2 SYNOPSIS

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

COMPOUND NAME: Coxsackievirus A21 (V937)

PROTOCOL TITLE: A Phase 2, Randomized Clinical Study of Intravenous or Intratumoral Administration of V937 in Combination with Pembrolizumab (MK-3475) Versus Pembrolizumab Alone in Participants with Advanced/Metastatic Melanoma

STUDY IDENTIFIERS:

IND: 14547	EudraCT: 2019-002034-36	WHO: N/A	NCT: 04152863
UTN: N/A	EU CT: N/A	Other: N/A	

STUDY PHASE: 2

INDICATION: The treatment of participants with advanced/metastatic melanoma.

STUDY CENTERS: This study was conducted at 30 centers in 11 countries.

STUDY STATUS: This study was terminated due to the Sponsor's development decision; eligible participants who were receiving pembrolizumab were enrolled in a pembrolizumab extension study to continue receiving pembrolizumab monotherapy for up to 35 cycles. This report is based on the final analysis.

First Patient, First Visit	Last Patient, Last Visit	Database Lock Date
05-JUN-2020	12-JUL-2023	05-SEP-2023

NOTE: Patient = Participant

METHODOLOGY: This was an active-controlled, parallel-group, multisite, open-label study of pembrolizumab in combination with V937 administered IV (Arm 1=IV pembro + IV V937) or ITu (Arm 2=IV pembro + ITu V937) versus pembrolizumab alone (Arm 3=IV pembro alone) in participants with a histologically or cytologically confirmed diagnosis of Stage III or IV melanoma. The study enrolled 85 participants with advanced/metastatic melanoma with cutaneous, subcutaneous, or nodal lesions that were amenable to ITu injection by visual inspection, palpation, or ultrasound guidance. Participants needed to have 1 measurable lesion that was amenable to ITu injection and biopsy, as well as 1 measurable discrete and/or distant lesion (bystander lesion) that was amenable to biopsy to evaluate any abscopal effect. This study evaluated the efficacy, safety, and tolerability of V937 in combination with pembrolizumab versus pembrolizumab alone.

After a screening period of up to 28 days, participants were randomized 1:1:1 to: Arm 1: IV pembro + IV V937; Arm 2: IV pembro + ITu V937; or Arm 3: IV pembro alone. The first treatment cycle was 28 days, and each subsequent treatment cycle was 21 days Participants were treated for up to 35 cycles (approximately 2 years) after initiation of treatment with pembrolizumab alone or in combination with V937. V937 was given for a total of 8 cycles. Discontinuation Follow-Up was 30 days after the last dose.

Intervention	Unit Dose and Frequency	Route of Administration
V937 + Pembrolizumab (Arm 1)	1×10^9 $TCID_{50}$ on D1, D3, D5, and D8 of C1 (28 days), and then D1 of C2-C8 (21 days each) + pembrolizumab 200 mg on C1D8 and then every 21 days	V937: IV Pembrolizumab: IV
V937 + Pembrolizumab (Arm 2)	3×10^8 $TCID_{50}$ V937 on D1, D3, D5, and D8 of C1 (28 days), and then D1 of C2-C8 (21 days each) + pembrolizumab 200 mg on C1D8 and then every 21 days	V937: ITu Pembrolizumab: IV
Pembrolizumab (Arm 3)	200 mg on D8 of C1 (28 days) and then every 21 days	IV
Note: V937 will be administered 0.5 to 4 hours after pembrolizumab infusion (as appropriate). C=cycle; D=day; ITu=intratumorally; IV=intravenous, $TCID_{50}$ =50% tissue culture infectious dose.		

Part of this study was conducted during the COVID-19 pandemic. The Sponsor continued to follow its Standard Operating Procedures for study conduct, monitoring, and oversight during the pandemic and employed a risk-based approach to assess and mitigate impact on study conduct.

ELIGIBILITY CRITERIA: The study included male and female participants ≥18 years of age with histologically or cytologically confirmed Stage III or Stage IV advanced/metastatic melanoma. Participants must have been naïve to anti-PD-(L)1 treatment, TVEC, and other oncolytic viruses; had at least 1 cutaneous or subcutaneous lesion amenable to ITu injection and biopsy; had at least 1 measurable, distant, and/or discrete noninjected lesion that was amenable to biopsy via visual inspection or amenable to biopsy via image guidance; and had a performance status of 0 or 1 on the Eastern Cooperative Oncology Group Performance Scale.

OBJECTIVES AND ENDPOINTS: The following objectives and endpoints were evaluated in participants with advanced/metastatic melanoma who were anti-PD-(L)1-treatment–naïve. Hypotheses are aligned with objectives in the objectives and endpoints table.

