Poster c12

Real-World Outcomes of Patients With Metastatic Castration-Resistant Prostate Cancer (mCRPC) and Tumors Harboring Androgen Receptor (*AR*) Ligand-Binding Domain (LBD) Mutations

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Objectives

- To determine the prevalence of missense *AR* LBD mutations and explore testing and treatment patterns in a real-world sample of US patients with mCRPC
- To compare real-world overall survival (rwOS) in patients with *AR* LBD missense mutations (excluding L702H alone) compared with patients without any missense mutations in the *AR* LBD

Key Findings

- 20% of patients had an *AR* LBD missense mutation
- Prevalence of *AR* LBD mutations was higher in later lines of treatment; however, there was a decreased prevalence of testing in later lines of therapy, and retesting rates were low
- Patients with *AR* LBD–mutated mCRPC had notably shorter rwOS than those whose tumors did not harbor *AR* LBD mutations, indicating an unmet need for this population

Limitations

- Small sample sizes prevented additional subgroup analyses of real-world outcomes by specific treatment exposure
- Analysis was restricted to patients who received Guardant360 (G360) testing
- This study utilized claims data, which are collected primarily for billing purposes, not scientific research purposes. As with all retrospective claims analyses, administrative claims data are subject to coding errors, which may result in potential misclassification of mCRPC status, covariates, and/or study outcomes

Conclusions

- These observations suggest that *AR* LBD mutations may go undetected with current testing practices
- Prognosis as measured by rwOS was worse in patients with *AR* LBD mutations compared with patients without any *AR* LBD mutations
- As treatment paradigms shift with earlier novel hormonal agent (NHA) use and additional subgroups of *AR* LBD missense mutations become of greater interest, further studies are warranted to better understand the clinical impact of all *AR* LBD mutations

References

1. CDC. Cancer Statistics At a Glance. Accessed January 2, 2024. https://gis.cdc.gov/Cancer/USCS/#/AtAGlance/value,1,1,1,1,2,1. **2.** Snaterse G, et al. *Prostate Cancer Prostatic Dis*. 2023;26(2):293-301. **3.** Lallous N, et al. *Genome Biol*. 2016;17:10. **4.** Shiota M, et al. *Endocr Relat Cancer*. 2022;29(10):R143-R155. **5.** Zhen JT, et al. *Cancer*. 2018;124(15):3105-3117. **6.** Taavitsainen S, et al. *JCO Precis Oncol*. 2019;3:PO.19.00014. **7.** Freedland SJ, et al. *Curr Med Res Opin*. 2021;37(4):609-622.

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Background

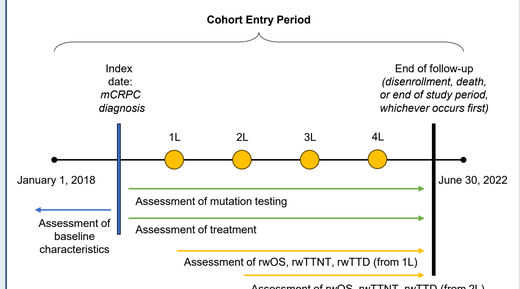
- In the United States, prostate cancer is the most common cancer among men and is the second leading cause of cancer-related death[1]
- It is estimated that approximately 20%–25% of men with mCRPC will develop mutations in the *AR* LBD (amino acids 671–920); L702H, H875Y, and T878A are the most common and are associated with disease progression and poor prognosis[2–4]
- Genetic testing for patients with prostate cancer has been adopted more slowly compared with other forms of cancer, such as breast and colon cancer[5]
- Recent research has shown that genomic testing is becoming increasingly more important in patients with advanced prostate cancer, with circulating tumor DNA (ctDNA) sequencing providing a minimally invasive method to identify molecular characteristics of tumors[6]
- This study characterized testing practices, mutation prevalence, treatment patterns, and real-world outcomes in patients with mCRPC whose ctDNA tested positive or negative for missense mutations in the *AR* LBD

