPS≥1%	42/71	59 (46.8–70.7)	28/71	39 (28.0–51.7)	19.72 (9.14-30.29)
PD-L1 TPS 1-49%	22/44	50 (34.6–65.4)	15/44	34 (20.5–49.9)	15.91 (2.66-29.16)
PD-L1 TPS ≥50%	20/27	74 (53.7–88.9)	13/27	48 (28.7–68.1)	25.93% (9.88-41.97)

BICR, blinded independent central review; CI, confidence interval; ITT, intention-to-treat; ORR, overall response rate; PD-L1, programmed cell death ligand-1; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TPS, tumor proportion score.

4.4.2. Progression Free Survival (PFS)

The PFS was evaluated using RECIST v1.1 based on Investigator assessment. Within the ITT population a numerical trend was observed favoring the dostarlimab with chemotherapy arm versus the pembrolizumab with chemotherapy arm. The median PFS by investigator assessment for the dostarlimab combination arm was 8.8 months vs 6.7 months in the pembrolizumab combination arm, achieving a HR of 0.7 (95% CI 0.50, 0.98) as shown in Table 6.

Table 6 PFS per RECIST v1.1 Based on Investigator Assessment

Variable	Dostarlimab + CT (N=121)	Pembrolizumab + CT (N=122)
mPFS, months (95% CI)	8.8 (6.7, 10.4)	6.7 (4.9, 7.1)
HR (95% CI)	0.70 (0.50, 0.98)	
Survival Probability, 95% CI		
3 months	0.83 (0.74, 0.88)	0.74 (0.65, 0.81)
6 months	0.61 (0.52, 0.70)	0.52 (0.42, 0.61)
9 months	0.46 (0.36, 0.56)	0.36 (0.26, 0.45)
12 months	0.37 (0.27, 0.48)	0.21(0.10, 0.35)

CI, confidence interval; HR, Hazard Ratio; (m)PFS, (median) progression free survival; PD-L1, programmed cell death ligand-1; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TPS, tumor proportion score.

Progression-free survival probabilities at all time points were numerically higher for the dostarlimab combination arm compared to the pembrolizumab combination arm, with differences ranging from 9-16%. The progression-free survival probability at 12 months was 37% (95% CI: 27, 48) for the dostarlimab combination compared to 21% (95% CI: 10, 35) for the pembrolizumab combination.

Subgroup analyses by PD-L1 expression status demonstrated numerically higher PFS in the dostarlimab combination arm compared with the pembrolizumab combination arm for patients with PD-L1 TPS ≥1%, as shown in Table 7.

Table 7 PFS per RECIST v1.1 per Investigator Assessment by PD-L1 TPS status

	Dostarlimab + CT (N=121)		Pembrolizumab + CT (N=122)		
	Events, n/N	mPFS, months (95% CI)	Events, n/N	mPFS, months (95% CI)	HR (95% CI)
PD-L1 TPS<1%	29/50 (58)	7.0 (4.9–9.7)	32/51 (63)	6.9 (4.7–9.6)	0.77 (0.46–1.28)
PD-L1 TPS≥1%	35/71 (49)	10.4 (6.8–13.6)	42/71 (59)	6.1 (4.8–7.1)	0.66 (0.41–1.03)
PD-L1 TPS 1-49%	22/44 (50)	9.0 (5.3–NR)	26/44 (59)	5.4 (3.2–11.3)	0.67 (0.38–1.19)
PD-L1 TPS ≥50%	13/27 (48)	10.4 (5.8–NR)	16/27 (59)	6.7 (4.2–NR)	0.60 (0.27–1.29)

CI, confidence interval; HR, Hazard Ratio; (m)PFS, (median) progression free survival; NR, not reached; PD-L1, programmed cell death ligand-1; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TPS, tumor proportion score.

4.4.3. Overall Survival Analysis

OS is not yet matured and will be reported at a later date.

4.4.4. Efficacy Conclusions

The results of PERLA show a similar ORR across both treatment arms, with a numerical trend towards higher ORR for patients receiving dostarlimab plus chemotherapy compared to pembrolizumab plus chemotherapy in the overall study population and PD-L1-positive subgroups (TPS ≥1%).

The PFS was also similar between patients treated with dostarlimab plus chemotherapy and those treated with pembrolizumab plus chemotherapy. Across PD-L1-positive subgroups the PFS was broadly consistent, with some small differences observed.

4.5. Clinical Safety

Safety of dostarlimab in PERLA was evaluated in the safety population, consisting of all participants who received at least 1 dose of study intervention (N=243).

The safety profiles of dostarlimab plus chemotherapy and pembrolizumab plus chemotherapy were similar (Table 8). The proportion of patients experiencing any TEAEs was the same for both treatment groups (97%).

There was a numerical trend in favor of dostarlimab in the proportion of patients experiencing SAEs (38% and 45%, respectively), as well as AEs leading to treatment discontinuation (25% and 32%, respectively), while a numerical trend favoring pembrolizumab was observed in the proportion of patients experiencing TRAEs. Fatal TRAEs (related to any study treatment) were infrequent in both groups (2% for dostarlimab plus chemotherapy and 4% for pembrolizumab plus chemotherapy). A summary of TEAEs is provided in Table 8 below.

