



Original Investigation | Oncology

Antitumor Activity and Safety of Dostarlimab Monotherapy in Patients With Mismatch Repair Deficient Solid Tumors

A Nonrandomized Controlled Trial

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Abstract

IMPORTANCE Mismatch repair deficiency (dMMR) occurs in various cancers, and these tumors are attractive candidates for anti-programmed cell death 1 therapies, such as dostarlimab, a recently approved immune checkpoint inhibitor.

OBJECTIVE To assess the antitumor activity and safety of dostarlimab in patients with advanced or recurrent dMMR solid tumors.

DESIGN, SETTING, AND PARTICIPANTS The GARNET trial was a phase 1, open-label, single-group, multicenter study that began enrolling May 8, 2017. Participants had advanced or recurrent dMMR and microsatellite instability-high (MSI-H) or polymerase epsilon (POLE)-altered solid tumors. The data cut for this interim analysis was from November 1, 2021, with median follow-up of 27.7 months.

INTERVENTIONS Patients received 500 mg of dostarlimab intravenously every 3 weeks for 4 doses, then 1000 mg every 6 weeks until disease progression, discontinuation, or withdrawal.

MAIN OUTCOMES AND MEASURES The primary objective was to evaluate objective response rate and duration of response in patients with dMMR solid tumors by blinded independent central review using Response Evaluation Criteria in Solid Tumors, version 1.1.

RESULTS The efficacy population included 327 patients (median [range] age, 63 [24-85] years; 235 [71.9%] female; 7 [2.1%] Asian, 6 [1.8%] Black, and 206 [63.0%] White patients), with 141 patients (43.1%) with dMMR endometrial cancer, 105 patients (32.1%) with dMMR colorectal cancer, and 81 patients (24.8%) with other dMMR tumor types. All patients had at least 1 previous line of therapy. Objective response rate assessed per blinded independent central review for dMMR solid tumors was 44.0% (95% CI, 38.6% to 49.6%). Median duration of response was not reached (range, ≥ 1.18 to ≥ 47.21 months); 72.2% of responders (104 of 144) had a response lasting 12 or more months. Median progression-free survival was 6.9 months (95% CI, 4.2 to 13.6 months); probability of progression-free survival at 24 months was 40.6% (95% CI, 35.0% to 46.1%). Median overall survival was not reached (95% CI, 31.6 months to not reached). The most frequent immune-related adverse events were hypothyroidism (25 [6.9%]), alanine aminotransferase increase (21 [5.8%]), and arthralgia (17 [4.7%]). No new safety concerns were identified.

CONCLUSIONS AND RELEVANCE In this nonrandomized controlled trial, dostarlimab was a well-tolerated treatment option with rapid, robust, and durable antitumor activity in patients with diverse

(continued)

Key Points

Question What is the antitumor activity and safety of dostarlimab monotherapy for patients with mismatch repair deficient and microsatellite instability-high solid tumors?

Findings In this nonrandomized, open-label, single-group, multicenter clinical trial with 327 participants, the objective response rate was 44.0% in patients with mismatch repair deficient solid tumors, with a median duration of response that was not reached at a median follow-up of 27.7 months. Safety was consistent with the drug class; no new safety signals were observed.

Meaning In this study, dostarlimab monotherapy demonstrated durable antitumor activity across multiple tumor types in patients with mismatch repair deficient and microsatellite instability-high advanced or recurrent solid tumors.

+ Supplemental content

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Abstract (continued)

dMMR solid tumors. These findings suggest that dostarlimab provides meaningful long-term benefit in a population with high unmet need.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: [NCT02715284](https://clinicaltrials.gov/ct2/show/study/NCT02715284)

JAMA Network Open. 2023;6(11):e2341165. doi:10.1001/jamanetworkopen.2023.41165

Introduction

Classification and treatment of cancers have historically been based on tumor type and histological subtype. However, advancements in precision medicine have led to the development of biomarker-driven tumor-agnostic treatments.¹ This change is reflected by biomarker-linked approvals, including the recent US Food and Drug Administration tissue-agnostic drug approvals for tumors characterized by defective mismatch repair (MMR) machinery.¹

In MMR protein-deficient (dMMR) tumors, mismatches accumulate and lead to genome instability with many mutations in microsatellites, leading to microsatellite instability (MSI), which can have either a sporadic origin (somatic mutation or promoter hypermethylation) or an inherited origin (Lynch syndrome).² Tumors with dMMR and/or high MSI (MSI-H) have been found to have increased tumor-infiltrating lymphocytes and increased expression of programmed cell death 1 (PD-1) receptor and its ligands (PD-L1 and PD-L2). Simultaneously, the MSI-driven oncogenic pathway leads to a high tumor mutational burden (TMB), with highly immunogenic neoantigens arising from frameshift mutations. Together, these features make these dMMR and MSI-H tumors attractive candidates for anti-PD-1 and anti-PD-L1 checkpoint inhibition.²⁻⁵ The highest incidence of dMMR and MSI-H has been reported in endometrial cancer (EC; 25%-30%) and colorectal cancer (CRC; 10%-15%) of all stages.⁴⁻⁷ However, dMMR and MSI-H is also found in other cancers, including gastric, small intestine, urothelial, central nervous system, and several other solid tumors.^{6,7} Regardless of tumor type, patients with advanced dMMR and MSI-H tumors that failed to respond to systemic therapy have limited treatment options, and there is a high unmet therapeutic need in these settings.⁸

Alterations in other DNA proofreading proteins can also be associated with hypermutagenesis and may lead to tumors that are susceptible to response to anti-PD-1/PD-L1 therapy.⁹⁻¹¹ Defective proofreading polymerase epsilon (POLE) alterations are rare and have been predominantly described in MMR proficient (MMRp) CRC and EC as sporadic and germline events.⁹⁻¹¹ Although patients with pathogenic POLE alterations have been shown to benefit from immune checkpoint inhibitor therapy, the overall number of patients with POLE alterations of advanced solid tumors in trials has been small, and thus there is a gap in knowledge of anti-PD-1 therapy in regards to POLE alteration.⁹⁻¹¹

The Study of TSR-042, an Anti-PD-1 Monoclonal Antibody, in Participants With Advanced Solid Tumors (GARNET) Trial is a phase 1, multicenter, open-label, single-group study of dostarlimab monotherapy, an anti-PD-1 monoclonal antibody, in patients with advanced and recurrent solid tumors.^{12,13} GARNET has prospectively evaluated dostarlimab in patients with dMMR and MSI-H recurrent or advanced solid tumors.^{13,14} In the United States, dostarlimab is approved for patients with dMMR recurrent or advanced solid tumors that have progressed on or following prior treatment and who have no satisfactory alternative treatment options. It is also approved in adult patients with dMMR (United States) or dMMR and MSI-H (European Union and United Kingdom) recurrent or advanced EC that has progressed on or following prior treatment with a platinum-containing regimen.¹⁵⁻¹⁸ Here, we report on a prespecified population for an interim analysis of dostarlimab among patients with dMMR and MSI-H or POLE-altered solid tumors.

