Pembrolizumab Monotherapy for Docetaxel-Pretreated Metastatic Castration-Resistant Prostate Cancer: Updated Analyses With 4 Years of Follow-Up From Cohorts 1-3 of the KEYNOTE-199 Study

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Background

- Previous analysis of the open-label, multinational, multicohort, phase 2 KEYNOTE-199 study showed that pembrolizumab monotherapy demonstrated antitumor activity, provided disease control, and exhibited acceptable safety in 3 cohorts of patients with metastatic castration-resistant prostate cancer (mCRPC) who were previously treated with next-generation hormonal agents (NHAs) and docetaxel[1]
  - Cohort 1: RECIST-measurable disease and PD-L1–positive status
  - Cohort 2: RECIST-measurable disease and PD-L1–negative status
  - Cohort 3: Bone-predominant disease irrespective of PD-L1 status
- Because long-term outcomes with immunotherapy are of interest, we present updated results for cohorts 1-3 of KEYNOTE-199 with 4 years of follow-up

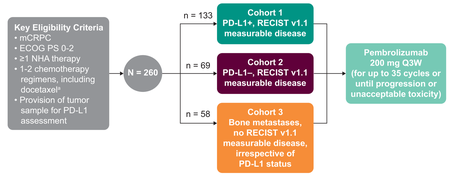
Objective

- To evaluate long-term antitumor activity and safety of pembrolizumab monotherapy in patients with RECIST-measurable or bone-predominant mCRPC previously treated with NHAs and docetaxel

Methods

Study Design, Patients, and Treatment

Figure 1. KEYNOTE-199 Study Design



Primary End Point
Cohorts 1 and 2
- ORR per RECIST v1.1 by BICR

Secondary End Points
Cohorts 1 and 2
- ORR per PCWG3-modified RECIST v1.1 by BICR
- DOR per RECIST v1.1 by BICR

All Cohorts
- DCR[c] per RECIST v1.1 by BICR and PCWG3-modified RECIST v1.1 by BICR
- rPFS per PCWG3-modified RECIST v1.1 by BICR
- PSA response rate[d]
- OS
- Safety and tolerability

BICR, blinded independent central review; CR, complete response; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; 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; rPFS, radiographic progression-free survival; SD, stable disease.

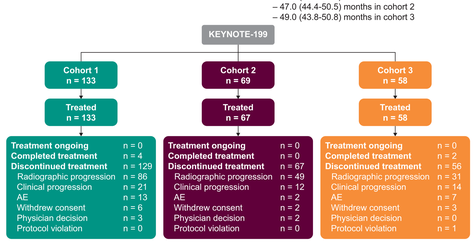
[a]A maximum of 3 lines of prior treatment for mCRPC was allowed.
[b]DCR defined as the proportion of patients who experienced CR or PR of any duration or SD or non-CR/non-PD disease for ≥6 months.
[c]PSA response rate defined as a reduction in the PSA level from baseline by ≥50%, as confirmed by additional PSA evaluation ≥3 weeks later.

- Both efficacy and safety were analyzed in patients who received ≥1 dose of pembrolizumab
- The database cutoff date was November 4, 2020

Results

Patients

Figure 2. Patient Disposition



AE, adverse event.
[a]Defined as the time from date of first dose to database cutoff date.

Table 1. Baseline Demographics and Disease Characteristics

Characteristic	Cohort 1 PD-L1 Positive n = 133	Cohort 2 PD-L1 Negative n = 67	Cohort 3 Bone Predominant n = 58
Age, median (range), years	68 (48-85)	68 (53-86)	71 (53-90)
ECOG PS 0/1/2, %	32/56/12	37/55/6[a]	45/45/10
Gleason score ≤7/≥8/unknown, %	30/64/6	27/66/7	41/53/5
PSA value, median (range), ng/mL	116 (0.1-5000)	116 (1-3583)	43 (0.1-2539)
Visceral disease liver/no liver, %	38/23	16/27	0/5
No. of previous chemotherapy regimens, 1/>1, %	67/33	73/27	78/22
Previous NHA[b]			
Enzalutamide only, %	31	40	28
Abiraterone only, %	43	36	48
Enzalutamide + abiraterone, %	26	24	24

[a]ECOG PS score was missing for 1 patient in cohort 2.
[b]1 patient in cohort 1 received an NHA other than enzalutamide or abiraterone.