Primary Objective(s)	**Primary Endpoint(s)**
• Objective: To evaluate the ORR of participants treated with IV V937 administered in combination with pembrolizumab, ITu V937 administered in combination with pembrolizumab, or pembrolizumab alone per RECIST 1.1 by BICR. • Hypothesis: V937 administered either IV in combination with pembrolizumab or ITu in combination with pembrolizumab results in a superior ORR per RECIST 1.1 based on BICR, compared to pembrolizumab alone.	• Objective response is a confirmed CR or PR
Secondary Objective(s)	**Secondary Endpoint(s)**
• To evaluate PFS and DOR of participants treated with IV V937 in combination with pembrolizumab, ITu V937 in combination with pembrolizumab, or pembrolizumab alone per RECIST 1.1 by BICR.	• PFS, defined as the time from randomization to the first documented PD or death from any cause, whichever occurs first. • DOR, defined as the time from the first documented evidence of CR or PR until PD or death due to any cause, whichever occurs first, in participants demonstrating CR or PR
• To evaluate ORR, PFS, and DOR of participants treated with IV V937 in combination with pembrolizumab, ITu V937 in combination with pembrolizumab, or pembrolizumab alone, per RECIST 1.1, as assessed by the investigator.	• Objective response • PFS • DOR
• To evaluate OS of participants treated with IV V937 in combination with pembrolizumab, ITu V937 in combination with pembrolizumab, or pembrolizumab alone.	• OS, defined as the time from randomization to the date of death from any cause

• Objective: To assess the safety and tolerability of participants treated with IV V937 in combination with pembrolizumab, ITu V937 in combination with pembrolizumab, or pembrolizumab alone.	• AEs • Discontinuing study intervention due to an AE

NUMBER OF PARTICIPANTS (planned and analyzed): The planned enrollment total was 135 participants. As of the LPLV for this report, 85 participants were randomized 1:1:1 to 3 arms (28 participants each in the IV pembro + IV V937 arm and in the IV pembro + ITu V937 arm; 29 participants in the IV pembro arm).

STATISTICAL AND ANALYTICAL METHODS: The analyses of efficacy endpoints (ORR, PFS, OS, and DOR) were based on the ITT population. All randomized participants were included in this population, and participants were analyzed in the treatment arm to which they were randomized. The stratified Miettinen and Nurminen method was used for the ORR comparison (Arm 1 vs Arm 3; Arm 2 vs Arm 3). The difference in ORR, 90% CI and p-values from the stratified Miettinen and Nurminen method with strata weighted by sample size were reported. The nonparametric KM method was used to estimate the PFS and OS curves in each treatment group. The treatment difference in 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 (ie, HR) between the treatment arms. The HR and its 95% CI from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate were reported. Summary statistics using the KM method were used to estimate DOR.

The APaT population was used for the analysis of safety data in this study. The APaT population included all randomized participants who received at least 1 dose of study treatment. Participants were analyzed in the treatment arm corresponding to the study treatment they actually received.

RESULTS:

Participant Disposition:

- Arm 1 (IV pembro + IV V937): 28 randomized, 28 treated, 2 (7.1%) completed treatment, 26 (92.9%) discontinued treatment
- Arm 2 (IV pembro + ITu V937): 28 randomized, 28 treated, 2 (7.1%) completed treatment, 26 (92.9%) discontinued treatment
- Arm 3 (IV pembro): 29 randomized, 26 treated, 2 (7.7) completed treatment, 24 (92.3% discontinued treatment

Demographics and Baseline Characteristics:

Arm 1 (IV pembro + IV V937)

- **Overall Median Age (Range)**: 65.0 years (41 to 86 years)
- **Sex:** 20 (71.4%) male, 8 (28.6%) female
- **Ethnicity**: 25 (89.3%) not Hispanic or Latino, 2 (7.1%) Hispanic or Latino
- **Race**: 2 (7.1%) Asian, 3 (10.7%) Black or African American, 23 (82.1%) White

Arm 2 (IV pembro + ITu V937)

- **Overall Median Age (Range)**: 57.5 years (32 to 88 years)
- **Sex:** 18 (64.3%) male, 10 (35.7%) female
- **Ethnicity**: 21 (75.0%) not Hispanic or Latino, 6 (21.4%) Hispanic or Latino
- **Race**: 3 (10.7%) Black or African American, 24 (85.7%) White

Arm 3 (IV pembro)

- **Overall Median Age (Range)**: 62.0 years (34 to 86 years)
- **Sex:** 18 (62.1%) male, 11 (37.9%) female
- **Ethnicity:** 26 (89.7%) not Hispanic or Latino, 3 (10.3%) Hispanic or Latino
- **Race**: 1 (3.4%) Asian, 2 (6.9%) Black or African American, 26 (89.7%) White

Efficacy:

