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Real-world outcomes in patients with metastatic castration-resistant prostate cancer (mCRPC) and tumors with androgen receptor (*AR*) 878/875 mutations

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Objectives

- Characterize the real-world detection rate of *AR* 878/875 mutations in mCRPC
- Compare clinical outcomes in patients with mCRPC and tumors harboring *AR* T878 and/or H875 missense mutations (*AR* 878/875+) and patients with mCRPC whose tumors do not have these mutations (*AR* 878/875-)

Key Findings

- In this real-world mCRPC cohort, 11% of patients had *AR* 878/875+ tumors
  - The *AR* 878/875+ detection rate increased from 6.3% in 2014 to 10.5% in 2020 in patients with prostate cancer
- In matched cohorts of *AR* 878/875+ patients with mutations detected prior to first-line (1L) mCRPC therapy vs *AR* 878/875- patients:
  - Median (95% CI) real-world overall survival (rwOS) from 1L treatment initiation was 16.1 months (11.4–26.8) vs 50.7 months (45.4–59.8; $P<0.0001$)
  - Median time to next treatment (TTNT; 95% CI) was 5.0 months (4.1–7.2) vs 11.7 months (9.7–14.4; $P=0.0183$)
- In the subcohort of matched *AR* 878/875+ and *AR* 878/875- patients who received novel hormonal agent (NHA)-containing 1L treatment:
  - Median (95% CI) rwOS from 1L initiation was 16.4 months (6.9–not reached [NR]) vs 59.9 months (43.5–NR; $P=0.0007$)
  - Median TTNT (95% CI) was 4.5 months (1.8–13.1) vs 13.9 months (9.1–20.9; $P=0.0274$)

Conclusions

- In this retrospective, real-world study, 11% of patients with mCRPC were *AR* 878/875+ by circulating tumor DNA testing, with detection rates increasing in recent years
- By matched comparative analysis, rwOS and TTNT were significantly shorter in patients with mCRPC and tumor *AR* 878/875 mutations detected early in the course of treatment than patients whose tumors did not harbor these mutations, indicating that new treatment options are needed for this patient population

References

1. Boudadi K and Antonarakis ES. *Clin Med Insights Oncol.* 2016;10(Suppl1):1-9.
2. Jernberg E, et al. *Endocr Connect.* 2017;6(8):R146-R161.
3. Iacus S, et al. *Political Analysis.* 2012;20(1):1-24.
4. van Walraven C, et al. *Med Care.* 2009;47(6):626-633.

Acknowledgments

This study is sponsored by Arvinas Androgen Receptor, Inc. Poster development support was provided by Britt Anderson, PhD, of Apollo Medical Communications and funded by Arvinas, Inc.

Disclosures

JML has served on advisory boards in a personal capacity for 4D Pharma, Arvinas, Astellas, AstraZeneca, Gilead, Janssen, Myovant, Pfizer, and Seagen, and has been a product investigator in an institutional role for Arvinas, Gilead, Pfizer, and Seagen.

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Presented at the European Society for Medical Oncology (ESMO) Annual Congress, Paris, France, September 9–13, 2022

Background

- NHAs, eg, abiraterone and enzalutamide, are standard treatment for mCRPC, but many patients develop drug resistance, including due to mutations in the ligand-binding domain of *AR*, and have a poor prognosis[1]
- *AR* 878/875 missense mutations are associated with resistance to current NHA therapies and disease progression[2]
- However, there are limited real-world data characterizing the incidence and clinical implications of these *AR* mutations in men with prostate cancer

Methods

- In this retrospective, exploratory study, patients with mCRPC were identified in the GuardantINFORM database, which combines genomic information from Guardant360 tests with real-world administrative claims data
- The study dataset included patients with Guardant360 tests administered between March 11, 2014, and June 30, 2021
- For each patient, the index date was defined as the earliest diagnosis of mCRPC
- Inclusion criteria:
  - ≥18 years of age as of the index date
  - ≥1 Guardant360 test, with prostate cancer entered as cancer type on test requisition form, administered at any point during disease journey
  - Diagnosed/treated at a clinical site in the United States
- Matched (1:2) cohorts of *AR* 878/875+ and *AR* 878/875- patients were created based on:
  - Age (± 5 years)
  - Elixhauser Comorbidity Index weighted score (± 1 standard deviation)
  - NHA prior to 1L mCRPC
  - Earliest year of metastatic diagnosis (± 1 year) using coarsened exact matching[3]
- Outcomes were compared in unmatched *AR* 878/875+ vs *AR* 878/875- cohorts and in matched *AR* 878/875+ patients who had the mutation detected prior to 1L mCRPC treatment vs *AR* 878/875- patients
- Kaplan-Meier curves were generated and the Wilcoxon test was used to compare clinical outcomes between cohorts