Methods

Study Design

GARNET is a phase 1, single-group study of dostarlimab monotherapy in patients with advanced and recurrent solid tumors. The trial protocol and statistical analysis plan are available in [Supplement 1](#).

In parts 1 and 2A of the trial, the recommended therapeutic dose (RTD) was determined to be 500 mg intravenously every 3 weeks for 4 cycles, then 1000 mg intravenously every 6 weeks until discontinuation.¹⁹ Part 2B of the ongoing GARNET study explores antitumor activity and safety in prespecified tumor types using the RTD. Cohort A1 enrolled patients with dMMR and MSI-H EC, and cohort F enrolled patients with dMMR and MSI-H non-EC or POLE-altered solid tumors. Key inclusion and exclusion criteria, enrolling sites, sample size, and brief statistical analysis overview can be found in eAppendix 1 in [Supplement 2](#). Data from the first and second prespecified interim analyses, which included the endometrial cancer cohorts (cohort A1 [dMMR and MSI-H EC] and cohort A2 [MMRp/microsatellite stable (MSS) EC]), were published prior to this prespecified third interim analysis.^{14,20}

The study was initiated on April 10, 2017; enrollment in cohort A1 is complete, whereas cohort F is open for enrollment. Data analysis of this interim analysis was performed using a data cut date of November 1, 2021, with a median follow-up of 27.7 months.

Full sample size information for cohorts A1 and F can be found in eAppendix 1 in [Supplement 2](#) and has been previously published for cohort A1.¹⁴ In short, a total sample size of 300 patients evaluable for antitumor activity from cohorts A1 and F combined allowed the lower-limit boundary of the exact 95% CI to exclude a response rate of 30% or less, assuming the observed objective response rate (ORR) was 35%.

The trial was performed in accordance with the principles of the Declaration of Helsinki, Good Clinical Practices, and all local laws. Part 2B of the study was overseen by an independent data and safety monitoring committee. The study protocol and/or other relevant documents received approval by the institutional ethics committee, institutional review board, and/or relevant competent authorities at each site. Written informed consent was obtained from all subjects or a legal surrogate. This trial follows the Transparent Reporting of Evaluations With Nonrandomized Designs ([TREND](#)) reporting guidelines for nonrandomized trial studies.

Biomarker Screening

Patients were screened prospectively for MMR/MSI status using immunohistochemistry (IHC), polymerase chain reaction, or next-generation sequencing. For patients enrolled after protocol amendment 5, eligibility was determined by IHC performed in a certified local laboratory or by central testing if local IHC testing was not available.^{7,21-24}

Patients enrolled on the study based on POLE-alteration status must have had local results available showing tumor alteration in the exonuclease domain of the *POLE* gene (amino acid residues 268-471) prior to screening for assignment into cohort F (prospective POLE alteration). Additional biomarker screening information can be found in eAppendix 1 in [Supplement 2](#).

Patients

A total of 363 patients with dMMR and MSI-H and/or POLE-altered tumors were enrolled and received dostarlimab ([Figure 1](#)). The efficacy population consisted of 347 patients with dMMR and MSI-H and/or POLE-altered tumors, which included 327 patients with dMMR tumors.

Objectives

Efficacy End Points

The primary end point for each cohort (A1 and F) was to evaluate the antitumor activity of dostarlimab in dMMR tumors in terms of ORR and duration of response (DOR) by blinded independent central review (BICR) using Response Evaluation Criteria in Solid Tumors (RECIST)

version 1.1 in the efficacy population. Durable responses were defined as those responses with a duration of 12 months or longer.

Prespecified secondary end points included a combined analysis of ORR and DOR by BICR using RECIST version 1.1 in dMMR tumors from cohorts A1 and F in the efficacy population. Additional prespecified secondary end points for cohorts A1 and F, individually, included disease control rate and progression-free survival (PFS), and overall survival (OS) in the efficacy population.

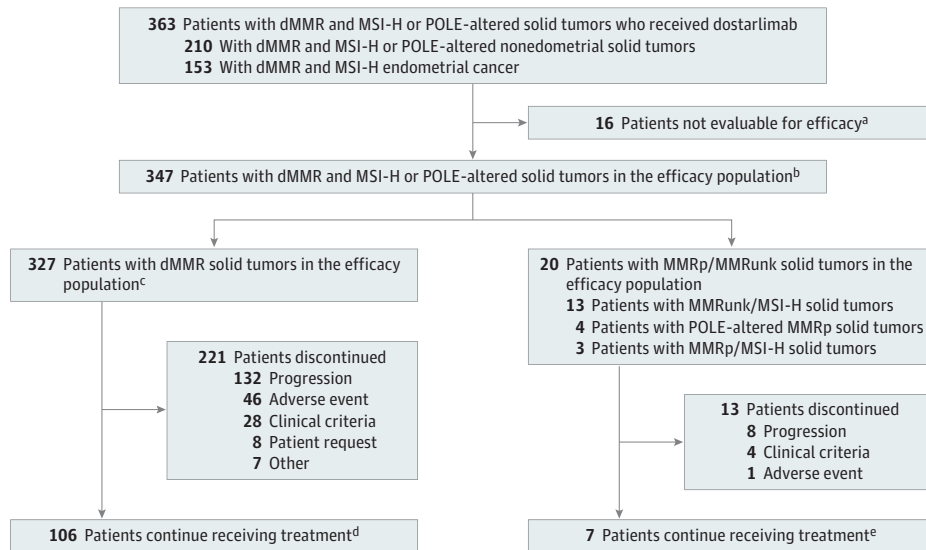
Post Hoc Analyses

Post hoc and exploratory analyses included evaluation of the antitumor activity of dostarlimab in terms of ORR, DOR, PFS, and OS by tumor type (EC, CRC, non-CRC/non-EC, gastrointestinal, pancreatic, small intestinal, and ovarian). These analyses were also conducted by biomarker status, including POLE-altered tumors (both prospective and retrospective POLE-altered tumors), PD-L1, and TMB status as well as MSI-H tumors with discordant or unknown MMR results.

