Statin use and survival in patients with metastatic castration-resistant prostate cancer treated with abiraterone or enzalutamide after docetaxel failure: the international retrospective observational STABEN study

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ABSTRACT

Background: Statins may potentiate the effects of anti-hormonal agents for metastatic castration-resistant prostate cancer (mCRPC) through further disruption of essential steroidogenic processes. We investigated the effects of statin use on clinical outcomes in patients with mCRPC receiving abiraterone or enzalutamide.

Materials and methods: This was a retrospective multicenter study including patients that received abiraterone or enzalutamide for mCRPC. The effect of concurrent
statin use on outcomes was evaluated. The associations of statins with early (≤12 weeks) prostate-specific antigen (PSA) declines (> 30%), cancer-specific survival and overall survival (OS) were evaluated after controlling for known prognostic factors.

Results: Five hundred and ninety-eight patients treated with second-line abiraterone or enzalutamide after docetaxel for mCRPC were included. A total of 199 men (33.3%) received statins during abiraterone/enzalutamide treatment. Median OS was 20.8 months (95% CI = 18.3–23.2) for patients who received statins, versus 12.9 months (95% CI = 11.4–14.6) for patients who did not receive statins (P < 0.001). After adjusting for age, alkaline phosphatase, PSA, neutrophil-to-lymphocytes ratio, Charlson comorbidity score, Gleason score, visceral disease, hemoglobin, opiate use and abiraterone versus enzalutamide treatment, the use of statin therapy was associated with a 53% reduction in the overall risk of death (hazard ratio [HR] = 0.47; 95% CI = 0.35–0.63; P < 0.001). Statin use was also associated with a 63% increased odds of a > 30% PSA decline within the first 12 weeks of treatment (OR = 1.63; 95% CI = 1.03–2.60; P = 0.039).

Conclusions: In this retrospective cohort, statin use was significantly associated with both prolonged OS and cancer-specific survival and increased early > 30% PSA declines. Prospective validation is warranted.

INTRODUCTION

In developed countries, prostate cancer is the most prevalent malignancy in men, with 142,000 patients dying each year, and an 8.8% cumulative lifetime incidence [1]. Statins are a therapeutic class of medications that are commonly prescribed to lower circulating cholesterol levels through inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase [2], and have an established role in primary and secondary cardiovascular prevention [3]. Over the past decade, a preponderance of evidence from numerous studies, mostly conducted in patients with hormone-sensitive disease, has shown that statin use in prostate cancer patients is associated with longer cancer-specific and overall survival (OS) [4]. The putative mechanism for this observed improvement in survival is that statins may impair prostate cancer growth via multiple cholesterol- and non-cholesterol-mediated effects [4]. In a recently published study of a large, registry-based cohort, which included >30,000 prostate cancer patients [5], statin use was predictive of improved cancer-specific and OS, after adjusting for stage, Gleason score and primary treatment at diagnosis. Conversely, there is little evidence regarding the effects of statins among patients with castration-resistant prostate cancer (CRPC), and the potential synergism with active systemic treatments (e.g., abiraterone and enzalutamide).

Abiraterone works by inhibiting residual adrenal and intra-tumoral androgen synthesis via CYP17A blockade [6], while enzalutamide acts by inhibiting binding of testosterone to the androgen receptor (AR) as well as by blocking androgen-mediated change and nuclear translocation of AR [7]. In one small retrospective study, statin use was significantly associated with longer OS and early PSA declines in men who received abiraterone [8]. In contrast, this OS advantage has not been consistently observed in other studies [9, 10]. Furthermore, there is prospective evidence from a phase III trial suggesting that statins may be discontinued in the palliative care setting with no detrimental effect on survival [11].

In view of the potential additive effect of statins with novel hormonal agents and of the unknown value of continuing versus discontinuing statin therapy in patients with metastatic CRPC (mCRPC), a multi-center retrospective study was conducted to further explore the effects of statin use on PSA response and survival outcomes during second-line (post-docetaxel) treatment with abiraterone or enzalutamide, after adjusting for multiple known predictive factors in the second-line setting [12].

RESULTS

Patients’ characteristics and outcomes

Six hundred and forty-two patients were initially included in this dataset. Of these, 44 patients were excluded because statin use could not be ascertained. Baseline characteristics and outcomes are presented for the remaining 598 patients in Table 1A–1D. Notably, > 50% of patients came from one treatment center (BCCA) and an additional 21% of patients came from a second center (Federico II Napoli). Median age of the population was 72 years (range, 42–96). Most of the study patients received abiraterone. Median duration of second-line treatment with abiraterone or enzalutamide was 8.3 months (range, 0.4–47.5), with 52% of patients having a > 30% PSA decrease within the first 12 weeks of treatment. At the time of this analysis, 513 (85.8%) patients had died, with a median OS of 16.1 months (95% confidence interval
[CI] = 13.8–17.0. Cancer-specific survival was 16.2 months (95% CI: 14.3–17.1).

