Original Study

TEAM Study: Upfront Docetaxel Treatment in Patients With Metastatic Hormone-Sensitive Prostate Cancer: A Real-World, Multicenter, Retrospective Analysis

Chiara Pisano,[1,*] Fabio Turco,[2,*] Elena Arnaudo,[2] Elena Fea,[1] Paola Vanella,[1] Fiorella Ruatta,[3] Roberto Filippi,[2,4] Federica Brusa,[5] Veronica Prati,[6] Federica Vana,[7] Alessia Mennitto,[8] Carlo Cattrini,[8] Francesca Vignani,[9] Rossana Dionisio,[9] Massimiliano Icardi,[10] Pamela Guglielmini,[11] Roberta Buosi,[11] Ilaria Stevani,[11] Roberto Vormola,[12] Gianmauro Numico,[1] Ilaria Depetris,[4] Alessandro Comandone,[7] Alessandra Gennari,[8] Mario Airoldi,[10] Maura Rossi,[11] Giorgio Vellani,[12] Cinzia Ortega,[6] Marcello Tucci,[5] Massimo Di Maio,[9] Consuelo Buttigliero[2]

Abstract

Metastatic hormone-sensitive prostate cancer benefits from upfront treatment intensification. To date, we do not have a validated prognostic model to guide treatment choice. In our study, docetaxel-treated patients with high Gleason score, high disease burden, pain or unfavorable laboratory parameters at baseline had worse outcomes. These results may be useful in tailoring treatment in this setting.

Background: Treatment of metastatic hormone-sensitive prostate cancer (mHSPC) dramatically changed. PEACE-1 and ARASENS trials established triplet therapy efficacy. Identifying prognostic factors supporting treatment choice is pivotal. **Methods:** TEAM is an observational, retrospective study to evaluate prognostic role of variables in mHSPC patients receiving upfront docetaxel in 11 Italian centers. Outcome measures were progression-free survival (PFS) and overall-survival (OS). **Results:** From September 2014 to December 2020, 147 patients were included. Median PFS and OS were 11.6 and 37.4 months. At univariate analysis, PFS-related variables were Gleason Score (GS) ($P = .001$), opioid use ($P = .004$), bone metastases number ($P < .001$), baseline PSA ($P = .006$), Hb ($P < .001$), ALP ($P < .001$) and LDH ($P = .002$), time between ADT and docetaxel start ($P = .018$), 3-month PSA ($P < .001$) and ALP ($P < .001$), and number of docetaxel cycles ($P < .001$). OS-related variables were PSA at diagnosis ($P = .024$), primary

[1]Department of Medical Oncology, S Croce e Carle Hospital, Cuneo, Italy
[2]Department of Oncology, San Luigi Gonzaga University Hospital, University of Turin, Orbassano, Italy
[3]Department of Medical Oncology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy
[4]Division of Medical Oncology 1, Department of Oncology, Città della Salute e della Scienza Hospital, Turin, Italy
[5]Department of Medical Oncology, Cardinal Massaia Hospital, Asti, Italy
[6]Department of Medical Oncology, Michele e Pietro Ferrero Hospital, Verduno-Azienda Sanitaria Locale CN2, Alba-Bra, Cuneo, Italy
[7]Department of Oncology, San Giovanni Bosco Hospital, Turin, Italy
[8]Medical Oncology-Department of Translational Medicine (DIMET), Università del Piemonte Orientale (UPO), Maggiore della Carità University Hospital, Novara, Italy
[9]Department of Oncology, Ordine Mauriziano Hospital, University of Turin, Turin, Italy
[10]Division of Medical Oncology 2, Department of Oncology, Città della Salute e della Scienza Hospital, Turin, Italy
[11]Oncology Unit, S. Spirito Hospital, Casale Monferrato, Alessandria, Italy
[12]Department of Oncology, Ivrea Community Hospital, Ivrea, Italy

Submitted: Jul 8, 2023; Revised: Aug 18, 2023; Accepted: Aug 28, 2023; Epub: 7 September 2023

Address for correspondence: Marcello Tucci, MD, Department of Medical Oncology, Cardinal Massaia Hospital, Corso Dante Alighieri 202, Asti, 14100 Italy
E-mail contact: marcello.tucci@gmail.com

* C.P. and F.T. contributed equally to this work.

1558-7673/$ - see front matter
https://doi.org/10.1016/j.clgc.2023.08.006

tumor treatment ($P = .022$), baseline pain ($P = .015$), opioid use ($P < .001$), bone metastases number ($P < .001$), baseline Hb ($P < .001$), ALP ($P < .001$) and LDH ($P = .001$), NLR ratio ($P = .039$), 3-month PSA ($P < .001$) and ALP ($P < .001$) and docetaxel cycles number ($P < .001$). At multivariate analysis, independent prognostic variables were GS, opioid use, baseline LDH and time between ADT and docetaxel initiation for PFS, and baseline Hb and LDH for OS. **Conclusion:** Patients receiving upfront docetaxel with high GS, high disease burden, pain or opioid use, baseline unfavorable laboratory values had worse outcomes. Patients had greater docetaxel benefit when initiated early after ADT start. These parameters could be taken into account when selecting candidates for triplet therapy.

Clinical Genitourinary Cancer, Vol. 22, No. 2, 56–67
Keywords: Docetaxel, Metastatic hormone-sensitive prostate cancer, Prognostic factors, Triplet therapy

Introduction

Metastatic hormone-sensitive prostate cancer (mHSPC) includes a spectrum of conditions with overall survival (OS) ranging from 2 to 6 years.[1,2]

Several randomized phase III trials showed that the addition of docetaxel[3-10] or androgen-receptor signaling inhibitors (ARSI), such as abiraterone,[11-14] enzalutamide[15-19] or apalutamide,[20,21] to androgen deprivation therapy (ADT) improved OS compared to ADT alone. Docetaxel showed efficacy especially in high-volume disease according to CHAARTED criteria (presence of visceral metastasis or ≥4 bone lesions with ≥1 beyond axial skeleton). ARSI demonstrated efficacy irrespective of disease volume. Furthermore, the combination of ADT and primary radiotherapy showed to improve OS compared with ADT in de-novo low-burden disease.[13]

To date, the only criteria that directs treatment choice in mHSPC is disease volume. Docetaxel should be performed in high-volume disease while prostate radiotherapy exclusively in low-volume patients. Recently 2 phase III clinical trials demonstrated that ADT + ARSI + docetaxel improves OS compared to ADT + docetaxel[14,22] Both studies investigated the addition of ARSI to ADT + docetaxel, but they did not evaluate if triplet therapy improves outcomes compared to ADT + ARSI. To understand in which patient chemotherapy could be avoided is a crucial point. We do not have a validated prognostic model able to identify mHSPC patients who can benefit most from treatment intensification.[23] Our study aims to evaluate the prognostic role of a number of baseline and on-treatment variables in docetaxel-treated mHSPC patients.

Materials and Methods

Study Population

TEAM is an observational, retrospective, multicenter study enrolling mHSCP patients treated with upfront docetaxel. The protocol was approved by the Ethics Committees of eleven Oncology Centers in Piedmont region, in the north of Italy. Patients included were male aged ≥18 years with a histological diagnosis of prostate adenocarcinoma and metastatic disease documented by instrumental investigations (computed tomography, magnetic resonance imaging, bone scan, positron emission tomography with ^{18}F-choline or ^{68}Ga-PSMA). The following information were collected for each patient: age, baseline Prostate Specific Antigen (PSA), Gleason Score (GS), TNM staging according to 8th Edition, any treatments performed on primary tumor (TPT), baseline variables before starting upfront docetaxel included in Halabi's nomogram [24] such as Eastern Cooperative Oncology Group Performance Status (ECOG PS), opioids use, pain according to Numerical Rating Scale (NRS), albumin, Haemoglobin (Hb), alkaline phosphatase (ALP), PSA, lactate dehydrogenase (LDH) values, metastatic sites (bone, lymph node, visceral, other), Platelets to Lymphocyte Ratio (PLR), Neutrophil to Lymphocyte Ratio (NLR), time between ADT and docetaxel start, Body Mass Index (BMI), and bone-protecting agents (BPAs) use. Change in ALP and PSA during docetaxel were investigated. We finally collected outcome and follow-up data.

Sample Size and Statistical Analysis

According to preliminary estimations, between 100 and 200 patients were expected to be included. Primary endpoint was progression-free survival (PFS). Different powers for PFS analysis, corresponding to different number of events collected for analysis, were generated in study protocol. In detail, for univariate PFS analysis of a dichotomic variable classifying patients in 2 groups of equal size, with 2-sided alpha error 0.05, in case of 100 PFS events statistical power was 93.6% for Hazard Ratio (HR) 0.50, 72.4% for HR 0.60 and 52.7% for HR 0.67. In case of 125 PFS events, statistical power was 97.4% for HR 0.50, 81.8% for HR 0.60 and 62.4% for HR 0.67. Descriptive statistics were reported as mean or median values, ranges for continuous variables and as percentages for categorical variables. Median follow-up was estimated according to the Schemper method (reverse Kaplan Meier). PFS was defined as time from the start of upfront docetaxel treatment to the date of progression, the date of death for patients who died without documented progression, or the last date of follow-up for patients who were alive or lost without progression. The secondary endpoint was OS, defined as time from the date of upfront docetaxel treatment beginning to the date of death or the last date follow-up for patients alive or lost. Survivals were estimated with Kaplan-Meier method and compared across groups using log-rank test. Cox proportional hazards models were used to estimate HR for PFS and OS univariate and multivariate analysis. Only variables statistically significant at univariate analysis were included in multivariate analysis. All statistical tests were 2-tailed and *P*-values <.05 were considered statistically significant. No correction was performed for multiplicity. All analyses were performed with IBM SPSS for Windows, Version 25.0.

Figure 1 PFS (A) and OS (B) in overall population.

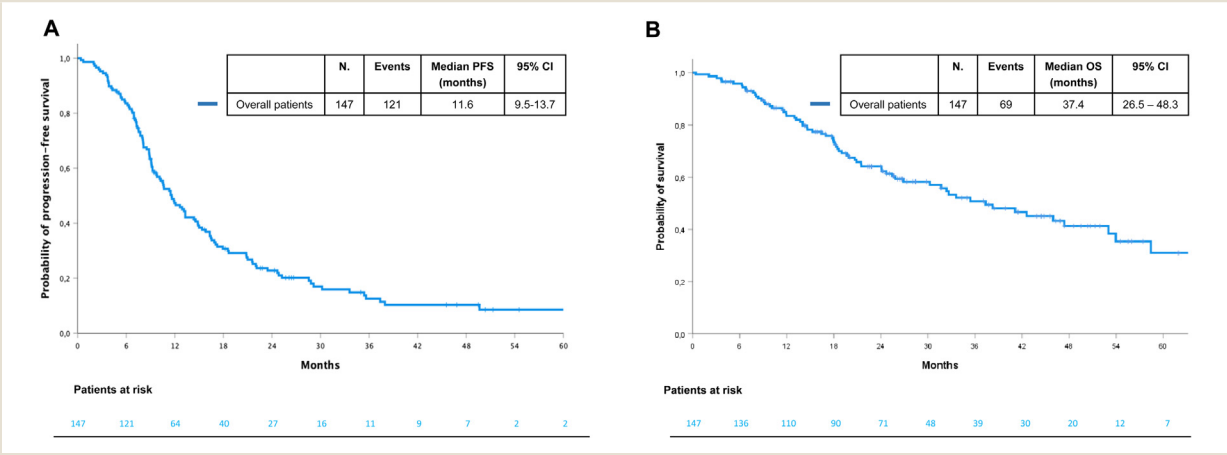
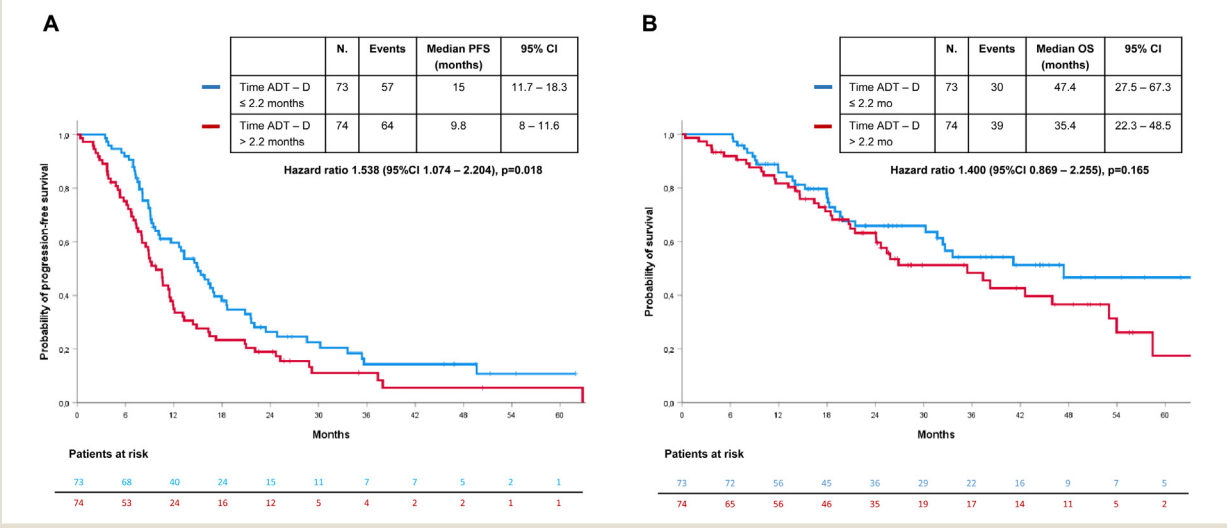


Figure 2 Prognostic impact of time between ADT start and docetaxel initiation, PFS (A) and OS (B).



Results

Patients' Characteristics

From September 2014 to December 2021, 147 patients were included in our analysis. Patients' characteristics are summarized in Table 1.

Median age was 67.5 years (range 41.1-82.4). Median PSA at diagnosis was 103.4 ng/mL.

10.2% and 10.2% of patients had received primary surgery or radiotherapy, respectively.

94.6% patients had high-volume disease. The majority of patients had bone metastases (15.9% 1-5, 17.9% 6-19, 60% ≥20). 17.7% patients had visceral metastases (14.3% lung, 6.1% liver, 2% both) and 69.2% had node metastases.

ECOG PS was 0 in 66.2% and 1 in 31.7% of cases. Baseline pain was absent (NRS 0), mild (NRS 1-3), moderate (NRS 4-6) and severe (NRS 7-10) in 27.1%, 57.1%, 11.3%, and 4.5% of cases, respectively.

Median time from ADT to docetaxel start was 2.2 months (range 0-7.5 months). Globally, 80.3% of patients completed the planned 6 docetaxel cycles.

Survival

Median follow-up was 28 months. In the overall population, median PFS (mPFS) and median OS (mOS) were 11.6 (95% CI, 9.5-13.7) and 37.4 (95% CI, 26.5-48.3) months, respectively (Figure 1).

