

# Prevalence and Severity of Hot Flashes and Their Association With Prostate-Specific Antigen Response: Results From the Initial Treatment Phase of LIBERTAS, a Phase 3 Study in Metastatic Hormone-Sensitive Prostate Cancer

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## Key Takeaway



Results from the initial treatment phase of LIBERTAS, which combines APA with continuous ADT, demonstrate a rapid onset of hot flashes in patients with mHSPC. The LIBERTAS study is now fully enrolled, and the first clinical data on ADT de-escalation in patients experiencing a deep PSA decline are expected in late 2026 or early 2027

## Conclusions



Patients had a deep and rapid PSA decline with APA + continuous ADT



Hot flash incidence and overall burden were high and increased from BL to 6 months during initial treatment with APA + continuous ADT; this increase occurred regardless of PSA response



Hot flash severity increased more in patients who had not received ADT before the study versus those who did receive prestudy ADT. Further analysis after study unblinding will help to clarify the factors contributing to hot flashes in the main phase of LIBERTAS



LIBERTAS will explore the de-escalation of ADT, in a randomized manner, and resulting impact on PSA response, clinical outcomes, and quality of life



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Poster

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Supplementary material

## Introduction

- Apalutamide (APA) with continuous androgen deprivation therapy (ADT) showed rapid and deep prostate-specific antigen (PSA) decline in patients with metastatic hormone-sensitive prostate cancer (mHSPC)\*1,2. 38% and 23% of patients treated with APA + ADT achieved a deep PSA decline of >0.02 to 0.2 ng/mL, and ≤0.02 ng/mL by 3 months, respectively, in the TITAN study<sup>2</sup>
  - This deep PSA response, the highest observed for any androgen receptor pathway inhibitor, was associated with improved OS and sustained quality of life<sup>1,3,4</sup>
- ADT-related side effects cause a significant burden on patients, with hot flashes, potentially leading to distress and negative downstream effects on sleep, energy levels, and quality of life<sup>5,6</sup>
- LIBERTAS, an ongoing ADT de-escalation study, is evaluating APA + intermittent ADT vs APA + continuous ADT in patients with mHSPC who have deep PSA decline (PSA <0.2 ng/mL) after initial treatment with APA + continuous ADT
- Here we report PSA and hot flash data for the initial 6-month treatment phase

## Results\*\*

### Patients

- For the initial treatment phase, 420 patients (73 sites, 9 countries) were enrolled (Full analysis; Table 1)
- Patients were enrolled based on conventional imaging and/or NGL; patients who had prostate-specific membrane antigen positron emission tomography at screening had a lower disease burden (such as BL PSA and disease volume) versus the overall population (data not shown)
- At BL, 59% of patients reported hot flash

Table 1: BL characteristics

	Full analysis N=420	With hot flash at BL n=248	Without hot flash at BL n=172
Age, years			
Median (IQR)	70 (64-75)	69 (63-75)	72 (67-77)
≥75, n (%)	124 (30)	66 (27)	58 (34)
Race, n (%) <sup>a</sup>			
White	297 (71)	177 (71)	120 (70)
Asian	39 (9)	22 (9)	17 (10)
Black or African American	36 (9)	21 (9)	15 (9)
Median (IQR) time from mHSPC diagnosis to initial treatment, mo	2.3 (1.4-3.5)	2.6 (1.5-3.5)	2.0 (1.3-3.2)
ECOG PS, n (%)			
0	312 (74)	181 (73)	131 (76)
1	105 (25)	65 (26)	40 (23)
2	3 (0.7)	2 (0.8)	1 (0.6)
Gleason score at diagnosis, n (%) <sup>b</sup>			
≤7	139 (33)	82 (33)	57 (33)
>7	269 (64)	159 (64)	110 (64)
Metastasis stage at diagnosis, n (%) <sup>c</sup>			
M0 or MX	146 (35)	78 (31)	68 (40)
M1	273 (65)	170 (69)	103 (60)
Bone metastasis at BL, n (%)	344 (82)	217 (88)	127 (74)
Visceral metastasis at BL, n (%)	68 (16)	44 (18)	24 (14)
High volume, n (%) <sup>d</sup>	202 (48)	123 (50)	79 (46)