Table 8 Summary of Treatment Emergent Adverse Events (all subjects)

	Dostarlimab + CT (N=121)	Pembrolizumab + CT (N=122)
Any AE	117 (97%)	118 (97%)
TRAEs[a]	99 (82%)	96 (79%)
AEs leading to any treatment discontinuation	30 (25%)	39 (32%)
TRAEs with Grade >=3[a]	43 (36%)	51 (42%)
Any SAE	46 (38%)	55 (45%)
Fatal SAEs[b]	15 (12%)	12 (10%)
Fatal TRSAEs [a,b,c]	3 (2%)	5 (4%)
irSAEs Grade >=3	6 (5%)	10 (8%)

[a]AEs described as treatment-related could be related to any study treatment agent.
[b]Patients who had a fatal SAE recorded and death was not recorded as due unequivocally to disease under study.
[c]Fatal TRSAEs for dostarlimab + CT were immune-mediated lung disease, pneumonitis, and urosepsis and for pembrolizumab + CT were myelosuppression, pneumonia, respiratory failure, septic shock, and thrombocytopenia (one patient each).
AE = adverse event; CT = chemotherapy; ir(S)AE = immune-related (serious) adverse event; SAE = serious adverse event; TRAE = treatment-related adverse event; TRSAE = treatment-related serious adverse event

4.5.1. Safety Conclusions

Overall, dostarlimab demonstrated an acceptable safety profile with manageable toxicity. The safety profile of dostarlimab in combination with chemotherapy was consistent with that of pembrolizumab in combination with chemotherapy and the known safety profiles of the individual agents.

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6.2 Phase 2 PERLA Study Press Release – 07 December 2022

GSK

Press release

For media and investors only

Issued: 07 December 2022, London UK

PERLA phase II trial of *Jemperli* (dostarlimab) plus chemotherapy shows positive results in first-line metastatic non-squamous non-small cell lung cancer

- PERLA is the largest global head-to-head trial of PD-1 inhibitors in this patient population
- Confirmed objective response rate was 46% in patients treated with investigational dostarlimab combination versus 37% in the pembrolizumab combination
- Key secondary endpoint of median progression-free survival was 8.8 months in the dostarlimab treatment arm versus 6.7 months in the pembrolizumab treatment arm

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GSK plc (LSE/NYSE: GSK) today announced results from the PERLA phase II clinical trial investigating dostarlimab in combination with chemotherapy versus pembrolizumab in combination with chemotherapy as a first-line treatment for patients with metastatic non-squamous non-small cell lung cancer (NSCLC). Dostarlimab plus chemotherapy achieved very promising results for the primary endpoint of confirmed objective response rate (ORR) as well as for the key secondary endpoint of median progression-free survival (mPFS).

The PERLA phase II trial is a randomised, double-blind trial of 243 patients and is the largest global head-to-head trial of programmed death receptor-1 (PD-1) inhibitors in this patient population. The findings from the primary analysis were presented today at the European Society for Medical Oncology (ESMO) Immuno-Oncology Congress 2022 in Geneva, Switzerland.

Hesham Abdullah, Senior Vice President, Global Head of Oncology Development, GSK said: "The head-to-head data from the PERLA trial showed that dostarlimab combined with chemotherapy provided robust anti-tumour activity in patients with previously untreated metastatic non-squamous non-small cell lung cancer. The positive results from this trial inform our future development plans and highlight the potential for dostarlimab to be our foundational immuno-oncology therapy as a single-agent and in combination with standards of care and novel therapies within our pipeline."

The primary endpoint was overall ORR by Response Evaluation Criteria in Solid Tumours (RECIST) as determined by blinded independent central review (BICR) and was 46% (n=56/121) in the dostarlimab treatment arm versus 37% (n=45/122) in the pembrolizumab treatment arm (difference in ORR: 9.32%; 80% CI: 1.46% to 17.18%).

The key secondary endpoint, mPFS, was 8.8 months (95% CI: 6.7 to 10.4) in the dostarlimab treatment arm versus 6.7 months (95% CI: 4.9 to 7.1) in the pembrolizumab treatment arm (HR 0.70 [95% CI: 0.50 to 0.98]).

The table below summarizes key results across all pre-specified programmed death ligand-1 (PD-L1) expression cohorts, as measured by Tumor Proportion Score (TPS).

GSK

Press release

For media and investors only

	ORR by RECIST (BICR) (95% CI)		mPFS (Investigator Assessed) (95% CI)		PFS HR (95% CI)
Pre-specified PD-L1 expression cohorts measured by TPS	dostarlimab + chemo	pembrolizumab + chemo	dostarlimab + chemo (CI)	pembrolizumab + chemo (CI)	
Overall Population	**46% (37.2–55.6)**	**37% (28.3–46.1)**	**8.8 months (6.7–10.4)**	**6.7 months (4.9–7.1)**	**HR 0.70 (0.50–0.98)**
TPS <1%	28%	33%	7.0 months (4.9–9.7)	6.9 months (4.7–9.6)	0.77 (0.46–1.28)
TPS ≥1%	59%	39%	10.4 months (6.8–13.6)	6.1 months (4.8–7.1)	0.66 (0.41–1.03)
TPS 1% to 49%	50%	34%	9.0 months (5.3–NR)	5.4 months (3.2–11.3)	0.67 (0.38–1.19)
TPS ≥50%	74%	48%	10.4 months (5.8–NR)	6.7 months (4.2–NR)	0.60 (0.27–1.29)