Table 1 Patients' Characteristics

At the Time of Diagnosis	
Age (years) (n = 147)	67.5 (41.1-82.4)
Median (range)	67.5 (41.1-82.4)
Age categories – n (%)	
<75	129 (87.8%)
≥75	18 (12.2%)
PSA (ng/mL) (n = 146)	
Median (range)	103.40 (0.04-6965)
Gleason score (n = 137) – n (%)	
6	2 (1.5%)
7	17 (12.4%)
8	44 (32.1%)
9	58 (42.3%)
10	16 (11.7%)
Gleason score categories (n = 137)	
<8	19 (13.9%)
≥8	118 (86.1%)
Neuroendocrine aspects (n = 143) – n (%)	
Absent	132 (92.3%)
Present	11 (7.7%)
Surgery on primary tumor (n = 147) – n (%)	
No	132 (89.8%)
Yes	15 (10.2%)
Radiotherapy on primary tumor (n = 147) – n (%)	
No	132 (89.8%)
Yes	15 (10.2%)

At the time of docetaxel initiation	
Bone metastases (n = 147) – n (%)	
No	9 (6.3%)
Yes	138 (93.7%)
Bone—axial skeleton (n = 142) – n (%)	
No	9 (6.3%)
Yes	132 (89.8%)
Bone—other sites (n = 142) – n (%)	
No	37 (26.1%)
Yes	105 (73.9%)
N. bone metastases (n = 145) – n (%)	
0	9 (6.2%)
1-5	23 (15.9%)
6-19	26 (17.9%)
≥20	87 (60%)
Bone metastases categories – n (%)	
<20	58 (40%)
≥20	87 (60%)
Visceral metastases (n = 147) – n (%)	
No	121 (82.3%)
Yes	26 (17.7%)
Visceral metastases sites (n = 26) – n (%)	
Lung	21 (14.3%)
Liver	9 (6.1%)
Lung + liver	3 (2%)

(continued on next column)

Table 1 (continued)

At the time of docetaxel initiation	
Nodes metastases (n = 146) – n (%)	
No	45 (30.8%)
Yes	101 (69.2%)
Metastases other sites (n = 147) – n (%)	
No	136 (92.5%)
Yes	11 (7.5%)
ECOG PS (n = 145) – n (%)	
0	96 (66.2%)
1	46 (31.7%)
2	3 (2.1%)
ECOG PS categories	
0	96 (66.2%)
1-2	49 (33.8%)
Pain (NRS) (n = 133) – n (%)	
0	36 (27.1%)
1-3	76 (57.1%)
4-6	15 (11.3%)
7-10	6 (4.5%)
Pain categories (NRS) – n (%)	
0-3	112 (84.2%)
4-10	21 (15.8%)
Use of opioids (n = 146) – n (%)	
No	117 (80.1%)
Yes	29 (19.9%)
BMI (Kg x m^{-2}) (n = 144)	
Median (range)	25.36 (17.95-38.83)
BMI categories – n (%)	
<30	121 (84%)
≥30	23 (16%)
PSA (ng/mL) (n = 146)	
Median (range)	15.3 (0.00-4571)
Hb (g/dL) (n = 145)	
Median (range)	13.5 (6.7-17.3)
Hb categories – n (%)	
<12	36 (24.8%)
≥12	109 (75.2%)
NLR (n = 136)	
Median (range)	2.5 (0.6-24.04)
NLR categories (n = 136) – n (%)	
<4	103 (75.7%)
≥4	33 (24.3%)
PLR (n = 136)	
Median (range)	131.19 (24.04-2159.29)
PLR categories (n = 136) – n (%)	
<190	100 (73.5%)
≥190	36 (26.5%)
Albumin (mg/L) (n = 60)	
Median (range)	3900 (2713-5100)

(continued on next column)

Table 1 (continued)

At the time of docetaxel initiation	
Albumin categories (g/L) – n (%)	
<3900	27 (45%)
≥3900	33 (55%)
ALP (U/L) (n = 123)	
Median (range)	149 (46-3489)
ALP categories (ULN = 120 U/L) (n = 123) – n (%)	
≤ULN	57 (46.3%)
>ULN	66 (53.7%)
LDH (U/L) (n = 85)	
Median (range)	317 (150-6293)
LDH categories (ULN = 243 U/L) (n = 85) – n (%)	
≤243	28 (32.9%)
>243	57 (67.1%)
Median time from ADT to D initiation (mo) (n = 147)	
Median (range)	2.2 (0-7.5)

During docetaxel treatment	
3-mo ALP (U/L) (n = 98)	
Median (range)	82.5 (30-1454)
3-mo ALP categories (ULN = 120 U/L) (n = 98)–n (%)	
≤ULN	70 (71.4%)
>ULN	28 (28.6%)
3-mo PSA (ng/mL) (n = 139)	
Median (range)	1.3 (0.00-1053)
3-mo PSA categories (ng/mL) (n = 139) – n (%)	
≤1.3	71 (51.1%)
>1.3	68 (48.9%)
N. D cycles (n = 147)	
<6	29 (19.7%)
≥6	118 (80.3%)
Progression to D (n = 145) – n (%)	
No	32 (22.1%)
Yes	113 (77.9%)
Deceased patients (n = 147) – n (%)	
No	75 (51%)
Yes	72 (49%)
Subsequent treatments (n = 116)	
Cabazitaxel	17 (14.7%)
Abiraterone acetate	36 (31%)
Enzalutamide	36 (31%)
Docetaxel rechallange	5 (4.3%)
Others	4 (3.4%)
None	18 (15.5%)

ADT = Androgen-Deprivation Therapy; ALP = Alkaline Phosphatase; BMI = Body Mass Index; D = docetaxel; ECOG PS = Eastern Cooperative Oncology Group Performance Status; Hb = Hemoglobin; LDH = Lactate Dehydrogenase; NRS = Numerical Rating Scale; NLR = Neutrophil to Lymphocyte ratio; PSA = Prostate Specific Antigen; PLR = Platelet to Lymphocyte ratio; ULN = Upper Limit of Normal.

We analyzed survival outcomes stratifying patients according to predefined variables.

Univariate Analysis for PFS. Results are summarized in Table 2 (Supplemental Figure 3S-24S). GS was associated with PFS: 49.6 months in patients with GS <8 vs. 10.7 months in those with GS ≥8 (HR 3.137, 95% CI, 1.520-6.473, $P = .001$).

A mPFS of 8.5 months was reported in patients treated with opioids compared with 12.6 months in those who were not (HR 1.893, 95% CI, 1.210-2.963, $P = .004$).

Patients with <20 bone metastases achieved a mPFS of 16.9 months vs. 9.2 months in patients with ≥20 bone lesions (HR 1.870, 95% CI 1.284-2.725, $P < .001$). Node and visceral metastases were not prognostic.

PSA at diagnosis was not prognostic for PFS. Conversely, patients with baseline PSA ≥15.3 ng/mL had a mPFS of 9.4 months compared with patients with baseline PSA <15.3 ng/mL, who achieved a mPFS of 14.9 months (HR 0.600, 95% CI, 0.410-0.860, $P = .006$). Patients with low baseline ALP, LDH, and high baseline Hb had a statistically longer PFS. For patients with Hb <12 vs. ≥12 g/dL, mPFS was 8 vs. 14.6 months, respectively (HR 0.474, 95% CI, 0.316-0.710, $P < .001$). In patients with baseline ALP values >120 U/L, mPFS was 8.8 months compared with 17.9 months of patients with baseline ALP values ≤120 U/L (HR 0.447, 95% CI, 0.297-0.674, $P < .001$). Patients with baseline LDH >243 U/L achieved a mPFS of 8.8 months vs. 24.8 months of patients with baseline LDH ≤243 U/L (HR 2.276, 95% CI, 1.321-3.920, $P = .002$). Baseline albumin, NLR and PLR did not significantly affect PFS. Patients who received ≥6 cycles of docetaxel had a significantly better mPFS compared with those who received <6 cycles (13.3 vs. 7.5 months, respectively; HR 0.361, 95% CI, 0.234-0.557, $P < .001$). PSA and ALP levels at 3 months were prognostic for PFS. mPFS was 16.5 vs. 9.4 months for patients with PSA levels <1.4 ng/mL vs. ≥1.4 ng/mL, respectively (HR 2.240, 95% CI, 1.529-3.282, $P < .001$), and 13.3 vs. 8.5 months for patients with ALP levels ≤ upper limit of normal (ULN) vs. >ULN (HR 2.902, 95% CI, 1.738-4.846, $P < .001$). Notably, patients who started docetaxel ≤2.2 months after ADT start had a significantly longer PFS (15 months) than those who started docetaxel ≥2.2 months after (9.8 months) (HR 1.538, 95% CI, 1.074-2.204, $P = .018$) (Figure 2).

Univariate Analysis for OS. Results are summarized in Table 3 (Supplementary Figures 3S-24S). Patients who received surgery or radiotherapy had a significantly better OS compared to those who did not (NR vs. 33.6 months; HR 0.388, 95% CI, 0.168-0.898, $P = .022$).

Pain showed a prognostic role even for OS: in patients with mild pain mOS was 38.2 months vs. 18.3 months in patients with moderate or severe pain (HR 2.070, 95% CI, 1.139-3.762, $P = .015$); for patients using opioids mOS was 17 months vs. 42.6 months in opioids-naïve patients (HR 2.952, 95% CI, 1.713-5.088, $P < .001$).

Patients with <20 bone metastases achieved a mOS of 65.7 months vs. 21.5 months of patients with ≥20 lesions (HR 2.596,

Table 2 Prognostic Role of Patients' Characteristics, at Baseline and During Docetaxel Treatment: Univariate Analysis for PFS

Patients' Characteristics	Events (N)	Median (mo)	HR (95% CI)	*P*-Value
At the time of diagnosis				
Age (n = 147)				
<75 (n = 129)	105	11.6	1.125	.661
≥75 (n = 18)	16	9.4	(0.663-1.908)	
PSA (ng/mL) (n = 146)				
< median (n = 73)	30	30.2	1.375	.069
≥ median (n = 74)	39	13.3	(0.960-1.971)	
GS (n = 137)				
<8 (n = 19)	8	49.6	3.137	**.001**
≥8 (n = 118)	103	10.7	(1.520-6.473)	
Treatment on primary[a] (n = 147)				
No (n = 123)	105	10.6	0.601	.056
Yes (n = 24)	16	18.7	(0.354-1.019)	
Bone protecting agents (n = 146)				
No (n = 112)	92	11.5	0.992	.969
Yes (n = 34)	28	11.6	(0.645-1.526)	
At the time of docetaxel start				
ECOG PS (n = 145)				
0 (n = 96)	79	11.9	1.162	.444
1-2 (n = 49)	40	11.5	(0.790-1.711)	
Pain NRS (n = 133)				
0-3 (n = 112)	90	11.9	1.583	.074
4-10 (n = 21)	18	9.1	(0.951-2.635)	
Opioids use (n = 146)				
No (n = 117)	95	12.6	1.893	**.004**
Yes (n = 29)	25	8.5	(1.210-2.963)	
BMI (Kg x m^{-2}) (n = 144)				
<30 (n = 121)	98	11.6	1.028	.911
≥30 (n = 23)	20	11.6	(0.634-1.665)	
N. bone metastases (n = 145)				
<20 (n = 58)	47	16.9	1.870	**<.001**
≥20 (n = 87)	73	9.2	(1.284-2.725)	
Node metastases (n = 146)				
No (n = 45)	35	12.1	1.262	.252
Yes (n = 101)	86	11.3	(0.847-1.880)	
Visceral metastases (n = 147)				
No (n = 121)	100	11.6	1.088	.725
Yes (n = 26)	21	10.1	(0.679-1.745)	
PSA (ng/mL) (n = 146)				
≥15.3 (n = 73)	61	9.4	0.598	**.006**
<15.3 (n = 73)	59	14.9	(0.415-0.864)	
Hb (g/dL) (n = 145)				
<12 (n = 36)	34	8.0	0.474	**<.001**
≥12 (n = 109)	86	14.6	(0.316-0.710)	
NLR (n = 136)				
<4 (n = 103)	84	11.5	0.840	.435
≥4 (n = 33)	27	12.1	(0.543-1.302)	
PLR (n = 136)				
<190 (n = 100)	80	11.9	1.059	.787
≥190 (n = 36)	31	10.5	(0.697-1.609)	

(*continued on next page*)

Table 2 (*continued*)

Patients' Characteristics	Events (N)	Median (mo)	HR (95% CI)	*P*-Value
Albumin (mg/L) (n = 60)				
<3900 (n = 27)	25	11.5	0.811	.462
≥3900 (n = 33)	26	10.7	(0.464-1.418)	
ALP (U/L) (n = 123)				
>120 (n = 66)	56	8.8	0.447	**<.001**
≤120 (n = 57)	43	17.9	(0.297-0.674)	
LDH (U/L) (n = 85)				
>243 (n = 57)	49	8.8	2.276	**.002**
≤243 (n = 28)	19	24.8	(1.321-3.920)	
Time ADT – D start (mo) (n = 147)				
≤2.2 (n = 73)	57	15	1.538	**.018**
>2.2 (n = 74)	64	9.8	(1.074-2.204)	
During docetaxel treatment				
3-mo PSA (ng/mL) (n = 139)				
<1.4 (n = 71)	53	16.5	2.240	**<.001**
≥1.4 (n = 68)	60	9.4	(1.529-3.282)	
3-mo ALP[b] (U/L) (n = 98)				
≤ULN (n = 70)	54	13.3	2.902	**<.001**
>ULN (n = 28)	27	8.5	(1.738-4.846)	
N. D cycles (n = 147)				
<6 (n = 29)	28	7.5	0.361	**<.001**
≥6 (n = 118)	93	13.3	(0.234-0.557)	

ADT = Androgen Deprivation Therapy; ALP = Alkaline Phosphatase; BMI = Body Mass Index; D = docetaxel; ECOG PS = Eastern Cooperative Oncology Group Performance Status; Hb = Hemoglobin; NRS = Numerical Rating Scale; LDH = Lactate Dehydrogenase; NLR = Neutrophil to Lymphocyte ratio; PSA = Prostate Specific Antigen; PLR = Platelet to Lymphocyte ratio; ULN = Upper Limit of Normal.
[a] Treatment on primary: radical surgery or radiotherapy.
[b] Three-months ALP: excluding patients progressed within 3 months.

95% CI, 1.529-4.407, $P < .001$). Node and visceral involvement were not prognostic.

Patients with PSA values at diagnosis <103.4 ng/mL had mOS of 53.9 months vs. 32.6 months of patients with values ≥ 103.4 ng/mL (HR 1.723, 95% CI, 1.067-2.783, $P = .024$). Baseline PSA did not correlate with OS.

Low baseline ALP, LDH, NLR and high baseline Hb correlated with statistically longer OS. For patients with Hb <12 vs. ≥12 g/dL, mOS was 14 vs. 47.4 months, respectively (HR 0.303, 95% CI, 0.184-0.498, $P < .001$). In patients with baseline ALP >120 U/L, mOS was 18.5 months compared with 65.7 months of patients with baseline ALP ≤120 U/L (HR 0.279, 95% CI, 0.155-0.503 $P < .001$). Patients with baseline LDH >243 U/L achieved a mOS of 18.5 months vs. 65.7 months of patients with baseline LDH ≤243 U/L (HR 3.208, 95% CI, 1.535-6.701, $P = .001$). Conversely, baseline albumin and PLR did not significantly affect survival. Patients who received ≥6 cycles of docetaxel achieved a significantly better mOS compared with those who received <6 cycles (46 vs. 16.4 months, respectively; HR 0.371, 95% CI, 0.125-0.641, $P < .001$). PSA and ALP achieved at 3 months were associated with OS. mOS was 65.7 vs. 24.1 months for patients who recorded PSA levels <1.4 vs. ≥ 1.4 ng/mL, respectively (HR 2.689, 95% CI, 1.589-4.549, $P < .001$), and 53 vs. 19 months for patients with ALP levels ≤ ULN vs. >ULN (HR 3.361, 95% CI, 1.843-6.130, $P < .001$). There were no differences in OS regarding time of docetaxel initiation (mOS 47.4 vs. 35.4 months for ≤2.2 vs. >2.2 months, respectively; HR 1.400, 95% CI, 0.869-2.255, $P = .165$) (Figure 2).

Multivariate Analysis. At multivariate analysis, GS (HR 3.655, 95% CI, 1.444-9.251, $P = .006$), opioids use (HR 2.276, 95% CI, 1.143-4.534, $P = .19$), baseline LDH (HR 2.304, 95% CI, 1.182-4.491, $P = .14$), and time between ADT and docetaxel start (HR 2.600, 95% CI, 1.440-4.695, $P = .002$) were significantly and independently associated with PFS. Baseline Hb (HR 0.344, 95% CI, 0.149-0.793, $P = .012$) and baseline LDH (HR 3.362, 95% CI, 1.338-8.447, $P = .010$) were independent variables associated with OS (Table 4).