IQR, interquartile range. Percentages may not equal 100 due to rounding. <sup>a</sup>Other patients were American Indian or Alaska Native (n=2), other (n=22), multiple (n=11), and not reported/unknown (n=13) in the full analysis set; American Indian or Alaska Native (n=2), other (n=13), multiple (n=6), and not reported/unknown (n=7) in "with hot flash at BL"; and other (n=9), multiple (n=5), and not reported/unknown (n=6) in "without hot flash at BL". <sup>b</sup>Missing data: full analysis (n=12), "with hot flash at BL" (n=7), "without hot flash at BL" (n=5). <sup>c</sup>Missing data: full analysis (n=1), "without hot flash at BL" (n=1). <sup>d</sup>Defined as either visceral metastases or ≥4 bone lesions, including ≥1 outside of the vertebral column or pelvis based on the CHAARTED criteria. <sup>e</sup>Missing data: full analysis (n=3), "without hot flash at BL" (n=3).

### Prestudy ADT for mHSPC

- In the full analysis set, prestudy ADT for mHSPC was received by 65% of patients; it was received by more patients with hot flashes at BL (73%) versus without hot flashes at BL (54%) (Table 2)
- Median time from start of prestudy ADT to start of initial study treatment was <2 months and was similar in patients with and without hot flash at BL (Table 2)

### Serum testosterone

- At BL, median serum testosterone was above castration level (0.7 nmol/L threshold) in patients without hot flash at BL and below in patients with hot flash at BL (Table 2)
- At 6 months, median serum testosterone levels were below castration levels regardless of hot flash at BL (Table 2)

## Methods

- LIBERTAS is a prospective, open-label, randomized study in patients with mHSPC (Figure 1)
- During the initial 6-month treatment phase, patients received APA (240 mg/d) + continuous ADT
- Patients with confirmed PSA <0.2 ng/mL after the initial treatment phase were randomized 1:1 to APA + intermittent ADT or APA + continuous ADT in the main treatment phase
- Treatment cycles were 28 days each
- Hot flash diary was collected per protocol across all sites/visits and was completed for ≥7 days consecutively prior to cycle 1 day 1 (baseline [BL]), cycle 4 day 1 (3 months), and cycle 7 day 1 (6 months) during the initial treatment phase
- The coprimary end points are radiographic progression-free survival and hot flash burden reduction after 18 months of APA + intermittent ADT. Secondary end points and eligibility criteria are available at <https://clinicaltrials.gov/study/NCT05884398>

### Deep PSA decline with 6 months of APA + continuous ADT

- More than two thirds of patients achieved PSA <0.2 ng/mL; the proportion was similar for patients with and without hot flash at BL (Table 2)
- Median time to achieve PSA <0.2 ng/mL was less than 3 months regardless of hot flash at BL
- Approximately one fifth of patients achieved PSA <0.02 ng/mL; the proportion was similar for patients with and without hot flash at BL