**Statin use**

Approximately one-third of the evaluable study population (199 of 598 patients) received statins during treatment, with 107 patients receiving atorvastatin (18% of patients). Importantly, statin use was documented by the local investigator using prescription data in almost 91% of cases. Only eleven patients were reported to have started statin after abiraterone or enzalutamide or to have interrupted statins before suspending abiraterone/enzalutamide treatment (2% of

**Table 1A: Summary statistics**

| Characteristic                          | Statistic     | N   | All Patients | Abiraterone | Enzalutamide |
|----------------------------------------|---------------|-----|--------------|-------------|--------------|
| **Site**                               |               |     |              |             |              |
| Federico II Napoli                      | N             | 598 | 127 (21.2)   | 91 (19.0)   | 36 (30.5)    |
| Pascale Napoli                          |               |     | 17 (2.8)     | 14 (2.9)    | 3 (2.5)      |
| University Bari                         |               |     | 21 (3.5)     | 13 (2.7)    | 8 (6.8)      |
| St. Gallen                              |               |     | 29 (4.9)     | 27 (5.6)    | 2 (1.7)      |
| UNC                                     |               |     | 41 (6.9)     | 20 (4.2)    | 21 (17.8)    |
| UCLA                                    |               |     | 15 (2.5)     | 9 (1.9)     | 6 (5.1)      |
| BCCH                                    |               |     | 342 (57.2)   | 301 (62.7)  | 41 (34.8)    |
| Gallarate                               |               |     | 6 (1.0)      | 5 (1.0)     | 1 (0.9)      |
| **Age**                                 |               |     |              |             |              |
| Mean (std dev)                          | N             | 598 | 72.5 (9.0)   | 72.6 (9.0)  | 72.0 (8.8)   |
| Median (range)                          |               |     | 72 (42.96)   | 72 (42.96)  | 72 (43, 90)  |
| **Gleason Score**                       |               |     |              |             |              |
| N (%) ≥8                                | N             | 540 | 306 (56.7)   | 248/431 (57.5) | 58/109 (53.2) |
| **Charlson Score**                      |               |     |              |             |              |
| Median (range)                          | N             | 598 | 10 (6.17)    | 10 (6.17)   | 10 (6.15)    |
| N (%) ≥10                               |               |     | 341 (57.0)   | 274/480 (57.1) | 67/118 (56.8) |
| **Baseline PSA**                        |               |     |              |             |              |
| Median (range)                          | N             | 588 | 87.3 (0, 7938) | 97.8 (0, 7938) | 61 (1.9, 2220) |
| **Alkaline Phosphatase**                |               |     |              |             |              |
| Median (range)                          | N             | 448 | 119 (8.9, 2189) | 120 (8.9, 2189) | 105 (39, 1791) |
| **LDH**                                 |               |     |              |             |              |
| Median (range)                          | N             | 259 | 264 (90, 2598) | 262 (90, 2598) | 266 (103, 2219) |
| **Neutrophils/Lymphocyte Ratio**        |               |     |              |             |              |
| Median (range)                          | N             | 530 | 3.4 (0.2, 37.5) | 3.5 (0.2, 34.5) | 2.7 (1.0, 37.5) |
| **Hemoglobin**                          |               |     |              |             |              |
| Median (range)                          | N             | 555 | 11.9 (5.7, 15.8) | 11.9 (5.7, 15.8) | 11.8 (7.1, 15.6) |
| **Baseline PSA**                        |               |     |              |             |              |
| Median (range)                          | N             | 390 | 18.4 (0.2, 65.5) | 18.6 (0.2, 65.5) | 16.0 (0.8, 59.8) |
| **Months, Castration-sensitive Disease**|               |     |              |             |              |
| Median (range)                          | N             | 474 | 37.0 (0, 162.0) | 39.3 (0, 161.3) | 25.0 (0, 162.0) |
| **Opiate Use**                          |               |     |              |             |              |
| N (%) Yes                               | N             | 587 | 191/587 (32.5) | 152/476 (31.9) | 39/111 (35.1) |
| **Visceral Disease**                    |               |     |              |             |              |
| N (%) Yes                               | N             | 598 | 46 (7.7)     | 31/480 (6.5) | 15/118 (12.7) |
| **Treatment with abiraterone/enzalutamide ± statins** |       |     |              |             |              |
| **Treatment**                           |               |     |              |             |              |
| N (%) Abiraterone                       | N             | 598 | 480 (80.3)   | 480 (100.0) | 0 (0.0)      |
| N (%) Yes                               | N             | 598 | 199/598 (33.3) | 157/480 (32.7) | 42/118 (35.6) |
| Atorvastatin                            |               |     | 107 (53.8)   | 93 (59.2)   | 14 (33.3)    |
| Lovastatin                              |               |     | 3 (1.5)      | 2 (1.3)     | 1 (2.4)      |
| Pravastatin                             |               |     | 11 (5.5)     | 8 (5.1)     | 3 (7.1)      |
| Rosuvastatin                            |               |     | 33 (16.6)    | 30 (19.1)   | 3 (7.1)      |
| Simvastatin                             |               |     | 22 (11.1)    | 20 (12.7)   | 2 (4.8)      |
| Unknown                                 |               |     | 23 (11.6)    | 4 (2.6)     | 19 (45.2)    |
| **Dose of Statins**                     |               |     |              |             |              |
| Median (range)                          | N             | 122 | 20 (5, 80)   | 20 (5, 80)  | 20 (5, 40)   |
| **Simvastatin Equivalent Dose**         |               |     |              |             |              |
| Median (range)                          | N             | 122 | 30 (8, 120)  | 30 (8, 120) | 30 (10, 60)  |
| Statins Prior to Abiraterone/Enzalutamide|               |     |              |             |              |
| N (%) Yes                               | N             | 196 | 191/196 (97.5) | 151/154 (98.1) | 40/42 (95.2) |
| **Statin Use Suspended during abiraterone/enzalutamide treatment** |       |     |              |             |              |
| N (%) Yes                               | N             | 196 | 3/196 (1.5)  | 2/154 (1.3) | 1/42 (2.4)   |
| Months, Duration of Abiraterone/Enzalutamide Treatment | Median (range) | 183 | 8.3 (0.4, 47.5) | 8.5 (0.4, 47.5) | 7.1 (1.4, 33.4) |
| **Use Hydrophilic Statin**              |               |     |              |             |              |
| N (%) Yes                               | N             | 176 | 44 (25.0)    | 38/153 (24.8) | 6/23 (26.1)  |
| **Source of Statin Use Data**           |               |     |              |             |              |
| Prescription data                       |               |     | 543 (90.8%)  | 444 (92.5%) | 99 (83.8%)   |
| Claims                                  |               |     | 55 (9.2%)    | 36 (7.5%)   | 19 (16.1%)   |