Treatment-emergent adverse events (TEAEs) for dostarlimab in the PERLA phase II trial were consistent with previous trials of similar regimens. The rate of TEAEs was 97% for both the dostarlimab and pembrolizumab treatments arms of the trial. The rate of Grade 3 or higher TEAEs was 59% in the dostarlimab treatment arm and 60% in the pembrolizumab treatment arm. The most common TEAEs were anaemia, asthenia, nausea, constipation, cough, dyspnoea, vomiting, decreased appetite, and neutropenia.

Solange Peters, M.D., Ph.D., Professor and Chair of Medical Oncology, University Hospital of Lausanne, Switzerland and ESMO President, said: "Understanding the role of immuno-oncology treatments in the NSCLC patient population is a significant goal we're committed to in the oncology community. Despite advancements in treatment options, unmet need persists for health care providers and their patients. The data results presented at ESMO-IO add to the body of evidence of immuno-oncology agents such as dostarlimab and enhance our knowledge in this important area of research."

GSK is also studying dostarlimab in earlier lines of treatment for endometrial cancer and in combination with other therapeutic agents for patients with advanced/metastatic cancers. This research includes the recently announced positive headline RUBY Phase III trial results in patients with primary advanced or recurrent endometrial cancer, as well as the COSTAR Lung phase III trial comparing cobolimab, an investigational anti-TIM-3 targeting monoclonal antibody, plus dostarlimab plus docetaxel to dostarlimab plus docetaxel to docetaxel alone in patients with advanced NSCLC who have progressed on prior anti-PD-(L)1 therapy and chemotherapy.

About PERLA

The PERLA phase II trial is a global, randomised, double-blind trial of 243 patients evaluating the efficacy and safety of dostarlimab plus chemotherapy versus pembrolizumab plus chemotherapy in patients with metastatic non-squamous NSCLC without a known sensitising epidermal growth factor receptor, anaplastic lymphoma kinase, or receptor tyrosine kinase-1 mutation, V600E mutation of the BRAF gene or other genomic mutation for which an approved targeted therapy is available. The primary endpoint was objective response rate of dostarlimab plus chemotherapy versus pembrolizumab plus chemotherapy assessed by blinded independent central review per RECIST v1.1. Secondary endpoints include investigator-assessed progression-free survival per RECIST v1.1, overall survival, and safety.

About NSCLC

GSK

Press release

For media and investors only

Lung cancer is one of the most commonly diagnosed cancers worldwide, with more than 2 million new cases diagnosed globally in 2020[1]. It is the most common cause of cancer-related death in men and women worldwide, with relatively poor survival outcomes as evidenced by a five-year survival rate of 21%[2]. Approximately 85% of lung cancer cases are NSCLC[3,4]. NSCLC develops when once-healthy cells in the lungs begin to grow abnormally and form a tumour. When NSCLC spreads, or metastasizes, it can become more difficult treat, resulting in a significant need for new treatment approaches.

About *Jemperli* (dostarlimab)
Jemperli is a programmed death receptor-1 (PD-1)-blocking antibody that binds to the PD-1 receptor and blocks its interaction with the PD-1 ligands PD-L1 and PD-L2. *Jemperli* is being investigated in registrational enabling studies, as monotherapy and as part of combination regimens, including in women with recurrent or primary advanced endometrial cancer, women with stage III or IV non-mucinous epithelial ovarian cancer, and in patients with other advanced solid tumours or metastatic cancers. *Jemperli* is not approved anywhere in the world in combination with chemotherapy in first-line patients with metastatic non-squamous NSCLC or in combination with other agents to treat patients with advanced NSCLC who have progressed on prior anti-PD-L1 therapy and chemotherapy.

Jemperli was discovered by AnaptysBio and licensed to TESARO, Inc., under a Collaboration and Exclusive License Agreement signed in March 2014. The collaboration has resulted in three monospecific antibody therapies that have progressed into the clinic. These are: *Jemperli* (GSK4057190), a PD-1 antagonist; cobolimab, (GSK4069889), a TIM-3 antagonist; and GSK4074386, a LAG-3 antagonist. GSK is responsible for the ongoing research, development, commercialization, and manufacturing of each of these Products under the Agreement.

Important Information for *Jemperli* in the EU

Indication

Jemperli is indicated as monotherapy for the treatment of adult patients with mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) recurrent or advanced endometrial cancer that has progressed on or following prior treatment with a platinum -containing regimen.

Refer to the *Jemperli* Reference Information for a full list of adverse events and the complete important safety information in the EU.