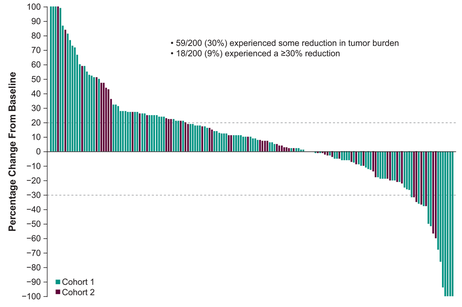
Efficacy

Table 2. Summary of Confirmed Response by Cohort

	Cohort 1 PD-L1 Positive n = 133	Cohort 2 PD-L1 Negative n = 67	Cohort 3 Bone Predominant n = 58
RECIST v1.1, n (%)			
ORR	8 (6)	2 (3)	NA
CR	4 (3)	0 (0)	NA
PR	4 (3)	2 (3)	NA
SD of any duration	23 (17)	14 (21)	0 (0)
Non-CR/non-PD of any duration	NA	NA	21 (36)
DCR (CR + PR + SD/non-CR/non-PD ≥6 months)	13 (10)	3 (4)	12 (21)
PD	80 (60)	43 (64)	32 (55)
Nonevaluable[a]	2 (2)	1 (1)	1 (2)
No assessment[b]	20 (15)	7 (10)	4 (7)
PCWG3-modified RECIST v1.1, n (%)			
ORR	8 (6)	2 (3)	NA
CR	3 (2)	0 (0)	NA
PR	5 (4)	2 (3)	NA
SD of any duration	28 (21)	25 (37)	0 (0)
Non-CR/non-PD of any duration	NA	NA	34 (59)
DCR (CR + PR + SD/non-CR/non-PD ≥6 months)	14 (11)	3 (4)	14 (24)
PD	73 (55)	31 (46)	19 (33)
Nonevaluable[a]	4 (3)	2 (3)	1 (2)
No assessment[b]	20 (15)	7 (10)	4 (7)
PSA response rate for patients who had PSA measurement at baseline	**n = 124**	**n = 61**	**n = 58**
Response rate, n (%)	8 (6)	5 (8)	1 (2)

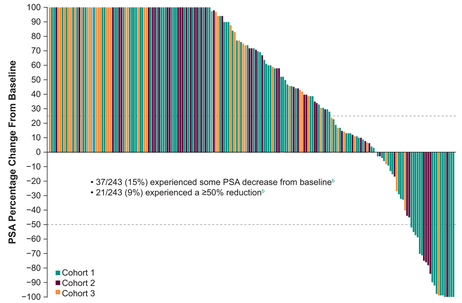
NA, not applicable.
[a]Nonevaluable patients for whom imaging quality was poor or who had insufficient follow-up (<6 months) with best overall response (unconfirmed) of SD, CR, or PR.
[b]"No assessment" counts patients who had a baseline assessment but no postbaseline assessment on the data cutoff date, including missing, discontinuing, or death before first postbaseline imaging.

Figure 3. Target Lesion Change From Baseline for RECIST-Measurable Disease (confirmed and unconfirmed)[a]



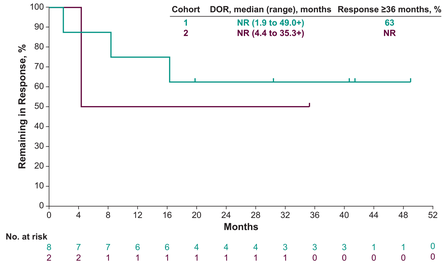
[a]Plot is based on patients who had RECIST-evaluable disease at baseline and ≥1 evaluable postbaseline imaging assessment (n = 168).

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



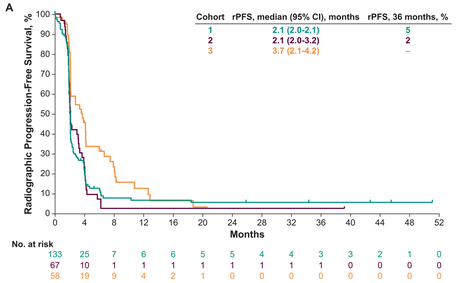
[a]Plot is based on patients who had a PSA measurement at baseline and ≥1 postbaseline PSA measurement (n = 193).
[b]Calculation is based on patients who had nonmissing PSA measurements at baseline.

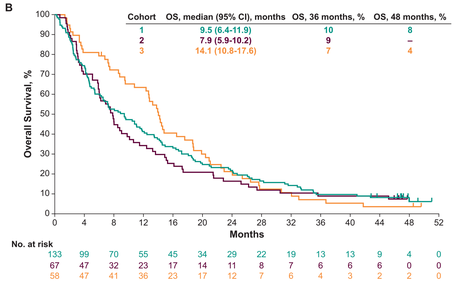
Figure 5. Kaplan-Meier Estimate of DOR per RECIST v1.1 by BICR



NR, not reached.
"+" indicates ongoing response.

