Impact of androgen receptor pathway inhibitors (ARPIs) on mental health in Veterans with metastatic hormone-sensitive prostate cancer (mHSPC)

Phoebe A. Tsao[1,2], Kyle Kumbier[1], Stephanie Visnic[1], Jordan Sparks[1], Joshi J. Alumkal[2], Amy S.B. Bohnert[1,3,4], Megan E. V. Caram[1,2]

[1]VA Center for Clinical Management and Research, VA Ann Arbor Healthcare System, Ann Arbor, MI
[2]Division of Hematology/Oncology, Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, MI
[3]Department of Anesthesiology, University of Michigan Medical School, Ann Arbor, MI
[4]Department of Psychiatry, University of Michigan Medical School, Ann Arbor, MI

Background:
Androgen deprivation therapy (ADT) is the backbone treatment for mHSPC. Its use is associated with the development of depression and anxiety due to testosterone loss and its negative impacts on quality of life. ARPIs, when added to ADT, are now a critical aspect of the standard of care for mHSPC. Given ARPIs further alter the testosterone axis, we sought to understand the impact of ARPIs on mental health compared to ADT alone.

Methods:
We used national Veterans Health Administration data and a validated natural language processing algorithm to identify Veterans with mHSPC diagnosed between 2018-2022 who received either ADT alone or ADT + ARPI as first-line therapy for mHSPC. The ADT + ARPI group was defined as Veterans who started an ARPI ≤120 days of starting ADT for mHSPC. Veterans receiving care for a second malignancy and those with preexisting mental health conditions were excluded. We compared the incidence of mental health diagnoses in the 2 years after starting ADT in those who received ADT alone v. ADT + ARPI using Chi-square and Fisher's exact tests.

Results:
We identified 3337 Veterans without a preexisting mental health diagnosis who received ADT for mHSPC – 2235 (67.0%) received ADT alone and 1102 (33.0%) ADT + ARPI. Those who received ADT alone were older (median 75 years, interquartile range [IQR] 70-83 v. 75 years, IQR 70-80), had a higher comorbidity burden (NCI Charlson comorbidity index ≥2 35.3% v. 30.1%), had a lower baseline prostate specific antigen (median 30 v. 49 ng/dl), and received treatment earlier in the study window (2018-2019 47.7% v. 28.6%) (Table 1). More Veterans who received ADT + ARPI (23.1%) were diagnosed with a new mental health condition in the 2 years after starting ADT compared to those who received ADT alone (20.4%), although this did not reach statistical significance (p=0.07) (Table 2, Figure 1). Depression was the most common diagnosis (9.4% ADT alone, 10.2% ADT + ARPI), followed by adjustment disorder (6.9% ADT alone, 8.4% ADT + ARPI) and anxiety (6.0% ADT alone, 7.2% ADT + ARPI) in both groups.

Conclusions:
Veterans who received ADT + ARPI as first-line treatment for mHSPC trended towards having more incident mental health diagnoses compared to those who received ADT alone, although this was not statistically significant. Overall, more than 20% of Veterans with mHSPC were diagnosed with a new mental health condition after starting treatment for mHSPC. Further work to account for covariates and to understand the impact of ARPIs in those with preexisting mental health diagnoses is warranted.

Funding Acknowledgements: The Stewart J. Rahr Foundation – PCF VAlor Young Investigator Award

Conflicts of Interest: None

Table 1. Demographics and clinical characteristics.

	ADT alone (n = 2,235)	ADT + ARPI (n = 1,102)	p-value
Age, years (median, IQR)	75 (70-83)	75 (70-80)	<0.001
Race (n, %)			0.8
White	1,486 (66%)	728 (66%)	
Black	582 (26%)	286 (26%)	
Other	57 (2.6%)	25 (2.3%)	
Unknown	110 (4.9%)	63 (5.7%)	
Marital status (N, %)			0.6
Married	1,175 (53%)	597 (54%)	
Not married	1,048 (47%)	501 (45%)	
Unknown	12 (0.5%)	4 (0.4%)	
NCI Charlson comorbidity index (n, %)			0.003
0	860 (38%)	487 (44%)	
1	586 (26%)	283 (26%)	
≥2	789 (35%)	332 (30%)	
Urban v. rural home zip code (n, %)			0.6
Urban	1,559 (70%)	766 (70%)	
Rural	673 (30%)	333 (30%)	
Unknown	3 (0.1%)	3 (0.3%)	
Baseline PSA[1] (median, IQR)	30 (6-136)	49 (12-246)	<0.001
Missing baseline PSA (n, %)	474 (21%)	123 (11%)	
Year of treatment initiation for mHSPC (n, %)			<0.001
2018	566 (25%)	132 (12%)	
2019	499 (22%)	183 (17%)	
2020	371 (17%)	183 (17%)	
2021	418 (19%)	273 (25%)	
2022	381 (17%)	331 (30%)	