### Hot flash

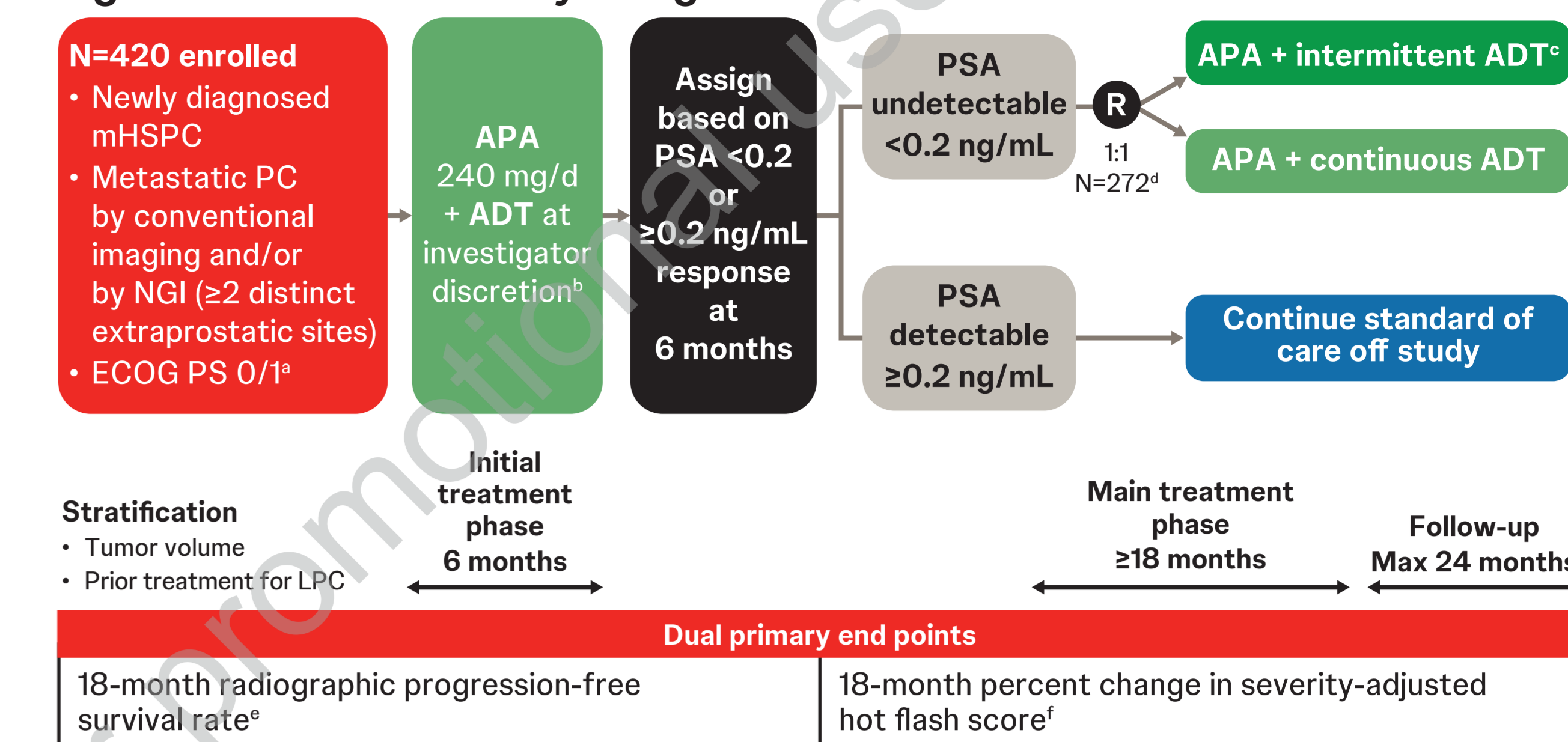
- Hot flash diary was partially or entirely completed by 96%, 93%, and 97% of patients at BL, 3 months, and 6 months
- Hot flash incidence and median severity-adjusted hot flash score increased substantially from BL to 6 months (Tables 2 and 3)
- Peak hot flash severity increased from BL to 6 months (Figure 2)
- The majority of patients experienced a deterioration in hot flash during the initial treatment phase regardless of hot flash at BL