Characteristics of the study population grouped by treatment.

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Table 1B: Outcomes of the study population, grouped by treatment

| Characteristic                        | Statistic | All Patients | Abiraterone | Enzalutamide |
|---------------------------------------|-----------|--------------|-------------|--------------|
|                                      | N (%)     | N (%)        | N (%)       | N (%)        |
| >30% PSA Decline at Week 4           | 209 (40.3)| 169/419 (40.3)| 40/100 (40.0)|
| >30% PSA Decline at Week 8           | 223 (46.5)| 184/391 (47.1)| 39/89 (43.8) |
| >30% PSA Decline at Week 12          | 231 (49.3)| 184/383 (48.0)| 47/86 (54.7) |
| >30% PSA Decline at 4,8 or 12 Weeks†| 299/574 (52.1)| 243/465 (52.3)| 56/109 (51.4)|
| Overall Survival                     |           | 513 (85.8)   | 424 (88.3)  | 89 (75.4)    |
|                                       | Median (95% CI) | 16.1 (13.8, 17.0)| 15.8 (13.7, 17.0)| 16.5 (12.1, 20.1)|
|                                       | 6-mo OS (95% CI) | 81.7 (78.3, 84.6)| 82.4 (78.7, 85.6)| 78.5 (69.9, 84.9)|
|                                       | 1-year OS (95% CI) | 61.0 (56.9, 64.8)| 61.3 (56.7, 65.5)| 59.7 (50.1, 68.1)|
|                                       | 2-year OS (95% CI) | 31.2 (27.5, 35.1)| 30.5 (26.3, 34.7)| 34.7 (25.8, 43.7)|
| Cause of Death                       | Prostate Cancer | 468 (91.2)   | 390/424 (92.0)| 78/89 (87.6) |
| Cancer-Specific Survival             |           | 16.5 (15.3, 17.7)| 16.4 (14.6, 17.7)| 17.6 (13.6, 21.4)|
|                                       | 6-mo OS (95% CI) | 82.7 (79.4, 85.6)| 83.4 (79.7, 86.5)| 80.0 (71.4, 86.2)|
|                                       | 1-year OS (95% CI) | 63.2 (59.1, 67.0)| 63.3 (58.7, 67.5)| 63.2 (53.5, 71.4)|
|                                       | 2-year OS (95% CI) | 33.8 (29.8, 37.8)| 33.0 (28.6, 37.4)| 37.4 (28.0, 46.8)|
| Vascular Events                      | Cardiovascular N (%) | 20 (3.3)     | 15 (3.1)    | 5 (4.2)     |
|                                       | Cerebrovascular N (%) | 13 (2.2)    | 12 (2.5)    | 1 (0.9)     |
|                                       | Either N (%)       | 33 (5.5)    | 27 (5.6)    | 6 (5.1)     |

*denominator is number of patients with a PSA assessment at week 4, 8 or 12.