Safety Analyses

Safety analyses included incidence of treatment-emergent adverse events, immune-related adverse events (irAEs) of interest, and serious adverse events occurring while patients were receiving treatment or up to 90 days after the end of treatment.

Figure 1. Enrollment and Outcomes



dMMR indicates mismatch repair deficient; MMRp, mismatch repair proficient; MMRunk, mismatch repair status unknown; MSI-H, microsatellite instability-high; POLE, polymerase epsilon.

^a Sixteen patients had no measurable disease per blinded independent central review (BICR) at baseline and were excluded from the efficacy population.

^b All patients with dMMR and MSI-H or POLE-altered solid tumors who had received at least 1 dose of dostarlimab, had at least 1 BICR-confirmed measurable lesion at baseline, and had the opportunity to be followed up for at least 6 months as of the data cutoff date were included in the efficacy population, regardless of whether the patient had a postbaseline tumor assessment.

^c Total of 327 patients with dMMR solid tumors (including 2 who were also POLE-altered).

^d Total of 106 patients with dMMR solid tumors (including 2 who also had POLE alterations).

^e Seven patients with MMR unknown/MSI-H tumors or MMRp tumors (including 2 who had POLE alterations).

Statistical Analysis

Point estimates and exact 2-sided 95% CIs were provided for ORR; DOR was analyzed using the Kaplan-Meier method. Patients who did not achieve a confirmed response, either complete response (CR) or partial response (PR), were excluded from the DOR analysis. Median follow-up time was calculated using the reverse Kaplan-Meier method. Time-to-event analyses were performed using Kaplan-Meier methods. All statistical outputs were generated using SAS version 9.4 (SAS Institute). No formal hypothesis-testing analysis of adverse event incidence rates was performed. Additional information can be found in eAppendix 1 in [Supplement 2](#) and the trial protocol ([Supplement 1](#)).

Results

Patients

Demographic and baseline characteristics of the efficacy population are included in **Table 1**. The median age was 63 years (range, 24-85 years), and all patients had received at least 1 prior line of therapy. Among the 327 patients with dMMR tumors, there were 235 (71.9%) female patients; 7 (2.1%) Asian patients, 6 (1.8%) Black patients, and 206 (63.0%) White patients. Overall, 141 (43.1%) had EC, 105 (32.1%) had CRC, and 81 (24.8%) had other tumor types.

Because of a change in study design after protocol amendment 5, cohorts A1 and F also included patients with MSI-H/MMR unknown tumors or discordant MMR/MSI status. Cohort F also included patients prospectively enrolled based on POLE exonuclease domain alteration status. Cohorts A1 and F included a total of 347 patients in the efficacy population; specifically, in addition to the 327 dMMR tumors, there were 13 patients enrolled with MSI-H/MMR unknown tumors (2 EC and 11 non-EC), 3 patients with MSI-H/MMRp tumors, and 4 patients with POLE-altered tumors that were MMRp. Included among the 327 tumors that were dMMR, there were 5 tumors that were also POLE altered (Figure 1 and Table 1).

Antitumor Activity

Prespecified Efficacy Analyses

At the time of the data cut, the ORR as assessed per BICR for dMMR solid tumors ($n = 327$) was 44.0% (144 of 327; 95% CI, 38.6%-49.6%) (**Table 2** and eTable 1 in [Supplement 2](#)): there were 43 CRs (13.1%) and 101 PRs (30.9%). The disease control rate was 58.4%.

The median DOR (mDOR) for patients with dMMR solid tumors ($n = 327$) was not reached (range, ≥ 1.18 to ≥ 47.21 months). Responses were durable, with 104 of 144 responders (72.2%) having a response that lasted 12 months or longer. The probability of remaining in response at 6 months was 95.7%, at 12 months was 92.4%, and at 24 months was 84.7% (eTable 1 and eFigure 1 in [Supplement 2](#)).

The mPFS as assessed per BICR for all patients with dMMR solid tumors ($n = 327$) was 6.9 months (95% CI, 4.2-13.6 months) (**Figure 2** and eTable 2 in [Supplement 2](#)). The probabilities of PFS at 6, 12, 24, and 36 months were 50.5% (95% CI, 44.9%-55.9%), 45.8% (95% CI, 40.2%-51.2%), 40.6% (95% CI, 35.0%-46.1%), and 39.7% (95% CI, 33.9%-45.3%), respectively (Figure 2 and eTable 2 in [Supplement 2](#)). The median OS (mOS) for all patients with dMMR solid tumors ($n = 327$) was not reached (95% CI, 31.6 months to not reached) (Figure 2 and eTable 3 in [Supplement 2](#)). The probabilities of OS at 6, 12, 24, and 36 months were 82.6% (95% CI, 78.0%-86.2%), 70.6% (95% CI, 65.3%-75.3%), 58.4% (95% CI, 52.5%-63.9%), and 55.9% (95% CI, 49.7%-61.7%), respectively (Figure 2 and eTable 3 in [Supplement 2](#)).

Post Hoc Analyses

When included in the analysis, the results of the antitumor activity outcomes for the full efficacy population, which includes patients with dMMR and MSI-H or POLE-altered tumors ($n = 347$), were similar to the dMMR population, with an ORR of 44.1% (153 of 347; 95% CI, 38.8%-49.5%) (eTable 1 in [Supplement 2](#)). The mDOR was not reached (range, ≥ 1.18 to ≥ 47.21 months) (Table 2), mPFS was

7.0 months (95% CI, 4.2-13.8 months) (eTable 2 in Supplement 2), and mOS (n = 363) was not reached (95% CI, 39.9 months to not reached) (eTable 3 in Supplement 2).