About GSK
GSK is a global biopharma company with a purpose to unite science, technology, and talent to get ahead of disease together. Find out more at gsk.com/company

GSK enquiries

Media:	Tim Foley	+44 (0) 20 8047 5502	(London)
	Dan Smith	+44 (0) 20 8047 5502	(London)
	Kathleen Quinn	+1 202 603 5003	(Washington DC)
	Lyndsay Meyer	+1 202 302 4595	(Washington DC)

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[1] WHO Globocan 2020
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GSK

Press release

For media and investors only

Investor Relations:	Nick Stone	+44 (0) 7717 618834	(London)
	James Dodwell	+44 (0) 20 8047 2406	(London)
	Mick Readey	+44 (0) 7990 339653	(London)
	Josh Williams	+44 (0) 7385 415719	(London)
	Jeff McLaughlin	+1 215 751 7002	(Philadelphia)
	Frannie DeFranco	+1 215 751 4855	(Philadelphia)

Cautionary statement regarding forward-looking statements

GSK cautions investors that any forward-looking statements or projections made by GSK, including those made in this announcement, are subject to risks and uncertainties that may cause actual results to differ materially from those projected. Such factors include, but are not limited to, those described in the Company's Annual Report on Form 20-F for 2021, GSK's Q3 Results for 2022 and any impacts of the COVID-19 pandemic.

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Registered Office:
980 Great West Road
Brentford, Middlesex
TW8 9GS

6.3 Phase 3 RUBY Study Press Release – 02 December 2022

GSK

Stock-exchange announcement

For media and investors only

Issued: 2 December 2022, London UK

Jemperli (dostarlimab) RUBY phase III trial met its primary endpoint in a planned interim analysis in patients with primary advanced or recurrent endometrial cancer

- Results showed a statistically significant and clinically meaningful improvement in investigator-assessed progression-free survival
- RUBY is the only first-line trial to show improvement in progression-free survival for an immuno-oncology therapy in combination with standard-of-care chemotherapy in primary advanced or recurrent endometrial cancer
- Regulatory submissions based on the trial results are planned for the first half of 2023

GSK plc (LSE/NYSE: GSK) today announced positive headline results from the planned interim analysis of Part 1 of the RUBY/ENGOT-EN6/GOG3031/NSGO phase III trial investigating *Jemperli* (dostarlimab) plus standard-of-care chemotherapy (carboplatin-paclitaxel) followed by *Jemperli* compared to chemotherapy plus placebo followed by placebo in adult patients with primary advanced or recurrent endometrial cancer. The trial met its primary endpoint of investigator-assessed progression-free survival (PFS). It showed a statistically significant and clinically meaningful benefit in the prespecified mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) patient subgroup and in the overall population. A clinically relevant benefit in PFS was also observed in the mismatch repair proficient (MMRp)/microsatellite stable (MSS) patient subgroup.

While the overall survival (OS) data were immature at the time of this analysis, a favourable trend was observed in the overall population, including both the dMMR/MSI-H and MMRp/MSS subgroups.

The safety and tolerability profile of dostarlimab in the RUBY phase III trial was consistent with clinical trials of similar regimens. The most common treatment-emergent adverse events in patients receiving dostarlimab plus chemotherapy were nausea, alopecia, fatigue, peripheral neuropathy, anaemia, arthralgia, constipation and diarrhoea.

Hesham Abdullah, Senior Vice President, Global Head of Oncology Development, GSK, said: "Patients with primary advanced or recurrent endometrial cancer have limited treatment options. Long-term outcomes remain poor, and new treatment options are urgently needed to evolve the current standard of care, which is platinum-based chemotherapy. Based on these positive headline results from the RUBY phase III trial, GSK intends to seek regulatory approvals for a potential new indication for dostarlimab in the treatment of primary advanced or recurrent endometrial cancer."

Regulatory submissions based on the trial results are anticipated in the first half of 2023. Full results from the trial will be published in a medical journal and presented at an upcoming scientific meeting.

RUBY is part of an international collaboration between the European Network of Gynaecological Oncological Trial groups (ENGOT), a research network of the European Society of Gynaecological Oncology (ESGO) that consists of 22 trial groups from 31 European countries that perform cooperative clinical trials, and the GOG Foundation, a non-profit organisation dedicated to transforming the standard of care in gynaecologic oncology.

About endometrial cancer

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Stock-exchange announcement

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Endometrial cancer is found in the inner lining of the uterus, known as the endometrium. It is the most common gynaecologic cancer in the US and the second most common gynaecologic cancer globally.[I] Approximately 15-20% of women with endometrial cancer will be diagnosed with advanced disease at the time of diagnosis.[II]

About RUBY
RUBY is a two-part global, randomised, double-blind, multicentre phase III trial of patients with primary advanced or recurrent endometrial cancer. Part 1 is evaluating dostarlimab plus carboplatin-paclitaxel followed by dostarlimab versus carboplatin-paclitaxel plus placebo followed by placebo. Part 2 is evaluating dostarlimab plus carboplatin-paclitaxel followed by dostarlimab plus niraparib versus placebo plus carboplatin-paclitaxel followed by placebo. The primary endpoints in Part 1 are investigator-assessed PFS based on the Response Evaluation Criteria in Solid Tumours v1.1 and OS. In Part 2, the primary endpoint is investigator-assessed PFS. Secondary endpoints in Part 1 and Part 2 include PFS per blinded independent central review, overall response rate, duration of response, disease control rate, patient-reported outcomes, and safety and tolerability.

