2 SYNOPSIS

SPONSOR: Merck, Sharp & Dohme Corp., Whitehouse Station, NJ USA (MSD)

COMPOUND NAME: Pembrolizumab

PROTOCOL TITLE: Adjuvant Therapy with Pembrolizumab versus Placebo in Resected High-risk Stage II Melanoma: A Randomized, Double-blind Phase 3 Study (KEYNOTE 716)

STUDY IDENTIFIERS:

IND: 110,080	EudraCT: 2018-000669-35	NCT: NCT03553836

STUDY PHASE: 3

INDICATION: Adjuvant treatment of high-risk Stage II melanoma

STUDY CENTERS: This study was conducted at 160 centers in 16 countries.

STUDY STATUS: This study is ongoing; report based on the 21-JUN-2021 interim analysis.

First Patient, First Visit	Data Cutoff Date	Database Lock Date
12-SEP-2018	21-JUN-2021	28-JUL-2021

NOTE: Patient = Participant

METHODOLOGY: Part of this study was conducted during the coronavirus disease 2019 (COVID-19) pandemic. The Sponsor continued to follow its standard operating procedures for study conduct, monitoring, and oversight during the pandemic and used a risk-based approach to assess and mitigate impact on study conduct.

KEYNOTE-716 is a randomized, placebo-controlled, parallel-group, crossover/rechallenge, multicenter study of adjuvant pembrolizumab in participants 12 years of age and older with resected high-risk Stage II cutaneous melanoma. Participants must have had newly diagnosed, pathologically confirmed, and completely resected melanoma with negative margins, and could not have received prior systemic therapy for Stage II melanoma.

The treatment phase of the study consists of 2 parts:

- Part 1 (Adjuvant Treatment): Pembrolizumab or placebo administered every 3 weeks (Q3W) for 17 cycles.

- Part 2 (Crossover/Rechallenge after First Recurrence): Pembrolizumab administered Q3W for 17 cycles after resection of recurrent disease if feasible (local recurrence, including local metastatic lymph nodes, or distant metastasis) or up to 35 cycles of pembrolizumab Q3W for unresectable disease recurrence (unresectable local [regional metastatic lymph nodes, in-transit, satellite, and/or microsatellite metastases] or unresectable distant recurrence).

This report includes efficacy and safety results from Part 1 only.

The study treatments are shown below. Participants under 18 years of age who were randomized to receive pembrolizumab at the beginning of Part 1 remained on the pediatric dose of pembrolizumab throughout Part 1.

Study Treatments

Study Treatment Name	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period	Use
Pembrolizumab	Solution for infusion	25 mg/mL vial	2 mg/kg (maximum 200 mg) Q3W for pediatric participants (≥12 and <18 years old); 200 mg Q3W for adults (≥18 years of age)	IV infusion via infusion pump	Part 1: 17 cycles Part 2: 17 or 35 cycles	Experimental
Saline placebo	Solution for infusion	None	None	IV infusion via infusion pump	Part 1: 17 cycles	Placebo

IV=intravenous; Q3W=every 3 weeks

ELIGIBILITY CRITERIA: Male and female participants ≥12 years of age with surgically resected Stage IIB or IIC cutaneous melanoma who met the following key criteria were eligible for enrollment in the study:

- Histologically/pathologically confirmed, newly diagnosed Stage IIB or IIC cutaneous melanoma (tumor stage of T3b, T4a, or T4b) with pathologically confirmed negative sentinel lymph node biopsy, and no evidence of regional [N0] or distant metastatic [M0] disease per American Joint Committee on Cancer eighth edition guidelines.
- Not previously treated for melanoma beyond complete surgical resection.
- No more than 12 weeks between final surgical resection and randomization, with complete surgical wound healing.
- No evidence of metastatic disease on imaging as determined by investigator assessment; suspicious lesions amenable to biopsy confirmed negative for malignancy.

- Performance status of 0 or 1 on the Eastern Cooperative Oncology Group Performance Scale at the time of enrollment, Lansky Performance Status score ≥50 (for participants ≤16 years old.), or a Karnofsky Performance Status score ≥50 (for participants >16 and <18 years old).