Table 2: ADT prior to study initiation, testosterone, PSA decline, and hot flash

	Full analysis N=420	With hot flash at BL n=248	Without hot flash at BL n=172
<b>Prestudy ADT</b>			
Prestudy ADT for mHSPC, n (%)	274 (65)	181 (73)	93 (54)
Median time from ADT initiation to initial treatment (IQR), mo <sup>a</sup>	1.6 (1.0-2.6)	1.7 (1.2-2.6)	1.4 (0.8-2.2)
<b>Testosterone</b>			
Median (IQR) serum testosterone at BL, nmol/L <sup>b</sup>	0.8 (0.4-11.2)	0.6 (0.4-6.2)	5.2 (0.5-13.4)
Median (IQR) serum testosterone at 6 mo, nmol/L <sup>b</sup>	0.5 (0.4-0.8)	0.5 (0.4-0.8)	0.5 (0.4-0.8)
<b>PSA</b>			
Median (IQR) PSA at BL, ng/mL	7.3 (1.7-43.7)	4.9 (1.1-36.6)	11.8 (3.2-61.6)
Confirmed PSA <0.2 ng/mL during initial treatment phase, n (%) <sup>c</sup>	294 (70)	174 (70)	120 (70)
Median (IQR) time to confirmed PSA <0.2 ng/mL, mo	2.8 (1.9-3.7)	2.8 (1.9-3.7)	2.8 (1.9-3.7)
Confirmed PSA <0.02 ng/mL during initial treatment phase, n (%) <sup>c</sup>	88 (21)	55 (22)	33 (19)
Median (IQR) time to confirmed PSA <0.02 ng/mL, mo	4.6 (3.7-5.1)	4.6 (3.7-5.1)	4.6 (3.7-5.1)
<b>Hot flash</b>			
Hot flash incidence, n/n (%)			
At BL	248/404 (61)	248/248 (100)	0/156 (0)
At 6 months	295/344 (86)	184/206 (89)	111/138 (80)
Median (IQR) severity-adjusted hot flash score <sup>d</sup>			
At BL	0.6 (0-3.7)	2.5 (0.8-7.6)	NA
At 6 months	5.2 (1.3-11.4)	6.2 (2.0-12.5)	3.7 (0.9-10.0)
Deterioration in hot flash during initial treatment phase, n/n (%) <sup>e</sup>			
Increase of ≥2 average hot flashes per day from BL	194/314 (62)	117/199 (59)	77/115 (67)
≥50% increase in severity-adjusted hot flash score from BL <sup>f</sup>	NA	135/199 (68)	NA

NA, not applicable. <sup>a</sup>Includes only dosing periods with nonmissing start and end dates. <sup>b</sup>BL n=413 and 6 mo n=246 in the full analysis set; BL n=242 and 6 mo n=147 in "with hot flash at BL"; and BL n=171 and 6 mo n=99 in "without hot flash at BL". The American Urological Association supports using a total testosterone level below 300 ng/dL (10.4 nmol/L) as a reasonable cutoff to aid in the diagnosis of low testosterone. <sup>c</sup>Best response during the initial treatment phase. <sup>d</sup>Total severity score: each hot flash event multiplied by severity factor (1-mild, 2-moderate, 3-severe, 4-very severe) and summed across collection days. Average daily: total severity score divided by number of collection days. <sup>e</sup>Patients were included if hot flash data were available from all 3 visits (BL, cycle 4 day 1, and cycle 7 day 1). <sup>f</sup>Calculated only for patients with hot flash at baseline.

Figure 1: LIBERTAS study design



ECOG PS, Eastern Cooperative Oncology Group performance status; LPC, localized prostate cancer; NGL, next-generation imaging. <sup>a</sup>Patients with ECOG PS 2 or 3 were eligible for the study if the ECOG PS score was related to stable physical limitations and not related to prostate cancer or associated therapy. <sup>b</sup>Choice of gonadotropin hormone-releasing hormone agonist or antagonist at discretion of investigator. <sup>c</sup>ADT can be restarted in the APA + intermittent ADT group for participants with new or worsening cancer symptoms, PSA increase to >10 ng/mL (or return to BL level when PSA was <10 ng/mL before start of ADT), or PSA doubling time <6 months. <sup>d</sup>272 patients were randomized including 1 patient without assignment of randomized treatment (intent-to-treat population n=271). <sup>e</sup>Radiographic progression assessed using conventional imaging. <sup>f</sup>Evaluated with hot flash diary data.

### Relationship between PSA response and hot flash

- Hot flash incidence and median severity-adjusted hot flash score were similar at BL and increased from BL to 6 months regardless of PSA response (Table 3)
- Median severity-adjusted hot flash score was higher at 6 months in nonresponders versus responders