Discussion

Recently, 2 studies highlighted the so-called "triplet therapy" efficacy in mHSPC. In PEACE-1 trial, ADT + docetaxel + abiraterone improved OS in de novo mHSPC compared to ADT + docetaxel, especially in high-volume patients. In ARASENS study, ADT + docetaxel + darolutamide increased OS compared to ADT + docetaxel.[25,26] A recent post hoc analysis of ARASENS trial stratified patients by volume and risk showing that treatment intensification increases OS in high-volume and high/low-risk patients, but not in low-volume patients.[27]

Table 3 Prognostic Role of Patients' Characteristics, at Baseline and During Docetaxel Treatment: Univariate Analysis for OS

Patients' Characteristics	Events (N)	Median (mo)	HR (95% CI)	*P*-Value
At the time of diagnosis				
Age (n = 147)				
<75 (n = 129)	59	41.1	1.539	.206
≥75 (n = 18)	10	20.9	(0.785-3.017)	
PSA (ng/mL) (n = 147)				
< median (n = 73)	30	53.9	1.723	**.024**
≥ median (n = 74)	39	32.6	(1.067-2.783)	
GS (n = 137)				
<8 (n = 19)	6	35.4	1.492	.349
≥8 (n = 118)	58	37.4	(0.642-3.467)	
Treatment on primary[a] (n = 147)				
No (n = 123)	63	33.6	0.388	**.022**
Yes (n = 24)	6	NR	(0.168-0.898)	
Bone protecting agents (n = 146)				
No (n = 112)	56	38.2	0.674	.214
Yes (n = 34)	12	32.6	(0.360-1.261)	
At the time of docetaxel start				
ECOG PS (n = 145)				
0 (n = 96)	49	41.1	1.026	.926
1-2 (n = 49)	18	35.4	(0.595-1.769)	
Pain NRS (n = 133)				
0-3 (n = 112)	52	38.2	2.070	**.015**
4-10 (n = 21)	14	18.3	(1.139-3.762)	
Opioids use (n = 146)				
No (n = 117)	49	42.6	2.952	**<.001**
Yes (n = 29)	19	17	(1.713-5.088)	
BMI (Kg x m^{-2}) (n = 144)				
<30 (n = 121)	58	35.4	0.833	.610
≥30 (n = 23)	9	NR	(0.412-1.683)	
N. bone metastases (n = 145)				
<20 (n = 58)	20	65.7	2.596	**<.001**
≥20 (n = 87)	48	21.5	(1.529-4.407)	
Node metastases (n = 146)				
No (n = 45)	16	NR	1.527	.136
Yes (n = 101)	53	33.6	(0.872-2.673)	
Visceral metastases (n = 147)				
No (n = 121)	57	41.1	1.086	.797
Yes (n = 26)	12	32.4	(0.578-2.039)	
PSA (ng/mL) (n = 146)				
≥15.3 (n = 73)	35	32.4	0.648	.075
<15.3 (n = 73)	33	41.1	(0.401-1.049)	
Hb (g/dL) (n = 145)				
<12 (n = 36)	26	14	0.303	**<.001**
≥12 (n = 109)	42	47.4	(0.184-0.498)	
NLR (n = 136)				
<4 (n = 103)	42	42.6	1.734	**.039**
≥4 (n = 33)	21	24.1	(1.020-2.946)	
PLR (n = 136)				
<190 (n = 100)	41	53	1.582	.085
≥190 (n = 36)	22	25.9	(0.934-2.679)	

(*continued on next page*)

Table 3 (*continued*)

Patients' Characteristics	Events (N)	Median (mo)	HR (95% CI)	*P*-Value
Albumin (mg/L) (n = 60)				
<3900 (n = 27)	14	42.6	1.217	.584
≥3900 (n = 33)	18	30.2	(0.602-2.463)	
ALP (U/L) (n = 123)				
>120 (n = 66)	40	18.5	0.279	**<.001**
≤120 (n = 57)	17	65.7	(0.155-0.503)	
LDH (U/L) (n = 85)				
>243 (n = 57)	36	18.5	3.208	**.001**
≤243 (n = 28)	10	65.7	(1.535-6.701)	
Time ADT – D start (mo) (n = 147)				
≤2.2 (n = 73)	30	47.4	1.400	.165
>2.2 (n = 74)	39	35.4	(0.869-2.255)	
During docetaxel treatment				
3-mo PSA (ng/mL) (n = 139)				
<1.4 (n = 71)	25	65.7	2.689	**<.001**
≥1.4 (n = 68)	36	24.1	(1.589-4.549)	
3-mo ALP[b] (U/L) (n = 93)				
≤ULN (n = 67)	23	53.9	3.280	**<.001**
>ULN (n = 26)	19	20.9	(1.759-6.117)	
N. D cycles (n = 147)				
<6 (n = 29)	18	16.4	0.371	**<.001**
≥6 (n = 118)	51	46	(0.215-0.641)	

ADT = Androgen Deprivation Therapy; ALP = Alkaline Phosphatase; BMI = Body Mass Index; D = docetaxel; ECOG PS = Eastern Cooperative Oncology Group Performance Status; Hb = Hemoglobin; LDH = Lactate Dehydrogenase; NRS = Numerical Rating Scale; NLR = Neutrophil to Lymphocyte ratio; PLR = Platelet to Lymphocyte ratio; PSA = Prostate Specific Antigen; ULN = Upper Limit of Normal.
[a] Treatment on primary: radical surgery or radiotherapy.
[b] Three-months ALP: excluding patients progressed within 3 months.

ARASENS and PEACE-1 trials leave some unresolved questions. Since both studies predominantly enrolled de novo metastatic patients, it is unclear whether this approach can result in equal benefit in recurrent disease. Besides, there are still no evidences of triplets benefit over ADT + ARSI.

Identifying prognostic factors to select patients for whom docetaxel can be spared is of paramount interest since triplet therapy toxicity is mainly docetaxel-related. However, risk factors in mHSPC have yet to be studied and to date there are no validated prognostic models. Glass et al.[28] reported the oldest prognostic model, which differentiated 3 groups based on bone disease localization, ECOG PS, baseline PSA and GS. In 2015 Gravis et al.[23] identified pain intensity, bone and visceral metastases, ECOG PS 0 vs. ≥1, de novo vs. recurrent disease, PSA, Hb, ALP, and LDH levels as independent risk factors in mHSPC. Table 5S (Supplementary material) summarizes studies evaluating variables associated with mHSPC survival.

Our study included a homogenous population with high volume (94.6%) and de novo (83.6%) mHSPC. Due to a more aggressive disease, mPFS, and mOS were lower than those observed in pivotal trials.[3,4,6] The presence of a high number of bone metastases (≥20) showed an unfavorable prognostic correlation at univariate analysis for PFS and OS. This finding is in agreement with CHAARTED results[4,10] and most recent meta-analyses supporting treatment intensification in high-volume patients.[25,26] The same result did not emerge for visceral metastases, likely due to the small subgroup (Table 5S Supplemental material).

Among biological features, GS ≥8 demonstrated a negative prognostic association with PFS, also at multivariate analysis. These results are not surprising, higher GS correlates with greater disease aggressiveness.[29]

Pain and opioids need are known negative prognostic factors in mCRPC.[24] Recently, a negative prognostic impact of baseline pain on PFS and OS was also shown in de novo mHSPC.[2] In our study, opioid use correlated with worse PFS and OS and maintained independent prognostic value at multivariate analysis for PFS, confirming pain importance in patients candidate for docetaxel treatment.

Among biochemical variables, high ALP and LDH and low Hb pretreatment values were associated with worse prognosis. ALP correlates with higher bone metastatic burden. In a recent meta-analysis, elevated ALP correlated with a worse prognosis in both high- and low-volume disease.[30] Notably, in Gravis' study ALP proved to have the greatest ability to predict OS.[23] Similarly, LDH is a marker of aggressive and high burden disease. In a recent systematic review and meta-analysis, low levels of Hb were correlated with worse OS, PFS and cancer-specific survival, both in low- and high-volume disease, hypothesizing a synergistic effect with tumor hypoxia in deregulating gene expression in favor of tumor progression.[31]

Table 4 Prognostic Role of Patients' Characteristics: Multivariate Analysis for PFS and OS

PFS			
Covariates		**HR (95% CI)**	***P*-Value**
GS at diagnosis	<8 vs. ≥8	3.655 (1.444-9.251)	**.006**
Baseline opioid use	no vs. yes	2.276 (1.143-4.534)	**.019**
N. bone metastases	<20 vs. ≥20	1.175 (0.619-2.229)	.623
Baseline PSA (ng/mL)	≥15.3 vs. <15.3 ng/mL	0.771 (0.438-1.355)	.366
Baseline Hb (g/dL)	<12 vs. ≥12 g/dL	0.751 (0.383-1.472)	.404
Baseline ALP (U/L)	>120 vs. ≤120 U/L	0.603 (0.328-1.109)	.104
Baseline LDH (U/L)	>243 vs. ≤243 U/L	2.304 (1.182-4.491)	**.014**
Time from ADT to D initiation (mo)	≤2.2 vs. 2.2 mo	2.600 (1.440-4.695)	**.002**

OS			
Covariates		**HR (95% CI)**	***P*-value**
PSA at diagnosis (ng/mL)	<103.4 (median) vs. ≥ 103.4	0.906 (0.446-1.843)	.785
Treatment on primary tumor[a]	no vs. yes	1.171 (0.410-3.343)	.768
Baseline pain (NRS)	0-3 vs. 4-10	1.308 (0.475-3.599)	.603
Baseline opioid use	no vs. yes	2.369 (0.982-5.713)	.055
Bone metastases	<20 vs. ≥20	1.144 (0.485-2.700)	.759
Baseline Hb (g/dL)	<12 vs. ≥12 g/dL	0.344 (0.149-0.793)	**.012**
Baseline NLR	<4 vs. ≥4	0.920 (0.432-1.961)	.830
Baseline ALP (U/L)	>120 vs. ≤120 U/L	0.592 (0.243-1.441)	.248
Baseline LDH (U/L)	>243 vs. ≤243 U/L	3.362 (1.338-8.447)	**.010**

ADT = Androgen Deprivation Therapy; ALP = Alkaline Phosphatase; D = docetaxel; GS = Gleason Score; Hb = Hemoglobin; LDH = Lactate Dehydrogenase; NRS = Numerical Rating Scale; NLR = Neutrophil to Lymphocyte ratio; OS = overall survival; PSA = Prostate Specific Antigen; PFS = progression-free survival.
[a] Treatment on primary tumor: radical surgery or radiotherapy.

We found a significant association at univariate analysis for PFS and OS for the number of docetaxel cycles administered. Patients completing 6 cycles had better outcomes, thus the decision to interrupt treatment in case of poor tolerability should take into account the likely negative impact on treatment outcome.

Similar to other reports, our results confirm the prognostic significance of rapid kinetics of PSA and ALP decrease.[32-34]

Of particular interest, patients who started docetaxel ≤2.2 months after ADT start had a significantly better PFS. This finding was confirmed at multivariate analysis. Comparing baseline characteristics, no significant differences seem to emerge between patients who received docetaxel ≤2.2 months after ADT initiation compared to those who started docetaxel later (Table 6S, Supplementary material). A retrospective study based on CHAARTED population showed that docetaxel administration within 6 days after ADT initiation resulted in greater freedom from CRPC compared with patients who started docetaxel beyond 14 days.[35]

There is a strong biological rationale for combining ADT and docetaxel. HSPC is characterized by the coexistence of both AR-positive and negative cells. Docetaxel is able to deeply interfere with AR. An early docetaxel start could inhibit both androgen-independent and dependent clones.[36]

Although our work is one of the widest real-world data collections on mHSPC patients treated with docetaxel, it bears the important limitations of the small sample size and retrospective design. For the number of events used in PFS analysis (121), the statistical power was quite high in case of variables associated with a strong prognostic role (e.g. HR 0.50), but was quite small for weaker prognostic variables. In addition, it would have been interesting to evaluate the prognostic role of variables subdividing our population by disease volume and mode of presentation. However, the small number of patients with low-volume and recurrent disease limits the interpretation of these results; studies with larger populations are needed. Furthermore, our study does not compare patients treated or not with docetaxel to clearly estimate its benefit according to prognostic factors. For these reasons, it should be considered as simply hypotheses-generating about the suggestion of administering upfront docetaxel in patients with negative prognostic features. However, in patient's candidate for upfront docetaxel, in absence of clinical contra-indications, it should be started as soon as possible.

Conclusions

Our study suggests that patients treated with upfront docetaxel who had high GS, high disease burden, baseline pain or opioid use and baseline unfavorable laboratory values (high LDH and ALP, low Hb) had worse outcomes. Patients completing 6 docetaxel cycles had better prognosis. For patients receiving docetaxel, our study hypothesizes a greater benefit for its early initiation. These parameters could be taken into account in selecting patients for triplet therapy.

Clinical Practice Points

- Treatment of metastatic hormone-sensitive prostate cancer (mHSPC) has dramatically changed. Several randomized phase III trials showed that the addition of docetaxel or androgen-receptor

signaling inhibitors (ARSI) to androgen deprivation therapy (ADT) improved OS compared to ADT alone. In addition, PEACE-1 and ARASENS trials have now established the efficacy of triplet therapy.

To date, the only criteria that directs treatment choice in mHSPC is disease volume. Identifying prognostic factors to help guiding treatment choice and understanding in which patient chemotherapy can be avoided is of paramount interest.

- TEAM is an observational, retrospective study which aims to evaluate prognostic role of several baseline and on-treatment variables in patients with mHSPC receiving upfront docetaxel. From September 2014 to December 2020, 147 patients from 11 Italian centers were included (94.6% high-volume, 89.8% de novo), representing one of the widest real-world data collections on mHSPC patients treated with docetaxel.
- In this series, patients treated with upfront docetaxel who had high Gleason Score, high disease burden, pain or opioid use, baseline unfavorable laboratory values (high lactate dehydrogenase and lactate dehydrogenase, low hemoglobin) had worse outcomes. For patients candidate to upfront docetaxel, our study suggests a greater benefit for its early administration. These parameters could be taken into account when selecting candidates for triplet therapy.

Authors' Contributions

Conceptualization and design: Chiara Pisano, Fabio Turco, Consuelo Buttigliero, Cinzia Ortega, Marcello Tucci, Massimo Di Maio. Acquisition of data: Chiara Pisano, Fabio Turco, Elena Arnaudo, Elena Fea, Paola Vanella, Fiorella Ruatta, Roberto Filippi, Federica Brusa, Veronica Prati, Federica Vana, Alessia Mennitto, Carlo Cattrini, Francesca Vignani, Rossana Dionisio, Massimiliano Icardi, Guglielmini Pamela, Roberta Buosi, Ilaria Stevani, Roberto Vormola, Gianmauro Numico, Ilaria Depetris, Alessandro Comandone, Alessandra Gennari, Mario Airoldi, Maura Rossi, Giorgio Vellani, Cinzia Ortega, Marcello Tucci, Massimo Di Maio, Consuelo Buttigliero. Analysis and interpretation of data: Chiara Pisano, Fabio Turco, Elena Arnaudo, Consuelo Buttigliero, Cinzia Ortega, Marcello Tucci, Massimo Di Maio. Drafting of the manuscript: Chiara Pisano, Fabio Turco. Critical revision of the manuscript for important intellectual content: Consuelo Buttigliero, Cinzia Ortega, Marcello Tucci, Massimo Di Maio. Statistical analysis: Consuelo Buttigliero, Massimo Di Maio. Supervision: Consuelo Buttigliero, Cinzia Ortega, Marcello Tucci, Massimo Di Maio. The final manuscript version was approved by all authors.

Ethics Approval and Consent to Participate

The protocol was approved by the Ethics Committees of eleven Oncology Centers in Piedmont region, in the north of Italy.

Disclosure

All authors have no conflict of interest to declare.

