

Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Characteristics of Patients With Complete and Incomplete Data

| Variable | Overall population n=745 | Patients with available data n=678 | P value |
|------------------------------------------|-----------------------------|------------------------------------------|---------|
| Median age at baseline, yrs (IQR) | 77.6 (68.1-83.6) | 77.3 (67.8-83.1) | 0.96 |
| Race, No. (%) | | | 0.99 |
| Caucasian | 699 (93.8) | 635 (93.6) | |
| Other | 19 (2.5) | 18 (2.7) | |
| Not available | 27 (3.7) | 25 (3.6) | |
| Gleason score, No. (%) | | | 0.98 |
| ≤6 | 62 (8.3) | 57 (8.4) | |
| 7 | 218 (29.3) | 200 (29.5) | |
| ≥8 | 337 (45.2) | 310 (45.7) | |
| Not available | 128 (17.2) | 111 (16.4) | |
| Prior local therapy, No. (%) | | | 0.93 |
| No | 353 (47.4) | 328 (48.4) | |
| Surgery | 196 (26.3) | 177 (26.1) | |
| Radiotherapy | 181 (24.3) | 173 (25.5) | |
| Not available | 15 (2.0) | 0 | |
| De novo, No. (%) | | | 0.70 |
| No | 483 (64.9) | 433 (63.9) | |
| Yes | 262 (35.1) | 245 (36.1) | |
| Treatment for mHSPC, No. (%) | | | 0.82 |
| ADT | 617 (82.8) | 602 (88.8) | |
| ADT+D | 81 (10.8) | 76 (11.2) | |
| Not available | 47 (6.4) | 0 | |
| Volume of disease at baseline, No. (%) | | | 0.99 |
| Low | 276 (37.0) | 269 (39.7) | |
| High | 420 (56.4) | 409 (60.3) | |
| Not available | 49 (6.6) | 0 | |
| Visceral metastases at baseline, No. (%) | | | 0.99 |
| No | 680 (91.3) | 619 (91.3) | |
| Yes | 65 (8.7) | 59 (8.7) | |
| Liver metastases at baseline, No. (%) | | | 0.62 |
| No | 709 (95.2) | 649 (95.7) | |
| Yes | 36 (4.8) | 29 (4.3) | |
| ECOG PS at baseline, No. (%) | | | 0.55 |
| 0 | 324 (43.5) | 316 (46.7) | |
| ≥1 | 369 (49.5) | 362 (53.3) | |
| Not available | 52 (7.0) | 0 | |
| Pain intensity at baseline, No. (%) | | | 0.94 |
| VAS 0-3 | 514 (69.0) | 506 (74.6) | |
| VAS 4-5 | 112 (15.0) | 107 (15.8) | |
| VAS >5 | 70 (9.4) | 65 (9.6) | |
| Not available | 49 (6.6) | 0 | |
| Use of opioids at baseline, No. (%) | | | 0.79 |
| No | 598 (80.3) | 585 (86.3) | |
| Yes | 99 (13.3) | 93 (13.7) | |
| Not available | 48 (6.4) | 0 | |
| Median PSA at baseline, ng/mL (IQR) | 32 (10.0-98.5) | 32.3 (10.2 – 99.7) | 0.95 |
| Use of BRI, No. (%) | | | 0.36 |
| No | 529 (71) | 504 (74.3) | |

| | | | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|--------------------|------|
| Zoledronic Acid | 84 (11.3) | 70 (11.3) | |
| Denosumab | 132 (17.7) | 104 (14.2) | |
| Median time from start of AA to start of BRI, days (IQR) | 15 (0-68) | 15 (0-67) | 0.99 |
| Median time of BRI administration, days (IQR) | 741 (362-1182) | 738 (357-1174) | 0.94 |
| Median AA cycles, n (IQR) | 9 (4-20) | 9 (4-20) | 0.99 |
| Pain palliation, No. (%) | | | 0.87 |
| No | 198 (26.6) | 190 (28) | |
| Yes | 497 (66.7) | 486 (71.7) | |
| Not available | 50 (6.7) | 2 (0.3) | |
| Number of treatments received after AA, Median (IQR) | 1 (0-2) | 1 (0-2) | 0.99 |
| 0-1 | 511 (68.6) | 488 (72) | |
| >1 | 225 (30.2) | 190 (28) | 0.29 |
| Not available | 9 (1.2) | 0 | |
| Median FU in overall population, months (CI) | 23.5 (19.8-24.9) | 23.5 (19.7 – 24.8) | 0.94 |
| <p>Abbreviations: AA = abiraterone acetate plus prednisone; ADT = androgen deprivation therapy; BRI = bone resorption inhibitors; CI = confidence interval; D = docetaxel; ECOG PS = Eastern Cooperative Oncology Group performance status; FU = follow-up; IQR = interquartile range; mHSPC = metastatic hormone-sensitive prostate cancer; NA = not available; PSA = prostate-specific antigen; VAS = visual analogue scale; yrs = years.</p> <p>Note: High volume is defined as ≥ 4 bone metastases of which at least 1 out of the pelvis and axis and/or visceral metastases); low volume is defined as not high volume.</p> | | | |