Analyses were completed to determine the ORR, mDOR, mPFS, and mOS by tumor type in the full efficacy population (n = 347). ORR was similar across tumor types: 45.5% in patients with EC (65 of 143), 43.5% in patients with CRC (50 of 115), 45.5% in patients with gastric cancer (10 of 22), 39.1% in patients with small-intestinal cancer (9 of 23), 41.7% in patients with pancreatic cancer (5 of 12), 42.9% in patients with ovarian cancer (3 of 7), and 44.0% in a combined analysis of other tumor types (11 of 25) (Table 2). DOR, mPFS, and mOS were also similar across tumor types (Table 2 and eFigures 2 and 3 in Supplement 2). Because of the small number of patients with ovarian cancer (n = 7), an analysis of PFS and OS could not be completed; however, ORR was 42.9% (3 of 7; 95% CI,

Table 1. Combined Cohort Analysis: Demographics and Baseline Characteristics

Characteristic	Patients, No. (%)	
	dMMR solid tumors (n = 327)	dMMR and MSI-H and/or POLE-altered (n = 347)
Age, median (range), y	63 (24-85)	63 (24-85)
Sex		
Female	235 (71.9)	241 (69.5)
Male	92 (28.1)	106 (30.5)
Race		
American Indian or Alaska Native	3 (0.9)	3 (0.9)
Asian	7 (2.1)	7 (2.0)
Black	6 (1.8)	6 (1.7)
Native Hawaiian or Other Pacific Islander	0	0
White	206 (63.0)	223 (64.3)
Other, unknown, or not reported	105 (32.1)	108 (31.1)
Ethnicity		
Hispanic or Latino	10 (3.1)	10 (2.9)
Not Hispanic or Latino	205 (62.7)	222 (64.0)
Unknown or not reported	112 (34.3)	115 (33.1)
ECOG performance status		
0	129 (39.4)	138 (39.8)
1	198 (60.6)	208 (60.0)
Prior lines of therapy ^a		
1	137 (41.9)	141 (40.6)
2	118 (36.1)	131 (37.8)
≥3	72 (22.0)	75 (21.6)
Prior therapy type		
Surgery	279 (85.3)	296 (85.3)
Radiotherapy	140 (42.8)	147 (42.4)
Tumor types		
Endometrial cancer	141 (43.1)	143 (41.2)
Colorectal cancer	105 (32.1)	115 (33.1)
Gastric and gastroesophageal junction cancer	21 (6.4)	22 (6.3)
Small-intestinal cancer	19 (5.8)	23 (6.6)
Pancreatic carcinoma	11 (3.4)	12 (3.5)
Biliary neoplasm	10 (3.1)	11 (3.2)
Ovarian cancer	7 (2.1)	7 (2.0)
Other ^b	13 (4.0)	14 (4.0) ^b
Biomarkers, No.		
dMMR	327 ^c	327 ^c
MSI-H/MMRunk	NA	13 ^d
MSI-H/MMRp	NA	3 ^d
POLE alteration and MMRp	NA	4

Abbreviations: dMMR, mismatch repair deficient; ECOG, Eastern Cooperative Oncology Group; MMRp, mismatch repair proficient; MMRunk, mismatch repair status unknown; MSI-H, microsatellite instability-high; NA, not applicable; POLE, polymerase epsilon.

^a Includes lines of therapy in the adjuvant setting.

^b Includes adrenal cortical carcinoma, cancer of unknown origin, esophageal cancer, mesothelioma, breast cancer, malignant neoplasm of the female genitals, renal cell carcinoma, sarcoma, and thymic tumor.

^c Includes 3 patients with endometrial cancer and 2 patients with nonendometrial cancer that was POLE altered and dMMR by IHC. The 3 patients with endometrial cancer were retrospectively identified as having POLE alterations.

^d Excludes patients with POLE alterations.

9.9%-81.6%), and mDOR was not reached (range, ≥ 6.0 to ≥ 36.4 months). An analysis of PFS per best overall response can be found in eAppendix 2 and eTable 4 in Supplement 2.

Eleven patients with POLE alterations were enrolled (eFigure 4 and eTable 5 in Supplement 2). All had alterations in the exonuclease domain. The ORR for patients with POLE-altered solid tumors was 54.5% (6 of 11; 95% CI, 23.4%-83.3%). With a median duration of follow-up of 38.7 months, neither the mDOR (range, 16.9 to ≥ 44.4 months) or mOS (95% CI, 1.8 months to not reached) were reached (eTable 6 and eFigure 5 in Supplement 2). Median PFS was 19.5 months (95% CI, 1.2 months to not reached) (eTable 6 in Supplement 2). Three of 6 patients with MMRp/POLE-altered tumors achieved a response (including 1 patient with CRC who achieved a CR), and 3 of 5 patients with dMMR/POLE-altered tumors achieved a response (eFigure 5 in Supplement 2).

An exploratory analysis of the biomarkers TMB and PD-L1 was performed. It is included in eAppendix 3, eFigures 6 to 9, and eTable 7 in Supplement 2.

Safety

The safety profile of dostarlimab in dMMR and MSI-H or POLE-altered solid tumors was consistent with other anti-PD-(L)1 antibodies, and no new safety concerns were identified. Most treatment-related adverse events (TRAEs) were grade 1 or 2; 16.3% of patients (59 of 363) experienced a grade 3 or greater TRAE (Table 3). Twenty-five patients (6.9%) experienced a TRAE that led to discontinuation; the most frequent TRAEs leading to discontinuation were alanine aminotransferase increase (5 patients [1.4%]) and pneumonitis (4 [1.1%]). The most common grade 3 or greater TRAEs were anemia (9 [2.5%]), alanine aminotransferase increase (7 [1.9%]), and lipase increase (5 [1.4%]). irAEs were experienced by 34.2% of patients (124 of 363); 11.0% of these (40) were grade 3 or greater. The most frequent irAEs were hypothyroidism (25 [6.9%]), alanine aminotransferase increase (21 [5.8%]), and arthralgia (17 [4.7%]). A recent analysis showed no increase in toxic effects at the transition from receiving 500 mg every 3 weeks to receiving 1000 mg every 6 weeks dosing.²⁵

There were 2 deaths attributed by investigators to study treatment. One patient with biliary neoplasm had hepatic ischemia, and 1 patient with CRC died of suicide.