References

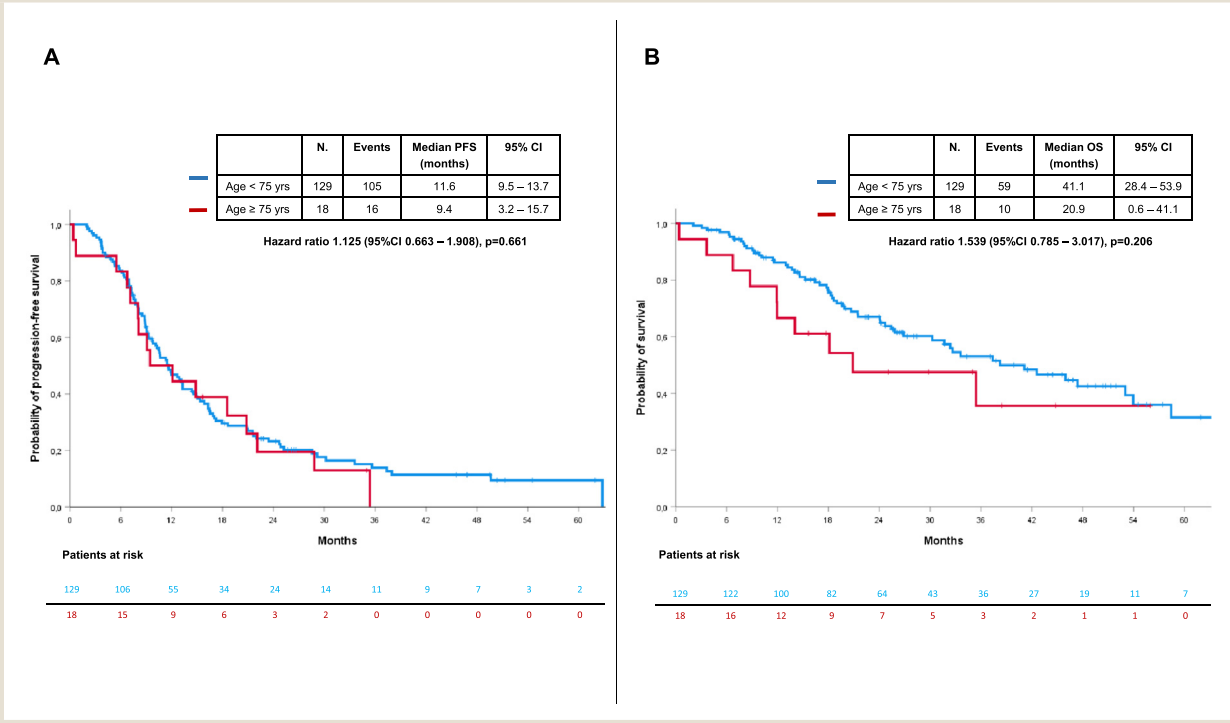
1. Clarke NW, Ali A, Ingleby FC, et al. Addition of docetaxel to hormonal therapy in low- and high-burden metastatic hormone sensitive prostate cancer: long-term survival results from the STAMPEDE trial. *Ann Oncol*. 2019;30(12):1992–2003. doi:10.1093/annonc/mdz396.
2. Iacovelli R, Ciccarese C, Caffo O, et al. The prognostic value of pain in castration-sensitive prostate cancer. *Prostate Cancer Prostatic Dis*. 2020;23(4):654–660. doi:10.1038/s41391-020-0255-x.
3. Gravis G, Fizazi K, Joly F, et al. Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2013;14(2):149–158. doi:10.1016/S1470-2045(12)70560-0.
4. Sweeney CJ, Chen YH, Carducci M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. *N Engl J Med*. 2015;373(8):737–746. doi:10.1056/NEJMoa1503747.
5. Kyriakopoulos CE, Chen YH, Carducci MA, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer: long-term survival analysis of the randomized phase III E3805 CHAARTED trial. *J Clin Oncol*. 2018;36(11):1080–1087. doi:10.1200/JCO.2017.75.3657.
6. James ND, Sydes MR, Clarke NW, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. *Lancet*. 2016;387(10024):1163–1177. doi:10.1016/S0140-6736(15)01037-5.
7. Gravis G, Boher JM, Joly F, et al. Androgen deprivation therapy (ADT) plus docetaxel versus ADT alone in metastatic non castrate prostate cancer: impact of metastatic burden and long-term survival analysis of the randomized phase 3 getugafu15 trial. *Eur Urol*. 2016;70(2):256–262. doi:10.1016/j.eururo.2015.11.005.
8. Vale CL, Burdett S, Rydzewska LHM, et al. Addition of docetaxel or bisphosphonates to standard of care in men with localised or metastatic, hormone-sensitive prostate cancer: a systematic review and meta-analyses of aggregate data. *Lancet Oncol*. 2016;17(2):243–256. doi:10.1016/S1470-2045(15)00489-1.
9. Tucci M, Bertaglia V, Vignani F, et al. Addition of docetaxel to androgen deprivation therapy for patients with hormone-sensitive metastatic prostate cancer: a systematic review and meta-analysis. *Eur Urol*. 2016;69(4):563–573. doi:10.1016/j.eururo.2015.09.013.
10. Gravis G, Boher JM, Chen YH, et al. Burden of metastatic castrate naive prostate cancer patients, to identify men more likely to benefit from early docetaxel: further analyses of CHAARTED and GETUG-AFU15 studies. *Eur Urol*. 2018;73(6):847–855. doi:10.1016/j.eururo.2018.02.001.
11. Fizazi K, Tran N, Fein L, et al. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. *N Engl J Med*. 2017;377(4):352–360. doi:10.1056/NEJMoa1704174.
12. James ND, de Bono JS, Spears MR, et al. Abiraterone for prostate cancer not previously treated with hormone therapy. *N Engl J Med*. 2017;377(4):338–351. doi:10.1056/NEJMoa1702900.
13. Parker CC, James ND, Brawley CD, et al. Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. *Lancet*. 2018;392(10162):2353–2366. doi:10.1016/S0140-6736(18)32486-3.
14. Fizazi K, Foulon S, Carles J, et al. Abiraterone plus prednisone added to androgen deprivation therapy and docetaxel in de novo metastatic castration-sensitive prostate cancer (PEACE-1): a multicentre, open-label, randomised, phase 3 study with a 2 x 2 factorial design. *Lancet*. 2022;399(10336):1695–1707. doi:10.1016/S0140-6736(22)00367-1.
15. Davis ID, Martin AJ, Stockler MR, et al. Enzalutamide with standard first-line therapy in metastatic prostate cancer. *N Engl J Med*. 2019;381(2):121–131. doi:10.1056/NEJMoa1903835.
16. Davis ID, Martin AJ, Zielinski RR, et al. Updated overall survival outcomes in ENZAMET (ANZUP 1304), an international, cooperative group trial of enzalutamide in metastatic hormone-sensitive prostate cancer (mHSPC). *J Clin Oncol*. 2022;40(Suppl 17). doi:10.1200/JCO.2022.40.17_suppl.LBA5004.
17. Armstrong AJ, Szmulewitz RZ, Petrylak DP, et al. ARCHES: a randomized, phase III study of androgen deprivation therapy with enzalutamide or placebo in men with metastatic hormone-sensitive prostate cancer. *J Clin Oncol*. 2019;37(32):2974–2986. doi:10.1200/JCO.19.00799.
18. Armstrong AJ, Shore ND, Szmulewitz RZ, et al. Efficacy of enzalutamide plus androgen deprivation therapy in metastatic hormone-sensitive prostate cancer by pattern of metastatic spread: ARCHES post hoc analyses. *J Urol*. 2021;205(5):1361–1371. doi:10.1097/JU.0000000000001568.
19. Armstrong AJ, Azad AA, Iguchi T, et al. Improved survival with enzalutamide in patients with metastatic hormone-sensitive prostate cancer. *J Clin Oncol*. 2022;40(15):1616–1622. doi:10.1200/JCO.22.00193.
20. Chi KN, Agarwal N, Bjartell A, et al. Apalutamide for metastatic, castration-sensitive prostate cancer. *N Engl J Med*. 2019;381(1):13–24. doi:10.1056/NEJMoa1903307.
21. Chi KN, Chowdhury S, Bjartell A, et al. Apalutamide in patients with metastatic castration-sensitive prostate cancer: final survival analysis of the randomized, double-blind, phase III TITAN study. *J Clin Oncol*. 2021;39(20):2294–2303. doi:10.1200/JCO.20.03488.
22. Smith MR, Hussain M, Saad F, et al. Darolutamide and survival in metastatic, hormone-sensitive prostate cancer. *N Engl J Med*. 2022;386(12):1132–1142. doi:10.1056/NEJMoa2119115.
23. Gravis G, Boher JM, Fizazi K, et al. Prognostic factors for survival in noncastrate metastatic prostate cancer: validation of the glass model and development of a novel simplified prognostic model. *Eur Urol*. 2015;68(2):196–204. doi:10.1016/j.eururo.2014.09.022.

24. Halabi S, Lin CY, Kelly WK, et al. Updated prognostic model for predicting overall survival in first-line chemotherapy for patients with metastatic castration-resistant prostate cancer. *J Clin Oncol*. 2014;32(7):671–677. doi:10.1200/JCO.2013.52.3696.
25. Ciccarese C, Iacovelli R, Sternberg CN, et al. Triplet therapy with androgen deprivation, docetaxel, and androgen receptor signalling inhibitors in metastatic castration-sensitive prostate cancer: a meta-analysis. *Eur J Cancer*. 2022;173:276–284. doi:10.1016/j.ejca.2022.07.011.
26. Maiorano BA, De Giorgi U, Roviello G, et al. Addition of androgen receptor-targeted agents to androgen-deprivation therapy and docetaxel in metastatic hormone-sensitive prostate cancer: a systematic review and meta-analysis. *ESMO Open*. 2022;7(5):100575. doi:10.1016/j.esmoop.2022.100575.
27. Hussain M, Tombal B, Saad F, et al. Darolutamide plus androgen-deprivation therapy and docetaxel in metastatic hormone-sensitive prostate cancer by disease volume and risk subgroups in the phase III ARASENS trial. *J Clin Oncol*. 2023;41:JCO2300041. doi:10.1200/JCO.23.00041.
28. Glass TR, Tangen CM, Crawford ED, et al. Metastatic carcinoma of the prostate: identifying prognostic groups using recursive partitioning. *J Urol*. 2003;169(1):164–169. doi:10.1097/01.ju.0000042482.18153.30.
29. Lim B, Lee W, Kyung YS, et al. Biopsy-detected Gleason grade 5 tumor is an additional prognostic factor in metastatic hormone-sensitive prostate cancer. *J Cancer Res Clin Oncol*. 2022;148(3):727–734. doi:10.1007/s00432-021-03642-2.
30. Mori K, Janisch F, Parizi MK, et al. Prognostic value of alkaline phosphatase in hormone-sensitive prostate cancer: a systematic review and meta-analysis. *Int J Clin Oncol*. 2020;25(2):247–257. doi:10.1007/s10147-019-01578-9.
31. Mori K, Janisch F, Mostafaei H, et al. Prognostic value of hemoglobin in metastatic hormone-sensitive prostate cancer: a systematic review and meta-analysis. *Clin Genitourin Cancer*. 2020;18(4):e402–ee09. doi:10.1016/j.clgc.2019.12.002.
32. Narita S, Nomura K, Hatakeyama S, et al. Prognostic significance of early changes in serum biomarker levels in patients with newly diagnosed metastatic prostate cancer. *Sci Rep*. 2019;9(1):12071. doi:10.1038/s41598-019-48600-8.
33. Nagata Y, Matsukawa T, Tomisaki I, et al. Prognostic significance of 3-month prostate-specific antigen level following androgen-deprivation therapy in metastatic hormone-sensitive prostate cancer. *Anticancer Res*. 2022;42(2):1107–1114. doi:10.21873/anticanres.15573.
34. Fujimoto N, Shiota M, Matsukawa T, et al. Three-month prostate-specific antigen level after androgen deprivation therapy predicts survival in patients with metastatic castration-sensitive prostate cancer. *In Vivo*. 2021;35(2):1101–1108. doi:10.21873/invivo.12355.
35. Nasser NJ, Sun K, Scanlon KM, et al. Administering docetaxel for metastatic hormone-sensitive prostate cancer 1-6 days compared to more than 14 days after the start of LHRH agonist is associated with better clinical outcomes due to androgen flare. *Cancers (Basel)*. 2022;14(4):864. doi:10.3390/cancers14040864.
36. Sweeney C, Chen Y-H, Carducci MA, et al. Impact on overall survival (OS) with chemohormonal therapy versus hormonal therapy for hormone-sensitive newly metastatic prostate cancer (mPrCa): An ECOG-led phase III randomized trial. *J Clin Oncol*. 2014;32(Suppl 18) LBA2-LBA2. doi:10.1200/jco.2014.32.18_suppl.lba2.

Supplementary materials

Supplementary Table 5S, Table 6S Figure 3S-24S.

Supplemental Figure 3S Age at diagnosis: PFS (A) and OS (B).



Supplemental Table 5S Studies Investigating the Role of Prognostic Variables in mHSPC

Author (Year)	Type of Study	Population	N	Primary Endpoint	Prognostic Variables	HR (95%CI)	*P*-Value
Gravis (2015)	Retrospective	GETUG-AFU 15	385	OS	Pain intensity Visceral disease (yes vs. no) Bone disease (yes vs. no) PSA (<65 vs. ≥65 ng/mL) ALP (normal vs. abnormal) LDH (normal vs. abnormal) Hb (normal vs. abnormal) De novo (yes vs. no)	2.14 (1.54-2.98) 1.56 (1.05-2.32) 2.75 (1.66-4.53) 1.67 (1.24-2.26) 3.12 (2.29-4.24) 2.29 (1.54-3.41) 2.24 (1.61-3.10) 1.73 (1.21-2.49)	<.001 .03 <.001 .007 <.001 <.001 <.001 .003
Abdel-Rahman (2018)	Retrospective	CHAARTED	702	OS, PFS	Prostascore 3-5	-	<.05
Akamatsu (2019)	Retrospective	mHSPC (ADT only)	304 (DC) 520 (VC)	OS	EOD ≥2 and/or liver metastases LDH >250 vs. ≤250 Primary GS 5 vs. ≤4	3.44 (2.05-5.77) 2.22 (1.34-3.67) 1.72 (1.07-2.76)	<.001 .002 .024
Wallis (2021)	Retrospective	mHSPC De novo (11% DOC, 1% AA)	3556	OS	NLR (Q5 vs. Q1) PLR (Q5 vs. 1) Alb (normal vs. abnormal) Hb (normal vs. abnormal) PSA nadir <0.1 ng/mL (yes vs. no) 3-mo PSA decline ≥50% (yes vs. no)	1.55 (1.27-1.90) 1.36 (1.11-1.65) 0.60 (0.49-0.74) 0.55 (0.48-0.63) 0.27 (0.22-0.32) 0.26 (0.22-0.31)	<.001 <.001 <.001 <.001 <.001
Labe (2022)	Retrospective	mHSPC	13818 (NCDB) 9318 (SEER)	OS	M1c vs. M1a M1b vs. M1a T4 vs. T1 GG5 vs. GG1 PSA >20 vs. <10 ng/mL	2.26 (2.00-2.56) 1.57 (1.43-1.72) 1.27 (1.17-1.36) 1.93 (1.61-2.31) 1.32 (1.23-1.42)	<.0001 <.0001 <.0001 <.0001 <.0001
Narita (2022)	Retrospective	mHSPC	301 (95 DOC, 206 AA)	PFS2	Primary GS 5 (yes vs. no) Liver metastases (yes vs. no) ALP (≥397 vs. <397 U/L) LDH (≥230 vs. <230)	2.89 (1.70-4.92) 2.46 (1.16-5.20) 3.61 (1.98-6.59) 3.21 (1.90-5.41)	<.001 .034 .005 .002
Gravis (2018)	Metanalysis	GETUG-AFU 15 + CHAARTED	1175	OS	HV vs. LV	0.68 (0.56-0.82)	.017
Alhanafy (2018)	Prospective Observational	mHSPC	128	OS	HV vs. LV	2.1 (1.2-4.44)	.02
Shiota (2021)	Retrospective	mHSPC De novo	2400	OS	LV Hb (≤12 vs. >12 g/dL) GG (≤4 vs. 5) T (1-3 vs. 4) HV Hb (≤12 vs. >12 g/dL) GG (≤4 vs. 5) Liver metastases (yes vs. no) EOD (≤20 vs. >20 bone metastases)	 2.24 (1.30-3.88) 1.61 (1.005-2.57) 1.99 (1.23-3.20) 1.67 (1.31-2.13) 1.35 (1.05-1.75) 2.46 (1.34-4.52) 2.28 (1.69-3.08)	 .0039 .048 .005 <.0001 .021 .0038 <.0001

(*continued on next page*)

Supplemental Table 5S (*continued*)

