2 SYNOPSIS

Abbreviations are defined in the list of abbreviations located at the end of the Synopsis.

SPONSOR: Merck Sharp & Dohme LLC, Rahway, NJ, USA (hereafter called the Sponsor or MSD)

COMPOUND NAME: Favezelimab (+) pembrolizumab (MK-4280A)

PROTOCOL TITLE: A Phase 3 study of MK-4280A (coformulated favezelimab [MK-4280] plus pembrolizumab [MK-3475]) Versus Standard of Care in Previously Treated Metastatic PD-L1 positive Colorectal Cancer (KEYFORM-007)

STUDY IDENTIFIERS:

IND: 147726	EudraCT: 2021-001309-60	WHO/UTN: Not applicable	NCT: NCT05064059
jRCT: Not applicable	EU CT: Not applicable		

STUDY PHASE: Phase 3

INDICATION: Colon cancer Stage IV

STUDY CENTERS: This study was conducted at 155 centers in 21 countries. Of these centers, 125 centers randomized participants to study intervention.

STUDY STATUS: This study is complete. After enrollment of the global portion of the study was complete, the study remained open to enrollment in China alone until the target number of participants in China was enrolled to meet local regulatory requirements. This EoT report presents efficacy and safety results for the global population (includes all participants who were enrolled during the global enrollment period) and the China subpopulation (includes all China mainland participants who were enrolled during the global enrollment period and in the extension portion). Efficacy results for the global population are based on the FA (data cutoff: 15-AUG-2024) for the primary endpoint of OS and the IA (data cutoff: 21-AUG-2023) for the secondary endpoints of PFS, ORR, and DOR based on BICR assessment per RECIST 1.1. For the China subpopulation, efficacy results are based on the FA (data cutoff: 15-AUG-2024) for all endpoints, including OS, PFS, ORR, and DOR. A summary of all safety data collected is presented for the global population and the China subpopulation as of the EoT LPLV date of 21-FEB-2025. For participants enrolled during the global enrollment period, PRO results are presented for the PRO FAS population as of the EoT LPLV date of 21-FEB-2025.

First Participant First Visit	10-NOV-2021
Last Participant Last Visit	21-FEB-2025
Last Data Available	17-MAR-2025
Database Lock Date	24-MAR-2025

METHODOLOGY: MK-4280A-007 was a Phase 3, randomized, open-label, active-controlled, parallel-group, multicenter, safety and efficacy study of favezelimab + pembrolizumab versus SOC (either regorafenib or TAS-102) in participants with metastatic (Stage IV as defined by AJCC eight edition) colorectal adenocarcinoma whose tumors were positive for PD-L1 with CPS score ≥1, had pMMR status based on IHC testing at screening, and had progressed on or could not tolerate previous treatment with fluoropyrimidine (or capecitabine), oxaliplatin, and irinotecan, ±VEGF agent, ±EGFR agent (if RAS WT left-sided tumor), and +RAF inhibitors (if BRAF V600E mutated). PD-L1 and MMR status were tested centrally for eligibility.

The treatment phase of the study consisted of 2 arms: Arm A and Arm B. Participants were randomized 1:1 to receive either favezelimab + pembrolizumab (Arm A) or SOC (Arm B). Randomization was stratified by geographic region of the enrolling site (Asia Pacific, EMEA/Americas), presence of liver metastasis (yes, no), and time from initial diagnosis of metastatic disease to randomization (≥18 months, <18 months).

In Arm A, participants received favezelimab + pembrolizumab administered every 3 weeks for up to 35 cycles (approximately 2 years). Participants who attained a locally confirmed CR per RECIST 1.1 by 2 tumor scans at least 4 weeks apart and who had received at least 8 cycles (approximately 6 months) with favezelimab + pembrolizumab could discontinue intervention at the discretion of the investigator after receiving at least 2 cycles beyond the initial determination of a CR.

In Arm B, participants received the SOC treatment (either regorafenib or TAS-102) as per local and institutional guidelines according to the approved product labels. Participants in Arm B were not allowed to cross over to Arm A intervention.

AEs were monitored throughout the study and graded in severity according to the guidelines outlined in the NCI CTCAE v5.0. Each participant was monitored for AEs and SAEs, with specific events collected and designated as ECIs.