Table 2. Efficacy Results by Tumor Type for Patients With dMMR and MSI-H or POLE-Altered Tumors in the Efficacy Population

Tumor type	Patients, No.	No. (%)		ORR, % (95% CI)	mDOR (95% CI), mo	mPFS (95% CI), mo	mOS (95% CI), mo
		CR	PR				
Overall	347	46 (13.3)	107 (30.8)	44.1 (38.8-49.5)	NR (NR-NR)	7.0 (4.2-13.8)	NR (39.9-NR)
dMMR overall	327	43 (13.1)	101 (30.9)	44.0 (38.6-49.6)	NR (NR-NR)	6.9 (4.2-13.6)	NR (31.6-NR)
EC	143	23 (16.1)	42 (29.4)	45.5 (37.1-54.0)	NR (38.9-NR)	6.0 (4.1-18.0)	NR (25.7-NR)
Non-EC	204	23 (11.3)	65 (31.9)	43.1 (36.2-50.2)	NR (NR-NR)	7.1 (3.6-19.5)	NR (31.5-NR)
Colorectal cancer	115	14 (12.2)	36 (31.3)	43.5 (34.3-53.0)	NR (NR-NR)	8.4 (3.4-NR)	NR (NR-NR)
Gastric cancer	22	1 (4.5)	9 (40.9)	45.5 (24.4-67.8)	NR (17.5-NR)	5.5 (2.8-NR)	20.1 (6.7-NR)
Small-intestinal cancer	23	5 (21.7)	4 (17.4)	39.1 (19.7-61.5)	NR (8.3-NR)	8.1 (2.5-16.5)	31.6 (8.2-NR)
Pancreatic carcinoma	12	0	5 (41.7)	41.7 (15.2-72.3)	NR (NR-NR)	3.3 (2.6-NR)	12.7 (3.1-NR)
Ovarian cancer	7	0	3 (42.9)	42.9 (9.9-81.6)	NA ^a	NA ^a	NA ^a
Other ^b	25	3 (12.0)	8 (32.0)	44.0 (24.4-65.1)	4.5 (2.5-NR)	NR (8.8-NR)	NR (13.5-NR)

Abbreviations: CR, complete response; dMMR, mismatch repair deficient; EC, endometrial cancer; mDOR, median duration of response; mOS, median overall survival; mPFS, median progression-free survival; NA, not applicable; NR, not reached; ORR, objective response rate; POLE, polymerase epsilon; PR, partial response.

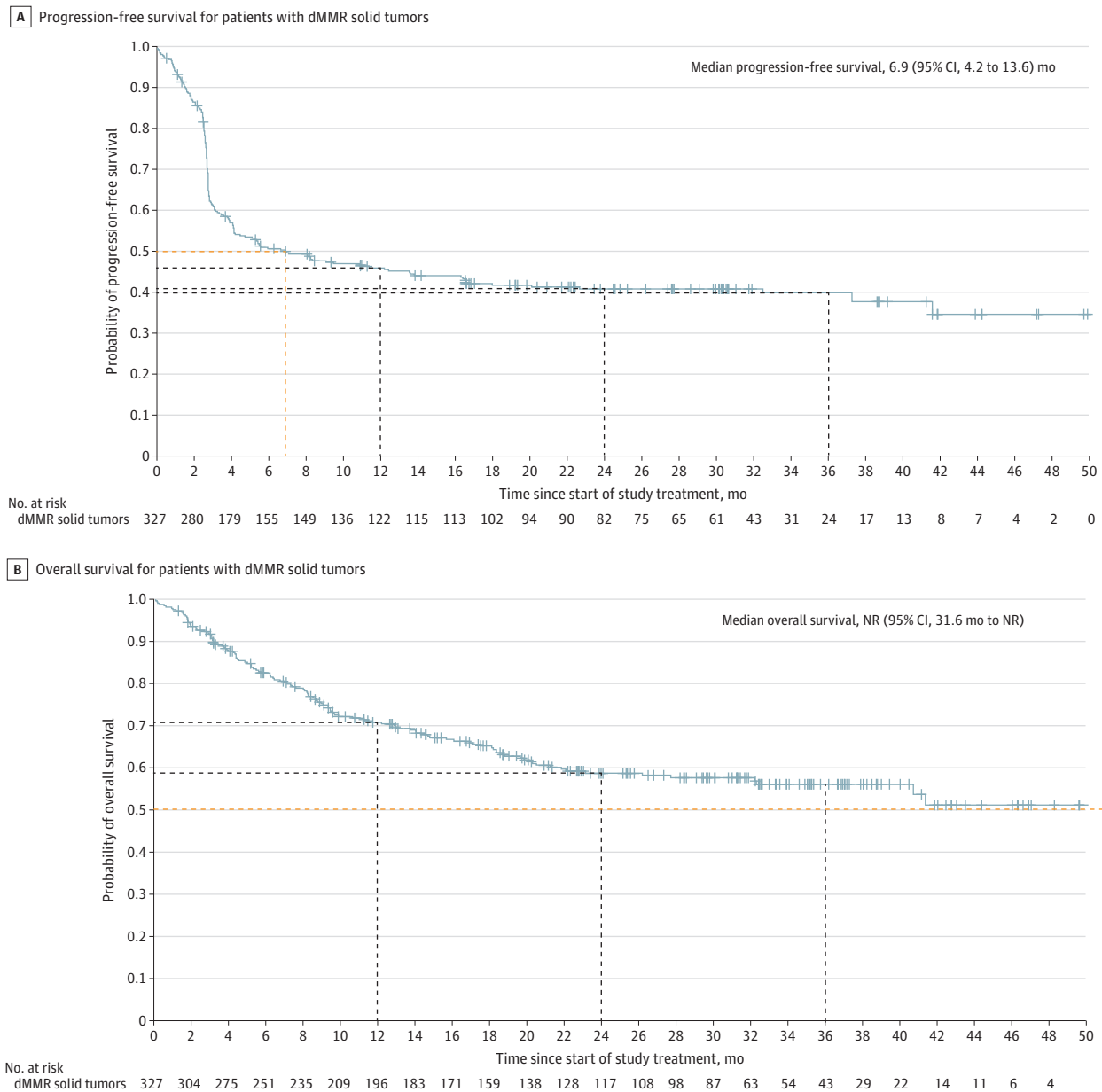
^b Other includes adrenal cortical carcinoma, biliary neoplasm, brain cancer, breast cancer, cancer of unknown primary, esophageal cancer, malignant neoplasm of the female genitals, mesothelioma, prostate cancer, renal cell carcinoma, sarcoma, and thymic tumor.

^a mDOR, mPFS, and mOS, all with 95% CIs, could not be calculated for the ovarian cancer subgroup because of the small size of the population. However, mDOR was not reached, with a range of 6.0 or greater to 36.4 or greater months.