About *Jemperli* (dostarlimab)
Jemperli is a programmed death receptor-1 (PD-1)-blocking antibody that binds to the PD-1 receptor and blocks its interaction with the PD-1 ligands PD-L1 and PD-L2.[III] Dostarlimab is being investigated in registrational enabling studies, as monotherapy and as part of combination regimens, including in women with recurrent or primary advanced endometrial cancer, women with Stage III or IV non-mucinous epithelial ovarian cancer, and patients with other advanced solid tumours or metastatic cancers.

In the US, dostarlimab is indicated for adult patients with dMMR recurrent or advanced endometrial cancer, as determined by an FDA-approved test, that have progressed on or following prior treatment with a platinum-containing regimen. Dostarlimab is also indicated in the US for patients with dMMR recurrent or advanced solid tumours, as determined by an FDA-approved test, that have progressed on or following prior treatment and who have no satisfactory alternative treatment options. These indications are approved in the US under accelerated approval based on tumour response rate and durability of response. Continued approval for these indications may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

Dostarlimab was discovered by AnaptysBio and licensed to TESARO, Inc., under a collaboration and exclusive license agreement signed in March 2014. The collaboration has resulted in three monospecific antibody therapies that have progressed into the clinic. These are: dostarlimab (GSK4057190), a PD-1 antagonist; cobolimab, (GSK4069889), a TIM-3 antagonist; and GSK4074386, a LAG-3 antagonist. GSK is responsible for the ongoing research, development, commercialisation, and manufacturing of each of these medicines under the agreement.

Important Information for *Jemperli* in the EU

Indication
Dostarlimab is indicated as monotherapy for the treatment of adult patients with mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) recurrent or advanced endometrial cancer that has progressed on or following prior treatment with a platinum-containing regimen.

Refer to the *Jemperli* EMA Reference Information for a full list of adverse events and the complete important safety information in the EU.

About GSK
GSK is a global biopharma company with a purpose to unite science, technology, and talent to get ahead of disease together. Find out more at gsk.com/company.

GSK enquiries

Media:	Tim Foley	+44 (0) 20 8047 5502	(London)
	Madeleine Breckon	+44 (0) 20 8047 5502	(London)
	Kathleen Quinn	+1 202 603 5003	(Washington DC)

GSK

Stock-exchange announcement

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	Lyndsay Meyer	+1 202 302 4595	(Washington DC)
Investor Relations:	Nick Stone	+44 (0) 7717 618834	(London)
	James Dodwell	+44 (0) 20 8047 2406	(London)
	Mick Readey	+44 (0) 7990 339653	(London)
	Josh Williams	+44 (0) 7385 415719	(London)
	Jeff McLaughlin	+1 215 751 7002	(Philadelphia)
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6.4 MSKCC Study 19-288 and GSK Study 53393 Inclusion and Exclusion Criteria

6.4.1 Ongoing MSKCC Study 19-288

For inclusion into the trial, patients were required to fulfill all of the following criteria. Patients must have:

1. Provided written informed consent for the trial.
2. ≥ 18 years of age on the date of signing informed consent.
3. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1.
4. Histologically confirmed locally advanced rectal cancer (LARC).
5. A rectal tumor that in standard practice would be treated with neoadjuvant therapy.

6. No evidence of distant metastases.
7. Radiologically measurable or clinically evaluable disease.
8. Tumor specimen that demonstrates mismatch repair deficiency (dMMR) by immunohistochemistry or microsatellite instability (MSI-H) as demonstrated by next generation sequencing or polymerase chain reaction.
9. Negative pregnancy test done 72 hours prior to beginning treatment, for women of childbearing potential only. Patients of childbearing potential must be willing to use an adequate method of contraception. Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives, or double barrier method (diaphragm plus condom). Contraception, for the course of the study starting with the first dose of study medication through 150 days after the last dose of study medication.

   Nonchildbearing potential is defined as follows (by other than medical reasons):

   - ≥ 45 years of age and has not had menses for > 1 year.
   - Patients who have been amenorrhoeic for < 2 years without history of a hysterectomy and oophorectomy must have a follicle stimulating hormone value in the postmenopausal range upon screening evaluation.
   - Post-hysterectomy, post-bilateral oophorectomy, or post-tubal ligation. Documented hysterectomy or oophorectomy must be confirmed with medical records of the actual procedure or confirmed by an ultrasound. Tubal ligation must be confirmed with medical records of the actual procedure, otherwise the patient must be willing to use 2 adequate barrier methods throughout the study.
10. If receiving corticosteroids, a stable dose for ≥ 4 weeks prior to initiating protocol therapy.
11. Demonstrated adequate organ function as defined in the Table below within 14 days of Cycle 1 Day 1. All screening labs should have been performed within 14 days of treatment initiation.