OBJECTIVES AND ENDPOINTS:

Primary Objective	**Primary Endpoint**
Objective: To compare RFS between treatment groups Hypothesis (H1): Pembrolizumab is superior to placebo with respect to RFS as assessed by the site investigator.	RFS: time from randomization to (1) any recurrence (local or regional [including invasive ipsilateral tumor and invasive locoregional tumor], or distant) as assessed by the investigator, or (2) death due to any cause (both cancer and noncancer causes of death)
Secondary Objectives	**Secondary Endpoints**
Objective: To compare DMFS between treatment groups Hypothesis (H2): Pembrolizumab is superior to placebo with respect to DMFS as assessed by the site investigator.	DMFS: The time from randomization to appearance of a distant metastasis as assessed by the investigator. A distant metastasis refers to cancer that has spread from the original (primary) tumor to distant organs or distant lymph nodes
Objective: To compare OS between treatment groups Hypothesis (H3): Pembrolizumab is superior to placebo with respect to OS.	OS: The time from randomization to death due to any cause
Objective: To assess the safety and tolerability of pembrolizumab compared to placebo in the proportion of AEs	▪ AEs ▪ Discontinuation of study treatment due to AEs

NUMBER OF PARTICIPANTS (planned and analyzed): The planned enrollment total was approximately 954 participants. As of the data cutoff (DCO) date for this report, 976 participants were randomized (487 in the pembrolizumab group and 489 in the placebo group).

STATISTICAL AND ANALYTICAL METHODS: The nonparametric Kaplan-Meier (KM) method was used to estimate the recurrence-free survival (RFS) curve in each treatment group. Treatment comparisons for RFS were evaluated using a stratified log-rank test with Efron's tie-handling method, and the hazard ratio was estimated using a stratified Cox model. RFS analysis was performed on the intent-to-treat (ITT) population.

Five efficacy interim analyses and a final analysis were planned for this study. The first interim analysis (IA1) was planned after enrollment was completed and approximately 128 RFS events were observed to test the superiority of pembrolizumab over placebo with respect to RFS as assessed by the investigator (primary hypothesis). The second interim analysis

(IA2) was planned after approximately 179 RFS events were observed, but the actual number at the final RFS analysis was 187.

The multiplicity strategy in this study will be applied to the primary (RFS) hypothesis and 2 secondary (distant metastasis-free survival [DMFS] and overall survival [OS]) hypotheses. The overall Type I error was strongly controlled at 2.5% (one-sided), with 2.5% initially allocated to the RFS hypothesis. The graphical method of Maurer and Bretz was used to control multiplicity for multiple hypotheses as well as interim analyses. According to this approach, when a particular null hypothesis is rejected, the alpha allocated to that hypothesis can be reallocated to other hypothesis tests.

Safety analysis followed a tiered approach. There were no Tier 1 events for this study. Point estimates and 95% confidence intervals (CIs) for between-treatment comparisons via the Miettinen and Nurminen method were provided for Tier 2 safety endpoints, and only point estimates by treatment group were provided for Tier 3 safety endpoints.

There were no changes in the planned analyses due to the COVID-19 pandemic.

RESULTS:

Participant Disposition:

- Pembrolizumab group: 487 participants were randomized, 483 were treated, 297 (61.5%) completed Part 1 study treatment, treatment was ongoing for 24 (5.0%), and treatment was discontinued for 162 (33.5%) participants. Twenty-seven (5.5%) participants were discontinued from the study, and 460 (94.5%) were ongoing in the study.
- Placebo group: 489 participants were randomized, 486 were treated, 353 (72.6%) completed Part 1 study treatment, treatment was ongoing for 17 (3.5%), and treatment was discontinued for 116 (23.9%) participants. Thirty (6.1%) participants were discontinued from the study, and 459 (93.9%) were ongoing in the study.