Discussion

This interim analysis provided a long-term follow-up of patients with dMMR and MSI-H and POLE-altered solid tumors who received dostarlimab. Dostarlimab demonstrated clinically meaningful antitumor activity in 327 patients with dMMR solid tumors across various tumor types in the efficacy population. This was a prespecified population based on previously seen responses by dMMR and MSI-H cancers to checkpoint inhibition.^{3,4,7,21} The study met its primary end point in dMMR solid tumors with an ORR of 44.0% (95% CI, 38.6%-49.6%). The lower limit of the 95% CI did not cross the prespecified threshold of 30%, allowing for rejection of the null hypothesis. The ORR was consistent in both EC and non-EC solid tumors. mDOR was not reached, with a probability of

Figure 2. Progression-Free Survival and Overall Survival for Patients With Mismatch Repair Deficient (dMMR) Solid Tumors



A, Dashed lines indicate study time points at 6, 12, 24, and 36 months. B, Dashed lines indicate study time points at 12, 24, and 36 months. Plus signs indicate censoring; NR, not reached.

remaining in response at 2 years of 84.7%, demonstrating that for responders, the responses were durable. The PFS Kaplan-Meier curve begins to plateau just below the median, consistent with observation of sustained CR and PR in most patients who achieved an objective response.

This study demonstrated similar ORR, mDOR, and mPFS in all tumor types, regardless of histology or cell of origin. With a median follow-up of 27.7 months for the dMMR population and of 29.1 months in the full population (dMMR and MSI-H or POLE-altered), mOS was not reached in either population, which suggests meaningful clinical benefit in this biomarker-selected patient population. This finding builds on the body of evidence for dMMR as a meaningful tumor-agnostic

Table 3. Safety Profile of Dostarlimab

Event	Patients with dMMR and MSI-H or POLE-altered solid tumors, No. (%) (n = 363) ^a
Any TEAE	358 (98.6)
Grade ≥3 TEAE	200 (55.1)
Any TRAE	257 (70.8)
Grade ≥3 TRAE	59 (16.3)
Any irAE	124 (34.2)
Grade ≥3 irAE	40 (11.0)
Treatment-related SAE	35 (9.6)
Any TRAE leading to discontinuation	25 (6.9)
TRAE leading to death ^b	2 (0.6)
TRAEs leading to discontinuation in ≥1% of patients	
Alanine aminotransferase increased	5 (1.4)
Pneumonitis	4 (1.1)
Any-grade TRAEs in ≥10% of patients	
Diarrhea	56 (15.4)
Asthenia	52 (14.3)
Pruritus	47 (12.9)
Fatigue	43 (11.8)
Hypothyroidism	37 (10.2)
Grade ≥3 TRAEs in ≥1% of patients	
Anemia	9 (2.5)
Alanine aminotransferase increased	7 (1.9)
Lipase increased	5 (1.3)
irAEs in ≥2% of patients ^c	
Hypothyroidism	25 (6.9)
Alanine aminotransferase increased	21 (5.8)
Arthralgia	17 (4.7)
Aspartate aminotransferase increased	16 (4.4)
Pruritus	12 (3.3)
Pneumonitis	11 (3.0)
Rash	11 (3.0)
Hyperthyroidism	10 (2.8)

Abbreviations: dMMR, mismatch repair deficient; irAE, immune-related adverse event; MSI-H, microsatellite instability-high; POLE, polymerase epsilon; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

^a Includes all patients with dMMR and MSI-H or POLE alterations who received at least 1 dose of dostarlimab.

^b One patient with biliary neoplasm had hepatic ischemia, and 1 patient with colorectal cancer died of suicide; these events were attributed by investigators to study treatment.

^c irAEs were defined as grade 2 and greater from a predefined list.

biomarker, thus providing additional evidence on the importance of testing for dMMR status through the use of a companion test, such as IHC.^{7,24}

Anti-PD-1 therapies have been tested in other studies of dMMR CRC or solid tumors (various primary origin), including pembrolizumab in KEYNOTE-164 and KEYNOTE-158 and nivolumab in CHECKMATE 142 and NCI-MATCH group Z1D.²⁶⁻³⁰ However, the trial designs and patient populations differed from GARNET. Specifically, KEYNOTE-158 and NCI-MATCH group Z1D did not include patients with CRC, whereas KEYNOTE-164 and CHECKMATE 142 were 100% CRC, and GARNET enrolled diverse tumor types for a combined analysis.²⁶⁻³⁰ Antitumor activity and safety comparisons across different studies have limitations and should be done with caution and awareness of the heterogeneity in study designs.

Few studies of immune checkpoint inhibitors have been conducted on patients with advanced disease harboring POLE alterations.⁹⁻¹¹ Although only a small number of patients were included (n = 11), GARNET is one of the largest reports of immune checkpoint inhibitors in POLE-altered cancers in a prospective clinical study. Dostarlimab demonstrated encouraging antitumor activity in patients with pathogenic POLE alterations in the exonuclease domain in GARNET, with ORR of 54.5%, DOR not reached with 3 years or longer of median follow-up, and PFS of 1 year or longer, consistent with reports of other immune checkpoint inhibitors.^{9,10} The POLE-altered population in this trial was small, thus limiting the certainty of the results.

This study has several points to highlight relative to other published studies of anti-PD-1 therapies in patients with dMMR and MSI-H advanced metastatic tumors.^{3,5,26-28,30} First, MMR status, as assessed by IHC, is an appropriate biomarker to select patients for treatment with dostarlimab because of consistently high antitumor activity results across tumor types. Second, to qualify for GARNET, patients were required to have evidence of prior treatment progression by BICR, ensuring that most patients treated with dostarlimab in this study had actively progressing tumors. Finally, this study suggests that TMB and PD-L1 may be biomarkers that, when added to MMR status, identify a population who are more likely to respond to dostarlimab; however, this addition requires validation in a prospective analysis.

Limitations

There are several limitations to this study. GARNET is a single-group trial of dostarlimab and was not designed to assess superiority or equivalence with other therapies. Cohorts A1 (dMMR and MSI-H EC) and F (dMMR and MSI-H or POLE-altered non-EC solid tumors) were a predefined biomarker-selected populations with inclusion by local IHC, polymerase chain reaction, or next-generation sequencing testing, without centralized analysis before inclusion, which, although a limitation, reflects typical laboratory practice. Evaluation was by RECIST version 1.1, and therefore does not permit assessment of the rate of patients with pseudo-progression; consequently these patients would be considered as an event in the PFS evaluation, potentially underestimating the true treatment activity of dostarlimab.³¹ Furthermore, the sample sizes were small for some individual tumor types, and therefore the results observed in this study may not reflect their broader populations.