Methods

- This was a retrospective analysis of the Guardant Inform Database (March 20, 2014–June 30, 2022; **Figure 1**)
- Data presented in this poster are for patients diagnosed since January 1, 2018, given the changes in treatment practices in more recent years
- Patient population:
  - Men (aged ≥18 years) with mCRPC who were tested with G360 next-generation sequencing identified using an algorithm developed by Freedland et al[7]
  - Diagnosed/treated at a clinical site in the United States with a first-line (1L) treatment
  - Patients with detectable ctDNA (ctDNA+)
- Patient subgroups:
  - Patients with any missense mutations in *AR* LBD, including the following as a subgroup:
    - Patients with *AR* LBD missense mutations, excluding L702H alone (eg, without co-occurring *AR* LBD mutations)
  - Patients without any mutations of the *AR* LBD
- Outcomes:
  - Mutation prevalence and characteristics
  - Treatment for metastatic cancers, such as NHAs, androgen deprivation therapy, first-generation AR antagonists, immunotherapy, radiotherapy, poly ADP-ribose polymerase (PARP) inhibitors, taxane chemotherapies, and non-taxane chemotherapies
  - Matched[a] real-world outcomes, including rwOS, time-to-next treatment (rwTTNT), and time-to-treatment discontinuation (rwTTD)

[a]1:5 coarsened exact matching was conducted between patients with any *AR* LBD mutations, excluding L702H alone, and patients without any *AR* LBD mutations on age (±5 years), Elixhauser Comorbidity Index weighted score (±1 SD), smoking status, prior use of NHA (including abiraterone, enzalutamide, apalutamide, darolutamide), and index year (±1 year)

Figure 1: Study design



1L=first line; 2L=second line; 3L=third line; 4L=fourth line; mCRPC=metastatic castration-resistant prostate cancer; rwOS=real-world overall survival; rwTTD=real-world time-to-treatment discontinuation; rwTTNT=real-world time-to-next treatment

Results

Mutation Characteristics and Treatment Patterns

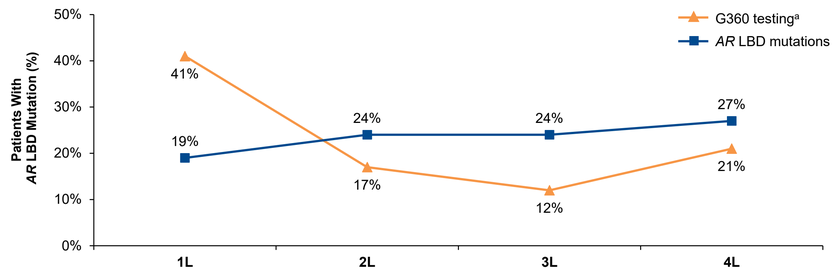
- 4833 patients with evidence of 1L treatment for mCRPC were identified in the database
- 20% had *AR* LBD mutations (**Table 1**)
- 41% of patients received a G360 test prior to 1L therapy, meaning 59% of patients received their first G360 test after 1L (**Figure 2**)
  - 65% of patients received a G360 test at some point after 1L therapy, with 15% of patients receiving >1 G360 test
- Mutation prevalence for *AR* LBD mutations was higher in patients tested prior to fourth line (4L) than 1L, while G360 testing rates decreased by lines of therapy (**Figure 2**)
- Among all patients with mCRPC, use of NHAs was lower in 4L than 1L (20% vs 33%), whereas use of taxanes was higher (31% vs 22%; **Table 2**)

Table 1: Prevalence of *AR* LBD mutations in patients with mCRPC from 2018 to 2022

Mutation	Prevalence, n (%)
Evidence of 1L mCRPC and received a G360 test since January 2018	4833 (100)
AR wild type[a]	2748 (57)
With *AR* LBD missense mutations	945 (20)
Other *AR* mutations	784 (16)
ctDNA negative	356 (7)

[a]Absence of any *AR* missense mutation, amplification, frame-shift mutation, rearrangement, etc
1L=first line; AR=androgen receptor; ctDNA=circulating tumor DNA; G360=Guardant360; LBD=ligand-binding domain; mCRPC=metastatic castration-resistant prostate cancer

Figure 2: Mutation testing rate and prevalence by line of therapy



[a]G360 testing received prior to the indicated line of therapy but after the preceding line of therapy (eg, prior to 1L, between 1L and 2L, between 2L and 3L, and after 3L)
1L=first line; 2L=second line; 3L=third line; 4L=fourth line; AR=androgen receptor; G360=Guardant360; LBD=ligand-binding domain