eTable 2. Univariate and Multivariate Analyses of Overall Survival in Overall Population

| Variable | Univariable Analysis | | Multivariable Analysis | |
|-------------------------------------------------------------|--------------------------------------|---------------|--------------------------------------|--------------|
| | HR (95%CI) | P value | HR (95%CI) | P value |
| Gleason grade (ref. ≤6) 7 ≥8 | 0.82 (0.58-1.16) 1.06 (0.76-1.49) | .26 .72 | NA | NA |
| Prior local therapy (ref. no) Surgery Radiotherapy | 0.62 (0.50-0.78) 0.73 (0.59-0.91) | <.001 .005 | 0.51 (0.39-0.68) 0.71 (0.55-0.93) | <.001 .03 |
| De-novo (ref. no) | 1.34 (1.12-1.61) | .001 | NS | NS |
| Treatment for mHSPC (ref. ADT alone) | 0.97 (0.74-1.29) | .87 | NA | NA |
| Volume of disease at baseline (ref. high volume) | 0.60 (0.50-0.72) | <.001 | 0.66 (0.54-0.80) | <.001 |
| Visceral metastases at baseline (ref. no) | 1.45 (1.08-1.95) | .01 | NS | NS |
| Liver metastases at baseline (ref. no) | 1.75 (1.20-2.54) | .004 | 2.04 (1.37-3.05) | .006 |
| ECOG PS at baseline (ref. 0) | 1.78 (1.49-2.13) | <.001 | 1.46 (1.20-1.78) | .003 |
| Pain intensity at baseline (ref. VAS 0-3) 4-5 >5 | 1.26 (1.00-1.59) 2.03 (1.54-2.66) | .057 <.001 | 1.13 (0.87-1.45) 1.88 (1.39-2.54) | .35 <.001 |
| Use of opioids at baseline (ref. no) | 1.64 (1.30-2.08) | <.001 | NS | NS |
| Use of BRI (ref. no) | 0.65 (0.54-0.79) | <.001 | 0.64 (0.52-0.79) | <.001 |
| PSA at baseline (as a continuous variable) | 1.05 (1.03-1.06) | <.001 | 1.03 (1.01-1.05) | .006 |
| Type of BRI used (ref. zoledronic acid) | 0.93 (0.66 – 1.30) | .79 | NA | NA |

Abbreviations: ADT = androgen deprivation therapy; BRI = bone resorption inhibitors; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; mHSPC = metastatic hormone-sensitive prostate cancer; HR = hazard ratio; NA = not available; NS = not significant; PSA = prostate-specific antigen; ref. = reference; VAS = visual analogue scale

Note: the multivariable analysis included a subset of patients (n=678) with all available covariates data.

High volume is defined as ≥4 bone metastases of which at least 1 out of the pelvis and axis and/or visceral metastases); low volume is defined as not high volume.

eTable 3. Univariate and Multivariate Analyses of Time to First Skeletal-related Event in Overall Population

| Variable | Univariable Analysis | | Multivariable Analysis | |
|-----------------------------------------------------|----------------------|---------|------------------------|---------|
| | HR (95%CI) | P value | HR (95%CI) | P value |
| Gleason grade (ref. ≤6) | | | | |
| 7 | 1.03 (0.65-1.63) | .88 | NA | NA |
| ≥8 | 1.13 (0.72-1.75) | .59 | | |
| Prior local therapy (ref. no) | | | | |
| Surgery | 0.79 (0.60-1.03) | .08 | NA | NA |
| Radiotherapy | 0.75 (0.56-1.01) | .05 | | |
| De-novo (ref. no) | 1.43 (1.13-1.81) | .002 | NA | NA |
| Treatment for mHSPC (ref. ADT alone) | 1.02 (0.71-1.47) | .90 | NA | NA |
| Volume of disease at baseline (ref. high volume) | 0.74 (0.58-0.95) | .02 | 0.73 (0.57-0.93) | .01 |
| Visceral metastases at baseline (ref. no) | 0.99 (0.63-1.56) | .96 | NA | NA |
| Liver metastases at baseline (ref. no) | 1.43 (0.83-2.44) | .19 | NA | NA |
| ECOG PS at baseline (ref. 0) | 1.53 (1.21-1.94) | .005 | NS | NS |
| Pain intensity at baseline (ref. VAS 0-3) | | | | |
| 4-5 | 1.51 (1.10-2.05) | .009 | 1.50 (1.10-2.04) | .001 |
| >5 | 3.42 (2.43-4.82) | <.001 | 3.52 (2.49-4.98) | <.001 |
| Use of opioids at baseline (ref. no) | 2.42 (1.81-3.23) | <.001 | NS | NS |
| Use of BRI (ref. no) | 1.27 (1.00-1.60) | .04 | NS | NS |
| PSA at baseline (as a continuous variable) | 1.02 (0.98-1.05) | .08 | NA | NA |

