Pembrolizumab Plus Olaparib in Patients With Docetaxel-Pretreated Metastatic Castration-Resistant Prostate Cancer: Update of KEYNOTE-365 Cohort A With a Minimum of 11 Months of Follow-Up for All Patients

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Background

- The phase 1b/2 KEYNOTE-365 trial (NCT02861573) examined the safety, tolerability, and efficacy of pembrolizumab combination therapy in men with metastatic castration-resistant prostate cancer (mCRPC)
  - In data previously reported from cohort A, pembrolizumab + olaparib demonstrated promising antitumor activity and acceptable safety in molecularly unselected patients treated with docetaxel for mCRPC[1,2]
- Here, we present updated results after a minimum of 11.4 months of follow-up for each patient

Objectives

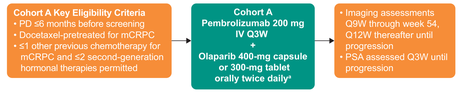
- To evaluate the safety and efficacy of pembrolizumab + olaparib in molecularly unselected patients with docetaxel-pretreated mCRPC

Methods

Study Design

- KEYNOTE-365 is a nonrandomized, multicenter, multicohort, open-label, phase 1b/2 study of pembrolizumab combination therapy in patients with mCRPC
  - Patients enrolled into cohort A were previously treated with docetaxel (prior treatment with 1 other chemotherapy for mCRPC; ≤2 next-generation hormone agent [NHAs] were permitted)
  - Treatment with pembrolizumab was given on day 1 of each 3-week dosing cycle for up to 35 cycles (~2 years); olaparib 400-mg capsules (first 41 patients enrolled) or 300-mg tablets orally twice daily was given continuously from day 1. Treatment was continued until confirmed disease progression, unacceptable toxicity, or withdrawal of consent
- Patients who discontinued 1 drug in the combination regimen because of treatment-related adverse events (TRAEs) were permitted to continue the other drug until discontinuation criteria were met

Figure 1. Study Design



Primary End Points
- Safety
- PSA response rate[b]
- ORR by RECIST v1.1 (BICR)

Secondary End Points
- Time to PSA progression
- DCR[c] by RECIST v1.1
- DOR by RECIST v1.1
- Composite response rate[d]
- rPFS by PCWG 3-modified RECIST v1.1
- OS

BICR, blinded independent central review; CR, complete response; DCR, disease control rate; DOR, duration of response; IV, intravenously; ORR, objective response rate; OS, overall survival; PCWG3, Prostate Cancer Working Group 3; PD, progressive disease; PR, partial response; PSA, prostate-specific antigen; Q3W, every 3 weeks; Q9W, every 9 weeks; Q12W, every 12 weeks; rPFS, radiographic progression-free survival; SD, stable disease.

[a]The first 41 patients were treated with the capsule formulation of olaparib; subsequent patients in this cohort received the tablet formulation. [b]Reduction in PSA ≥50% from baseline, measured twice ≥3 weeks apart. [c]Defined as CR + PR of any duration + SD or non-CR/non-PD ≥6 months per RECIST v1.1. [d]Defined as attainment of any 1 of the following: confirmed ORR per RECIST v1.1, confirmed PSA response, or confirmed decrease in circulating tumor cell count from ≥5 cells/7.5 mL blood to <5 cells/7.5 mL blood.

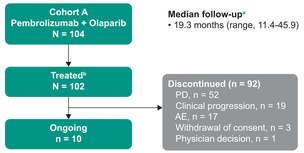
Statistical Analysis

- The Clopper-Pearson exact binomial method was used to assess point estimates and 95% CIs for ORR, DCR, composite response rate, and PSA response rate
- The Kaplan-Meier method was used to assess time to PSA progression, rPFS, and OS
- Efficacy and safety were assessed in all patients who received at least 1 dose of study treatment
- Database cutoff date: November 12, 2020

Results

Patient Disposition and Baseline Demographics

Figure 2. Patient Disposition



Median follow-up[a]
- 19.3 months (range, 11.4-45.9)

AE, adverse event.
[a]Time from enrollment to data cutoff.
[b]2 screening failures.

Table 1. Baseline Characteristics

Characteristic	Pembrolizumab + Olaparib N = 102
Age, median (range), years	69.5 (47-84)
≥65 years, n (%)	79 (77.5)
ECOG PS, n (%)	
0	48 (47.1)
1	48 (47.1)
2	6 (5.9)
PSA value, median (range), ng/mL	109.4 (1.2-5000.0)
PD-L1 status, n (%)	
Positive[a]	29 (28.4)
Negative	35 (34.3)
Unknown/NE	38 (37.3)
Disease measurability per RECIST v1.1, n (%)	58 (56.9)
Visceral disease, n (%)[b]	
Present	34 (33.3)
Not present	68 (66.7)
Prior use of cabazitaxel, n (%)	40 (39.2)
Prior use of abiraterone and/or enzalutamide, n (%)	
Abiraterone only	24 (23.5)
Enzalutamide only	24 (23.5)
Abiraterone and enzalutamide	46 (45.1)
Neither	8 (7.8)

CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; NE, not evaluable.
[a]PD-L1 positive was defined as CPS ≥1. CPS was defined as the number of PD-L1–staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100. [b]Soft tissue (not in brain, bone, or lymph node).