Results

Unmatched mCRPC cohorts

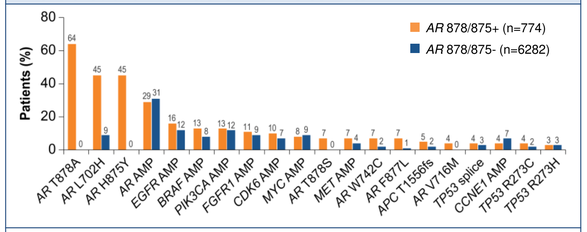
- The GuardantINFORM database contained 13,084 patients diagnosed with prostate cancer meeting the study entry criteria, of whom 7056 had confirmed mCRPC
- 774 (11%) of patients with mCRPC were *AR* 878/875+ and 6282 (89%) were *AR* 878/875-
  - The *AR* 878/875+ detection rate in patients with prostate cancer increased in recent years (from 6.3% in 2014 to 10.5% in 2020)
  - Patients in the *AR* 878/875+ mCRPC cohort had fewer comorbidities during the study and were more likely to have received an NHA prior to 1L therapy for mCRPC than patients in the *AR* 878/875- mCRPC cohort (**Table 1**)
  - *AR* L702H was the most common co-alteration in the *AR* 878/875+ mCRPC cohort (45%); *AR* L702H also occurred in 9% of patients in the *AR* 878/875- mCRPC cohort (**Figure 1**)
- In the unmatched cohorts, median (95% CI) rwOS from mCRPC diagnosis was 46.6 months (43.0–51.2) vs 51.6 months (50.1–54.2) for *AR* 878/875+ vs *AR* 878/875- patients ($P=0.1953$)

Table 1: Characteristics of unmatched *AR* 878/875+ and *AR* 878/875- mCRPC cohorts

Characteristic	*AR* 878/875+ (n=774)	*AR* 878/875- (n=6282)
Age (y), mean ± SD	73.9 ± 8.5	73.3 ± 8.3
Elixhauser Comorbidity Index Weighted VW score,[4] mean ± SD	10.8 ± 9.3	21.4 ± 11.6
Tobacco user, n (%)	371 (48)	2997 (48)
NHA use prior to 1L therapy for mCRPC, n (%)	265 (34)	1751 (28)
Site of metastasis, n (%)		
Bone	750 (97)	5757 (92)
Liver	143 (18)	1091 (17)
Lung	121 (16)	828 (13)
Brain	69 (9)	531 (8)

1L=first-line; *AR*=androgen receptor gene; mCRPC=metastatic castration-resistant prostate cancer; NHA=novel hormonal agent; SD=standard deviation; VW=van Walraven

Figure 1: Twenty most common co-occurring alterations in unmatched *AR* 878/875+ and *AR* 878/875- mCRPC cohorts

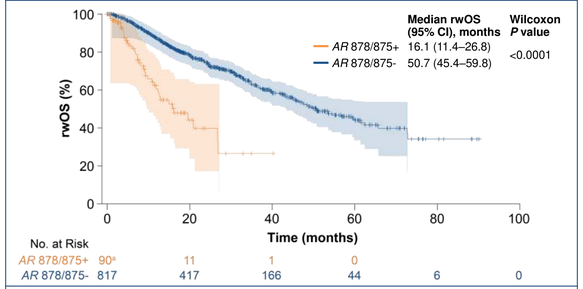


AMP=amplification; *AR*=androgen receptor gene; mCRPC=metastatic castration-resistant prostate cancer