Table 1C: Summary statistics

| Characteristic             | Statistic | N   | No Statins | N   | Statins |
|---------------------------|-----------|-----|------------|-----|---------|
| Site                      | Federico II of Napoli | 399 | 74 (18.6)  | 199 | 53 (26.6)|
|                           | Pascale Napoli       |     | 8 (2.0)    |     | 9 (4.5) |
|                           | University of Bari   |     | 14 (3.5)   |     | 7 (3.5) |
|                           | St. Gallen           |     | 25 (6.3)   |     | 4 (2.0) |
|                           | UNC                  |     | 27 (6.8)   |     | 14 (7.0)|
|                           | UCLA                 |     | 7 (1.8)    |     | 8 (4.0) |
|                           | BCCA                 |     | 241 (60.4)|     | 101 (50.8)|
|                           | Gallarate            |     | 3 (0.8)    |     | 3 (1.5) |
| Age                      | Mean (std dev)       | 399 | 71.9 (9.4) | 199 | 73.8 (7.9)|
|                           | Median (range)       |     | 72 (42, 96)|     | 74 (43, 94)|
| Gleason Score            | N (%) ≥8             | 354 | 204 (57.6)| 186 | 102 (54.8)|
| Charlson Score           | Median (range)       | 399 | 10 (6, 15)| 199 | 10 (6, 17)|
| PSA at Diagnosis         | Median (range)       | 391 | 95.3 (0, 7149)| 197 | 80 (0.2, 7938)|
| Alkaline Phosphatase     | Median (range)       | 312 | 113 (8.9, 2189)| 136 | 120 (25, 1791)|
| LDH                      | Median (range)       | 175 | 260 (103, 2598)| 136 | 272 (90, 2219)|
| Neutrophils/Lymphocyte Ratio | Median (range)     | 358 | 3.4 (0.2, 34.5)| 172 | 3.3 (0.2, 37.5)|
| Hemoglobin               | Median (range)       | 373 | 11.9 (5.7, 15.8)| 182 | 12.0 (7.9, 15.5)|
| Months, Castration-sensitive Disease | Median (range) | 259 | 18.4 (0.2, 65.5)| 131 | 18.4 (0.6, 65.4)|
| Months, Diagnosis to Metastases | Median (range) | 306 | 33.3 (0, 162.0)| 168 | 43.5 (0, 161.3)|
| Opiate Use               | N (%) Yes            | 389 | 124 (31.9)| 198 | 67 (33.8)|
| Visceral Disease         | N (%) Yes            | 399 | 33 (8.3)  | 199 | 13 (6.5) |
| Treatment                | N (%) Abiraterone    | 399 | 323 (81.0)| 199 | 157 (78.9)|
patients). The median simvastatin-equivalent daily dose administered was 30 mg.

**Association of statins with OS and cancer-related survival**

Median OS was significantly improved for mCPRC patients who received concomitant statins, when compared to patients not treated with statins (20.8 versus 12.9 months; hazard ratio [HR] = 0.57, 95% CI = 0.46–0.71, \( P < 0.001 \)) (Figure 1). Table 2A summarizes the results of univariable and multivariable models for OS. In the multivariable model, statin use remained strongly associated with OS with a 53% reduction in the risk of death. This association was similar in subgroup analyses and in the landmark analyses. Among the study patients who had died (\( n = 513 \)), over 91% of the deaths were attributable to prostate cancer, and thus

**Table 1D: Outcomes of the study population, grouped by statin use**

| Characteristic                                    | Statistic                      | N (%) Yes | N (%) No Statins | N (%) Statins |
|---------------------------------------------------|--------------------------------|-----------|------------------|---------------|
| >30% PSA Decline at Week 4                        | N (%) Yes                      | 349       | 130 (37.3)       | 170           |
| >30% PSA Decline at Week 8                        | N (%) Yes                      | 311       | 136 (43.7)       | 169           |
| >30% PSA Decline at Week 12                       | N (%) Yes                      | 305       | 148 (48.5)       | 164           |
| >30% PSA Decline at 4, 8 or 12 Weeks†             | N (%) Yes                      | 380       | 186 (49.0)       | 194           |
| Overall Survival                                  | N (%) Deaths                   | 399       | 347 (87.0)       | 199           |
| Median (95% CI)                                   | 12.9 (11.4, 14.6)              | 199       | 20.8 (18.3, 23.2) |
| 6-mo OS (95% CI)                                  | 78.6 (74.2, 82.3)              | 199       | 87.8 (82.3, 91.6) |
| 1-year OS (95% CI)                                | 53.8 (48.7, 58.7)              | 199       | 75.0 (68.3, 80.5) |
| 2-year OS (95% CI)                                | 25.9 (21.6, 30.5)              | 199       | 41.6 (34.5, 48.4) |
| Cause of Death                                    | Prostate Cancer                | 347       | 324 (93.4)       | 166           |
| Cancer-Specific Survival                          | Median (95% CI)                | 399       | 13.4 (12.1, 15.8) | 199           |
| 6-mo OS (95% CI)                                  | 79.3 (74.9, 83.0)              | 199       | 89.7 (84.5, 93.2) |
| 1-year OS (95% CI)                                | 56.0 (50.9, 60.9)              | 199       | 77.6 (71.0, 82.8) |
| 2-year OS (95% CI)                                | 27.8 (23.2, 32.5)              | 199       | 45.5 (38.1, 52.6) |
| Vascular Events                                   | Cardiovascular N (%)           | 399       | 8 (2.0)          | 199           |
|                                                                 | Cerebrovascular N (%)          | 399       | 3 (0.8)          | 199           |
|                                                                 | Either N (%)                   | 399       | 11 (2.8)         | 199           |

Characteristics of the study population, grouped by statin use.

*denominator is number of patients with a PSA response assessment at week 4, 8 or 12.
the cancer-specific survival was similar to OS. Median cancer-specific survival was also significantly improved for patients who received concomitant statins, when compared to patients not treated with statins (22.3 versus 13.4 months; HR = 0.43, 95% CI = 0.32 to 0.58, \( P < 0.001 \)) (Table 2B).

No statistically significant treatment effects were observed between enzalutamide versus abiraterone, nor were treatment differences observed based on type (atorvastatin versus other) or dose of statin.

**Association of statins with PSA response**

Among the 574 patients with available information, 299 (52.1%) experienced a PSA response (> 30% decline) within 12 weeks of abiraterone or enzalutamide initiation. Early PSA responses were observed significantly more often in patients that received statins, when compared to patients who did not receive statin therapy (58% versus 49%; odds ratio [OR] = 1.46, 95% CI = 1.02–2.08, \( P = 0.04 \)) (Table 3). The association between early PSA response and statin use remained significant in the multivariable analysis (OR = 1.63, 95% CI = 1.03–2.60, \( P = 0.04 \)).