Author (Year)	Type of Study	Population	N	Primary Endpoint	Prognostic Variables	HR (95%CI)	*P*-Value
Buelens (2019)	Prospective	mHSPC De novo	113 (27 DOC)	OS	LV vs. HV ALP (<120 vs. ≥120 U/L)	4.15 (0.84-20.5) 3.31 (1.16-9.44)	.047 .018
Salah (2021)	Retrospective	mHSPC De novo (24% DOC, 4% AA)	189	OS	NLR ≥4 vs. <4 ECOG PS ≥1 vs. 0 Hb <12 vs. ≥12 g/dL HV vs. LV	2.75 (1.01-7.87) 9.9 (4.0-24.5) 5.75 (2.62-14.29) 4.83 (1.53-15.27)	.047 <.001 <.001
Notario (2020)	Retrospective	mHSPC 100% DOC	100	OS	NLR <3 vs. ≥3 PLR <130 vs. ≥130	0.4 (0.1-12) 0.32 (0.12-0.90)	.09 .03
Lim (2022)	Retrospective	mHSPC	201	OS	GS 5 vs. ≤4 Bone metastases ≥4 vs. <4	1.67 (1.16-2.42) 1.67 (1.16-2.41)	.006 .006
Morozumi (2022)	Retrospective	mHSPC De novo	559	OS	Hb ≤10 vs. >10 g/dL LDH ≥350 vs. <350	2.52 (1.10-5.78) 6.01 (3.10-11.7)	.029 <.001
Iacovelli (2020)	Retrospective	mHSPC De novo 28.2% DOC	373	OS	Pain at diagnosis (yes vs. no)	2.01 (1.26-3.19)	.003
Abdel-Rahman (2018)	Retrospective	CHAARTED	790	OS	Local treatment (yes vs. no) GS <8 vs. ≥8 LV vs. HV	0.663 (0.443-0.992) 0.654 (0.457-0.936) 2.363 (1.625-3.438)	.045 .020 <.0001
Watanabe (2018)	Retrospective	mHSPC	107	PFS	Alb (<4 vs. ≥4 g/dL) Bone metastases (≥3 vs. <3)	2.199 (1.276-3.791) 2.944 (1.724-5.027)	<.001 <.001
Harshman (2018)	Retrospective	CHAARTED	719	OS	7-mo PSA ≤0.2 vs. >4 ng/mL 7-mo PSA >0.2–≤4 vs. >4 ng/mL LV vs. HV	0.18 (0.12-0.28) 0.33 (0.23-0.47) 0.5 (0.34-0.73)	<.001 <.001 <.001
Fujimoto (2021)	Retrospective	mHSPC	242	OS	3-mo PSA ≤2 vs. >2 ng/mL	2.292 (1.042-5.043)	.039

(*continued on next page*)

Supplemental Table 5S (*continued*)

Author (Year)	Type of Study	Population	N	Primary Endpoint	Prognostic Variables	HR (95%CI)	*P*-Value
Nagata (2022)	Retrospective	mHSPC De novo	145	OS	Age ≥80 vs. <80 years HV/HR vs. LV/LR 3-mo PSA ≥2.56 vs. <2.56	2.33 (1.39-3.92) 1.69 (1.01-2.82) 1.99 (1.22-3.23)	.001 .046 .006
Narita (2019)	Retrospective	mHSPC	330	OS	Hb ≤12 vs. >12 g/dL ALP ≥350 vs. <350 U/L LDH ≥220 vs. <220 GS ≥9 vs. <9 EOD ≥6 bone metastases 2-4 mo PSA >3.1 vs. ≤3.1 ng/mL 2-4 mo Hb <12 vs. ≥12 g/L 2-4 mo ALP ≥350 vs. <350 U/L	1.77 (1.20-2.62) 1.49 (1.01-2.19) 2.19 (1.50-3.21) 1.47 (1.01-2.14) 2.23 (1.46-3.41) 2.32 (1.57-3.42) 1.93 (1.31-2.83) 2.59 (1.70-3.94)	.004 .046 <.0001 .043 <.0001 <.0001 .001 <.0001
Sato (2018)	Retrospective	mHSPC De novo	60	OS	LogPSA change (basal–12 wk, continuum variable) 12-wk ALP (abnormal vs. normal)	0.68 (0.54-0.85) 3.57 (1.11-11.53)	.001 .030

ALP = Alkaline Phosphatase; Alb = albumin; AA = abiraterone acetate; DC = discovery cohort; DOC = docetaxel; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EOD = extent of disease; GG = grade group; Hb = Hemoglobin; HB = high volume; LDH = Lactate Dehydrogenase; LV = low volume; NLR = Neutrophil to Lymphocyte ratio; PLR = Platelet to Lymphocyte ratio; PSA = Prostate Specific Antigen; Q = quartile; VC = validation cohort.

REFERENCES OF TABLE 5S

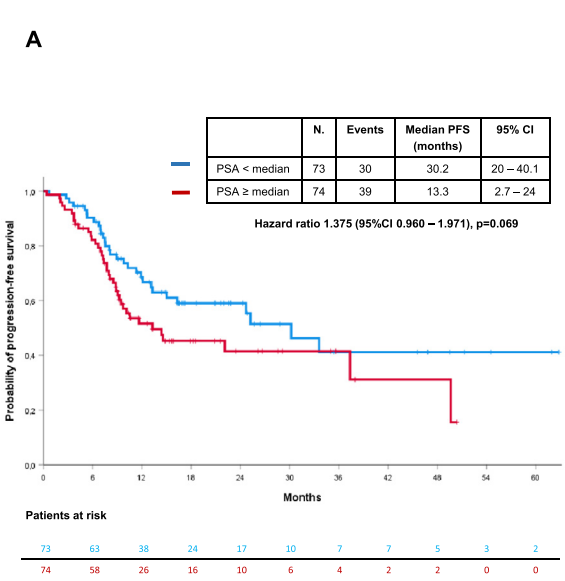
1. Gravis G, Boher JM, Fizazi K, Joly F, et al. **Prognostic factors for survival in noncastrate metastatic prostate cancer: validation of the glass model and development of a novel simplified prognostic model**. *Eur Urol* 2015, **68**(2):196-204.
2. Abdel-Rahman O, Cheung WY: **External validation of the prostascore model in patients with metastatic hormone-sensitive prostate cancer recruited to the CHAARTED study**. *BJU Int* 2018, **122**(3):394-400.
3. Akamatsu S, Kubota M, Uozumi R, et al **Development and validation of a novel prognostic model for predicting overall survival in treatment-naive castration-sensitive metastatic prostate cancer**. *Eur Urol Oncol* 2019, **2**(3):320-328.
4. Wallis CJD, Shayegan B, Morgan SC, et al. **Prognostic association between common laboratory tests and overall survival in elderly men with de novo metastatic castration sensitive prostate cancer: a population-based study in Canada**. *Cancers (Basel)* 2021, **13**(11).
5. Labe SA, Wang X, Lehrer EJ, et al. **Identification and validation of the prognostic impact of metastatic prostate cancer phenotypes**. *Clin Genitourin Cancer* 2022, **20**(4):371-380.
6. Narita S, Kimura T, Hatakeyama S, et al. **Real-world outcomes and risk stratification in patients with metastatic castration-sensitive prostate cancer treated with upfront abiraterone acetate and docetaxel**. *Int J Clin Oncol* 2022, **27**(9):1477-1486.
7. Gravis G, Boher JM, Chen YH, et al. **Burden of metastatic castrate naive prostate cancer patients, to identify men more likely to benefit from early docetaxel: further analyses of CHAARTED and GETUG-AFU15 studies**. *Eur Urol* 2018, **73**(6):847-855.
8. Alhanafy AM, Zanaty F, Ibrahem R, Omar S: **Prognostic factors for hormone sensitive metastatic prostate cancer: impact of disease volume**. *Asian Pac J Cancer Prev* 2018, **19**(4):1113-1118.
9. Shiota M, Terada N, Kitamura H, et al. **Novel metastatic burden-stratified risk model in de novo metastatic hormone-sensitive prostate cancer**. *Cancer Sci* 2021, **112**(9):3616-3626.
10. Buelens S, De Bleser E, Dhondt B, et al. **Importance of metastatic volume in prognostic models to predict survival in newly diagnosed metastatic prostate cancer**. *World J Urol* 2019, **37**(12):2565-2571.
11. Salah S, Abu-Hijlih R, Abuhijla F, Tamimi F, Al-Tell A, Shahait M: **Pretreatment neutrophil-to-lymphocyte ratio as a potential prognostic biomarker for newly diagnosed patients with metastatic castration-sensitive prostate cancer**. *Cancer Rep (Hoboken)* 2021, **4**(5):e1392.
12. Notario L, Piulats JM; Sala, N.; et al.: **667P impact of pretreatment neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) on overall survival (OS) in patients (p) with metastatic castration-sensitive prostate cancer (mCSPC) treated with docetaxel (D) plus androgen-deprivation therapy (ADT)**. *Ann Oncol*, **31**.
13. Lim B, Lee W, Kyung YS, You D, Jeong IG, Hong JH, Ahn H, Kim CS: **Biopsy-detected Gleason grade 5 tumor is an additional prognostic factor in metastatic hormone-sensitive prostate cancer**. *J Cancer Res Clin Oncol* 2022, **148**(3):727-734.
14. Morozumi K, Mitsuzuka K, Narita S, et al. **Impact of Gleason pattern 5 on prognosis for newly diagnosed metastatic hormone-sensitive prostate cancer with Gleason score >/=8**. *Int J Urol* 2022, **29**(4):324-331.
15. Iacovelli R, Ciccarese C, Caffo O, et al. **The prognostic value of pain in castration-sensitive prostate cancer**. *Prostate Cancer Prostatic Dis* 2020, **23**(4):654-660
16. Abdel-Rahman O, Cheung WY: **Impact of prior local treatment on the outcomes of metastatic hormone-sensitive prostate cancer: secondary analysis of a randomized controlled trial**. *Clin Genitourin Cancer* 2018, **16**(6):466-472.
17. Watanabe M, Kanao K.; Sugie, M.; et al. Sumitomo, M.: **Prognostic and predictive clinical factors for progression to castration refractory prostate cancer in patients with hormone sensitive prostate cancer**. *Ann Oncol* 2018, **29**.
18. Harshman LC, Chen YH, Liu G, et al: **Seven-month prostate-specific antigen is prognostic in metastatic hormone-sensitive prostate cancer treated with androgen deprivation with or without docetaxel**. *J Clin Oncol* 2018, **36**(4):376-382.
19. Fujimoto N, Shiota M, Matsukawa T, et al. **Three-month Prostate-specific antigen level after androgen deprivation therapy predicts survival in patients with metastatic castration-sensitive prostate cancer**. *In Vivo* 2021, **35**(2):1101-1108.
20. Nagata Y, Matsukawa T, Tomisaki I, Fujimoto N: **Prognostic significance of 3-month prostate-specific antigen level following androgen-deprivation therapy in metastatic hormone-sensitive prostate cancer**. *Anticancer Res* 2022, **42**(2):1107-1114.
21. Narita S, Nomura K, Hatakeyama S, et al. **Prognostic significance of early changes in serum biomarker levels in patients with newly diagnosed metastatic prostate cancer**. *Sci Rep* 2019, **9**(1):12071.
22. Sato H, Narita S, Tsuchiya N, et al. **Impact of early changes in serum biomarkers following androgen deprivation therapy on clinical outcomes in metastatic hormone-sensitive prostate cancer**. *BMC Urol* 2018, **18**(1):32.

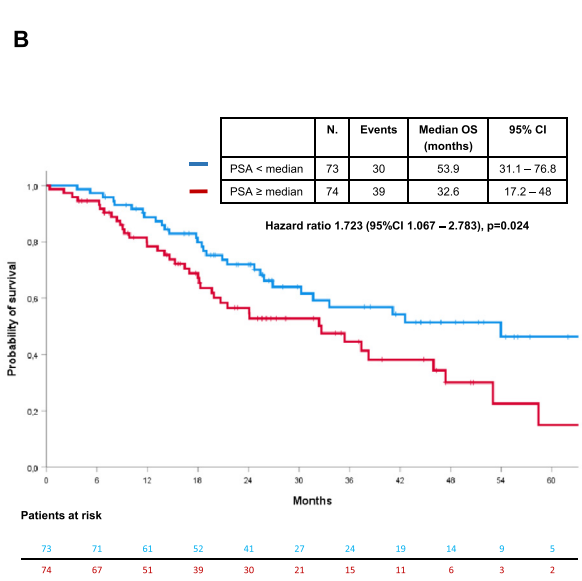
Table 6S Patients' Baseline Characteristics According to the Time From ADT to Docetaxel Initiation.

Patients' Characteristics	Time From ADT to D Initiation ≤2.2 Mo (n = 73)	Time From ADT to D Initiation >2.2 Mo (n = 74)	*P*-Value
Age (years)			
Median (range)	67.9 (46.9-77.8)	68.7 (47.4-82.4)	.86
PSA (ng/mL)			
Median (range)	109 (0.04-3590)	62.6 (0.97-5022)	.128
Gleason score – n (%)			
<8	10 (13.7%)	9 (12.2%)	.675
≥8	56 (76.7%)	62 (83.8%)	
Surgery on primary tumor – n (%)			
Yes	3 (4.1%)	12 (16.2%)	.016
No	70 (95.9%)	62 (83.8%)	
Radiotherapy on primary tumor – n (%)			
Yes	6 (8.2%)	9 (12.2%)	.43
No	67 (91.8%)	65 (87.8%)	
Bone metastases – n (%)			
Yes	69 (94.5%)	69 (93.2%)	.747
No	4 (5.5%)	5 (6.8%)	
Visceral metastases – n (%)			
Yes	14 (19.2%)	12 (16.2%)	.638
No	59 (80.8%)	62 (83.8%)	
Node metastases – n (%)			
Yes	59 (80.8%)	42 (56.8%)	<.001
No	13 (17.8%)	32 (43.2%)	
ECOG PS – n (%)			
0	43 (58.9%)	53 (71.6%)	.061
1-2	30 (41.1%)	19 (25.7%)	
Pain (NRS) – n (%)			
1-3	53 (72.6%)	59 (79.7%)	.22
4-10	13 (17.8%)	8 (10.8%)	
Hb (g/dL) – n (%)			
<12	21 (28.8%)	15 (20.3%)	.23
≥12	51 (69.7%)	58 (78.4%)	
Alb (mg/L)			
Median (range)	3928 (3500-4590)	3850 (2713-4380)	.17
ALP (U/L)			
Median (range)	189 (53-3348)	111 (46-742)	.109
LDH (U/L)			
Median (range)	327 (150-593)	266 (171-6293)	.355

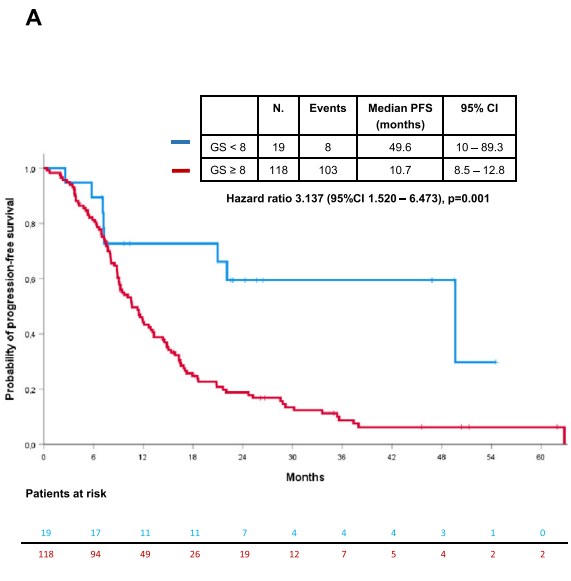
ALP = Alkaline Phosphatase; ADT = androgen deprivation therapy; D = docetaxel; ECOG PS = Eastern Cooperative Oncology Group Performance Status; Hb = Hemoglobin; LDH = Lactate Dehydrogenase; NRS = Numerical Rating Scale; PSA = Prostate Specific Antigen.

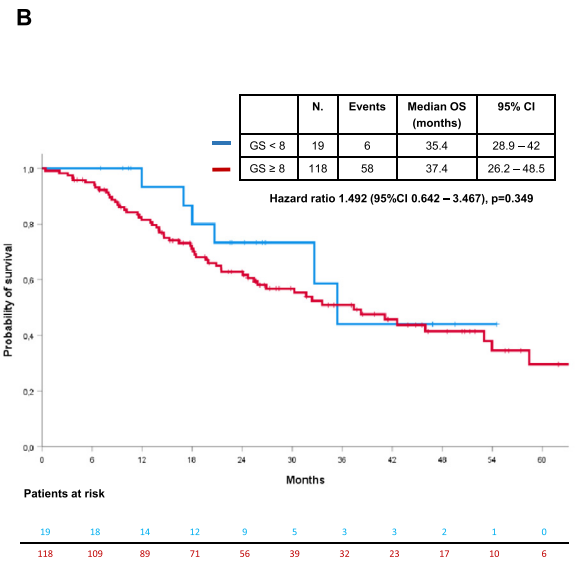
Supplemental Figure 4S PSA at diagnosis: PFS (A) and OS (B).