Conclusions

Advanced cancer that has progressed on or following prior chemotherapy with or without targeted therapy is typically associated with poor outcomes. The antitumor activity data presented here support the use of dostarlimab monotherapy in patients with dMMR solid tumors and provide evidence on the durability of response in this setting. The safety profile was manageable and consistent with prior reports. The additional post hoc tumor-specific and biomarker analyses provided in this report are of academic interest and suggest that prospective studies evaluating POLE alterations, as well as TMB and PD-L1 expression, may demonstrate that these biomarkers, in addition to dMMR and MSI-H, improve identification of patients most likely to benefit from

dostarlimab. In summary, dostarlimab provided clinically meaningful long-term benefit with a tolerable safety profile in dMMR solid tumors with a high unmet need.

ARTICLE INFORMATION

Accepted for Publication: August 14, 2023.

Published: November 2, 2023. doi:10.1001/jamanetworkopen.2023.41165

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Author Contributions: Dr André had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: André, Curigliano, Oaknin, Trigo, Boni, Zografos, Banerjee.

Critical review of the manuscript for important intellectual content: All authors.

Statistical analysis: Curigliano, Dewal, Antony, Zografos.

Administrative, technical, or material support: André, Ellard, Trigo, Kristeleit, Miller, Boni, Zografos.

Supervision: André, Berton, Curigliano, Oaknin, de Braud, Trigo, Gravina, Kristeleit, Moreno, Brown, Veneris.

Conflict of Interest Disclosures: Dr André reported receiving personal fees from Astellas, AstraZeneca, Aptitude Health, Bristol-Myers Squibb, Gritstone Oncology, GamaMabs Pharma SA, Gilead, GSK, Merck & Co Inc, Nordic Oncology, Pierre Fabre, Transgène, Servier, Seagen, Sanofi, Merck Serono, Amgen, and Roche/Ventana and receiving support for meetings from Bristol-Myers Squibb, Merck & Co Inc and Servier outside the submitted work. Dr Curigliano reported receiving personal fees from Bristol-Myers Squibb, Ellipsis, Seattle Genetics, Roche, Novartis, Pfizer, Eli Lilly and Co, AstraZeneca, Daichii Sankyo, and Gilead during the conduct of the study. Dr Sabatier reported receiving personal fees from AstraZeneca, Eisai, Novartis, Roche, MSD, and GSK; nonfinancial support from AstraZeneca, Bristol-Myers Squibb, GSK, Pfizer, and Roche; grants from AstraZeneca, and grants to the institution from AstraZeneca and Eisai outside the submitted work. Dr Tinker reported receiving institutional

grants from AstraZeneca and personal fees from GSK, Merck, Eisai, and AstraZeneca outside the submitted work. Dr Oaknin reported receiving personal fees from Agenus, AstraZeneca, Bristol-Myers Squibb, Clovis Oncology, Corcept Therapeutics, Deciphera Pharmaceuticals, Eisai, EMD Serono, F. Hoffmann-La Roche, Genmab, GSK, ImmunoGen, Itheos, MSD, Mersana Therapeutics, Novocure, OneXerna Therapeutics Inc, PharmaMar, Regeneron, Roche, Shattuck Labs, Seagen, and Sutro Biopharma and receiving institutional grants from AbbVie Deutschland, Ability Pharmaceuticals, Advaxis Inc, Aeterna Zentaris, Amgen, Aprea Therapeutics, Clovis Oncology, Eisai, F. Hoffmann-La Roche, GSK, ImmunoGen, Merck Sharp & Dohme de Espana, Millennium Pharmaceuticals, PharmaMar, and Regeneron Pharmaceuticals outside the submitted work. Dr Ellard reported owning stock in GSK outside the submitted work. Dr de Braud reported receiving personal fees from EMD Serono, Manarini, Novartis, MSD, Bristol-Myers Squibb, Incyte, Roche, Nerviano Medical Science, and Sanofi; receiving speakers bureau fees from AccMed, Amgen, Bristol-Myers Squibb, Healthcare Research & Pharmacoepidemiology, Incyte, Merck Group, MSD, Nadirex, Pfizer, Roche, Sanofi, and Servier; and receiving principal investigator fees from Basilea Pharmaceutica, Bristol-Myers Squibb, Exelixis, Daiichi Sankyo Development Limited, F. Hoffmann-LaRoche, Ignyta Operating, Janssen-Cilag International, Kymab, Loxo Oncology Inc, MedImmune, Merck KGAA, Merck Sharp & Dohme SpA, MSD, Novartis, Pfizer, and Tesaro outside the submitted work. Dr Trigo reported receiving institutional grants from AstraZeneca and MSD and receiving personal fees from Bristol-Myers Squibb, AstraZeneca, Boehringer, Takeda, MSD, and GSK during the conduct of the study. Dr Gravina reported receiving grants from Tesaro/GSK during the conduct of the study; receiving nonfinancial support from Pfizer; receiving grants from Janssen, AstraZeneca, Daiichi-Sankyo, Incyte, Exelixis, MSD, Pfizer, Roche, Bayer, Boehringer-Ingheleim, Hifibio, Merck, Sutro, and Taiho outside the submitted work. Dr Kristeleit reported receiving grants from Clovis Oncology and MSD; personal fees from GSK, Clovis Oncology, Tubulis, Merck, Celcuity, Leucid Bio, Duke St Bio, Seattle Genetics, Eisai, Basilea, Shattuck Labs, iTEOS, Incyte, Regeneron, AstraZeneca, PharmaMar, and MSD outside the submitted work. Dr Moreno reported receiving personal fees from Bristol-Myers Squibb, Bayer, Roche, Basilea, Janssen, Nanobiotix, Pieris, Regeneron/Sanofi, AstraZeneca, and Affimed outside the submitted work and receiving institutional funding from AbbVie, AceaBio, Adaptimmune, ADC Therapeutics, Aduro, Agenus, Amcure, Amgen, Astellas, AstraZeneca, Bayer, Beigene, Biolvent International, BMS, Boehringer, Celgene, Daichii Sankyo, Debiopharm, Eisai, e-Therapeutics, Exelixis, Forma Therapeutics, Genmab, GSK, Harpoon, Hutchison, Immutep, Incyte, Inovio, Iovance, Janssen, Kyowa Kirin, Eli Lilly and Co, Loxo Oncology Inc, MedSir, Menarini, Merck, Merus, Millennium, MSD, Nanobiotix, Nektar, Novartis, Odonate Therapeutics, Pfizer, PharmaMar, Principia, PsiOxus, Puma, Regeneron, Rigontec, Roche, Sanofi, Sierra Oncology, Synthon, Taiho, Takeda, Tesaro, Transgene, Turning Point Therapeutics, and Upshersmith outside the submitted work. Dr Abdeddaim reported receiving grants from MSD, GSK, Clovis Oncology, and AstraZeneca and receiving personal fees from AstraZeneca, Clovis Oncology, Merck, and GSK outside the submitted work. Dr Vano reported receiving personal fees from Bristol-Meyers Squibb, Janssen, Merck, Novartis, Roche, Sanofi, Viatrix, Pfizer, MSD, Ipsen, and Eisai outside the submitted work. Dr Samouëlian reported receiving personal fees from Merck. Dr Miller reported receiving consultant fees from AZD, Clovis Oncology, Ellipses, GSK, MSD, and Shionogi; speakers' bureau fees from AZD, Clovis Oncology, GSK, and Roche; travel grants from AZD and GSK; and trial funding from MSD. Dr Boni reported receiving institutional grants from AbbVie, ACEO, Adaptimmune, Alkermes, Amcure, Amgen, Array BioPharma, AstraZeneca, Bristol-Myers Squibb, Bayer, BioNTech, CytomX, Genmab, Roche/Genentech, GSK, Genentech/Roche, H3, Incyte, Janssen, Kura, Eli Lilly and Co, Loxo Oncology Inc, Nektar, Macrogenics, Menarini, Merck, Merus, Nanobiotix, Novartis, Pfizer, PharmaMar, Principia, Puma, Sanofi, Taiho, Tesaro, BeiGene, Transgene, Takeda, Innovio, MSD, PsiOxus, Seattle Genetics, Mersana, Daiichi, Astellas, Orca, Boston Therapeutics, Dynavax, DebioPharm, Boehringer Ingelheim, Regeneron, Millennium, Synthon, Spectrum, Rigontec, and Zenith; receiving personal fees from Puma Biotechnology, Ideaya Biosciences, Loxo Oncology Inc, START, CytomX Therapeutics, Guidepoint, OncoArt, Eli Lilly and Co, Janssen, NEX Oncology, and QuironSAlud, outside the submitted work. Dr Anton Torres reported personal fees from AstraZeneca-Daichii-Sanykio and personal fees from Pfizer during the conduct of the study, personal fees from Lilly and personal fees from Gilead outside the submitted work. Dr Gilbert reported receiving personal fees from Alkermes, AstraZeneca, Eisai-Merck, GSK, Merck, Eisai, Novovure, and Kora Health; receiving grants Pfizer, Merck Sharp & Dohme, Karyopharm, Tesaro, Alkermes, AstraZeneca, Clovis, IMV, ImmunoGen, Roche, Mersana, Esperas, Novovure, Oncoquest, K-Group Beta, and GSK outside the submitted work. Dr Brown reported serving on the research steering committee for Genentech, receiving research support from Caris Life Sciences, receiving personal fees from AstraZeneca, Verastem, Clovis, Eisai, and GSK/Tesaro outside the submitted work. Drs Dewal, Dabrowski, Antony, and Zografos reported being employees of GSK during the conduct of the study. Dr Veneris reported receiving personal fees from GSK during the conduct of the study and outside the submitted work. Dr Banerjee reported receiving funding from The Royal Marsden NHS Foundation Trust during the conduct of the study and receiving grants from AstraZeneca and GSK; receiving personal fees from Amgen, Clovis Oncology, GenMab, Merck Serono, GSK, AstraZeneca, Immunogen, MSD, Mersana, Novartis, OncXerna, Seagen, Shattuck Labs, Regeneron, Epsilogen, Novacure, Takeda, Roche, Pfizer, and Verastem outside the submitted work. No other disclosures were reported.

