7-Year Follow-Up of KEYNOTE-006: Pembrolizumab Versus Ipilimumab in Advanced Melanoma

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Background

- Pembrolizumab is a standard of care in the first-line treatment of advanced melanoma, and long-term outcomes of pembrolizumab-treated participants are of interest[1,2]
- After 5 years of follow-up of the phase 3 KEYNOTE-006 trial (NCT01866319), pembrolizumab continued to improve overall survival (OS) and progression-free survival (PFS) compared with ipilimumab[3] in participants with advanced melanoma
  - 5-year OS rates were 43% for pembrolizumab versus 33% with ipilimumab
  - All participants who attained complete response (CR) and completed 2 years of pembrolizumab were still alive after 5 years
- Here, we present results of 7 years of follow-up of survival for participants enrolled in KEYNOTE-006, including those who consented to transition to the KEYNOTE-587 extension study (NCT03486873)

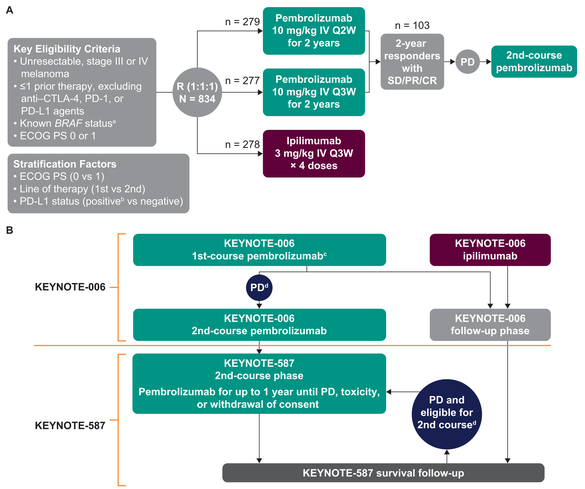
Objective

- To evaluate the long-term survival of participants with advanced melanoma from KEYNOTE-006, including those who transitioned to KEYNOTE-587

Methods

- KEYNOTE-006 was an open-label, randomized phase 3 study to compare the efficacy and safety of pembrolizumab versus ipilimumab in participants with advanced melanoma[4,5] (**Figure 1A**)
- Participants enrolled in KEYNOTE-006 who were ongoing at study end were eligible to transition to KEYNOTE-587 at KEYNOTE-006 closure for long-term follow-up of survival, progression, and start of new anticancer therapy (**Figure 1B**)
- KEYNOTE-587 is an open-label extension study for participants in pembrolizumab or pembrolizumab-based combination parent trials sponsored by Merck Sharp & Dohme, Corp., including KEYNOTE-006; results presented here pertain only to former participants in KEYNOTE-006
  - Participants who were ongoing on the second course of pembrolizumab treatment in KEYNOTE-006 (who had stable disease [SD] or better on the first course and then experienced progression) and participants in the survival follow-up phase who were eligible for the second course entered the second-course phase of KEYNOTE-587
  - Participants in the pembrolizumab or ipilimumab arms of KEYNOTE-006 who were in the follow-up phase of KEYNOTE-006 entered the survival follow-up phase of KEYNOTE-587
- In KEYNOTE-587, participants who were receiving pembrolizumab were followed up radiographically per the KEYNOTE-587 protocol, and those who were not on treatment underwent radiographic imaging per local standard of care

Figure 1. (A) KEYNOTE-006 and (B) Participant Flow From KEYNOTE-006 to KEYNOTE-587



CR, complete response; CTLA-4, cytotoxic T-lymphocyte–associated protein 4; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenously; LDH, lactate dehydrogenase; PD, progressive disease; PR, partial response; Q2W, every 2 weeks; Q3W, every 3 weeks, R, randomization.
[a]Prior anti-BRAF therapy was not required for participants with normal LDH levels and no clinically significant tumor-related symptoms or evidence of rapidly progressing disease.
[b]Defined as ≥1% staining in tumor and adjacent immune cells as assessed by the PD-L1 IHC 22CR pharmDx (Agilent).
[c]All participants from KEYNOTE-006 who enrolled in KEYNOTE-587 had completed the first course of pembrolizumab.
[d]Participants with SD or better on first-course pembrolizumab who had subsequent PD were eligible for a second course of pembrolizumab in KEYNOTE-006 or KEYNOTE-587.