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥ 1,500/mm^3
Platelets	≥ 100,000/mcL
Hemoglobin	> 9 g/dL or ≥ 5.6 mmol/L
Renal	
Serum creatinine OR Measured OR calculated[a] creatinine clearance (glomerular filtration rate [GFR] can also be used in place of creatinine or creatine clearance [CrCl])	≤ 1.5 × upper limit of normal (ULN) OR ≥ 60 mL/min for patient with creatinine levels > 1.5 × institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 × ULN OR direct bilirubin ≤ ULN for patients with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 × ULN
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	For patients not taking warfarin: INR ≤ 1.5 or PT ≤ 1.5 x ULN; and either PTT or aPTT ≤ 1.5 × ULN. Patients on warfarin may be included on a stable dose with a therapeutic INR < 3.5

a. Creatine clearance should be calculated per institutional standard.

Any of the following was regarded as a criterion for exclusion from the trial. Patients must not have:

1. Presence of metastatic or recurrent disease
2. Prior radiation therapy, chemotherapy, or surgery for tumor.
3. Tumor causing symptomatic bowel obstruction (patients who have a temporary diverting ostomy are eligible).
4. Other invasive malignancy ≤ 5 years prior to registration. Exceptions are non-melanoma skin cancer that has undergone potentially curative therapy and in situ cervical carcinoma.
5. Diagnosis of immunodeficiency or receiving systemic steroid therapy or any other form of non-physiologic dose immunosuppressive therapy within 7 days prior to first dose of trial treatment.
6. Active autoimmune disease requiring systemic treatment within the past 2 years or documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents at non-physiologic doses.
7. Active infection requiring systemic therapy.
8. Received prior therapy with an antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways.

9. Experienced ≥ Grade 3 immune-related adverse event (AE) with prior immunotherapy, except for non-clinically significant lab abnormalities.
10. Other anticancer or experimental therapy. No other experimental therapies (including chemotherapy, radiation, hormonal treatment, antibody therapy, immunotherapy, gene therapy, vaccine therapy, angiogenesis inhibitors, matrix metalloprotease inhibitors, thalidomide, anti-VEGF/Flk-1 monoclonal antibody or other experimental drugs) of any kind are permitted while the patient is receiving study treatment.
11. Known history of human immunodeficiency virus (HIV) (HIV 1/2 antibodies)
12. Known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HC virus RNA [qualitative] is detected).
13. Women who are pregnant or breastfeeding, or men expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening visit through 150 days after the last dose of study medication.
14. Concurrent medical or psychiatric condition or disease which, in the Investigator's judgement, would make them inappropriate candidates for entry into the study. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 90 days) myocardial infarction, chronic obstructive pulmonary disease, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, or any psychiatric disorder that prohibits obtaining informed consent.
15. Received a live vaccine within 30 days of planned start of study medication.
16. Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to enrollment.
17. History of interstitial lung disease.
18. Known hypersensitivity to dostarlimab components or excipients.

6.4.2 Planned GSK Study 53393

For inclusion into the trial, patients are required to fulfill all of the following criteria. Patients must have/be:

1. ≥ 18 years of age at the time of signing informed consent.
2. Histologically confirmed Stage II–III (T3-T4, N0, or T any, N+), LARC.
3. Radiologically and endoscopically evaluable disease.
4. A tumor demonstrating the presence of either:
    a) dMMR status; MMR status must be assessed by immunohistochemistry (IHC) for MMR protein expression (MLH1, MSH2, MSH6, PMS2) where loss of 1 or

more proteins indicates dMMR; MMR status may be determined either locally or by the central reference laboratory, or

b) MSI-H phenotype as determined by polymerase chain reaction or by tissue next-generation sequencing (NGS); MSI-H may be determined either locally or by the central reference laboratory.

NOTE: Patients who are known to have Lynch syndrome and have been found to carry a specific germline mutation in an MMR gene (MLH1, MSH2, MSH6, PMS2) are eligible to participate.

5. An archival formalin-fixed, paraffin-embedded (FFPE) tissue sample that must be available and submitted to the central reference laboratory for testing at Screening. If no archival tissue is available, a baseline biopsy will be required.
6. Willing to use adequate contraception.

- Contraceptive use by female patients should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

  Female patients:

- A female patient is eligible to participate if she is not pregnant or breastfeeding, and 1 of the following conditions applies:

  Is a woman of non-childbearing potential (WONCBP) as defined in the protocol.

  OR

  Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of < 1% per year), preferably with low user dependency, as described in the protocol, during the Treatment Period and for ≥ 120 days after the last dose of study intervention. The Investigator should evaluate the potential for contraceptive method failure (e.g., noncompliance, recently initiated) in relationship to the first dose of study intervention.

- A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 24 hours before the first dose of study intervention.
- If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the patient must be excluded from participation if the serum pregnancy result is positive.
- Additional requirements for pregnancy testing during and after study intervention will be provided in the protocol.

- The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

7. Capable of giving signed informed consent as described in the protocol, including compliance with the requirements and restrictions listed in the informed consent form and in this protocol.
8. An ECOG performance score of ≤ 1.
9. Adequate organ function, as defined in Table below. (NOTE: A complete blood count test should be obtained without transfusion or receipt of colony-stimulating factors within 2 weeks of obtaining the sample.)

   NOTE: Laboratory results obtained during the Screening Period should be used to determine eligibility criteria. In situations where laboratory results are outside the permitted range, the Investigator may opt to retest the patient and the subsequent within-range screening result may be used to confirm eligibility.