Matched mCRPC cohorts

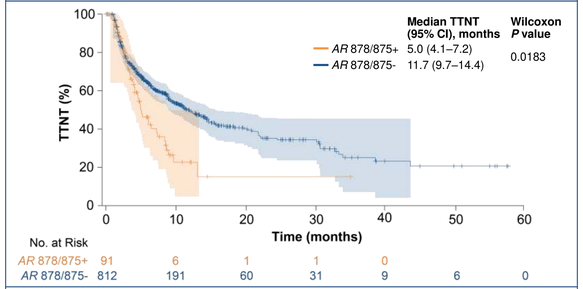
- The matched cohorts included 409 *AR* 878/875+ patients and 818 *AR* 878/875- patients
  - Characteristics were similar in matched cohorts
  - 91 of the *AR* 878/875+ patients had their mutation(s) detected prior to 1L mCRPC treatment
- rwOS (**Figure 2**) and TTNT (**Figure 3**) since 1L mCRPC treatment were significantly shorter in *AR* 878/875+ vs *AR* 878/875- patients
- In the subcohort of patients who received NHA-containing 1L therapy, rwOS (**Figure 4**) and TTNT (**Figure 5**) from 1L initiation were significantly shorter in *AR* 878/875+ vs *AR* 878/875- patients

Figure 2: rwOS since 1L mCRPC treatment in *AR* 878/875+ vs *AR* 878/875- patients (matched cohorts)



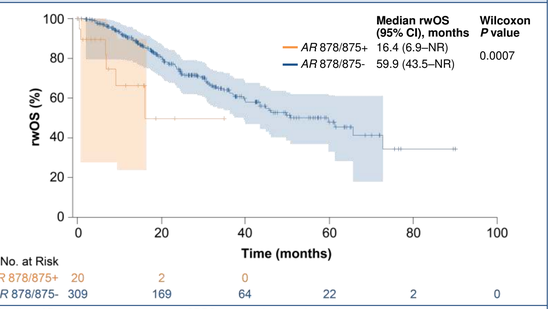
[a]1 *AR* 878/875+ patient was excluded from the rwOS analysis due to suspected erroneous data point.
1L=first-line; *AR*=androgen receptor gene; mCRPC=metastatic castration-resistant prostate cancer; rwOS=real-world overall survival

Figure 3: TTNT since 1L mCRPC treatment in *AR* 878/875+ vs *AR* 878/875- patients (matched cohorts)



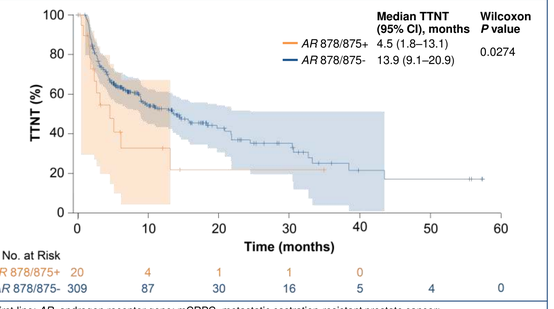
1L=first-line; *AR*=androgen receptor gene; mCRPC=metastatic castration-resistant prostate cancer; TTNT=time to next treatment

Figure 4: rwOS since 1L mCRPC treatment in *AR* 878/875+ vs *AR* 878/875- patients who received NHA-containing 1L treatment (matched cohorts)



1L=first-line; *AR*=androgen receptor gene; mCRPC=metastatic castration-resistant prostate cancer; NHA=novel hormonal agent; NR=not reached; rwOS=real-world overall survival

Figure 5: TTNT since 1L mCRPC treatment in *AR* 878/875+ vs *AR* 878/875- patients who received NHA-containing 1L treatment (matched cohorts)



1L=first-line; *AR*=androgen receptor gene; mCRPC=metastatic castration-resistant prostate cancer; NHA=novel hormonal agent; TTNT=time to next treatment

Study Limitations

- Limitations include the retrospective, real-world nature of the study, missing clinical information in administrative claims data, no information for patients not taking the Guardant360 test, changes in mCRPC standard of care during the study period (2014–2021), and patients with *AR* 878/875 mutations detected prior to 1L mCRPC therapy were not rematched prior to analysis