Phase 2 Study of Pembrolizumab in Docetaxel-Pretreated Patients With Metastatic Castration-Resistant Prostate Cancer: Updated Follow-Up of Cohorts 1-3 From KEYNOTE-199

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Background

- Pembrolizumab, a humanized monoclonal anti–PD-1 antibody, has demonstrated antitumor activity and an acceptable safety profile in patients with metastatic castration-resistant prostate cancer (mCRPC)[1,2]
- Cohorts 1, 2, and 3 of the phase 2 KEYNOTE-199 study (NCT02787005) were grouped to evaluate pembrolizumab monotherapy in patients with mCRPC previously treated with ≥1 next-generation hormonal agent (NHA) and 1 or 2 chemotherapy regimens, 1 of which must have included docetaxel
- Here we provide updated data for cohorts 1-3, based on longer follow-up and more events

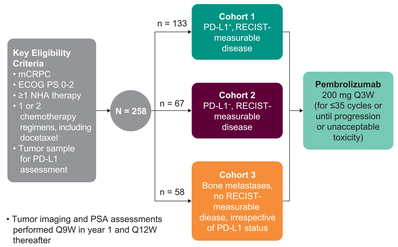
Objective

- To evaluate, using additional follow-up information, the 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

Figure 1. Study Design



Primary end point: ORR per RECIST v1.1 in cohorts 1 and 2 (separately and combined) by BICR
Secondary end points: DCR by BICR (RECIST v1.1); rPFS by BICR (PCWG3-modified RECIST v1.1), PSA response rate, OS, and safety (cohorts 1-3); DOR by BICR (RECIST v1.1, cohorts 1 and 2)

BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; DCR, disease control rate; DOR, duration of response; ORR, objective response rate; OS, overall survival; PCWG3, Prostate Cancer Working Group 3; PSA, prostate-specific antigen; Q3W, every 3 weeks; Q9W, every 9 weeks; Q12W, every 12 weeks; rPFS, radiographic progression-free survival.

[a]A maximum of 3 lines of prior treatment for mCRPC were allowed.

- PD-L1 expression was assessed centrally using the PD-L1 IHC 22C3 pharmDx assay (Agilent)
  - PD-L1 positivity was defined as a combined positive score ≥1, calculated as the number of PD-L1–positive cells (tumor cells, lymphocytes, macrophages) divided by the total number of tumor cells, multiplied by 100
- The analysis population comprised patients who received ≥1 dose of pembrolizumab
- Data cutoff was June 24, 2019

Results

Patients

- Time from enrollment to data cutoff, median (range), was 31.7 months (26.7-34.7)
  - Cohort 1: 31.3 months (26.7-34.7); cohort 2: 30.6 months (28.0-34.1); cohort 3: 32.6 months (27.4-34.4)

Table 1. Baseline Demographics and Disease Characteristics

	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 acetate only, %	43	36	48
Enzalutamide and abiraterone acetate, %	26	24	24

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

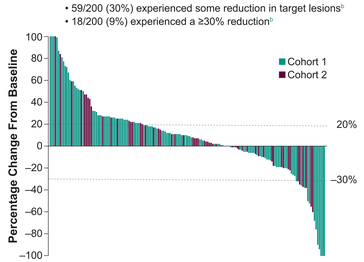
Efficacy

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	3 (2)	0	NA
PR	5 (4)	2 (3)	NA
SD of any duration	23 (17)	14 (21)	0 (0)
Non-CR/non-PD of any duration	0 (0)	0 (0)	21 (36)
DCR (CR + PR + SD/non-CR/non-PD ≥6 months)	14 (11)	4 (6)	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)
PSA response rate for patients with PSA measurement at baseline			
	n = 124	n = 61	n = 58
Response rate, n (%)	8 (6)	5 (8)	1 (2)

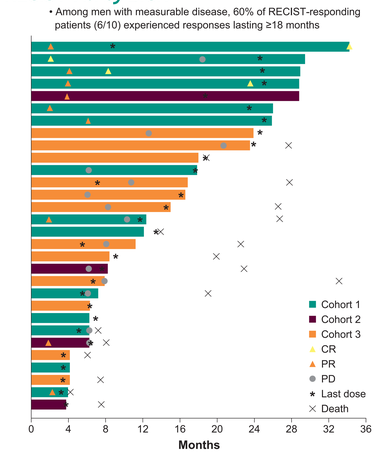
CR, complete response; NA, not applicable; PD, progressive disease; PR, partial response; SD, stable disease.
[a]Patients for whom imaging quality was poor or who had insufficient follow-up (<6 months) with best objective response (unconfirmed) of SD, CR, or PR.
[b]Patients who had a baseline assessment but no postbaseline assessment on the data cutoff date, including missing, discontinuing, or death before first postbaseline imaging.