System	Laboratory Value
Hematologic	
Absolute neutrophil count	≥ 1,500/µL (≥ 1.5 x 10^9/L)
Platelets	≥ 100,000/µL (≥ 100 x 10^9/L)
Hemoglobin	≥ 9 g/dL or ≥ 5.6 mmol/L
Renal[a]	
GFR	eGFR: ≥ 60 mL/min/1.73m^2 evaluated by CKD-EPI (National Kidney Foundation, 2021) or applicable country-specific formula OR mGFR using the Cockcroft-Gault formula or 51Cr EDTA methodology or non-BSA normalized GFR: ≥ 60 mL/min
Hepatic	
Total bilirubin	≤ 1.5 × ULN (isolated bilirubin > 1.5 x ULN is acceptable if bilirubin is fractionated and direct bilirubin < 35%)
AST and ALT	≤ 2.5 × ULN

a. eGFR should be calculated using the Chronic Kidney Disease Epidemiology Collaborative (CKD-Epi) method. Details will be provided in the Laboratory Manual. GFR may also be directly determined via 24-hour urine creatinine clearance or other equivalent method.
51Cr-EDTA=51Cr-ethylenediaminetetraacetic acid; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BSA=body surface area; CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; eGFR=estimated glomerular filtration rate; GFR= glomerular filtration rate; mGFR=measured glomerular filtration rate; ULN=upper limit of normal.

Any of the following is regarded as a criterion for exclusion from the trial. Patients must not have/be:

1. Distant metastatic disease.

2. Received prior radiation therapy, systemic therapy, or surgery for management of rectal cancer.
3. A tumor that, in the Investigator's judgment, is causing symptomatic bowel obstruction or otherwise requires urgent/emergent surgery.
4. A known additional malignancy that progressed or required active treatment within the past 2 years. Exceptions include adequately treated superficial skin cancers, superficial bladder cancers, and other in situ cancers.
5. Is immunocompromised in the opinion of the Investigator.
6. Has an active autoimmune disease that has required systemic treatment in the past 2 years (i.e., with 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) is not considered a form of systemic treatment.
7. Unable to undergo magnetic resonance imaging (MRI).
8. Experienced any of the following with prior immunotherapy: any immune-related AE ≥ Grade 3, immune-related severe neurologic events of any grade (e.g., myasthenic syndrome/myasthenia gravis, encephalitis, Guillain-Barré Syndrome, or transverse myelitis), exfoliative dermatitis of any grade (Stevens-Johnson Syndrome, toxic epidermal necrolysis, or drug reaction with eosinophilia and systemic symptoms [DRESS] syndrome), or myocarditis of any grade. Non-clinically significant laboratory abnormalities are not exclusionary.
9. Undergone any major surgical procedure, open biopsy, or experienced significant traumatic injury within 28 days prior to enrollment.
10. Any history of interstitial lung disease or pneumonitis.
11. Cirrhosis or current unstable liver or biliary disease per Investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal/gastric varices, or persistent jaundice.

    NOTE: Stable non-cirrhotic chronic liver disease (including Gilbert's syndrome or asymptomatic gallstones) is acceptable if patient otherwise meets entry criteria.
12. History or current evidence of any medical condition, therapy, or laboratory abnormality that might confound the study results, interfere with their participation for the full duration of the study intervention, or indicate it is not in the best interest of the patient to participate, in the opinion of the Investigator.
13. QTcF > 450 msec, or > 480 msec for patients with bundle branch block.
14. History of or evidence of cardiac abnormalities such as serious, uncontrolled cardiac arrhythmia or clinically significant electrocardiogram abnormalities within the 6 months prior to enrollment, including:

a. Second-degree (Type II) or third-degree atrioventricular block.

b. Cardiomyopathy, myocarditis, myocardial infraction, acute coronary syndromes (including unstable angina pectoris), coronary angioplasty, stenting, or bypass grafting.

c. Symptomatic pericarditis.

15. Receiving any other anticancer or experimental therapy. No other experimental therapies (including but not limited to chemotherapy, radiation, hormonal treatment, antibody therapy, immunotherapy, gene therapy, vaccine therapy, or other experimental drugs) of any kind are permitted while the patient is receiving study intervention.
16. Receiving immunosuppressive medication.
17. Received systemic corticosteroids (> 10 mg daily prednisone or equivalent) within 7 days of first dose of study intervention. Use of inhaled steroids, local injection of steroids, topical steroids, and steroidal eye drops are allowed.
18. Received any live vaccine within 30 days of enrollment. Vaccination against COVID-19 using vaccines that are authorized via the appropriate regulatory mechanisms (e.g., Emergency Use Authorization, Conditional Marketing Authorization, or Marketing Authorization Application) are not exclusionary. Note: mRNA and adenoviral-based COVID-19 vaccines are considered non-live. If a COVID-19 vaccine is administered at any time, the date of COVID-19 vaccination must be entered in the eCRF.
19. Documented presence of HBsAg at Screening or within 3 months prior to first dose of study intervention.
20. Positive hepatitis C virus (HCV) antibody test result at Screening or within 3 months prior to first dose of study intervention. NOTE: Patients with a positive HCV antibody test result due to prior resolved disease can be enrolled, only if a confirmatory negative HCV RNA test is obtained.
21. Positive HCV RNA test result at Screening or within 3 months prior to first dose of study intervention. NOTE: The HCV RNA test is optional and patients with negative HCV antibody test are not required to undergo HCV RNA testing as well.
22. Considered, in Investigator’s opinion, a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease, or active infection requiring systemic therapy. Specific examples include but are not limited to: uncontrolled major seizure disorder; unstable spinal cord compression; superior vena cava syndrome; or any psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study (including obtaining informed consent).