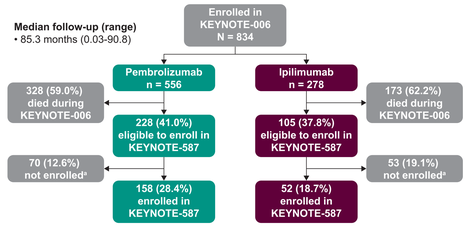
Statistical Analysis

- Efficacy was assessed in the intention-to-treat (ITT) population, which included all randomly assigned participants
- OS was the primary end point in KEYNOTE-587
- PFS and OS were estimated using the Kaplan-Meier method
  - For modified PFS (mPFS), participants without PD were censored at the date they were last known to be alive
  - Participants who did not enroll in KEYNOTE-587 were censored for OS and PFS at the date they were last known to be alive
- Hazard ratios and associated 95% CIs were assessed by a stratified Cox proportional hazards model with Efron's method of handling ties
- Database cutoff was April 19, 2021

Results

- 210 former participants of KEYNOTE-006 enrolled in KEYNOTE-587; 158 were from the pembrolizumab arm and 52 from the ipilimumab arm of KEYNOTE-006 (**Figure 2**)
  - All 158 participants who received pembrolizumab in KEYNOTE-006 and then enrolled in KEYNOTE-587 had completed the first course of pembrolizumab treatment in KEYNOTE-006
  - 103 participants completed ≥94 weeks of treatment with pembrolizumab
  - 16 patients received second-course pembrolizumab in KEYNOTE-587

Figure 2. Participant Disposition



[a]70 participants in the pembrolizumab arm and 53 participants in the ipilimumab arm were alive after KEYNOTE-006 but did not enroll in KEYNOTE-587.

Efficacy

Figure 3. Modified PFS

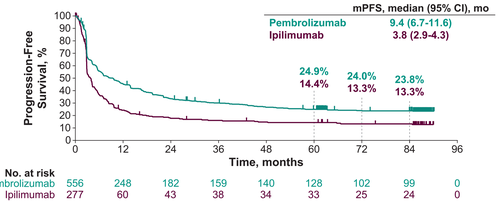
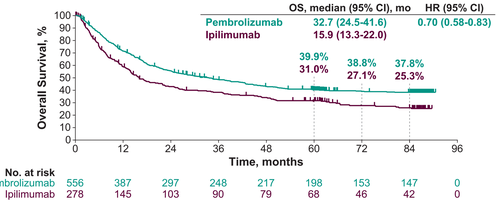


Figure 4. OS by Randomized Treatment in the Overall Population



HR, hazard ratio.

Table 1. Overall Survival in Subgroups by Baseline Characteristics

Characteristic	Events/n (%)		7-Year OS Rate, %		OS, Median (95% CI), mo		
	Pembrolizumab	Ipilimumab	Pembrolizumab	Ipilimumab	Pembrolizumab	Ipilimumab	HR (95% CI)
***BRAF* status**							
Wild type	216/355 (60.8)	112/170 (65.9)	36.5	25.7	28.1 (21.1-42.7)	13.9 (10.7-24.8)	0.71 (0.56-0.89)
Mutant (no prior BRAFi)[a]	52/108 (48.1)	35/55 (63.6)	49.7	27.7	78.5 (36.1-NE)	26.2 (16.0-64.0)	0.58 (0.38-0.89)
Mutant (prior BRAFi)	61/87 (70.1)	36/52 (69.2)	28.3	20.0	20.4 (12.8-35.6)	11.9 (6.0-17.8)	0.72 (0.47-1.08)
LDH							
Normal	206/369 (55.8)	108/179 (60.3)	42.0	30.5	42.9 (34.5-53.5)	33.1 (20.1-49.2)	0.76 (0.60-0.96)
Elevated	122/179 (68.2)	70/91 (76.9)	28.9	14.7	14.7 (10.1-19.5)	6.0 (5.0-8.0)	0.59 (0.44-0.79)
Total tumor size							
<10 cm	165/292 (56.5)	91/152 (59.9)	40.7	30.7	42.7 (28.1-51.9)	22.4 (16.0-38.5)	0.74 (0.58-0.96)
≥10 cm	76/106 (71.7)	41/51 (80.4)	26.1	15.9	9.5 (6.3-16.4)	5.9 (2.9-8.1)	0.67 (0.46-0.99)
Brain metastases							
Present	25/51 (49.0)	21/29 (72.4)	50.0	27.6	53.4 (16.6-NE)	10.8 (4.8-27.0)	0.49 (0.27-0.87)
Absent	303/500 (60.6)	161/248 (64.9)	36.8	25.0	32.7 (24.5-41.2)	17.1 (13.6-23.5)	0.72 (0.59-0.87)