Figure 6. Kaplan-Meier Estimates of (A) rPFS per PCWG3-modified RECIST by BICR and (B) OS





Safety

Table 3. Treatment-Related Adverse Events in Cohorts 1-3 Combined

n (%)	Total Population N = 258	
Any TRAE	158 (61)	
Grade 3-5 TRAE	41 (16)	
TRAEs that led to discontinuation	13 (5)	
TRAEs that led to death[a]	3 (1)	
TRAEs that occurred in ≥10 patients	Any Grade	Grade 3-5[b]
Fatigue	39 (15)	3 (1)
Diarrhea	29 (11)	3 (1)
Decreased appetite	27 (10)	2 (<1)
Nausea	25 (10)	0 (0)
Pruritis	17 (7)	1 (<1)
Asthenia	15 (6)	0 (0)
Vomiting	11 (4)	0 (0)
AST increased	11 (4)	1 (<1)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; TRAE, treatment-related adverse event.
[a]Cohort 1, sepsis; cohort 2, unknown; cohort 3, immune-related pneumonitis.
[b]Grade 3-5 TRAEs in ≥2 patients were colitis (n = 3), diarrhea (n =3), fatigue (n = 3), acute kidney injury (n = 2), ALT increased (n = 2), anemia (n = 2), decreased appetite (n = 2), hypophysitis (n = 2), neutropenia (n = 2), rash maculopapular (n = 2), and sepsis (n = 2).

Table 4. Immune-Mediated Adverse Events and Infusion Reactions in Cohorts 1-3 Combined

Immune-Mediated AE,[a] n (%)	Total Population N = 258	
	Any Grade	Grade 3-5
Any	42 (16)	16 (6)
Colitis	7 (3)	3 (1)
Hypothyroidism	7 (3)	1 (<1)
Hyperthyroidism	6 (2)	0 (0)
Pneumonitis	6 (2)	1 (<1)[b]
Severe skin reactions	6 (2)	4 (2)
Infusion reactions	5 (2)	1 (<1)
Adrenal insufficiency	3 (1)	0 (0)
Hypophysitis	3 (1)	2 (<1)
Hepatitis	1 (<1)	1 (<1)
Myositis	1 (<1)	0 (0)
Nephritis	1 (<1)	1 (<1)
Pancreatitis	1 (<1)	1 (<1)
Thyroiditis	1 (<1)	0 (0)
Type 1 diabetes mellitus	1 (<1)	1 (<1)

[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.
[b]Grade 5 AE.

Conclusions

- With 4 years of follow-up data, pembrolizumab monotherapy continued to show modest antitumor activity in patients with RECIST-measurable and bone-predominant mCRPC that was previously treated with NHAs and docetaxel
  - Cohort 1: ORR by RECIST v1.1, 6%; DCR by RECIST v1.1, 10%
  - Cohort 2: ORR by RECIST v1.1, 3%; DCR by RECIST v1.1, 4%
  - Cohort 3: DCR by RECIST v1.1, 21%
- Responses to pembrolizumab monotherapy were durable
  - Half of all patients (5/10) with a confirmed response remained in response for ≥24 months
  - 1 patient in cohort 1 remained in response for ≥48 months
- Median OS ranged from 7.9 to 14.1 months in all cohorts
- Pembrolizumab treatment was well tolerated; no new safety signals were observed
- The promising durability of response and DCR supports further exploration of pembrolizumab in combination with other agents for the treatment of mCRPC
  - Phase 3 combination studies with olaparib, docetaxel, and enzalutamide are in progress (KEYNOTE-641, NCT03834493; KEYNOTE-921, NCT03834506; KEYLYNK-010, NCT03834519)

References

1. Antonarakis ES et al. *J Clin Oncol.* 2020;38(suppl 6):104.

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Disclosures

E. S. Antonarakis has served as an advisor or consultant for Amgen, Astellas, AstraZeneca, Bayer, Clovis Oncology, Dendreon, Eli Lilly, ESSA, GlaxoSmithKline, Janssen, Medivation, Merck, and Sanofi; has received research funding from AstraZeneca, Bristol Myers Squibb, Celgene, Clovis Oncology, Dendreon, Genentech, Janssen, Johnson & Johnson, Merck, Novartis, Sanofi, and Tokai; and has received licensing/royalties from Qiagen.

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