Demographics and Baseline Characteristics:

- **Overall Median Age (range):** 61.0 years (16 to 87 years)
- **Sex:** 589 (60.3%) male, 387 (39.7%) female
- **Ethnicity:** 799 (81.9%) not Hispanic or Latino, 79 (8.1%) Hispanic or Latino, 87 (8.9%) not reported, 11 (1.1%) unknown
- **Race:** 1 (0.1%) American Indian or Alaska Native, 5 (0.5%) Asian, 8 (0.8%) black or African American, 1 (0.1%) multiple, 874 (89.5%) white, 87 (8.9%) missing

Efficacy:

- Consistent with the IA1 RFS results, adjuvant pembrolizumab treatment continued to result in a clinically meaningful improvement in RFS compared with placebo, with a 39% decreased risk of disease recurrence or death (HR=0.61; nominal p=0.00046). The RFS KM curves separated at Month 6 and remained separated through the period assessed. As of the DCO date, the median RFS was not yet reached in either treatment group.

- Fewer participants in the pembrolizumab group experienced disease recurrence during Part 1 of the study compared with the placebo group. The most frequent type of recurrence was distant, and the percentage of participants with this recurrence was lower, almost half of the number of participants, in the pembrolizumab group (31 [6.37%] participants) compared with the placebo group (60 [12.27%] participants). The percentage of Local/Regional/Locoregional recurrence was similar in the pembrolizumab and placebo groups. Eight deaths contributed to the RFS events; 3 deaths in the pembrolizumab group and 5 deaths in the placebo group.
- Of the 187 participants with an RFS event during Part 1 of the study, 94 (50.3%) participants underwent surgical resection, 24 (12.8%) participants received subsequent radiation therapy for palliation or control of recurrent/metastatic disease, and 86 (46.0%) participants received subsequent systemic therapy. In addition, 45 participants in the placebo group crossed over to pembrolizumab intervention, and 1 participant in the pembrolizumab group received pembrolizumab retreatment in Part 2 of the study.
- RFS results in prespecified subgroups at IA2 were generally consistent with the primary analysis and IA1. The subgroup analysis by region had small numbers of participants and events in the US compared with ex-US regions, resulting in a wide 95% CI for the HR.
- The KM curves of the RFS analysis by T-category (T3b, T4a and T4b) as well as by overall melanoma cancer stage, Stage IIB and Stage IIC, separated at 6 months. The comparatively smaller number of participants and RFS events in the Stage IIC (and T4b) subgroup limits the interpretation of the data when the subgroup is analyzed separately. The tails of the curves should be interpreted with caution due to the small number of participants at risk. With an additional 6 months of follow-up since IA1, the RFS benefit remains favorable for pembrolizumab in both subgroups, which supports the robustness of the RFS benefit.
- The results of a sensitivity analysis that included new primary melanomas as part of the RFS analysis were consistent with the primary analysis and with the results at IA1. The results of a second sensitivity analysis, in which a different censoring rule was applied, were also consistent with the primary analysis and IA1.
- Adjuvant pembrolizumab treatment resulted in a difference in LS means of -3.67 [95% CI: -5.91, -1.44] in global health status QoL at Week 48 compared with placebo. The change from baseline to Week 48 in physical functioning and the analysis of the EQ-5D-5L score at Week 48 were similar in the treatment groups.

Safety:

The overall frequency and type of adverse events (AEs) reported in KEYNOTE-716 were generally consistent with the established safety profile of pembrolizumab monotherapy. As expected for a comparison of active treatment versus placebo, higher incidences of AEs in the following categories were reported in the pembrolizumab group: drug-related AEs, Grade 3 to 5 AEs, drug-related Grade 3 to 5 AEs, drug-related serious AEs, and AEs and drug-related AEs leading to discontinuation of study intervention. The most frequently reported AEs in the pembrolizumab group (incidence ≥15%) were fatigue, diarrhea, pruritus, arthralgia, rash, hypothyroidism, and headache.

The overall nature and severity of the adverse events of special interest (AEOSIs) were similar to the established pembrolizumab monotherapy safety profile. Most AEOSIs were Grade 1 or 2 in severity and were generally manageable with treatment interruption, treatment discontinuation, and/or concomitant treatment with corticosteroids and hormone replacement therapy.

No deaths due to a drug-related AE were reported in either treatment group. One participant in the pembrolizumab group and 4 participants in the placebo group died due to nondrug-related AEs.