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
Arm A	MK-4280A	20 mg/mL favezelimab + 5 mg/mL pembrolizumab for a total protein content of 25 mg/mL	800 mg MK-4280 + 200 mg MK-3475	IV Infusion	Day 1, then Q3W, up to 35 infusions	Test Product
Arm B	regorafenib	40 mg/tablet	160 mg	Oral	4-week cycle: QD Days 1-21, no dose Days 22-28	Comparator
Arm B	TAS-102	15 mg trifluridine/6.14 mg tipiracil; 20 mg trifluridine/8.19 mg tipiracil	35 mg/m^2	Oral	4-week cycle: BID Days 1 to 5 and 8 to 12 of each 28-day treatment cycle (no dose days 6, 7, and 13-28)	Comparator

BID=twice daily; IV=intravenous; Q3W=every 3 weeks; QD=daily.

ELIGIBILITY CRITERIA: Participants were included in the study if they had histologically confirmed metastatic and unresectable colorectal adenocarcinoma (Stage IV as defined by AJCC eighth edition) and measurable disease per RECIST 1.1 as assessed by the local site investigator.

OBJECTIVES AND ENDPOINTS:

Primary Objective	Primary Endpoint
• To compare MK-4280A to standard of care (regorafenib or TAS-102) with respect to overall survival. • Hypothesis (H1): MK-4280A is superior to standard of care with respect to overall survival.	• Overall survival: The time from randomization to death due to any cause.
Secondary Objectives	**Secondary Endpoints**
• To compare MK-4280A to standard of care with respect to progression free survival per RECIST 1.1 as assessed by BICR. • Hypothesis (H2): MK-4280A is superior to standard of care with respect to progression free survival per RECIST 1.1 by BICR.	• Progression-free survival: The time from randomization to the first documented disease progression or death due to any cause, whichever occurs first.

• To compare MK-4280A to standard of care with respect to objective response rate per RECIST 1.1 as assessed by BICR • Hypothesis (H3): MK-4280A is superior to standard of care with respect to ORR per RECIST 1.1 by BICR.	• Objective response: complete response or partial response.
• To assess the efficacy of MK-4280A and standard of care with respect to duration of response per RECIST 1.1 by BICR.	• Duration of response: the time from first response (complete response or partial response) to subsequent disease progression or death from any cause, whichever occurs first.
• To determine the safety and tolerability of MK-4280A and standard of care.	• Adverse event • Study intervention discontinuation due to AEs
• To compare the change from baseline in global health status/QoL, physical functioning, appetite loss and bloating for MK-4280A versus standard of care.	• Score for the following Patient-Reported Outcomes scales/items: global health status/QoL (EORTC QLQ-C30 items 29 and 30), physical functioning (EORTC QLQ-C30 items 1-5), appetite loss (EORTC QLQ-C30 item 13) and bloating (EORTC QLQ-CR29 item 37).
• To compare the time to deterioration in global health status/QoL, physical functioning, appetite loss and bloating for MK-4280A versus standard of care.	• Time-to-deterioration, defined as the time from baseline to the first onset of a ≥10-point deterioration from baseline in global health status/QoL (EORTC QLQ-C30 items 29 and 30), physical functioning (EORTC QLQ-C30 items 1-5), appetite loss (EORTC QLQ-C30 item 13) and bloating (EORTC QLQ-CR29 item 37).
Tertiary/Exploratory Objectives	**Tertiary/Exploratory Endpoints**
CCI [redacted]	

NUMBER OF PARTICIPANTS (planned and analyzed):

The planned enrollment total for this study was 432 participants. As of the LPLV for this report:

- 441 participants were randomized and included in the global ITT population for efficacy analysis (221 in the favezelimab + pembrolizumab group, 220 in the SOC group), of which 30 were China mainland participants enrolled during the global enrollment period

- 431 participants were included in the global APaT population for safety analysis (221 in the favezelimab + pembrolizumab group, 210 in the SOC group)

- 94 participants were randomized and included in the China ITT population for efficacy analysis (50 in the favezelimab + pembrolizumab group, 44 in the SOC group), of which 64 were enrolled during the extension enrollment period

- 93 participants were included in the China APaT population for safety analysis (49 in the favezelimab + pembrolizumab group, 44 in the SOC group)

STATISTICAL AND ANALYSIS METHODS:

Global Population

The nonparametric KM method was used to estimate the OS and PFS curves. The treatment difference in OS and PFS was assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling was used to assess the magnitude of the treatment difference (HR). The HR and its 95% CI from the stratified Cox model with a single treatment covariate were reported. The stratification factors used for randomization were applied to both the stratified log-rank test and the stratified Cox model with small strata collapsed as prespecified in the sSAP. The stratified M&N method was used for the comparison of ORR. The difference in ORR and its 95% CI from the stratified M&N method with strata weighting by sample size were reported.