### Relationship between prestudy ADT for mHSPC and hot flash

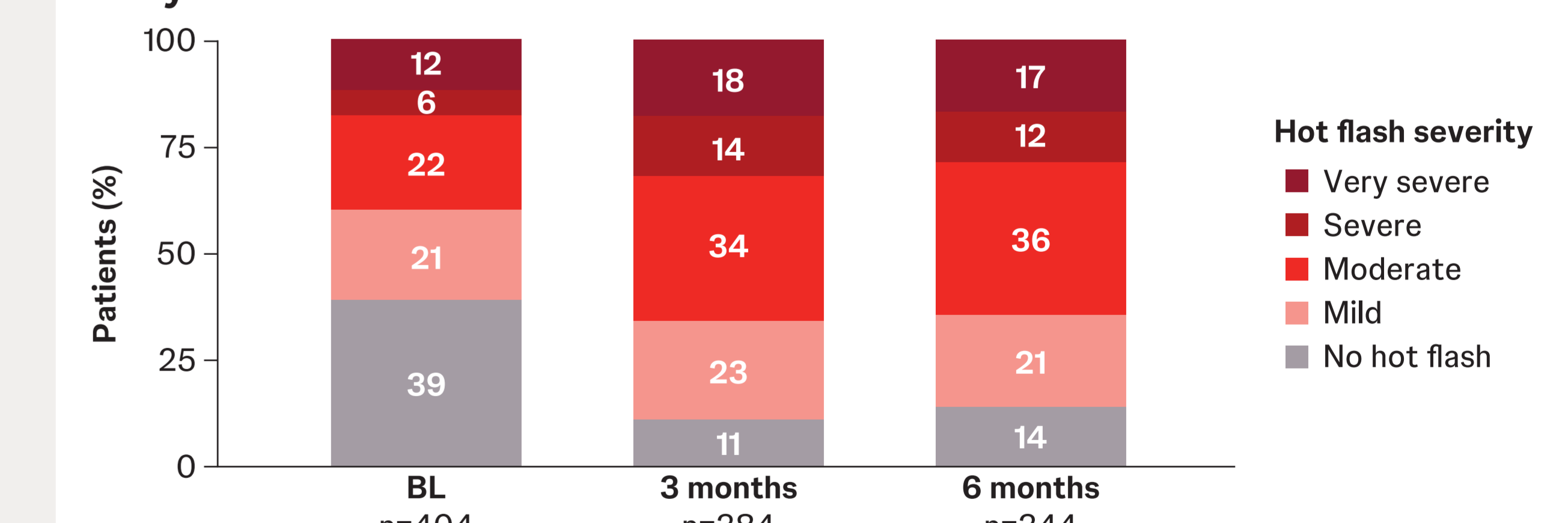
- Patients without prestudy ADT had lower BL hot flash incidence, peak hot flash severity, and median severity-adjusted hot flash score (Table 3 and Supplementary Figure 1)
  - Patients without prestudy ADT experienced a greater increase in BL hot flash incidence, peak hot flash severity, and median severity-adjusted hot flash score during initial treatment versus those without prestudy ADT
  - By 3 months, patients with and without prestudy ADT had similar median severity-adjusted hot flash scores, which remained steady until the end of the initial treatment phase (Supplementary Table 1)

Table 3: Incidence and overall hot flash burden determined by severity-adjusted hot flash score (combining frequency and severity) during initial treatment phase

	Hot flash incidence, n/n (%)		Median (IQR) severity-adjusted hot flash score <sup>a</sup>	
	BL	6 months	BL	6 months
<b>Full analysis</b> N=420	248/404 (61)	295/344 (86)	0.6 (0-3.7)	5.2 (1.3-11.4)
<b>PSA responders</b> n=271	161/261 (62)	223/262 (85)	0.6 (0-3.1)	4.5 (1.1-11.3)
<b>PSA nonresponders<sup>b</sup></b> n=149	87/143 (61)	72/82 (88)	0.5 (0-4.9)	7.1 (2.4-11.9)
<b>With prestudy ADT<sup>c</sup></b> n=274	181/263 (69)	190/227 (84)	1.1 (0-6.3)	4.9 (1.1-10.4)
<b>Without prestudy ADT<sup>c</sup></b> n=146	67/141 (48)	105/117 (90)	0 (0-1.1)	5.8 (1.5-12.7)

See Supplementary Table 1 for data at 3 months. <sup>a</sup>Total severity score: each hot flash event multiplied by severity factor (1-mild, 2-moderate, 3-severe, 4-very severe) and summed across collection days. Average daily: total severity score divided by number of collection days. <sup>b</sup>Nonresponders are patients with PSA ≥0.2 ng/mL response at 6 months. <sup>c</sup>Prior ADT for mHSPC.