In participants with advanced/metastatic melanoma:

- The treatment of IV pembrolizumab + IV V937 or IV pembrolizumab + ITu V937 showed a mixed clinical benefit in ORR by BICR compared with IV pembrolizumab alone.
  - The ORR based on BICR was greater in the IV pembro + IV V937 arm compared with the IV pembro arm (46.4% vs 34.5%) with a point estimate difference in the ORR percentage of 11.9%; 90% CI: -9.5, 32.5; nominal p-value= 0.1812.
  - The ORR based on BICR was similar in the IV pembro + ITu V937 arm compared with the IV pembro arm (39.3% vs 34.5%) with a point estimate difference in the ORR percentage of 4.8%; 90% CI: -16.2, 25.5; nominal p-value=0.3548.

  - The ORR based on BICR was greater in the IV pembro + IV V937 arm compared with the IV pembro + ITu pembro arm (46.4% vs 39.3%) with a point estimate difference in the ORR percentage of 7.1%; 90% CI: -14.6, 28.2.

- Median OS:

  - The median OS in the IV pembro + IV V937 arm and in the IV pembro arm was 17.5 months and not reached, respectively (HR: 1.64; 95% CI: 0.71, 3.79).

  - The median OS in the IV pembro + ITu V937 arm and in the IV pembro arm was 24.1 months and not reached, respectively (HR: 1.12; 95% CI: 0.47, 2.68).

  - The median OS in the IV pembro + IV V937 arm and in the IV pembro + ITu V937 arm was 17.5 and 24.1 months, respectively (HR: 1.39; 95% CI: 0.64, 3.02).

- The median PFS based on BICR:

  - Median PFS in the IV pembro + IV V937 arm and the IV pembro arm was 12.7 and 8.6 months, respectively (HR: 1.06; 95% CI: 0.5, 2.27).

  - Median PFS in the IV pembro + ITu V937 arm and the IV pembro arm was 7.3 and 8.6 months, respectively (HR: 1.08; 95% CI: 0.51, 2.29).

  - Median PFS in the IV pembro + IV V937 arm and the IV pembro + ITu V937 arm was 12.7 and 7.3 months, respectively (HR: 1.01; 95% CI: 0.50, 2.04).

- Median DOR based on BICR in the IV pembro + IV V937 arm, in the IV pembro + ITu V937 arm, and in the IV pembro arm was not reached. The median TTR in the IV pembro + IV V937 arm, in the IV pembro + ITu V937 arm, and in the IV pembro arm was 2.5, 2.4, and 2.4 months, respectively.

- ORR based on investigator assessment:

  - ORR in the IV pembro + IV V937 arm and the IV pembro arm was 39.3% and 41.4%, respectively. The point estimate of the difference in the ORR percentage between the IV pembro + IV V937 arm and the IV pembro arm was -2.1%; 90% CI: -23.1, 19.2.

  - ORR in the IV pembro + ITu V937 arm and the IV pembro arm was 39.3% and 41.4%, respectively. The point estimate of the difference in the ORR percentage between the IV pembro + ITu V937 arm and the IV pembro arm was -2.1%; 90% CI: -23.1, 19.2.

  - The ORR in the IV pembro + ITu V937 arm and in the IV pembro arm was equivalent. There was no difference in the ORR percentage between the IV pembro + IV V937 arm and the IV pembro + ITu V937 arm (0%; 90% CI: -21.2, 21.2).

- Median PFS based on investigator assessment:
  - Median PFS in the IV pembro + IV V937 arm and the IV pembro arm was 4.6 and 15.4 months, respectively (HR: 1.45; 95% CI: 0.70, 3.02).
  - Median PFS based on investigator assessment in the IV pembro + ITu V937 arm and the IV pembro arm was 6.5 and 15.4 months, respectively (HR: 1.29; 95% CI: 0.62, 2.68).
  - Median PFS based on investigator assessment in the IV pembro + IV V937 arm and the IV pembro + ITu V937 arm was 4.6 and 6.5 months, respectively (HR: 1.16; 95% CI: 0.60, 2.22).
- Median DOR based on investigator assessment in the IV pembro + IV V937 arm, in the IV pembro + ITu V937 arm, and in the IV pembro arm was not reached. The median TTR in the in the IV pembro + IV V937 arm, in the IV pembro + ITu V937 arm, and in the IV pembro arm was 2.6, 2.4, and 2.4 months, respectively.