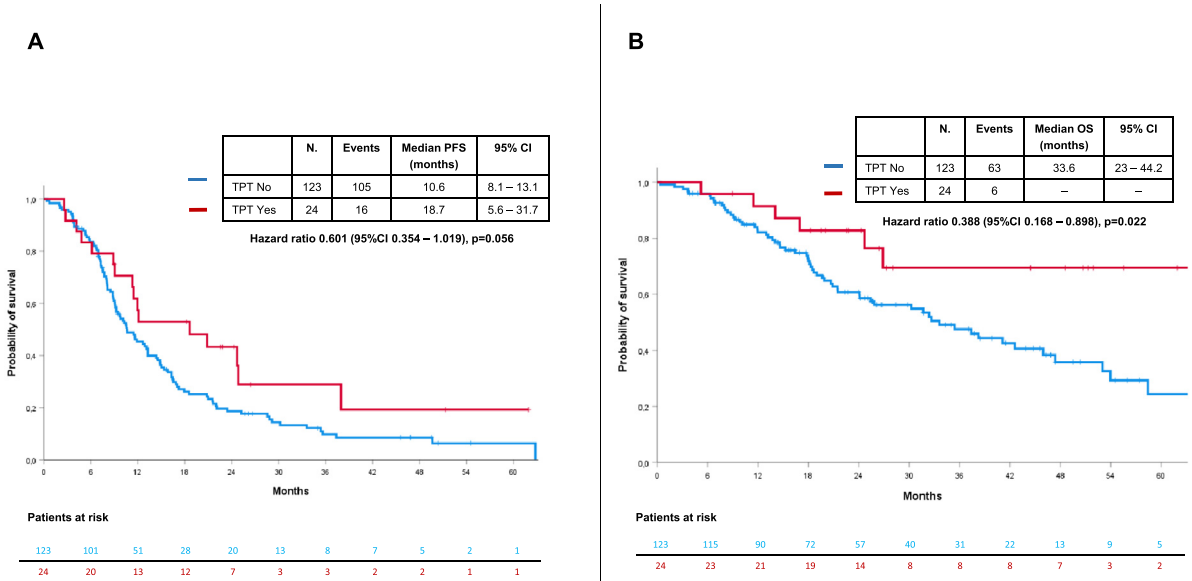


Supplemental Figure 5S Gleason score at diagnosis: PFS (A) and OS (B).

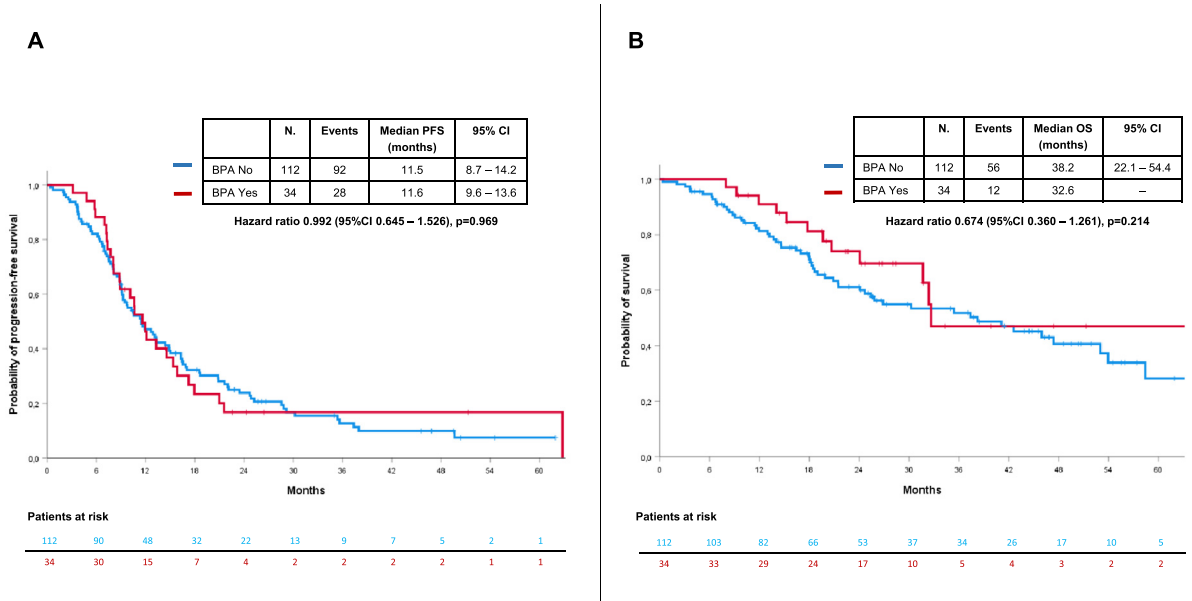




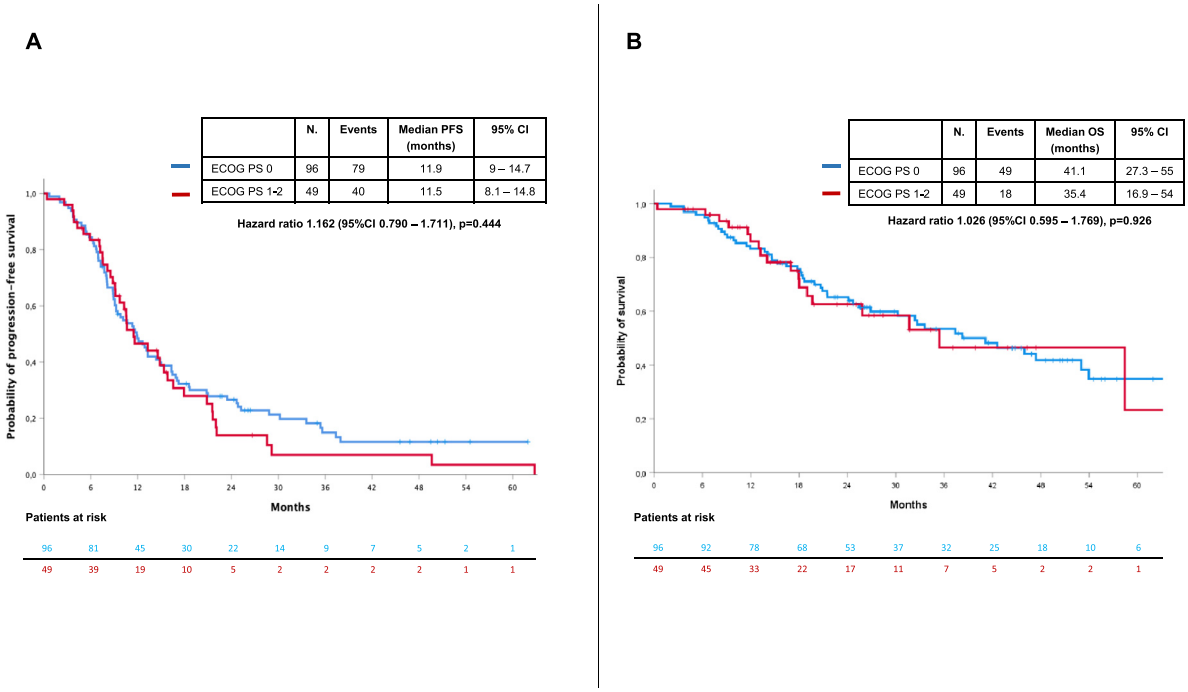
Supplemental Figure 6S Treatment on primary tumor (TPT): PFS (A) and OS (B).



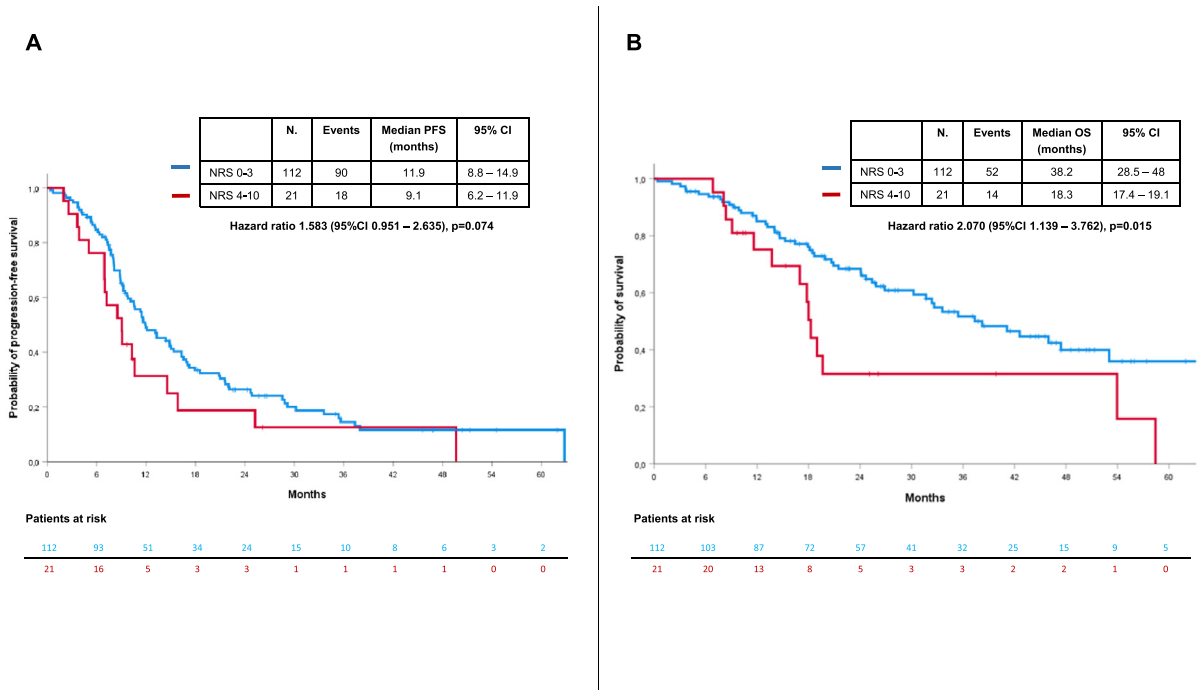
Supplemental Figure 7S Bone-protecting agents (BPA): PFS (A) and OS (B).



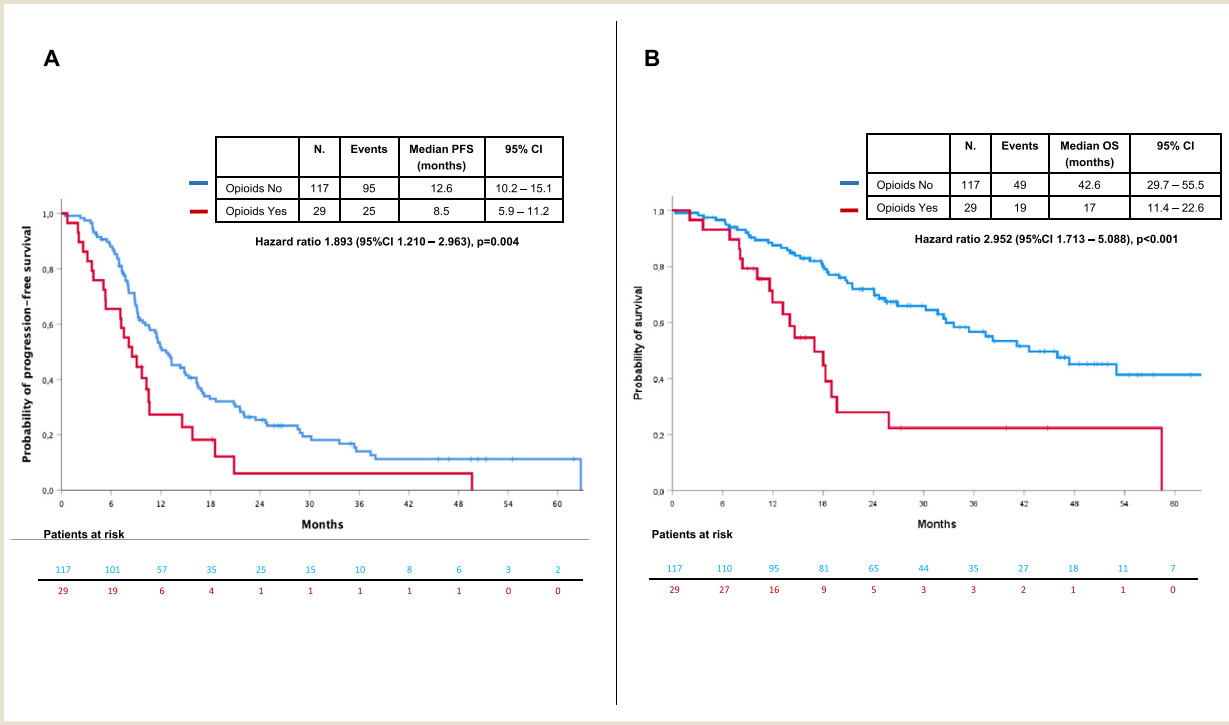
Supplemental Figure 8S ECOG PS: PFS (A) and OS (B).



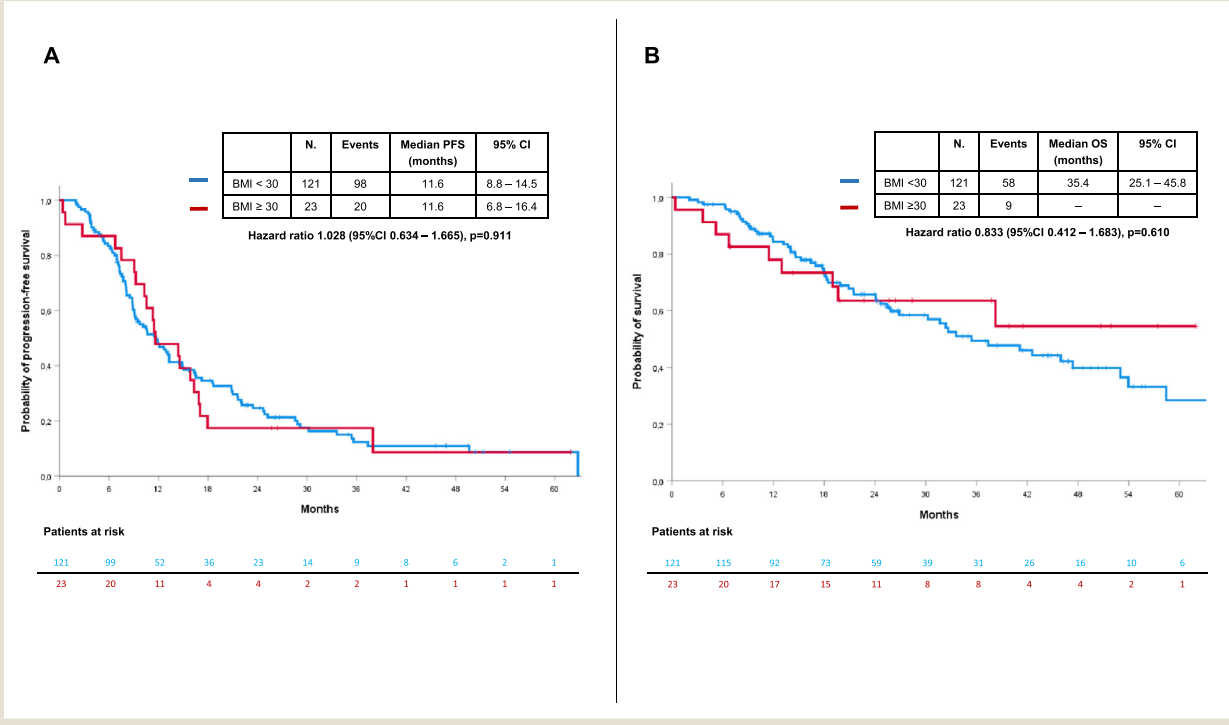
Supplemental Figure 9S Pain NRS: PFS (A) and OS (B).