**Association of statin use and cardiovascular or cerebrovascular events**

Thirty-three study patients experienced a cardiovascular or cerebrovascular event during the time period analyzed. Timing of events was not consistently reported, and therefore time-to-event analyses could not be performed. Among the 199 patients prescribed statins, 12 (6.0%) experienced a cardiovascular event, and 10 (5.0%) experienced a cerebrovascular event. In contrast, among the 399 patients not prescribed statin therapy, 8 (2.0%) experienced a cardiovascular event, and 3 (0.8%) experienced a cerebrovascular event. After adjusting for other factors in a multivariable model, concomitant statin use remained a significant predictive factor of increased risk of cardiovascular or cerebrovascular events (OR = 3.24, 95% CI = 1.15–9.17, \( p \)-value = 0.03) (Table 4).

**DISCUSSION**

Although statin use has been associated with reduced cancer-related mortality in a variety of malignancies [13], the potential synergism of statins with anti-cancer medications has been prospectively investigated only in a few clinical trials. Data from the recently published phase III double-blind, placebo-controlled LUNGSTAR trial failed to detect an OS or progression-free survival (PFS) benefit when pravastatin was added to first-line standard chemotherapy in patients with small-cell lung cancer [14]. Similarly, no benefit in overall survival associated with the use of statins added to chemotherapy was reported in two additional phase III trials conducted in advanced gastric [15] and colorectal [16] cancer patients, respectively.
# Table 2A: Cox regression analyses, outcome = overall survival

| Type                          | All Patients | Abiraterone | Enzalutamide |
|-------------------------------|--------------|-------------|--------------|
| Age                           | N = 598      | P = 0.28    | P = 0.98     |
| Months, Castrat.-Sensitive Dz | N = 480      | P = 0.28    | P = 0.98     |
| Months, Dx-Mets               | N = 367      | P = 0.28    | P = 0.98     |
| Alk Phos                      | N = 194      | P = 0.28    | P = 0.98     |
| LDH                           | N = 65       | P = 0.28    | P = 0.98     |
| Neutrophils/Lymphocyte Ratio  | N = 435      | P = 0.28    | P = 0.98     |
| Hemoglobin                    | N = 450      | P = 0.28    | P = 0.98     |
| Baseline PSA                  | N = 476      | P = 0.28    | P = 0.98     |
| Charlson Score                | N = 118      | P = 0.28    | P = 0.98     |
| Gleason Score                 | N = 109      | P = 0.28    | P = 0.98     |
| Visceral Disease              | N = 111      | P = 0.28    | P = 0.98     |
| Opiates                       | N = 111      | P = 0.28    | P = 0.98     |
| Treatment                     | N = 480      | P = 0.28    | P = 0.98     |
| Concomitant Statins           | N = 118      | P = 0.28    | P = 0.98     |
| Statin Type                   | N = 109      | P = 0.28    | P = 0.98     |
| Simvastatin Equivalent Dose   | N = 111      | P = 0.28    | P = 0.98     |
| Use of a hydrophilic statin   | N = 111      | P = 0.28    | P = 0.98     |

## Multivariable Model

| Age                           | N = 387      | P = 0.28    | P = 0.98     |
| Alk Phos                      | N = 476      | P = 0.28    | P = 0.98     |
| Neutrophils/Lymphocyte Ratio  | N = 435      | P = 0.28    | P = 0.98     |
| Hemoglobin                    | N = 450      | P = 0.28    | P = 0.98     |
| Baseline PSA                  | N = 476      | P = 0.28    | P = 0.98     |
| Charlson Score                | N = 118      | P = 0.28    | P = 0.98     |
| Gleason Score                 | N = 109      | P = 0.28    | P = 0.98     |
| Visceral Disease              | N = 111      | P = 0.28    | P = 0.98     |
| Opiates                       | N = 111      | P = 0.28    | P = 0.98     |
| Treatment                     | N = 480      | P = 0.28    | P = 0.98     |
| Concomitant Statins           | N = 118      | P = 0.28    | P = 0.98     |

## 3-Month Landmark Analysis – Multivariable Model

| Age                           | N = 360      | P = 0.28    | P = 0.98     |
| Alk Phos                      | N = 476      | P = 0.28    | P = 0.98     |
| Neutrophils/Lymphocyte Ratio  | N = 435      | P = 0.28    | P = 0.98     |
| Hemoglobin                    | N = 450      | P = 0.28    | P = 0.98     |
| Baseline PSA                  | N = 476      | P = 0.28    | P = 0.98     |
| Charlson Score                | N = 118      | P = 0.28    | P = 0.98     |
| Gleason Score                 | N = 109      | P = 0.28    | P = 0.98     |
| Visceral Disease              | N = 111      | P = 0.28    | P = 0.98     |
| Opiates                       | N = 111      | P = 0.28    | P = 0.98     |
| Treatment                     | N = 480      | P = 0.28    | P = 0.98     |
| Concomitant Statins           | N = 118      | P = 0.28    | P = 0.98     |
## Table 2B: Cox regression analyses, outcome = cancer-specific survival