Figure 2: Peak hot flash severity during initial treatment phase in the full analysis set



Hot flash severity was captured by the patients based on guidance provided. The severity grades were based on duration of hot flash, physical symptoms, emotional symptoms, and action taken. Highest severity is the most severe hot flash recorded at any time point associated with that analysis visit.

### Safety

- Safety was consistent with prior experience, with the exception of higher incidence of hot flash. Notably, this study has a high compliance rate of hot flash diary collections
- Hot flash reported as a treatment-emergent adverse event occurred in 41% of patients in the full analysis set; the majority (84%) were grade 1

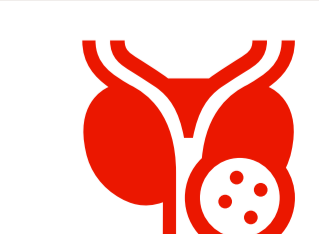
\*mHSPC is also known as metastatic castration-sensitive prostate cancer (mCSPC). \*\*All analyses are based on the August 11, 2025, data cut; data clean-up was not 100% completed at the time of the data cut.

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- Chowdhury S, et al. *Ann Oncol*. 2023;34:477-485. 2. Merseburger AS, et al. *BJU Int*. 2024;134:992-991. 3. Maughan BL, et al. *Prostate Cancer Prostatic Dis*. 2024 <https://doi.org/10.1038/s41391-024-00929-6>. 4. Small EJ, et al. *Eur Urol Oncol*. 2024;7:844-852. 5. Gonzalez BD, et al. *Cancer*. 2018;124(3):499-506. 6. Gillesen S, et al. *Eur Urol*. 2025;87:157-216. 7. Sweeney CJ, et al. *N Engl J Med*. 2015;373:737-746. 8. Mulholland JP, et al. *J Urol*. 2018;200:423-432.

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**Disclosures**  
Dr Morgans has provided consulting for Astellas, AstraZeneca, Bayer, BMS, Curium, Exelixis, Exact Sciences, Johnson & Johnson, Lantheus, MacroGenics, Merck, Novartis, Pfizer, Sumitomo Pharma, Inc, Telix, and Tolmar, and research for Astellas, Bayer, Johnson & Johnson, Lantheus, Pfizer, Sumitomo Pharma, Inc, and Telix.



# Supplementary material for: Prevalence and Severity of Hot Flashes and Their Association With Prostate-Specific Antigen Response: Results From the Initial Treatment Phase of LIBERTAS, a Phase 3 Study in Metastatic Hormone-Sensitive Prostate Cancer

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# Supplementary Table 1: Incidence and overall hot flash burden determined by severity-adjusted hot flash score (combining frequency and severity) during initial treatment phase

	Hot flash incidence, n/n (%)			Median (IQR) severity-adjusted hot flash score <sup>c</sup>		
	BL	3 months	6 months	BL	3 months	6 months
<b>Full analysis</b> N=420	248/404 (61)	340/384 (89)	295/344 (86)	0.6 (0-3.7)	5.0 (1.7-11.9)	5.2 (1.3-11.4)
<b>PSA responders</b> n=271	161/261 (62)	227/258 (88)	223/262 (85)	0.6 (0-3.1)	4.6 (1.5-11.7)	4.5 (1.1-11.3)
<b>PSA nonresponders<sup>a</sup></b> n=149	87/143 (61)	113/126 (90)	72/82 (88)	0.5 (0-4.9)	5.8 (2.0-12.7)	7.1 (2.4-11.9)
<b>With prestudy ADT<sup>b</sup></b> n=274	181/263 (69)	221/250 (88)	190/227 (84)	1.1 (0-6.3)	4.9 (1.6-11.2)	4.9 (1.1-10.4)
<b>Without prestudy ADT<sup>b</sup></b> n=146	67/141 (48)	119/134 (89)	105/117 (90)	0 (0-1.1)	5.5 (1.8-14.9)	5.8 (1.5-12.7)

<sup>a</sup>Nonresponders are patients with PSA  $\geq$ 0.2 ng/mL response at 6 months.