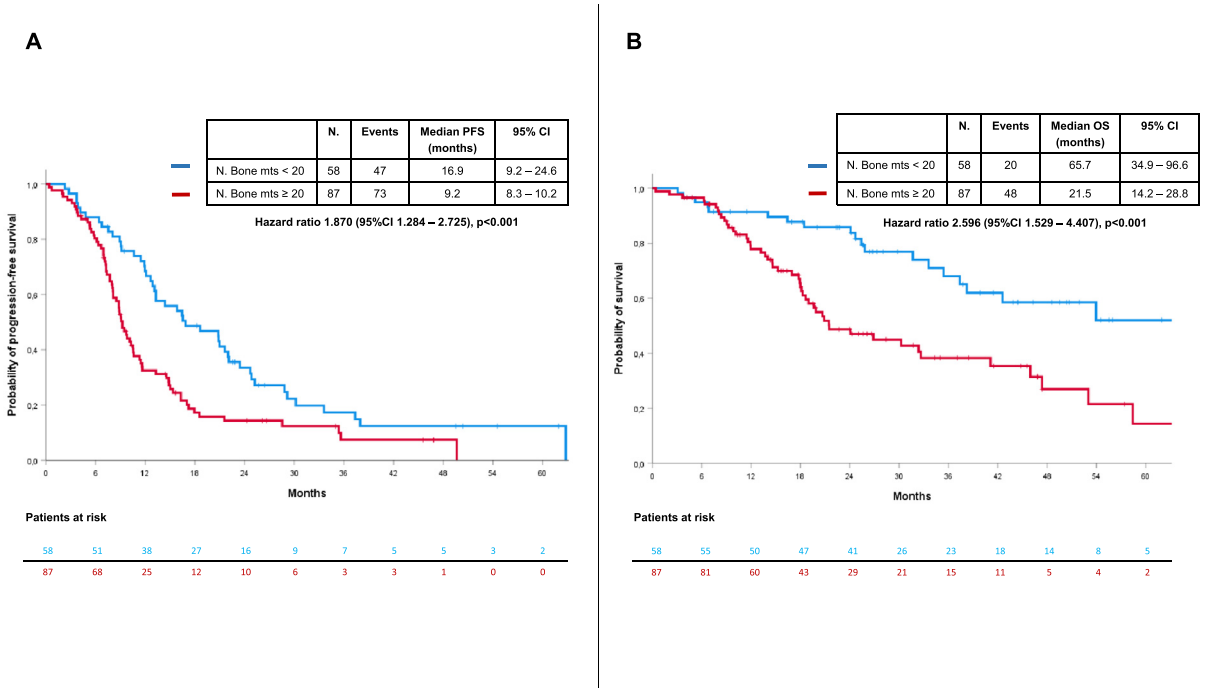
Supplemental Figure 10S Opioids use: PFS (A) and OS (B).



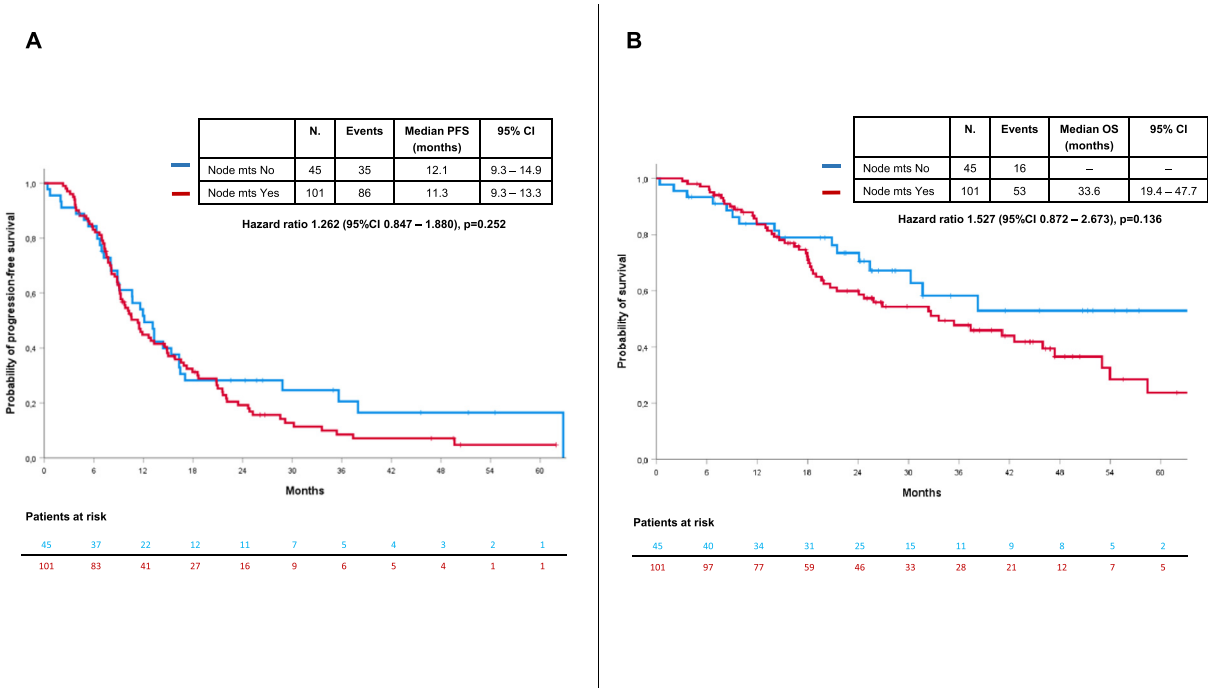
Supplemental Figure 11S BMI: PFS (A) and OS (B).



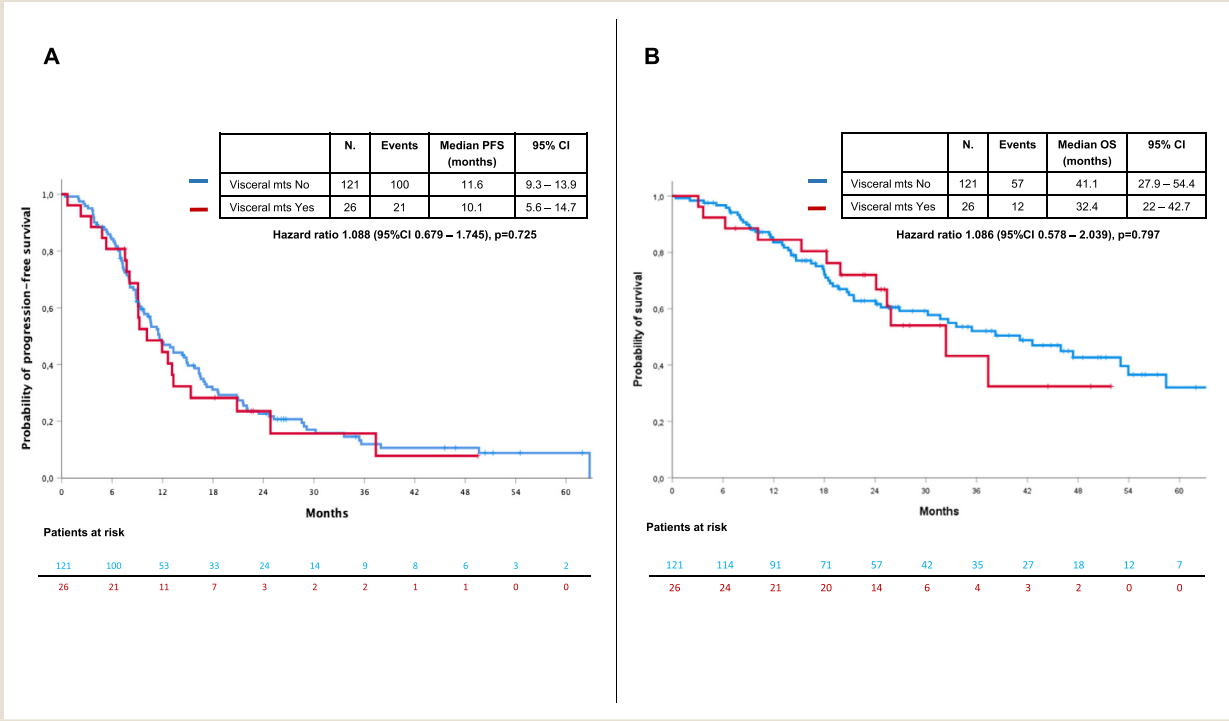
Supplemental Figure 12S Number of bone metastases: PFS (A) and OS (B).



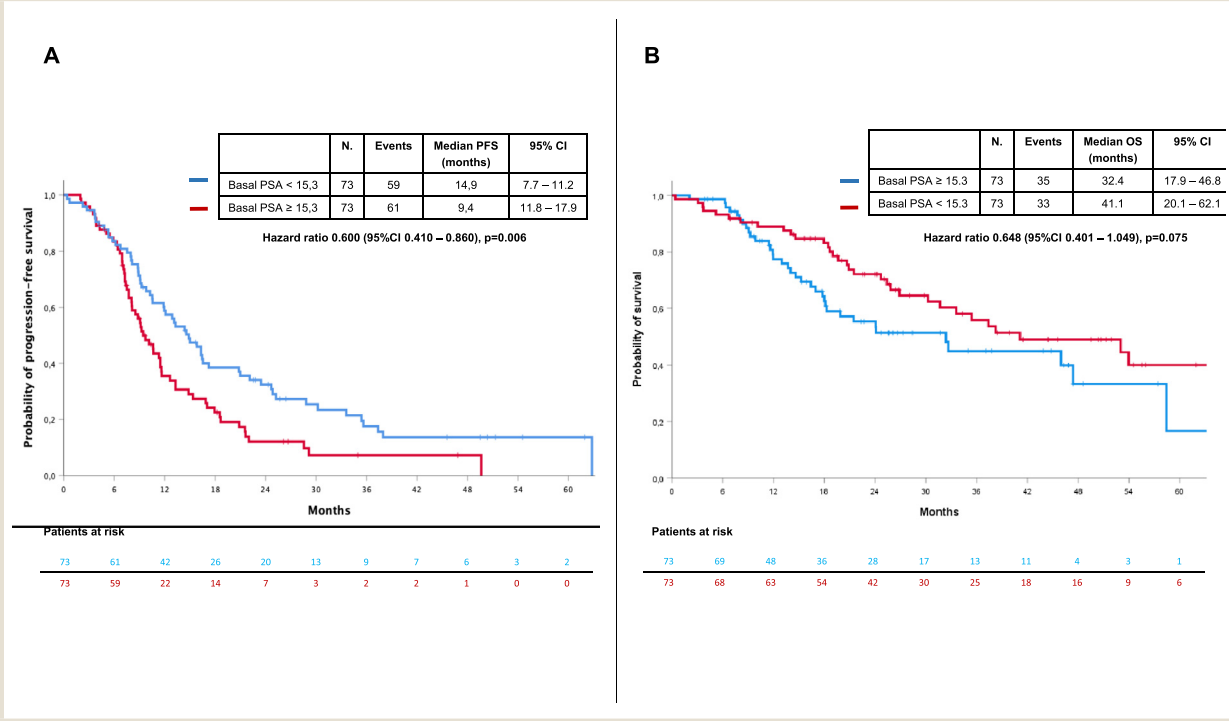
Supplemental Figure 13S Node metastases: PFS (A) and OS (B).



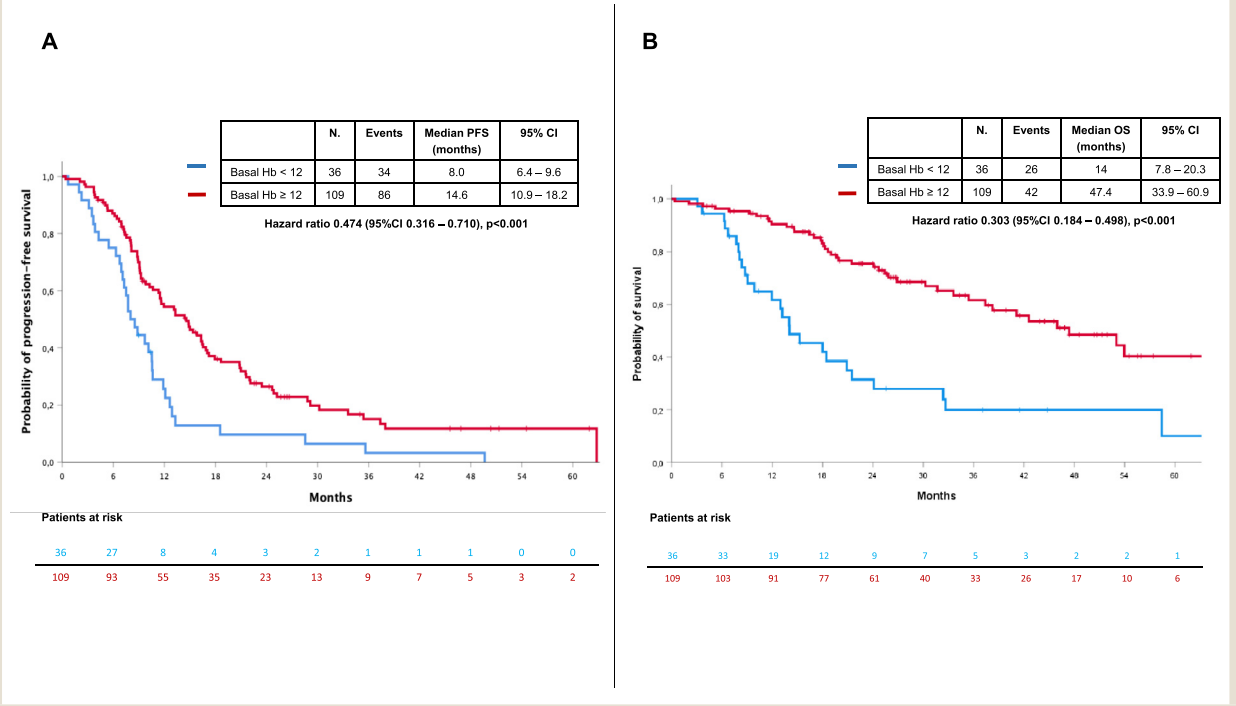
Supplemental Figure 14S Visceral metastases: PFS (A) and OS (B).



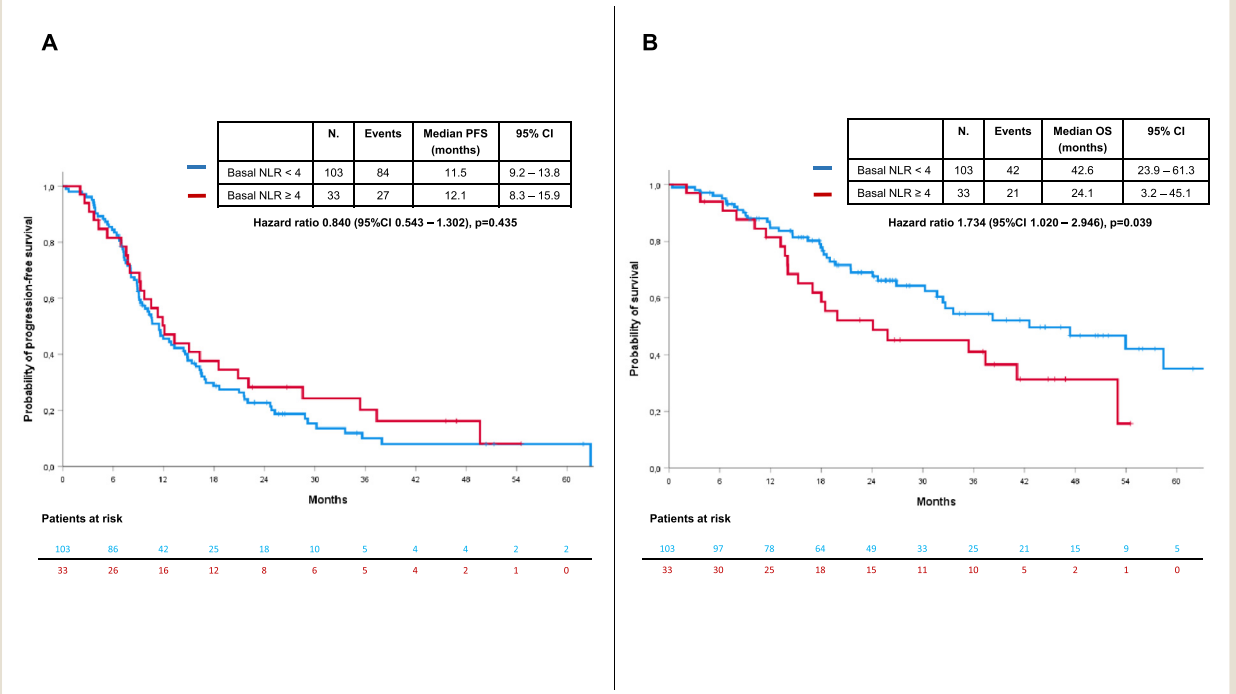
Supplemental Figure 15S Basal PSA: PFS (A) and OS (B).