| Type                                      | All Patients | Abiraterone Only | Enzalutamide Only |
|-------------------------------------------|--------------|------------------|-------------------|
| Age / decade                              |              |                  |                   |
| Months, Castrat.-Sensitive Dz <12 mos vs ≥12 mos |              |                  |                   |
| Months, Dx-Mets <36 mos vs ≥36 mos         |              |                  |                   |
| Alk Phos Log-transformed                   |              |                  |                   |
| LDH Log-transformed                        |              |                  |                   |
| Neutrophils/ Lymphocyte Ratio Log-transformed |              |                  |                   |
| Hemoglobin / unit                          |              |                  |                   |
| Baseline PSA Log-transformed               |              |                  |                   |
| Charlson Score / unit                      |              |                  |                   |
| Gleason Score ≥8 vs <8                     |              |                  |                   |
| Visceral Disease Yes vs No                 |              |                  |                   |
| Opiates Yes vs No                          |              |                  |                   |
| Treatment Enza vs Abi                      |              |                  |                   |
| Concomitant Statins Yes vs No              |              |                  |                   |
| Statin Type Atorvastatin vs Other          |              |                  |                   |
| Simvastatin Equivalent Dose / mg           |              |                  |                   |
| Use of a hydrophilic statin Yes vs No      |              |                  |                   |

### Multivariable Model

| Age / decade                              | All Patients | Abiraterone Only | Enzalutamide Only |
|-------------------------------------------|--------------|------------------|-------------------|
| Alk Phos Log-transformed                   |              |                  |                   |
| Neutrophils/ Lymphocyte Ratio Log-transformed |              |                  |                   |
| Hemoglobin / unit                          |              |                  |                   |
| Baseline PSA Log-transformed               |              |                  |                   |
| Charlson Score ≥10 vs <10                  |              |                  |                   |
| Gleason Score ≥8 vs <8                     |              |                  |                   |
| Visceral Disease Yes vs No                 |              |                  |                   |
| Opiates Yes vs No                          |              |                  |                   |
| Treatment Enza vs Abi                      |              |                  |                   |
| Concomitant Statins Yes vs No              |              |                  |                   |

### 3-Month Landmark Analysis – Multivariable Model

| Age / decade                              | All Patients | Abiraterone Only | Enzalutamide Only |
|-------------------------------------------|--------------|------------------|-------------------|
| Alk Phos Log-transformed                   |              |                  |                   |
| Neutrophils/ Lymphocyte Ratio Log-transformed |              |                  |                   |
| Hemoglobin / unit                          |              |                  |                   |
| Baseline PSA Log-transformed               |              |                  |                   |
| Charlson Score ≥10 vs <10                  |              |                  |                   |
| Gleason Score ≥8 vs <8                     |              |                  |                   |
| Visceral Disease Yes vs No                 |              |                  |                   |
| Opiates Yes vs No                          |              |                  |                   |
| Treatment Enza vs Abi                      |              |                  |                   |

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Table 3: Logistic regression analyses, outcome = early 30% PSA decline

|                                | All Patients | Abiraterone | Enzalutamide |
|--------------------------------|--------------|-------------|--------------|
|                                | N            | OR (95% CI) | P            | N            | OR (95% CI) | P            | N            | OR (95% CI) | P            |
| Age /decade                    | 574          | 1.05 (0.87, 1.27) | 0.63 | 465          | 1.20 (0.96, 1.48) | 0.10 | 109          | 0.60 (0.35, 1.02) | 0.059 |
| Months, Castration-sensitive Disease <12 mos vs ≥12 mos | 376          | 0.77 (0.49, 1.22) | 0.27 | 293          | 0.69 (0.41, 1.17) | 0.17 | 83           | 1.07 (0.40, 2.92) | 0.89 |
| Months, Disease-Metastases <36 mos vs ≥36 mos | 457          | 0.72 (0.49, 1.05) | 0.085 | 360          | 0.62 (0.40, 0.96) | 0.031 | 97           | 1.09 (0.46, 2.54) | 0.85 |
| Alk Phos Log-transformed       | 433          | 1.10 (0.85, 1.41) | 0.49 | 355          | 1.18 (0.89, 1.56) | 0.26 | 78           | 0.74 (0.39, 1.37) | 0.33 |
| LDH Log-transformed            | 255          | 0.72 (0.41, 1.26) | 0.24 | 192          | 0.91 (0.47, 1.75) | 0.78 | 63           | 0.44 (0.14, 1.42) | 0.17 |
| Neutrophils/Lymphocyte Ratio Log-transformed | 516          | 0.99 (0.76, 1.28) | 0.91 | 423          | 0.97 (0.73, 1.30) | 0.86 | 93           | 1.46 (0.68, 3.15) | 0.34 |
| Hemoglobin /unit               | 540          | 1.17 (1.04, 1.32) | 0.008 | 438          | 1.16 (1.01, 1.32) | 0.034 | 102          | 1.15 (0.90, 1.46) | 0.27 |
| Baseline PSA Log-transformed   | 572          | 1.02 (0.91, 1.14) | 0.75 | 464          | 1.03 (0.92, 1.17) | 0.60 | 108          | 1.00 (0.76, 1.32) | 0.99 |
| Charlson Score ≥10 vs <10      | 574          | 1.02 (0.94, 1.12) | 0.62 | 465          | 1.06 (0.96, 1.17) | 0.23 | 109          | 0.86 (0.67, 1.10) | 0.22 |
| Gleason Score ≥8 vs <8         | 520          | 0.58 (0.40, 0.85) | 0.005 | 419          | 0.54 (0.35, 0.83) | 0.005 | 101          | 0.88 (0.39, 2.01) | 0.76 |
| Visceral Disease Yes vs No     | 574          | 0.52 (0.27, 1.00) | 0.50 | 465          | 0.71 (0.33, 1.52) | 0.38 | 109          | 0.32 (0.09, 1.09) | 0.068 |
| Opiate Use Yes vs No           | 571          | 0.92 (0.62, 1.37) | 0.69 | 463          | 0.93 (0.60, 1.44) | 0.74 | 108          | 1.04 (0.38, 2.82) | 0.94 |
| Treatment Enzalutamide vs Abiraterone | 574          | 0.95 (0.61, 1.47) | 0.81 | -            | -            | -            | -            | -            | -            |
| Concomitant Statins Yes vs No  | 574          | 1.46 (1.02, 2.08) | 0.040 | 465          | 1.57 (1.05, 2.34) | 0.030 | 109          | 1.09 (0.48, 2.48) | 0.85 |
| Statin Type Atorvastatin vs Other | 194          | 0.76 (0.40, 1.42) | 0.38 | 154          | 0.77 (0.38, 1.58) | 0.48 | 40           | 0.59 (0.10, 3.59) | 0.56 |
| Dose of Statins /mg             | 122          | 1.00 (0.98, 1.01) | 0.60 | 99           | 1.00 (0.98, 1.02) | 0.93 | 23           | 0.92 (0.84, 1.02) | 0.11 |
| Use of a hydrophilic statin Yes vs No | 173          | 1.06 (0.52, 2.16) | 0.88 | 150          | 1.18 (0.55, 2.55) | 0.67 | 23           | 0.76 (0.10, 5.94) | 0.80 |