Figure 2. Target Lesion Change From Baseline for RECIST-Measurable Disease[a]



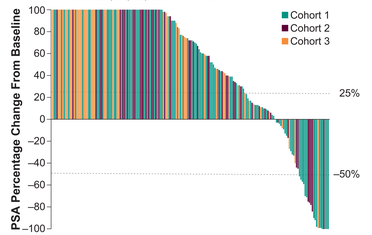
[a]Plot is based on patients who had RECIST-evaluable disease at baseline and ≥1 evaluable postbaseline imaging assessment (n = 168).
[b]Calculation is based on patients who had nonmissing target lesions at baseline.

Figure 3. Time to Response and Response Duration of Patients Who Achieved CR or PR or Had SD or Non-CR/Non-PD ≥6 Months per RECIST v1.1 by BICR



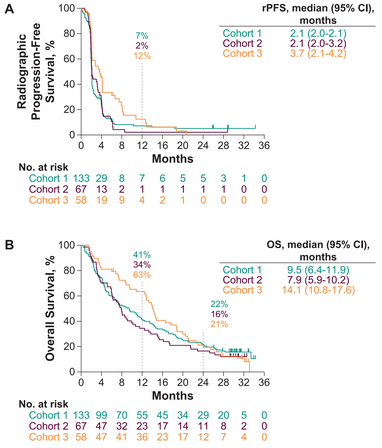
Rows without a symbol for CR or PR represent patients whose best overall response was SD or non-CR/non-PR. The length of the bar indicates time to the last imaging assessment.

Figure 4. PSA Percentage Change From Baseline[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 Estimates of (A) rPFS Based on BICR per PCWG3-Modified RECIST and (B) OS



Safety

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

n (%)	Total Population N = 258
Any TRAE	157 (61)
Grade 3-5 TRAE	41 (16)
TRAEs leading to discontinuation	13 (5)
TRAEs leading to death[a]	3 (1)

TRAEs occurring in ≥10 patients	Any Grade	Grade 3-5
Fatigue	39 (15)	3 (1)
Diarrhea	29 (11)	3 (1)
Decreased appetite	27 (10)	2 (<1)
Nausea	24 (9)	0 (0)
Pruritus	16 (6)	1 (<1)
Asthenia	15 (6)	0 (0)
Vomiting	11 (4)	0 (0)
AST level increased	11 (4)	1 (<1)
Anemia	10 (4)	2 (<1)

AST, aspartate aminotransferase; TRAE, treatment-related adverse event.
[a]Cohort 1, sepsis; cohort 2, unknown; cohort 3, immune-related pneumonitis.

Conclusions

- With additional follow-up, pembrolizumab monotherapy continued to show antitumor activity and disease control in patients with RECIST-measurable and bone-predominant mCRPC that was previously treated with NHAs and with docetaxel
- Median OS compared favorably with OS in other studies in this population with advanced disease
- The safety profile of pembrolizumab is acceptable and consistent with that of previous reports
- The promising durability of response 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 (KEYLYNK-010 [NCT03834519], KEYNOTE-921 [NCT03834506], KEYNOTE-641 [NCT03834493], respectively)

References

1. Antonarakis ES et al. *J Clin Oncol.* 2020;38:395-405.
2. Hansen AR et al. *Ann Oncol.* 2018;29:1807-1813.

Disclosures

J.C. Goh received honoraria from Merck; has stock in Immutep Ltd; has consultant/advisory roles for AstraZeneca, Tesaro, and BMS; and has received reimbursement for travel, accommodations, and expenses from AstraZeneca and Astellas.

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