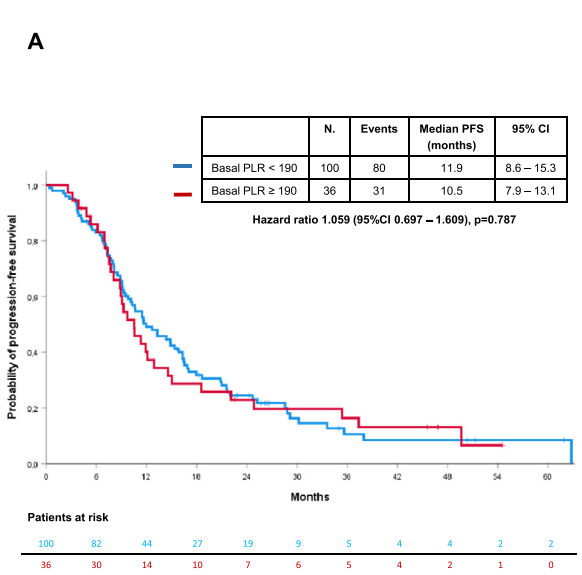
Supplemental Figure 16S Basal Hb: PFS (A) and OS (B).

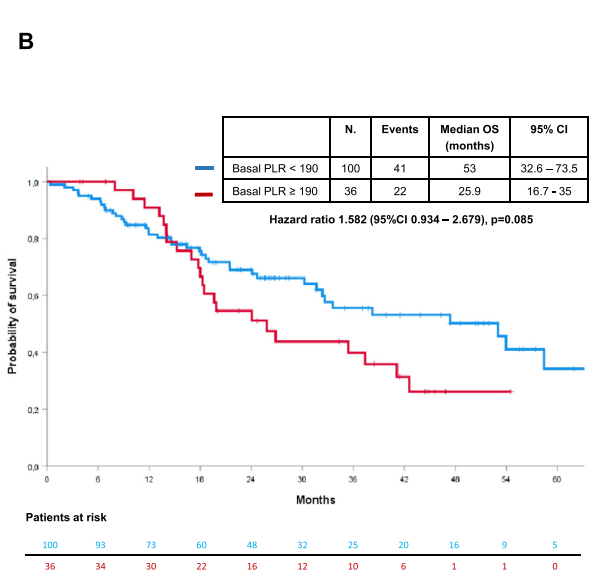


Supplemental Figure 17S Basal NLR: PFS (A) and OS (B).

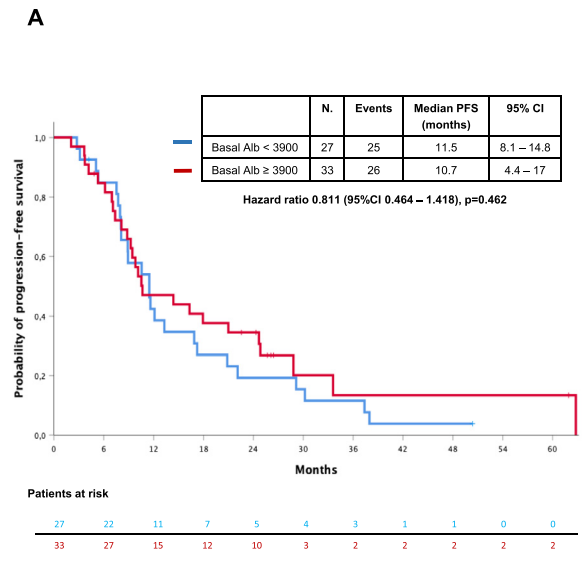


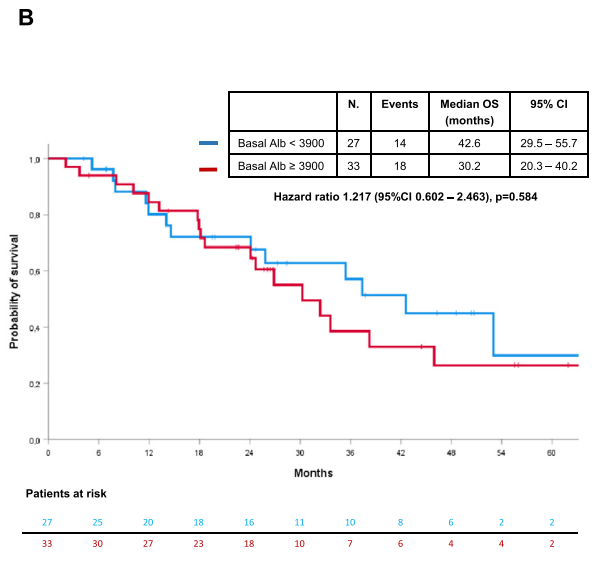
Supplemental Figure 18S Basal PLR: PFS (A) and OS (B).



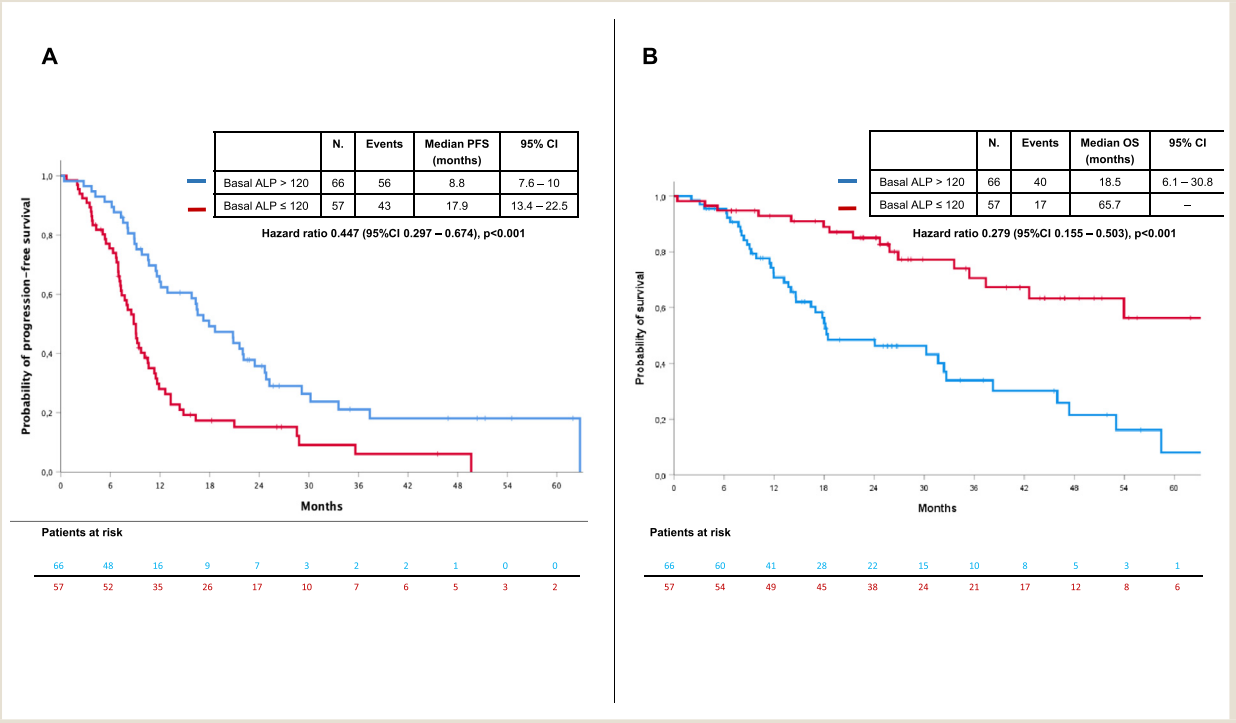


Supplemental Figure 19S Basal albumin: PFS (A) and OS (B).

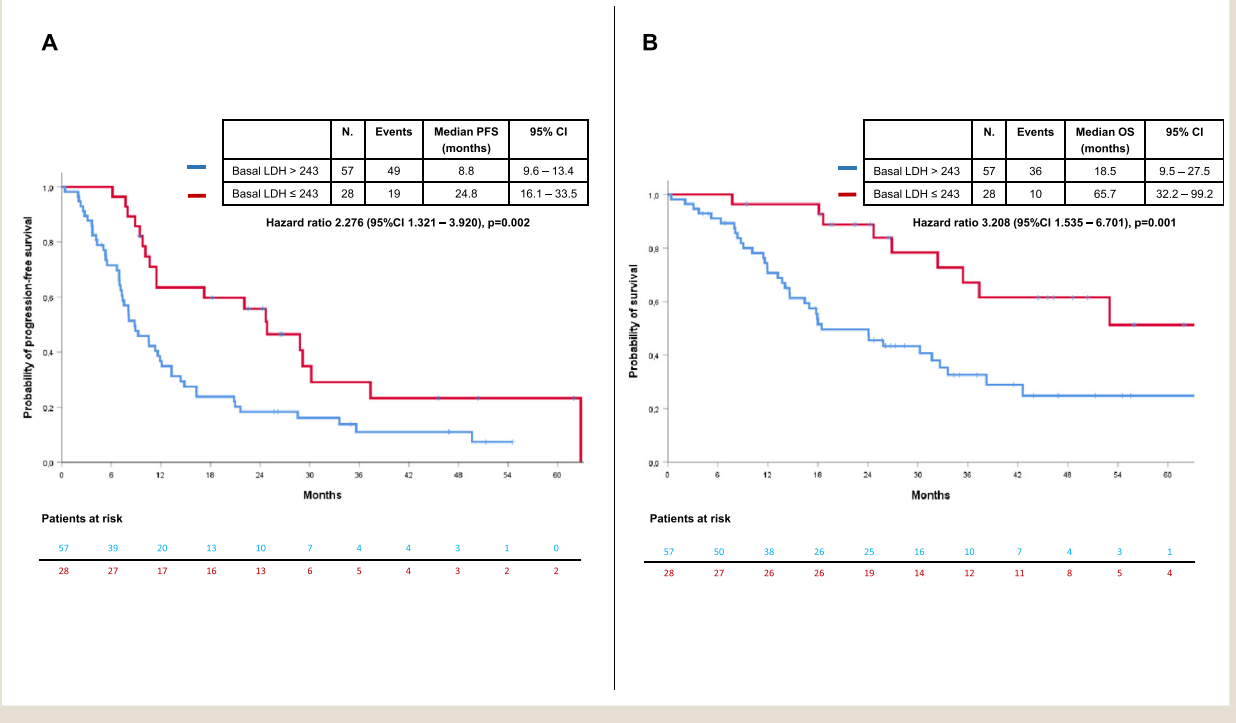




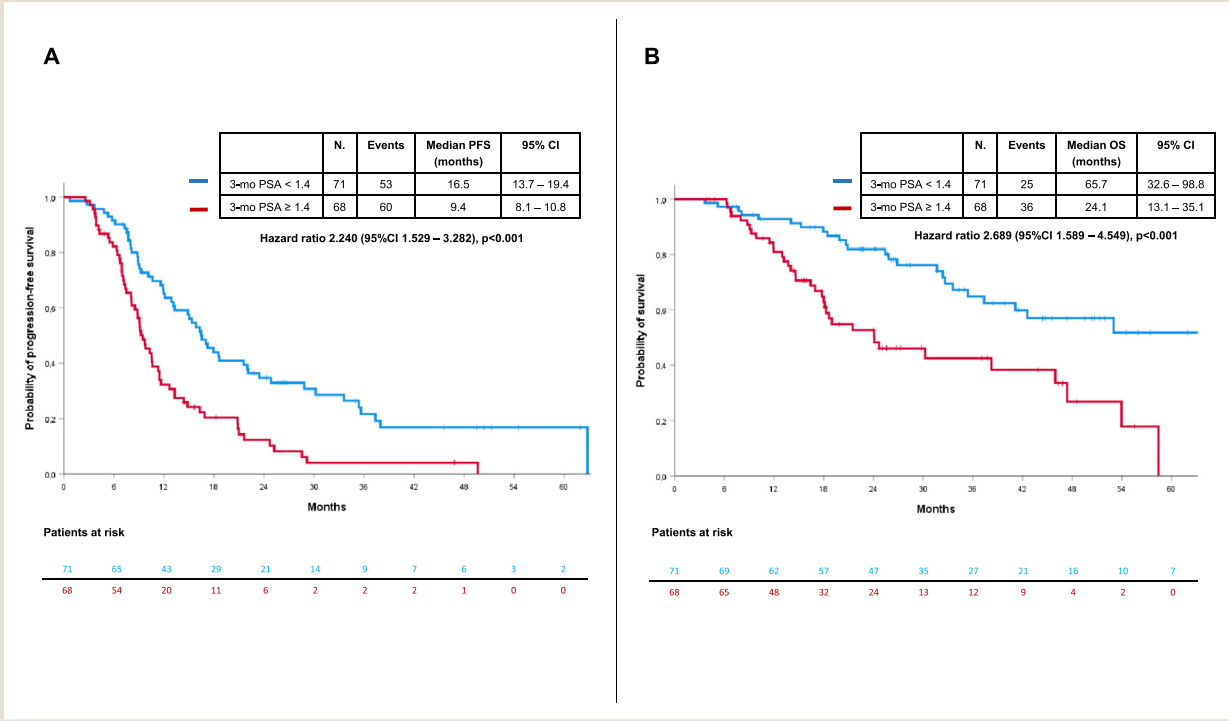
Supplemental Figure 20S Basal ALP: PFS (A) and OS (B).



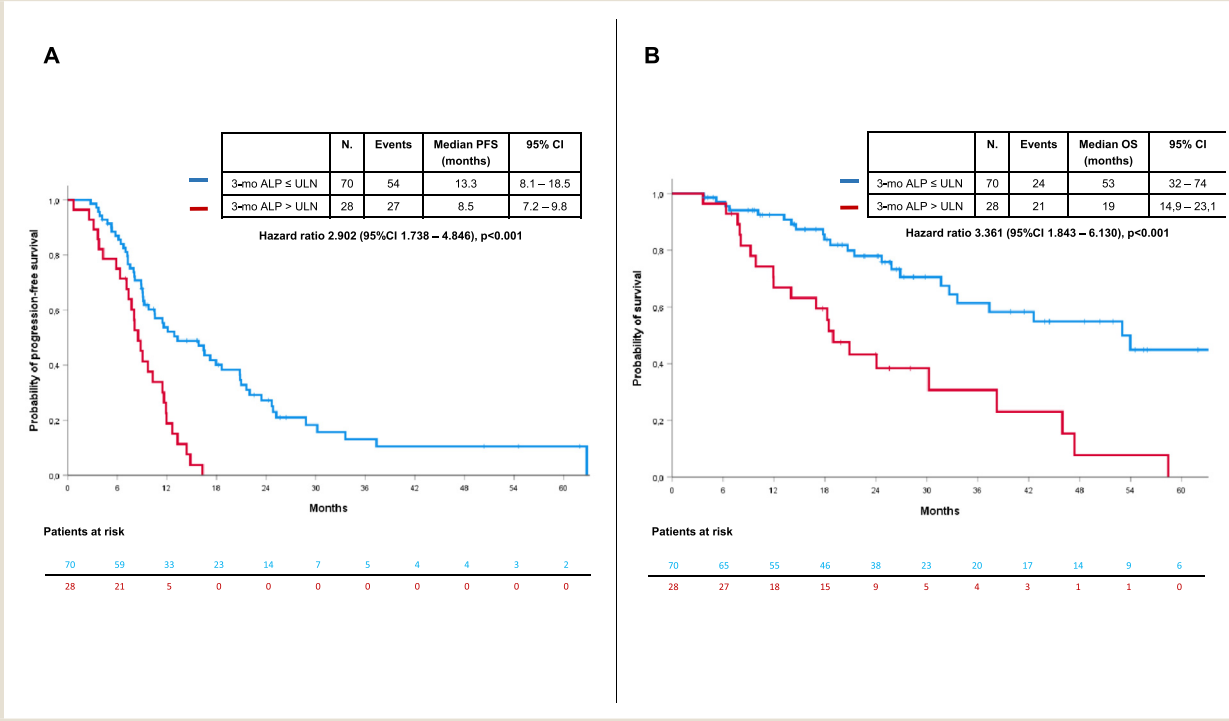
Supplemental Figure 21S Basal LDH: PFS (A) and OS (B).



Supplemental Figure 22S Three-months PSA: PFS (A) and OS (B).



Supplemental Figure 23S Three-months ALP: PFS (A) and OS (B).



Supplemental Figure 24S Number of docetaxel cycles: PFS (A) and OS (B).