<sup>b</sup>Prior ADT for mHSPC.

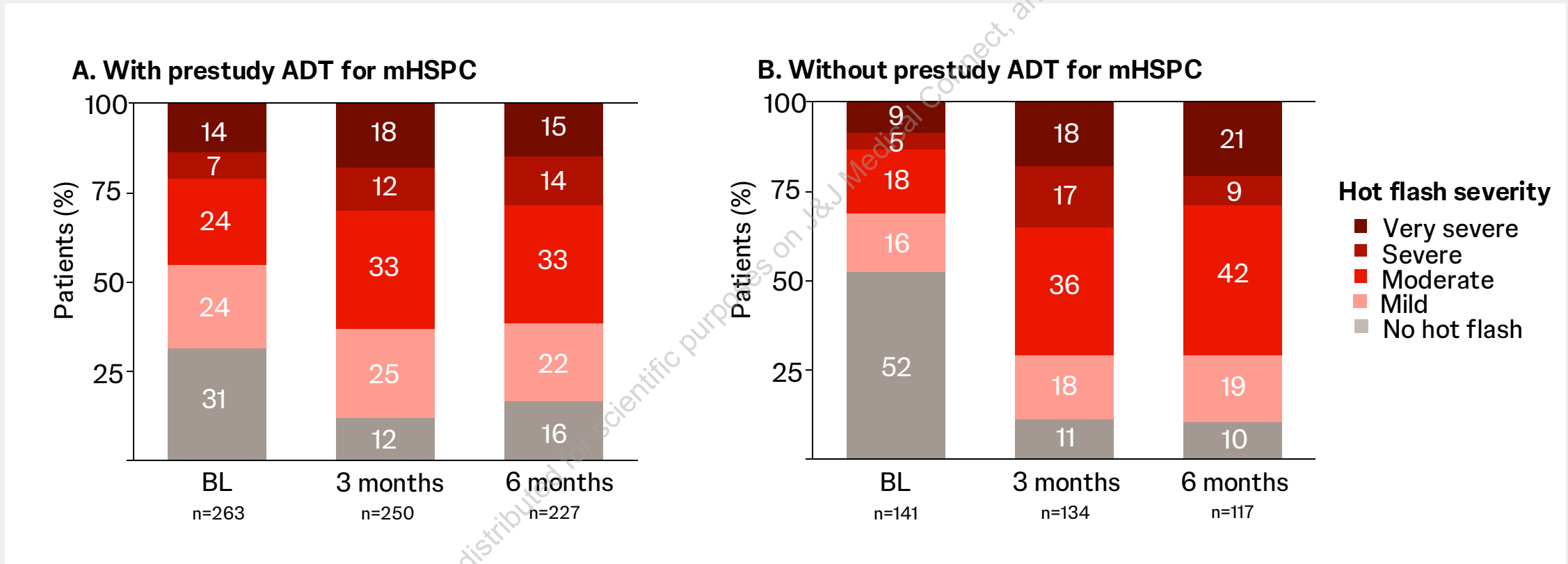
<sup>c</sup>Total severity score: each hot flash event multiplied by severity factor (1-mild, 2-moderate, 3-severe, 4-very severe) and summed across collection days. Average daily: total severity score divided by number of collection days.

All analyses are based on the August 11, 2025, data cut; data clean-up was not 100% completed at the time of the data cut.

mHSPC is also known as metastatic castration-sensitive prostate cancer (mCSPC).



# Supplementary Figure 1: Peak hot flash severity during initial treatment phase in patients with and without prestudy ADT for mHSPC



Hot flash severity was captured by the patients based on guidance provided. The severity grades were based on duration of hot flash, physical symptoms, emotional symptoms, and action taken. Highest severity is the most severe hot flash recorded at any time point associated with that analysis visit. All analyses are based on the August 11, 2025, data cut; data clean-up was not 100% completed at the time of the data cut. mHSPC is also known as metastatic castration-sensitive prostate cancer (mCSPC).



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