Safety:

- All participants in the IV pembro + IV V937 arm and in the IV pembro + ITu arm experienced at least 1 AE compared with 84.6% of participants in the IV pembro arm.
- Overall, the incidence of SAEs, drug-related SAEs, toxicity Grade 3 to 5 AEs, and drug-related toxicity Grade 3 to 5 AEs was higher in the IV pembro + IV V937 arm and in the IV pembro + ITu V937 arm compared with the IV pembro arm.
- Three deaths were reported in the IV pembro + IV V937 arm; no deaths occurred across all arms due to a drug-related AE.
- Study treatment was manageable as evidenced by the low rate of study interruption or discontinuation due to toxicity.
- The severity and outcome of AEOSIs were generally consistent with those previously reported for pembrolizumab monotherapy and was generally manageable with standard supportive care as appropriate, including corticosteroid use and hormone replacement therapy.
- No new indication-specific, immune-mediated AEs causally related to pembrolizumab were identified.
- Observed AEs were consistent with the known safety profile of V937 and with the established safety profile of pembrolizumab monotherapy.

Adverse Event Summary
(APaT Population)

	MK-3475 IV + V937 IV		MK-3475 IV + V937 IT		MK-3475 IV		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	28		28		26		82	
with one or more adverse events	28	(100.0)	28	(100.0)	22	(84.6)	78	(95.1)
with no adverse event	0	(0.0)	0	(0.0)	4	(15.4)	4	(4.9)
with drug-related[a] adverse events	20	(71.4)	20	(71.4)	22	(84.6)	62	(75.6)
with toxicity grade 3-5 adverse events	11	(39.3)	14	(50.0)	6	(23.1)	31	(37.8)
with toxicity grade 3-5 drug-related adverse events	5	(17.9)	4	(14.3)	1	(3.8)	10	(12.2)
with serious adverse events	8	(28.6)	5	(17.9)	4	(15.4)	17	(20.7)
with serious drug-related adverse events	4	(14.3)	1	(3.6)	0	(0.0)	5	(6.1)
with any dose modification[b] due to an adverse event	10	(35.7)	8	(28.6)	5	(19.2)	23	(28.0)
V937 dose modification	8	(28.6)	5	(17.9)	0	(0.0)	13	(15.9)
MK-3475 dose modification	10	(35.7)	7	(25.0)	5	(19.2)	22	(26.8)
who died	3	(10.7)	0	(0.0)	0	(0.0)	3	(3.7)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued any drug due to an adverse event	4	(14.3)	2	(7.1)	1	(3.8)	7	(8.5)
discontinued V937	1	(3.6)	1	(3.6)	0	(0.0)	2	(2.4)
discontinued MK-3475	4	(14.3)	2	(7.1)	1	(3.8)	7	(8.5)
discontinued any drug due to a drug-related adverse event	2	(7.1)	2	(7.1)	0	(0.0)	4	(4.9)
discontinued V937	0	(0.0)	1	(3.6)	0	(0.0)	1	(1.2)
discontinued MK-3475	2	(7.1)	2	(7.1)	0	(0.0)	4	(4.9)
discontinued any drug due to a serious adverse event	4	(14.3)	0	(0.0)	1	(3.8)	5	(6.1)
discontinued V937	1	(3.6)	0	(0.0)	0	(0.0)	1	(1.2)
discontinued MK-3475	4	(14.3)	0	(0.0)	1	(3.8)	5	(6.1)
discontinued any drug due to a serious drug-related adverse event	2	(7.1)	0	(0.0)	0	(0.0)	2	(2.4)
discontinued V937	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

Adverse Event Summary
(APaT Population)

	MK-3475 IV + V937 IV		MK-3475 IV + V937 IT		MK-3475 IV		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
discontinued MK-3475	2	(7.1)	0	(0.0)	0	(0.0)	2	(2.4)

[a] Determined by the investigator to be related to the drug.

[b] Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.

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: 12JUL2023

Source: [P011V937: adam-adsl; adae]

CONCLUSIONS:

Efficacy

- Combination treatment of pembrolizumab and V937 (IV or ITu administered) provides a mixed benefit in ORR compared with pembrolizumab alone.

Safety

- Study treatment is manageable with a safety profile generally consistent with the known safety profile of V937 and with the established safety profile of pembrolizumab monotherapy; no new safety concerns were identified.

LIST OF ABBREVIATIONS

Abbreviation/Term	Definition
AE	adverse event
AEOSI	adverse event of special interest
APaT	all-participants-as-treated
BICR	blinded independent central review
CI	confidence interval
CR	complete response
DOR	duration of response
HR	hazard ratio
ITT	intention-to-treat
ITu	intratumoral
IV	intravenous
KM	Kaplan-Meier
LPLV	last participant last visit
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-(L)1	programmed cell death (ligand) 1
pembro	pembrolizumab
PFS	progression-free survival
PR	partial response
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
TTR	time to response

PUBLICATION(S): As of the date of this report, there are no publications based on this study.

REPORT DATE: 04-JAN-2024

REVISED REPORT DATE: Not applicable