Funding/Support: This study was funded by GSK.

Role of the Funder/Sponsor: The trial was designed by GSK (originally designed and funded by Tesaro, acquired by GSK in 2019), in collaboration with the authors. The sponsor provided support for the statistical analyses of the data and funded a medical writer for the report. The authors performed the collection, analysis, and interpretation of the data. The authors had the final decision to submit the manuscript for publication. GSK had a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The manuscript was written by the authors, with medical writing assistance funded by GSK. GSK collaborated with the investigators in designing the trial, provided the study drug, coordinated the management of the study sites, funded the statistical analysis, and provided medical writing support. Authors employed by GSK, in coordination with all authors, were involved in preparation, review, approval, and decision to submit the manuscript.

Data Sharing Statement: See Supplement 3.

Additional Contributions: We thank the patients, their families, the clinical investigators, and site personnel who participated in this trial and Heather Ostendorff-Bach, PhD, of GSK, for coordinating compensated editorial and writing assistance provided by Shannon Morgan-Pelosi, PhD, and Jennifer Robertson, PhD, of Ashfield MedComms, an Inizio company.

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SUPPLEMENT 1.

Trial Protocol and Statistical Analysis Plan

SUPPLEMENT 2.

eAppendix 1. Sites and Investigators and Supplementary Methods

eFigure 1. Duration of Treatment for Responders With dMMR Solid Tumors

eTable 1. Antitumor Activity Analysis

eTable 2. Progression-Free Survival

eTable 3. Overall Survival

eFigure 2. Progression-Free Survival by Tumor Type

eFigure 3. Overall Survival by Tumor Type

eAppendix 2. Post Hoc Analysis of PFS by BOR

eTable 4. Progression-Free Survival by Best Overall Response per BICR in the Overall Efficacy Population

eFigure 4. Enrollment and Outcomes for Patients With POLE-Altered Tumors

eTable 5. Demographics and Baseline Characteristics of Patients With POLE Alterations

eTable 6. POLE-Altered Antitumor Activity Analysis by BICR

eFigure 5. Duration of Treatment for Patients With POLE-Altered Solid Tumors

eAppendix 3. Exploratory Analysis of Biomarkers

eFigure 6. Prevalence of TMB and PD-L1 in GARNET Cohorts A1 and F

eFigure 7. CPS and TMB Distribution by Cohort

eFigure 8. ORR by CPS as Continuous Variable

eFigure 9. ORR by TMB as Continuous Variable

eTable 7. Antitumor Activity Results by TMB and PD-L1 Status for dMMR EC and Non-EC Solid Tumors

SUPPLEMENT 3.

Data Sharing Statement