CCI [redacted]

The multiplicity strategy was applied to the primary hypothesis OS and secondary hypotheses PFS and ORR, with the overall Type-I error among the 3 hypotheses strongly controlled at 2.5% (one-sided), with 2.5% initially allocated to the OS hypothesis. The study used the graphical method of Maurer and Bretz to control multiplicity for multiple hypotheses as well as IAs. According to this approach, study hypotheses could be tested more than once, and when a particular null hypothesis was rejected, the α allocated to that hypothesis could be reallocated to other hypothesis tests.

Safety and tolerability were assessed by clinical review of all relevant parameters including AEs and laboratory tests. The analysis of safety results followed a tiered approach. Tier 1 safety endpoints were subject to inferential testing for statistical significance. Tier 2 parameters were assessed via point estimates with 95% CIs provided for between-group comparisons. Tier 3 safety parameters included AEs occurring in <10% of participants and continuous measures such as changes from baseline in laboratory and vital signs.

PRO analyses were performed as prespecified in the protocol and sSAP. Additional role functioning analyses were conducted.

China Subpopulation

Consistent with the statistical methods for efficacy analyses, no formal hypothesis testing was planned, and no multiplicity adjustment was applied. Unstratified methods were used for the China subpopulation analyses. CCI [redacted]

Safety analyses for the China subpopulation were the same as those for the global population.

RESULTS:

Participant Disposition:

Global Population

CCI [redacted]

Demographics and Baseline Characteristics:

The data presented below are based on the ITT analysis population.

Global Population

- Mean Age (Standard Deviation): 58.8 years (11.4).
- Median Age (Range): 59.0 years (24 to 83 years).
- Sex: 277 (62.8%) male, 164 (37.2%) female.

- Ethnicity: 393 (89.1%) not Hispanic or Latino, 36 (8.2%) Hispanic or Latino, 11 (2.5%) not reported, 1 (0.2%) unknown.

- Race: 132 (29.9%) Asian, 9 (2.0%) Black or African American, 2 (0.5%) multiple, 292 (66.2%) White, 6 (1.4%) missing.

China Subpopulation

- Mean Age (Standard Deviation): 56.5 years (10.8).

- Median Age (Range): 56.5 years (29 to 74 years).

- Sex: 57 (60.6%) male, 37 (39.4%) female.

- Ethnicity: 94 (100.0%) not Hispanic or Latino.

- Race: 94 (100.0%) Asian.

Efficacy and Patient-reported Outcomes:

Global Population

- At the FA, the favezelimab + pembrolizumab group did not demonstrate a statistically significant improvement for OS compared with SOC (HR = 0.98; [95% CI: 0.80, 1.20]; *p*=0.4183). The median OS by KM estimate for the favezelimab + pembrolizumab group compared with the SOC group was 7.3 months vs 8.5 months.

- At the IA, HR for PFS was 1.34 (95% CI: 1.09, 1.64; nominal *p*=0.9967). The median PFS by KM estimate for the favezelimab + pembrolizumab group compared with the SOC group was 2.1 months vs 2.6 months. PFS was not formally statistically tested per the prespecified multiplicity strategy.

- At the IA, ORR of the favezelimab + pembrolizumab group was 6.8% (95% CI: 3.8%, 10.9%), compared with 0.9% (95% CI: 0.1%, 3.2%) for the SOC group. The difference in objective response between favezelimab + pembrolizumab and SOC was 5.9% ([95% CI: 2.5%, 10.1%]; nominal *p*=0.0007). ORR was not formally statistically tested per the prespecified multiplicity strategy.

- At the IA, the median DOR was NR for the favezelimab + pembrolizumab group and was 12.4 months for the SOC group. The median TTR was 2.1 months for the favezelimab + pembrolizumab group and 2.0 months for the SOC group.

- Similar results were observed in both intervention groups in overall health-related QoL as evaluated by the EORTC QLQ-C30 (global health status/QoL, physical functioning, role functioning, and appetite loss), EORTC QLQ-C29 (bloating), and EQ-5D-5L VAS scores.

China Subpopulation

The following results were reported at the FA:

- The HR for OS was 0.94 (95% CI: 0.59, 1.50). The median OS by KM estimate for the favezelimab + pembrolizumab group compared with the SOC group was 9.6 months vs 9.2 months.