Table 2: Exposures to treatments (as monotherapy or combination therapy) from 1L to 4L for all patients with mCRPC

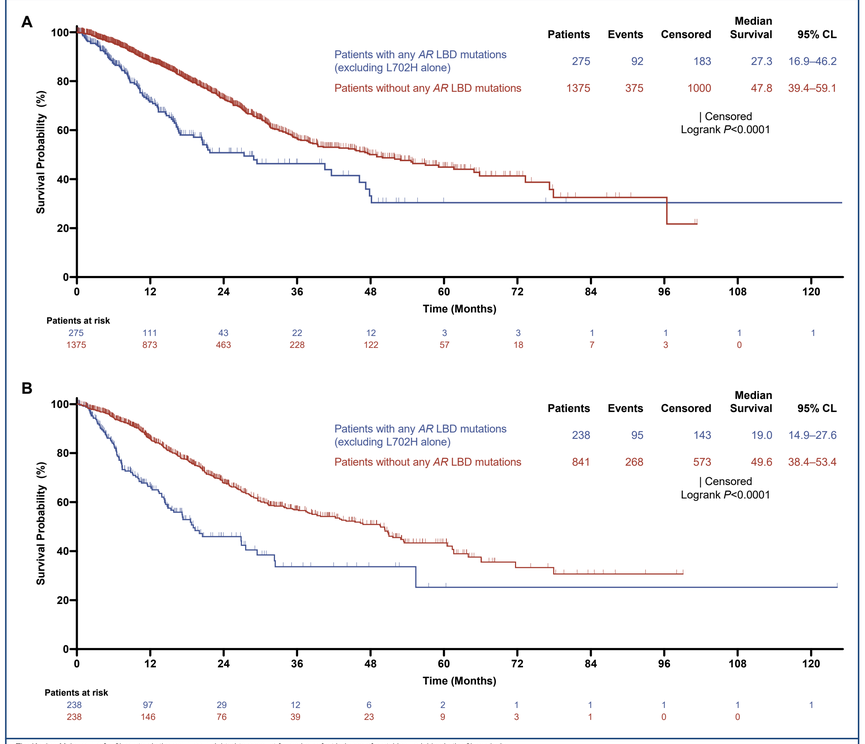
Treatments, n (%)	1L (n=4833)	2L (n=3185)	3L (n=2020)	4L (n=1255)
NHA	1599 (33)	847 (27)	456 (23)	246 (20)
ADT alone	1092 (23)	968 (30)	541 (27)	369 (29)
Taxane-based therapy	1074 (22)	826 (26)	668 (33)	395 (31)
Immunotherapy	540 (11)	172 (5)	110 (5)	71 (6)
First-generation AR antagonists[a]	363 (8)	145 (5)	75 (4)	32 (3)
Radiotherapy[b]	223 (5)	218 (7)	128 (6)	114 (9)
PARP	37 (1)	70 (2)	71 (4)	47 (4)

[a]Includes bicalutamide, nilutamide, or flutamide
[b]Radiotherapy includes RA-223, strontium, and samarium
1L=first line; 2L=second line; 3L=third line; 4L=fourth line; ADT=androgen deprivation therapy; AR=androgen receptor; mCRPC=metastatic castration-resistant prostate cancer; NHA=novel hormonal agent; PARP=poly ADP-ribose polymerase

Real-World Outcomes

- In the matched rwOS analysis, patients in the *AR* LBD group (n=275) had statistically significantly shorter 1L median rwOS than the control group (n=1375): 27.3 vs 47.8 months (*P*<0.0001; **Figure 3A**)
- Similar separations in the Kaplan-Meier curves were observed when considering rwOS from initiation of second-line (2L) therapy (**Figure 3B**)
  - Patients with any *AR* LBD mutations, excluding L702H alone, experienced shorter rwOS from 2L start than patients without any *AR* LBD mutations
- There were no significant differences in rwTTNT and rwTTD after matching

Figure 3: Matched adjustment Kaplan-Meier analysis of rwOS since (A) 1L systemic therapy initiation and (B) 2L systemic therapy initiation[a]



[a]The Kaplan-Meier curve for 2L systemic therapy was weighted to account for an imperfect balance of matching variables in the 2L analysis
1L=first line; 2L=second line; AR=androgen receptor; LBD=ligand-binding domain; rwOS=real-world overall survival