Biologically, statins can potentiate the efficacy of anti-androgen treatments, such as abiraterone and enzalutamide, in mCRPC through a number of potential mechanisms, including: inhibition of intra-tumoral de novo steroid biosynthesis [17], inhibition of biosynthesis of isoprenoids [18], as well as inhibition of the organic anionic transporters (e.g., SLCO2B1) [19] that are responsible for adrenal androgen dehydroepiandrosterone (DHEA) influx into cancer cells [20].

In one translational study, Harshman et al. [21] showed that statins impaired DHEA influx through competitive inhibition of the SLCO2B1 transporter both in androgen-dependent (LNCaP) and partially androgen-dependent (22RV1) prostate cancer cell lines. This was supported by their retrospective clinical study of 926 patients, treated with androgen deprivation, which demonstrated that patients who received statin therapy experienced longer median time to progression, when compared to patients not treated with a statin (27.5 versus 17.4 months; P < 0.001). Because abiraterone is also a SLCO2B1 substrate, the same research group [10] hypothesized that statin use could be a negative predictive factor for patients taking abiraterone. However, their retrospective study of 224 abiraterone-treated patients demonstrated that statin use trended toward longer treatment duration (14.2 versus 9.2 months; HR: 0.79,
Despite lack of validation in an independent cohort of 270 abiraterone-treated patients [10], the authors concluded that concomitant stain use did not negatively impact survival.

In our previous retrospective observational study (n = 187 mCRPC patients from 10 participating centers who received abiraterone), statin use was associated with longer OS in univariate (HR = 0.51, 95% CI = 0.37–0.72, P < 0.001) and multivariate analyses (HR = 0.40, 95% CI = 0.27–0.59, P < 0.001). Statin use was also significantly associated with early PSA declines (>50% declines at week 12 in statin users versus non-users: 72.1% vs. 38.5; P < 0.001). This study was limited by several factors, including the relatively small sample size, the lack of information about statin type and statin treatment duration, comorbidities, cardiovascular events, and prostate cancer–specific survival. To overcome these limitations, we designed a retrospective observational study to be conducted in an international setting that could better define concomitant treatment with statins. One of the purposes of the STABEN trial was to assess whether the potential advantage associated with statin use could be related to their known cardiovascular and cerebrovascular protective effect, of particular potential importance in an elderly population receiving abiraterone – an agent with known cardiovascular toxicity [22]. In the present retrospective study, multivariable models that included known prognostic factors in prostate cancer (e.g., baseline