Safety

- 6 patients died of AEs; the investigators considered 2 to be treatment related (myocardial infarction, unknown cause) and 4 not to be treatment related (colorectal cancer, general health deterioration, *Pneumocystis jirovecii* pneumonia, and unknown cause)

Table 2. TRAEs of All Grades (≥5% of the population) and Corresponding Grade 3-5 TRAEs

Event, n (%)	Pembrolizumab + Olaparib N = 102	
	Any Grade	Grade 3-5
Any TRAE	93 (91.2)	49 (48.0)
Anemia	42 (41.2)	28 (27.5)
Nausea	42 (41.2)	2 (2.0)
Decreased appetite	31 (30.4)	0 (0.0)
Fatigue	31 (30.4)	6 (5.9)
Asthenia	29 (28.4)	4 (3.9)
Vomiting	27 (26.5)	1 (1.0)
Diarrhea	23 (22.5)	0 (0.0)
Neutropenia	12 (11.8)	5 (4.9)
Pruritus	11 (10.8)	0 (0.0)
Rash	10 (9.8)	1 (1.0)
Blood creatinine increased	9 (8.8)	0 (0.0)
Weight decreased	9 (8.8)	0 (0.0)
Thrombocytopenia	7 (6.9)	2 (2.0)

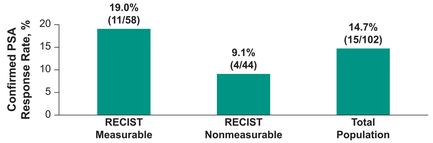
Table 3. Immune-Mediated Adverse Events[a]

Event, n (%)	Pembrolizumab + Olaparib N = 102	
	Any Grade	Grade 3-5
Any immune-mediated AE	12 (11.8)	4 (3.9)
Hypothyroidism	5 (4.9)	0 (0.0)
Adrenal insufficiency	2 (2.0)	1 (1.0)
Hyperthyroidism	2 (2.0)	0 (0.0)
Severe skin reaction	2 (1.0)	1 (1.0)
Pneumonitis	2 (2.0)	2 (2.0)
Colitis	1 (1.0)	0 (0.0)
Hypophysitis	1 (1.0)	0 (0.0)

[a]Based on a list of terms specified by the sponsor and included by the investigator regardless of attribution to study treatment or immune relatedness.

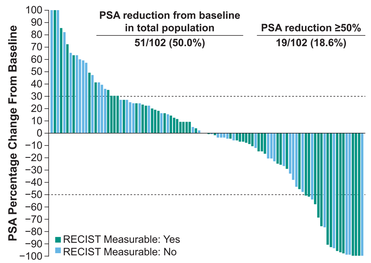
Efficacy

Figure 3. Confirmed PSA Response Rate[a]



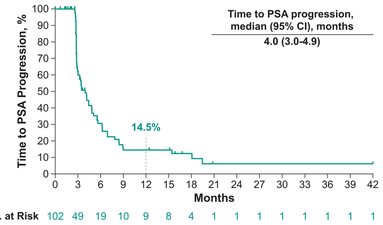
[a]Includes only patients with PSA measurement at baseline (N = 102).

Figure 4. PSA Percentage Change From Baseline (confirmed and unconfirmed)[a]



[a]Plot is based on patients who had a PSA measurement at baseline and ≥1 postbaseline PSA measurement (N = 102).

Figure 5. Kaplan-Meier Estimate of Confirmed Time to PSA Progression



No. at Risk 102 49 19 10 9 8 4 1 1 1 1 1 1 1 1

Table 4. Summary of Confirmed Response by BICR Assessment

	RECIST-Measurable Disease n = 58	RECIST-Nonmeasurable Disease n = 44	Total N = 102
ORR per RECIST v1.1, % (95% CI)	6.9 (1.9-16.7)	NA	NA
DCR per RECIST v1.1, % (95% CI)	25.9 (15.3-39.0)	27.3 (15.0-42.8)	26.5 (18.2-36.1)
CRR, % (95% CI)	24.1 (13.9-37.2)	9.1 (2.5-21.7)	17.6 (10.8-26.4)
Best response, n (%)			
CR	0 (0.0)	NA	NA
PR	4 (6.9)	NA	NA
SD of any duration	20 (34.5)	0 (0.0)	20 (19.6)
NN	0 (0.0)	24 (54.5)	24 (23.5)
SD or NN ≥6 months	11 (19.0)	12 (27.3)	23 (22.5)
PD	30 (51.7)	17 (38.6)	47 (46.1)
NE	0 (0.0)	2 (4.5)	2 (2.0)
No assessment[b]	4 (6.9)	1 (2.3)	5 (4.9)
Time to response, median (range), months	5.2 (2.1-8.8)	NA	NA
DOR, median (range), months	NR (7.2+ to 37.8+)[c]	NA	NA

CRR, composite response rate; NA, not applicable; NN, non–complete response/non–progressive disease; NR, not reached.
[a]Patients with insufficient data for response assessment. [b]2 patients had a response ≥12 months. [c]"+" indicates ongoing response.