Analysis of Adverse Event Summary
(APaT Population)

	Pembrolizumab		Placebo		Difference in % vs Placebo
	n	(%)	n	(%)	Estimate (95% CI)[a]
Participants in population	483		486		
with one or more adverse events	461	(95.4)	444	(91.4)	4.1 (1.0, 7.3)
with no adverse event	22	(4.6)	42	(8.6)	
with drug-related[b] adverse events	400	(82.8)	308	(63.4)	19.4 (14.0, 24.9)
with toxicity grade 3-5 adverse events	136	(28.2)	93	(19.1)	9.0 (3.7, 14.3)
with toxicity grade 3-5 drug-related adverse events	82	(17.0)	21	(4.3)	12.7 (8.9, 16.6)
with serious adverse events	101	(20.9)	91	(18.7)	2.2 (-2.8, 7.2)
with serious drug-related adverse events	46	(9.5)	9	(1.9)	7.7 (4.9, 10.8)
who died	1	(0.2)	4	(0.8)	-0.6 (-1.9, 0.4)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	
discontinued drug due to an adverse event	84	(17.4)	22	(4.5)	12.9 (9.1, 16.9)
discontinued drug due to a drug-related adverse event	79	(16.4)	12	(2.5)	
discontinued drug due to a serious adverse event	37	(7.7)	12	(2.5)	
discontinued drug due to a serious drug-related adverse event	32	(6.6)	4	(0.8)	

[a] Based on Miettinen & Nurminen method.
[b] Determined by the investigator to be related to the drug.
Estimated differences and confidence intervals are provided in accordance with the statistical analysis plan.
Grades are based on NCI CTCAE version 4.03.
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 V24.0 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: 21JUN2021.

Source: [P716V02MK3475: adam-adsl; adae]

CONCLUSIONS:

Efficacy Conclusions

Participants enrolled in KEYNOTE-716 are representative of a population with a high risk of disease recurrence. With a median duration of follow-up of 20.5 months, the IA2 supportive analyses were consistent with the primary RFS analysis at IA1 and confirm the robustness of the RFS results.

- Pembrolizumab administered as adjuvant therapy for resected high-risk Stage II cutaneous melanoma continues to provide a clinically meaningful improvement in RFS compared with placebo with an additional 6 months of follow-up.
- RFS results at IA2 are generally consistent regardless of tumor stage, age, gender, race, ECOG performance status, and region.
- Analysis of recurrence events shows approximately half the number of distant recurrence events for participants in the pembrolizumab group compared with those in the placebo group.

Safety Conclusions

With longer follow-up and treatment exposure, the safety results of IA2 are consistent with prior safety data from IA1 and further support the conclusion that pembrolizumab monotherapy administered in the adjuvant setting has an acceptable safety profile in patients with resected high-risk Stage II cutaneous melanoma, as shown by:

- Infrequent treatment interruption and discontinuation.
- The types and severity of AEOSIs are consistent with the established pembrolizumab monotherapy safety profile. AEOSIs were generally manageable with corticosteroids/hormone replacement therapy and/or with treatment interruption/discontinuation.
- No new safety concerns were identified for pembrolizumab monotherapy based on the IA2 safety data in the KEYNOTE-716.

PUBLICATIONS:

Luke JJ, Ascierto PA, Carlino MS, Gershenwald JE, Grob JJ, Hauschild A, et al. KEYNOTE-716: phase III study of adjuvant pembrolizumab versus placebo in resected high-risk Stage II melanoma. Future Oncol. 2020;16(3):4429-38.

Luke JJ, Rutkowski P, Queirolo P, Del Vecchio M, Mackiewicz J, Chiarion Sileni V, et al. LBA3 Pembrolizumab versus placebo after complete resection of high-risk stage II melanoma: Efficacy and safety results from the KEYNOTE-716 double-blind phase III trial. Presented at: European Society for Medical Oncology (ESMO) Congress; 2021 Sep 16-21. Ann Oncol. 2021;32(suppl 5):S1314-S1315. https://doi.org/10.1016/j.annonc.2021.08.2116

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