- The HR for PFS was 1.23 (95% CI: 0.78, 1.92). The median PFS by KM estimate was 2.1 months in both intervention groups.

- The ORR of the favezelimab + pembrolizumab group was 6.0% (95% CI: 1.3%, 16.5%); no responses were observed in the SOC group.

- The median DOR was 6.4 months for the favezelimab + pembrolizumab group; no responses were observed in the SOC group. The median TTR was 4.1 months for the favezelimab + pembrolizumab group.

Safety:

Global Population

No new safety concerns for the combination of favezelimab and pembrolizumab were identified. The safety profile for the combination of favezelimab and pembrolizumab is manageable and is generally consistent with the established safety profile of pembrolizumab monotherapy in nature and severity.

The key safety findings are as follows:

- The percentage of participants with AEs was comparable for the favezelimab + pembrolizumab group (92.8%) and the SOC group (94.8%).

- Most categories of AEs were comparable between groups. The favezelimab + pembrolizumab group had a higher percentage of participants with serious intervention-related AEs (17.2% vs 5.7%) than the SOC group, and a lower percentage of participants with intervention-related AEs (66.1% vs 79.5%), Grade 3 to 5 AEs (43.0% vs 60.5%), and Grade 3 to 5 intervention-related AEs (19.9% vs 36.2%) than the SOC group. The most frequently reported AEs observed were predominantly of mild to moderate intensity (Grade 1 or 2).

- A total of 14 deaths were reported (6 in the favezelimab + pembrolizumab group and 8 in the SOC group). Deaths due to intervention-related AEs were reported for 1 participant in the favezelimab + pembrolizumab group and 1 participant in the SOC group.

- As expected, the percentage of participants with AEOSIs was higher for the favezelimab + pembrolizumab group (38.0%) than the SOC group (6.2%). AEOSI were manageable with standard measures including steroid therapy, intervention interruption, and hormone replacement therapy.

China Subpopulation

- Safety results for the China participants were generally consistent with the global population. No new safety concerns were identified.

Adverse Event Summary
(APaT Population)

	Favezelimab + Pembrolizumab		SOC	
	n	(%)	n	(%)
Participants in population	221		210	
with one or more adverse events	205	(92.8)	199	(94.8)
with no adverse event	16	(7.2)	11	(5.2)
with drug-related[a] adverse events	146	(66.1)	167	(79.5)
with toxicity grade 3-5 adverse events	95	(43.0)	127	(60.5)
with toxicity grade 3-5 drug-related[a] adverse events	44	(19.9)	76	(36.2)
with serious adverse events	75	(33.9)	56	(26.7)
with serious drug-related[a] adverse events	38	(17.2)	12	(5.7)
who died	6	(2.7)	8	(3.8)
who died due to a drug-related[a] adverse event	1	(0.5)	1	(0.5)
discontinued drug due to an adverse event	21	(9.5)	19	(9.0)
discontinued drug due to a drug-related[a] adverse event	16	(7.2)	9	(4.3)
discontinued drug due to a serious adverse event	15	(6.8)	11	(5.2)
discontinued drug due to a serious drug-related[a] adverse event	11	(5.0)	4	(1.9)

[a] Determined by the investigator to be related to the drug.
Grades are based on NCI CTCAE version 5.0.
Non-serious adverse events up to 30 days of last treatment and serious adverse events up to 90 days of last treatment are included.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: 21FEB2025.

Source: [P007MK4280A: adam-adsl; adae]

Adverse Event Summary
(China APaT Population)

	Favezelimab + Pembrolizumab		SOC	
	n	(%)	n	(%)
Participants in population	49		44	
with one or more adverse events	46	(93.9)	44	(100.0)
with no adverse event	3	(6.1)	0	(0.0)
with drug-related[a] adverse events	37	(75.5)	43	(97.7)
with toxicity grade 3-5 adverse events	15	(30.6)	30	(68.2)
with toxicity grade 3-5 drug-related[a] adverse events	9	(18.4)	25	(56.8)
with serious adverse events	12	(24.5)	13	(29.5)
with serious drug-related[a] adverse events	7	(14.3)	8	(18.2)
who died	2	(4.1)	1	(2.3)
who died due to a drug-related[a] adverse event	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	5	(10.2)	4	(9.1)
discontinued drug due to a drug-related[a] adverse event	3	(6.1)	2	(4.5)
discontinued drug due to a serious adverse event	5	(10.2)	3	(6.8)
discontinued drug due to a serious drug-related[a] adverse event	3	(6.1)	2	(4.5)

[a] Determined by the investigator to be related to the drug.
Grades are based on NCI CTCAE version 5.0.
Non-serious adverse events up to 30 days of last treatment and serious adverse events up to 90 days of last treatment are included.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: 21FEB2025.