Figure 6. Target Lesion Change From Baseline (confirmed and unconfirmed) Based on BICR Assessment per RECIST v1.1 Among Patients With RECIST-Measurable Disease

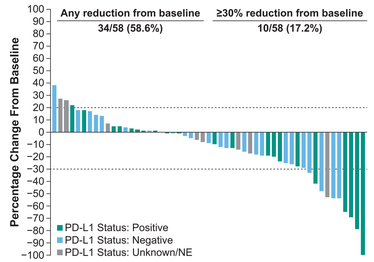
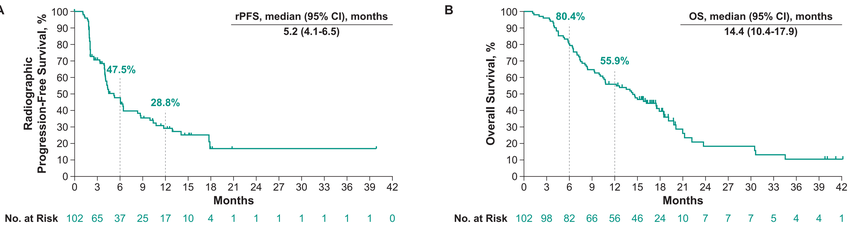


Figure 7. Kaplan-Meier Estimates of (A) rPFS Based on BICR Assessment per PCWG3-Modified RECIST v1.1 and (B) OS



No. at Risk 102 65 37 25 17 10 4 1 1 1 1 1 1 1 0
No. at Risk 102 98 82 66 56 46 24 10 7 7 7 5 4 4 1

Table 5. Time to Radiographic Bone Progression, Soft-Tissue Progression, Opiate Use, and Pathological Fracture

	N = 102		
	Median (95% CI),[a] months	12-Month Event-Free Survival Rate, %	24-Month Event-Free Survival Rate, %
Time to radiographic bone progression per PCWG3-modified RECIST v1.1 by BICR	10.5 (6.3-NR)	46.4	31.8
Time to soft-tissue progression per RECIST v1.1 by BICR	12.9 (7.0-NR)	52.1	19.9
Time to opiate use	7.2 (3.8-NR)	47.8	43.9
Time to pathological fracture	NR (NR-NR)	100	98.2

[a]Product-limit (Kaplan-Meier) method for censored data.

Conclusions

- With a minimum of 11.4 months follow-up, pembrolizumab + olaparib demonstrated antitumor activity and acceptable safety for men with molecularly unselected, docetaxel-pretreated mCRPC
- The safety and tolerability profile of pembrolizumab + olaparib combination therapy is consistent with the individual profiles of each agent[3,4]
  - Anemia was the most common grade 3-5 TRAE (27.5%)
  - 2 patients died of TRAEs (myocardial infarction, unknown cause)
- The confirmed PSA response rate was 14.7%, with an ORR of 6.9% and DCR of 26.5% by BICR per RECIST v1.1
- Among the patients with RECIST-measurable disease
  - 4 patients (6.9%) had a best response of PR
  - Any reduction in target lesion size occurred in 58.6% of patients; 17.2% of patients experienced a reduction ≥30%
- The promising rPFS and overall survival data support further evaluation of pembrolizumab + olaparib in molecularly unselected patients with mCRPC who received prior docetaxel treatment
  - The randomized, global, parallel-group, double-blind phase 3 KEYLYNK-010 trial (NCT03834519) is investigating combination pembrolizumab + olaparib versus abiraterone or enzalutamide in patients with mCRPC previously treated with abiraterone or enzalutamide who experienced disease progression on or after treatment with docetaxel for mCRPC

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Disclosures

E. Yu has served as a consultant or advisor for Janssen, Bayer, Merck Sharp & Dohme Corp., Seattle Genetics, Clovis Oncology, Advanced Accelerator Applications, Sanofi, AbbVie, and Myovant Sciences and has received research funding for his institution from Dendreon, Merck Sharp & Dohme Corp., Seattle Genetics, Daiichi Sankyo, Taiho Pharmaceuticals, Pharmacyclics, Blue Earth Diagnostics, and Bayer.

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