Abbreviations: ADT = androgen deprivation therapy; BRI = bone resorption inhibitors; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; mHSPC = metastatic hormone-sensitive prostate cancer; HR = hazard ratio; NA = not available; NS = not significant; PSA = prostate-specific antigen; ref. = reference; VAS = visual analogue scale
Note: the multivariable analysis included a subset of patients (n=685) with all available covariates data.
High volume is defined as ≥4 bone metastases of which at least 1 out of the pelvis and axis and/or visceral metastases; low volume is defined as not high volume.

eTable 4. Overall Survival Analysis According to BRI Use Stratified by Covariates

| Variables used for stratification | HR (95% CI) | P value |
|--------------------------------------------------|--------------------|----------------|
| Center | 0.75 (0.61-0.93) | .01 |
| Volume of disease at baseline (ref. high volume) | 0.67 (0.54-0.82) | .002 |
| Prior local therapy (ref. no) | 0.68 (0.56-0.83) | .001 |
| De-novo (ref. no) | 0.65 (0.54-0.78) | <.001 |
| Liver metastases at baseline (ref. no) | 0.65 (0.53-0.79) | <.001 |
| Visceral metastases at baseline (ref. no) | 0.66 (0.54-0.80) | <.001 |
| ECOG PS at baseline (ref. 0) | 0.66 (0.54-0.82) | .001 |
| Pain intensity at baseline (ref. VAS 0-3) | 0.61 (0.49-0.75) | <.001 |
| Use of opioid at baseline (ref. no) | 0.59 (0.48-0.73) | <.001 |
| PSA at baseline (> median value) | 0.66 (0.55-0.80) | <.001 |

Abbreviations: BRI = bone resorption inhibitors; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; HR = hazard ratio; PSA = prostate-specific antigen
 Note: Median PSA = 32 ng/ml. High volume is defined as ≥ 4 bone metastases of which at least 1 out of the pelvis and axis and/or visceral metastases); low volume is defined as not high volume.

eTable 5. Univariable and Multivariable Analyses of Overall Survival in Overall Population Stratified by Center

| Variable | Univariable Analysis | | Multivariable Analysis | |
|-------------------------------------------------------------|--------------------------------------|---------------|--------------------------------------|---------------|
| | HR (95%CI) | P value | HR (95%CI) | P value |
| Gleason grade (ref. ≤6) 7 ≥8 | 0.82 (0.58-1.16) 1.06 (0.76-1.49) | 0.26 0.72 | NA | NA |
| Prior local therapy (ref. no) Surgery Radiotherapy | 0.62 (0.50-0.78) 0.73 (0.59-0.91) | <.001 .005 | 0.58 (0.45-0.73) 0.79 (0.63-0.99) | <.001 .04 |
| De-novo (ref. no) | 1.34 (1.12-1.60) | .001 | NS | NS |
| Treatment for mHSPC (ref. ADT alone) | 1.26 (0.93-1.71) | .14 | NA | NA |
| Volume of disease at baseline (ref. high volume) | 0.72 (0.58-0.88) | .001 | 0.68 (0.55-0.84) | .004 |
| Visceral metastases at baseline (ref. no) | 1.43 (1.06-1.94) | .02 | NS | NS |
| Liver metastases at baseline (ref. no) | 1.96 (1.33-2.89) | .007 | 1.97 (1.29-3.01) | .002 |
| ECOG PS at baseline (ref. 0) | 1.62 (1.33-1.97) | <.001 | 1.42 (1.16-1.75) | .008 |
| Pain intensity at baseline (ref. VAS 0-3) 4-5 >5 | 1.43 (1.10-1.84) 1.96 (1.47-2.60) | .006 <.001 | 1.14 (0.87-1.49) 1.86 (1.37-2.52) | 0.33 <.001 |
| Use of opioids at baseline (ref. no) | 1.80 (1.41-2.86) | <.001 | NS | NS |
| Use of BRI (ref. no) | 0.75 (0.61-0.93) | 0.01 | 0.67 (0.51-0.88) | .004 |
| PSA at baseline (as a continuous variable) | 1.06 (1.05-1.07) | <.001 | 1.03 (1.01-1.04) | .001 |
| Type of BRI used (ref. zoledronic acid) | 0.97 (0.69-1.35) | .81 | NA | NA |