BRAFi, BRAF inhibitor; NE, not evaluable.
[a]Patients with *BRAF*-mutant melanoma with no prior BRAFi therapy were eligible for the study provided they had normal LDH levels and had no clinically significant tumor-related symptoms.

Figure 5. OS From Best Overall Response by Best Overall Response in the Combined Pembrolizumab Population

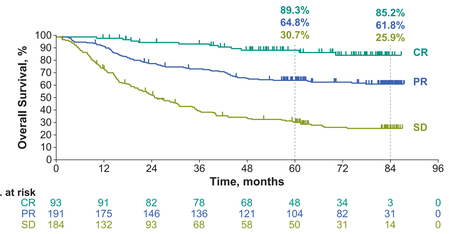


Figure 6. Modified PFS With Pembrolizumab in Participants Completing ≥94 Weeks of Treatment With SD or Better

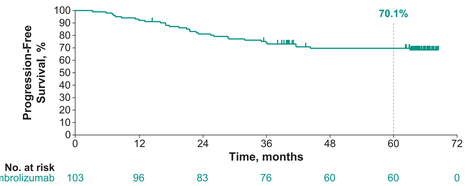


Figure 7. OS With Pembrolizumab in Participants Completing ≥94 Weeks of Treatment With SD or Better

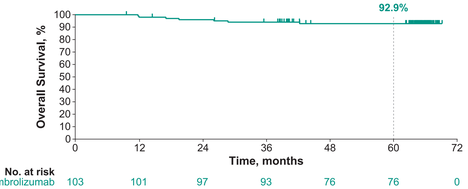


Table 2. Best Overall Response to First-Course and Second-Course Pembrolizumab

First-Course Best Overall Response	Second-Course Best Overall Response n= 16			
	CR	PR	SD	PD
7 CR	4	1	2	–
7 PR	–	4	1	2
2 SD	–	–	2	–

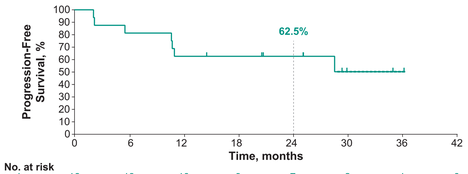
Table 3. Objective Response to Second-Course Treatment With Pembrolizumab per RECIST v1.1 by BICR

	Second Course n = 16
ORR, % (95% CI)	56.3 (29.9-80.2)
DCR, % (95% CI)[a]	87.5 (61.7-98.4)
Best overall response, n (%)	
CR	4 (25.0)
PR	5 (31.3)
SD	5 (31.3)
PD	2 (12.5)

BICR, blinded independent central review; ORR, objective response rate.
[a]Defined as CR + PR + SD.

- Median time (range) to second-course treatment was 45.1 months (29.5-66.7)

Figure 8. PFS for Participants Receiving a Second Course of Pembrolizumab



Conclusions

- After 7 years of follow-up, pembrolizumab continued to demonstrate improved OS compared with ipilimumab, with 7-year OS rates of 37.8% and 25.3%, respectively
  - Pembrolizumab continued to provide survival benefit, regardless of *BRAF* status, prior BRAFi therapy, and poor prognostic characteristics such as high LDH level, larger tumor size, or presence of brain metastases
  - For participants who completed ≥94 weeks of pembrolizumab with SD or better, 5-year PFS and OS rates were 70.1% and 92.9%, respectively
- Second-course pembrolizumab showed additional antitumor activity in some participants
- These results, which represent the longest follow-up from a phase 3 trial of immune-checkpoint inhibitor therapy for melanoma available to date, show that pembrolizumab continues to provide long-term OS benefit in participants with advanced melanoma, confirming pembrolizumab as a standard of care in this population

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