| Table 4: Logistic regression analyses of cardiovascular or cerebrovascular events | All Patients |
|---|---|---|---|
| **Type** |  | **N** | **OR (95% CI)** | **P** |
| Age | /decade | 598 | 2.24 (1.46, 3.46) | <0.001 |
| Months, Castration-sensitive Disease | <12 mos vs ≥12 mos | 390 | 0.55 (0.16, 1.97) | 0.36 |
| Months, Disease-Metastases | <36 mos vs ≥36 mos | 474 | 1.14 (0.51, 2.55) | 0.75 |
| Alk Phos | Log-transformed | 448 | 0.94 (0.54, 1.64) | 0.83 |
| LDH | Log-transformed | 259 | 0.89 (0.26, 3.03) | 0.85 |
| Neutrophils/Lymphocyte Ratio | Log-transformed | 530 | 1.38 (0.81, 2.36) | 0.24 |
| Hemoglobin | /unit | 555 | 1.02 (0.80, 1.31) | 0.85 |
| PSA at Diagnosis | Log-transformed | 587 | 0.94 (0.74, 1.18) | 0.57 |
| Charlson Score | /unit | 598 | 1.54 (1.29, 1.84) | <0.001 |
| | ≥10 vs <10 | 4.51 (1.72, 11.85) | 0.002 |
| Gleason Score | ≥8 vs <8 | 540 | 0.57 (0.27, 1.19) | 0.13 |
| Visceral Disease | Yes vs No | 598 | 0.36 (0.05, 2.71) | 0.32 |
| Opiate Use | Yes vs No | 587 | 0.68 (0.30, 1.54) | 0.35 |
| Treatment | Enalutamide vs Abiraterone | 598 | 0.90 (0.36, 2.23) | 0.82 |
| Concomitant Statins | Yes vs No | 598 | 4.38 (2.08, 9.24) | <0.001 |
| Statin Type | Atorvastatin vs Other | 199 | 1.58 (0.63, 3.96) | 0.33 |
| Dose of Statins | /mg | 123 | 1.02 (0.99, 1.04) | 0.22 |
| Use of a hydrophilic statin | Yes vs No | 176 | 0.73 (0.23, 2.30) | 0.58 |

**Multivariable Analysis**

| **Age** | /decade | 387 | 2.56 (1.11, 5.89) | 0.028 |
| **Alk Phos** | Log-transformed | 139 | 0.61 (3.19) | 0.43 |
| **Neutrophils/Lymphocyte Ratio** | Log-transformed | 124 | 0.52 (2.94) | 0.63 |
| **Hemoglobin** | /unit | 111 | 0.73 (1.70) | 0.62 |
| **PSA at Diagnosis** | Log-transformed | 65 | 0.45 (0.93) | 0.020 |
| **Charlson Score** | ≥10 vs <10 | 156 | 0.43 (5.70) | 0.50 |
| **Gleason Score** | ≥8 vs <8 | 77 | 0.24 (2.46) | 0.66 |
| **Visceral Disease** | Yes vs No | 64 | 0.07 (6.28) | 0.70 |
| **Opiate Use** | Yes vs No | 72 | 0.22 (2.38) | 0.59 |
| **Treatment** | Enalutamide vs Abiraterone | 58 | 0.12 (2.78) | 0.50 |
| **Concomitant Statins** | Yes vs No | 3.24 | 1.15 (9.17) | 0.027 |

95% CI, 0.57–1.09, P = 0.14). Despite lack of validation in an independent cohort of 270 abiraterone-treated patients [10], the authors concluded that concomitant stain use did not negatively impact survival.
Data analysis

Summary statistics were used to describe patient outcomes. Time-to-event outcomes were calculated from the first date of treatment with abiraterone or enzalutamide.

The primary objective of this study was to determine whether concomitant statin therapy was predictive of OS improvement for mCRPC patients treated with second-line abiraterone or enzalutamide. The secondary objective of the study was to determine whether concomitant statin therapy was predictive of early (>30% PSA decline) >30% PSA declines. The Kaplan-Meier method was used to estimate differences in survival between mCRPC patients treated who did and did not receive statin therapy, while Cox proportional hazards regression was used to investigate prognostic factors of overall survival. Logistic regression was used to investigate predictive factors of early >30% PSA declines. Using Cox proportional hazards, multivariable models were constructed to examine the effects of concomitant statins after adjusting for all other potential sources of variation. However, there were large numbers of missing data for some factors. Thus, a priori,
it was decided to include only those factors which had <30% missing data and were significant on univariate analysis, or those factors with <15% missing data overall. The impact of statins was then assessed after adjusting for factors included in the multivariable model. Supportive analyses were performed by including only those treated with abiraterone (~80% of the cohort), only those treated with enzalutamide, by performing a cancer-specific survival analysis and by performing a landmark analysis using 3-months as the landmark time. For the purposes of the landmark analysis, any patient who was not prescribed statin therapy at the time of abiraterone or enzalutamide initiation, experienced interruption of statin therapy, or received less than 3 months of statin therapy, was deemed to not have received statins. Data modifications were performed for statistical purposes. Specifically, a logarithmic transformation was used on covariates which were highly non-normal. Duration from prostate cancer diagnosis to detection of metastases, and duration of prostate cancer diagnosis to determination of castration-resistant disease were dichotomized. All analyses included site as a stratification factor. All tests were two-sided and a p-value of 0.05 or less was considered statistically significant. No p-value adjustments were performed due to multiple testing; however, inferences were performed understanding that multiple analyses were performed.

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CONFLICTS OF INTEREST

Omlin Aurelius: AO Advisory role (compensated, institutional): Astra Zeneca, Astellas, Bayer, Janssen, MSD, Pfizer, Roche, Sanofi Aventis. Research support (institutional): Teva, Janssen. Travel support: Astellas, Bayer, Sanofi Aventis

Silke Gillesen: Speaker bureau (uncompensated, institutional): Astellas, Roche and Sanofi; Speaker bureau (compensated, institutional): Ferring, Janssen, Novartis; Consultant (compensated, institutional): AAA International; Astellas; Bayer; Bristol-Myers Squibb; Clovis; CureVac; Ferring; Janssen; MaxiVax SA; Roche; Sanofi; Consultant (uncompensated, institutional): ESSA Pharmaceuticals; Nectra; ProteoMediX

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All other authors declare they have nothing to disclose.

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