Abbreviations: ADT = androgen deprivation therapy; BRI = bone resorption inhibitors; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; mHSPC = metastatic hormone-sensitive prostate cancer; HR = hazard ratio; NA = not available; NS = not significant; PSA = prostate-specific antigen; ref. = reference; VAS = visual analogue scale
Note: the multivariable analysis included a subset of patients (n=678) with all available covariates data. High volume is defined as ≥4 bone metastases of which at least 1 out of the pelvis and axis and/or visceral metastases; low volume is defined as not high volume.

eTable 6. Patient Characteristics and Overall Survival According to BRI Use Stratified by Center

| Center | Number of Patients | Median OS, months (95% CI) | % BRI administration | Mean subsequent treatments | % ECOG PS >1 | % high volume | Median baseline PSA (IQR) |
|--------|--------------------|----------------------------|----------------------|----------------------------|--------------|---------------|---------------------------|
| 1 | 24 | 26.8 (18.0-NR) | 20.8 | 0.6 | 45.8 | 66.7 | 67 (11.7-116.3) |
| 2 | 39 | 29.3 (24.5-NR) | 80.0 | 1.2 | 63.1 | 24.2 | 8.0 (3.5-36.0) |
| 3 | 26 | 37.4 (21.6-NR) | 11.5 | 0.8 | 46.1 | 46.1 | 15.5 (4.25-51.5) |
| 4 | 26 | 24.4 (16.4-NR) | 19.2 | 0.8 | 30.8 | 30.8 | 12.0 (4.0-39.3) |
| 5 | 126 | 36.5 (33.4-50.1) | 47.2 | 2.3 | 15.1 | 33.3 | 16.1 (3.4-45.2) |
| 6 | 393 | 21 (18.7-23.5) | 6.9 | 0.6 | 64.8 | 80.0 | 55.6 (21.2-155.2) |
| 7 | 10 | 34.8 (16.7-NR) | 70.0 | 1.2 | 40.0 | 50.0 | 24.9 (15.3-65.1) |
| 8 | 45 | 33.1 (22.8-49.2) | 73.0 | 3.3 | NA* | NA* | 15.4 (7.62-58.5) |

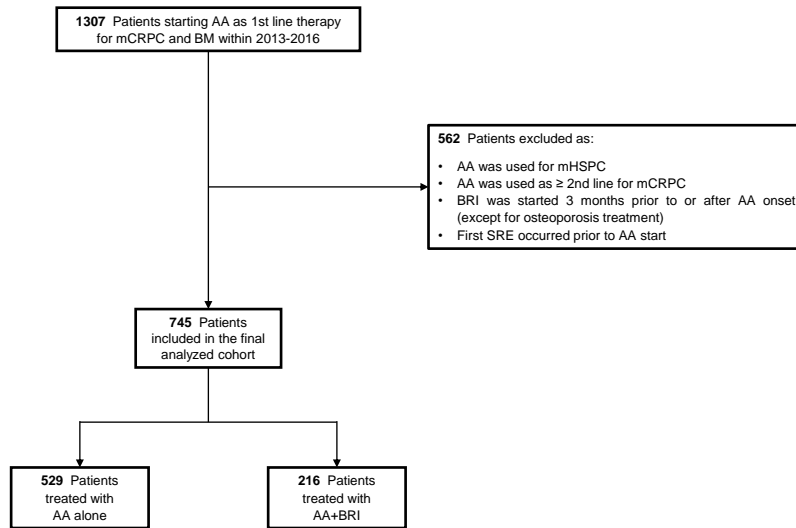
Abbreviations: BRI = bone resorption inhibitors; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; HR = hazard ratio; IQR = interquartile range; NA = not available; NR = not reached; PSA = prostate-specific antigen

Note: High volume is defined as ≥ 4 bone metastases of which at least 1 out of the pelvis and axis and/or visceral metastases); low volume is defined as not high volume.

* data for ECOG-PS and volume were not available for this center.

eFigure. Study Population Flowchart

eFigure 1. Study population flow.



Legend: AA = abiraterone acetate plus prednisone; BM = bone metastases; BRI = bone-resorption inhibitors (zoledronic acid or denosumab); mCRPC = metastatic castration-resistant prostate cancer; mHSPC = metastatic hormone-sensitive prostate cancer; SRE = skeletal-related event (definition: palliative radiotherapy or surgery to bone, pathological fractures, or spinal cord compression)

Note: Number of deaths prior to data cut-off date (September 15, 2019) were 369 among those treated with AA and 147 among those treated with AA+BRI.