[1]Baseline PSA was defined as the highest PSA value within a 120-day window centered on the start date of ADT

Abbreviations: ADT, androgen deprivation therapy; ARPI, androgen receptor pathway inhibitor; IQR, interquartile range; mHSPC, metastatic hormone-sensitive prostate cancer; NCI, National Cancer Institute; PSA, prostate specific antigen

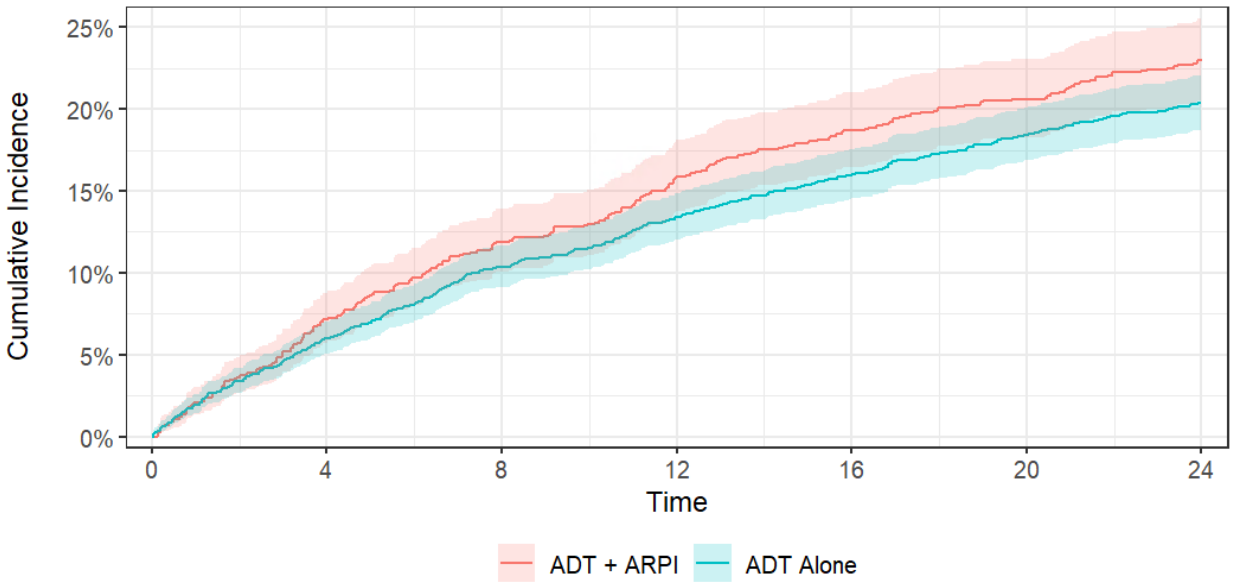
Table 2. Incident mental health diagnoses in Veterans receiving ADT v. ADT + ARPI for mHSPC.

	ADT alone (n = 2,235)	ADT + ARPI (n = 1,102)	p-value
Incident mental health diagnoses[1] (n, %)			
Any of the below	455 (20.4%)	254 (23.1%)	0.07
Depression	211 (9.4%)	112 (10.2%)	0.5
Anxiety	135 (6.0%)	79 (7.2%)	0.2
Post-traumatic stress disorder	87 (3.9%)	44 (4.0%)	0.9
Adjustment disorder	155 (6.9%)	93 (8.4%)	0.1
Substance use disorder	96 (4.3%)	58 (5.3%)	0.2
Bipolar disorder	8 (0.4%)	1 (<0.1%)	0.3
Schizophrenia	7 (0.3%)	2 (0.2%)	0.7
Attempted self-harm	1 (<0.1%)	0 (0.0%)	>0.9

[1]Any diagnoses that occurred ≤2 years of starting ADT

Abbreviations: ADT, androgen deprivation therapy; ARPI, androgen receptor pathway inhibitor; mHSPC, metastatic hormone-sensitive prostate cancer

Figure 1. Cumulative incidence of new mental health diagnoses in Veterans receiving ADT v. ADT + ARPI for mHSPC.



ADT + ARPI							
At Risk	1102	1023	971	927	896	875	848
Events	0	79	131	175	206	227	254
ADT Alone							
At Risk	2235	2101	2004	1935	1878	1823	1780
Events	0	134	231	300	358	412	455

Shaded areas reflect 95% confidence intervals.