Source: [P007MK4280A: adam-adsl; adae]

CONCLUSIONS:

Efficacy

The following key efficacy results were observed:

- In the global population, the combination of favezelimab + pembrolizumab did not demonstrate a statistically significant improvement in OS when compared with SOC in the ITT population consisting of treatment refractory PD-L1 positive (CPS ≥1) MSS mCRC.

- Efficacy results for the China participants were generally consistent with the global population.

Safety

Based on the results from this study in the global population and the China subpopulation, the following safety conclusions can be made:

- The safety profile for the combination of favezelimab and pembrolizumab is manageable and is generally consistent with the established safety profile of pembrolizumab monotherapy in nature and severity.

- No new safety risks were identified in association with the combination of favezelimab with pembrolizumab relative to the known safety profile of pembrolizumab.

- Safety results for the China participants were generally consistent with the global population with no new safety concerns identified.

LIST OF ABBREVIATIONS:

Abbreviation/Term	Definition
AE	adverse event
AEOSI	adverse event of special interest
AJCC	American Joint Committee on Cancer
APaT	All-Participants-as-Treated
BICR	blinded independent central review
CI	confidence interval
CPS	combined positive score
CR	complete response
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DOR	duration of response
ECI	event of clinical interest
eDMC	external data monitoring committee
EGFR	epidermal growth factor receptor
EMEA	Europe, Middle East, Africa
EORTC QLQ-CR29	European Organisation for Research and Treatment of Cancer's Quality of Life Questionnaire for Colorectal Cancer
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer's Quality of Life Questionnaire Core 30
EoT	end of trial
EQ-5D-5L	EuroQol 5-Dimensions 5-Levels
EU CT	European Union Clinical Trials
EudraCT	European Drug Regulatory Authorities Clinical Trials
FA	final analysis
FAS	full-analysis set
GCP	Good Clinical Practice
HR	hazard ratio
IA	interim analysis

Abbreviation/Term	Definition
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IHC	immunohistochemistry
IND	Investigational New Drug Application
ITT	intention-to-treat
jRCT	Japan Registry for Clinical Trials
KM	Kaplan-Meier
LPLV	last participant last visit
mCRC	metastatic colorectal cancer
M&N	Miettinen and Nurminen's
MMR	mismatch repair
MSD	Merck Sharp & Dohme LLC, Rahway, NJ, USA
MSS	microsatellite stable
NCI	National Cancer Institute
NCT	National Clinical Trial
NR	not reached
ORR	objective response rate
OS	overall survival
PD-L1	programmed cell death 1
PFS	progression-free survival
pMMR	proficient mismatch repair
PRO	patient reported outcome
QoL	quality of life
RECIST 1.1	Response Evaluation Criteria in Solid Tumors 1.1
SAE	serious adverse event
SOC	standard of care
sSAP	supplemental statistical analysis plan
TAS-102	combination of trifluridine and tipiracil hydrochloride (tradename Lonsurf®)
TTR	time to response
USA	United States of America
VAS	Visual Analog Scale
VEGF	vascular endothelial growth factor
WHO/UTN	World Health Organisation/Universal Trial Number
WT	wild type

PUBLICATION(S):

Segal NH, Passhak M, Kose F, Kubala E, Elez E, Kawakami H, et al. Co-formulated favezelimab plus pembrolizumab versus standard-of-care in previously treated, PD-L1-positive metastatic colorectal cancer: The phase 3, randomized KEYFORM-007 study [abstract]. Poster session presented at: 2025 American Society of Clinical Oncology (ASCO) Gastrointestinal Cancers Symposium; 2025 Jan 23-25; San Francisco, CA. J Clin Oncol. 2025;43(suppl 4).

Kim T, Taieb J, Passhak M, Kim T, Kim S, Geva R, et al. Phase 3 study of MK4280A (coformulated favezelimab and pembrolizumab) versus standard of care in previously treated PD-L1–positive metastatic colorectal cancer (mCRC) [abstract]. Presented at: European Society for Medical Oncology (ESMO) Congress; 2022 Sep 9-13; Paris (France). Ann Oncol. 2022;33(suppl 4):S277.

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