23. Known history of HIV infection, with the exception of patients who are positive for HIV and meet all of the following criteria:

    a. Is receiving a stable regimen of highly active anti-retroviral therapy (HAART);

    b. Has no requirement for concurrent antibiotics or antifungal agents for the prevention of opportunistic infections; and

    c. Has a CD4 count above 250 cells/mcL and an undetectable HIV viral load on standard polymerase chain reaction-based tests.

24. Pregnant, breastfeeding, or expecting to conceive children within the projected duration of the study, starting with the Screening Visit through 120 days after the last dose of study intervention.

25. History of severe allergic and/or anaphylactic reactions to chimeric, human or humanized antibodies, fusion proteins, or known allergies to dostarlimab or its excipients.

6.5 Dose Justification

The 2 approved indications for dostarlimab are dosed 500 mg once every 3 weeks (Q3W) for 4 cycles followed by 1000 mg dosed once every 6 weeks (Q6W).

Results from a dose-escalation and a fixed-dose study demonstrated that dostarlimab is interchangeable among 3 dosing regimens (500 mg Q3W; 500 mg Q3W for 4 cycles, followed by 1000 mg Q6W; 1000 mg Q6W), as well as safe and tolerable, in patients with recurrent or advanced dMMR solid tumors.

Similarity of the doses were explained by exposure-response data showed a generally flat relationship for both efficacy (e.g., ORR) and safety (e.g., top 5 occurring drug-related AEs). In addition, maximal target engagement, as measured by both direct receptor occupancy (RO) and functional downstream assays (IL-2 stimulations), was attained and maintained through the respective dosing intervals for both the 500 mg Q3W and 1000 mg Q6W dosing regimens. Safety results of dostarlimab at 500 mg on Day 1 Q3W for 4 cycles, followed by 1,000 mg Q6W are provided in Appendix 6.5.1.

6.5.1 Summary of Dostarlimab Safety in Mismatch Repair Deficient Endometrial Cancer

The safety of dostarlimab was evaluated in the GARNET Study in 104 patients with advanced or recurrent dMMR endometrial cancer who received ≥ 1 dose of dostarlimab (Jemperli USPI, 2022). Patients received dostarlimab 500 mg every 3 weeks for 4 doses followed by 1,000 mg every 6 weeks as an intravenous infusion until disease progression or unacceptable toxicity. Among patients receiving dostarlimab, 47% were exposed for 6 months or longer and 20% were exposed for > 1 year.

Serious adverse reactions occurred in 34% of patients receiving dostarlimab. Serious adverse reactions in > 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%).

Dostarlimab 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 treated with dostarlimab. Adverse reactions that required dosage interruption in ≥ 1% of patients who received dostarlimab were anemia, diarrhea, increased lipase, and pyrexia.

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. Immune-related adverse reactions, commonly associated with drugs in this class, occurred in 34% of patients; the most common immune-related adverse reactions were diarrhea (7.7%) and hypothyroidism (6.7%).

Table 11 summarizes the adverse reactions that occurred in ≥ 10% of patients with dMMR endometrial carcinoma on dostarlimab in the GARNET study.

Table 11: GARNET Study: Adverse Reactions in ≥ 10% of Patients with dMMR Endometrial Cancer Who Received Dostarlimab

	Dostarlimab (N=104)	
Adverse Reaction, %	**All Grades**	**Grade 3 or 4**
Anemia[a]	24	13
Nausea	30	0
Diarrhea	26	1.9
Constipation	20	0.9
Vomiting	18	1
Fatigue[b]	48	1.9
Urinary tract infection	13	0
Decreased appetite	14	0
Myalgia	12	0
Cough	14	0
Pruritus	14	1

a. Includes anemia, hemoglobin decreased, iron deficiency, and iron deficiency anemia.
b. Includes fatigue and asthenia.

6.6 Ongoing MSKCC Study 19-288: Primary Objective Statistics

The study is designed to have an 80% power to detect a 22.5% improvement in cCR12 rate (from 27.5 to 50%) with a type I error rate of 0.05. The historical control complete response rate of 27.5 was chosen based on a 62-patient study reported by de Rosa et al (de Rosa et al 2016).

6.6.1 Interim Analysis

The co-primary endpoint of ORR (PR + nCR + CR) was met at an interim analysis. The co-primary endpoint of ORR was assessed based on a one-sample hypothesis of ORR being < 25%, based on the FOxTROT trial (Foxtrot Collaborative 2012). For the MSKCC Study, successful rejection of this null hypothesis required 6 or more responders at the end of the first stage (6/15 patients, 40%) and 11 or more at the end of the second stage (11/30, 36.7%).