PSA Kinetics as Prognostic Markers of Overall Survival in Patients with Metastatic Castration-Resistant Prostate Cancer Treated with Abiraterone Acetate

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Background: Abiraterone acetate (AA) is widely used in the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC). However, a significant percentage of patients will still progress, highlighting the need to identify patients more likely to benefit from AA. Parameters linked to prostate-specific antigen (PSA) kinetics are promising prognostic markers. We have examined clinical and PSA-related factors potentially associated with overall survival (OS) in patients treated with AA.

Methods: Between 2011 and 2014, 104 patients with mCRPC treated with AA after progression to docetaxel at centers of the Catalan Institute of Oncology were included in this retrospective study. Patients were assessed monthly. Baseline characteristics and variables related to PSA kinetics were included in univariate and multivariate analyses of OS.

Results: Median OS was 16.4 months (range 12.4–20.6) for all patients. The univariate analysis identified the following baseline characteristics as significantly associated with OS: ECOG PS, location of metastases, time between starting androgen deprivation therapy and starting AA, time between stopping docetaxel treatment and starting AA, neutrophil-lymphocyte ratio (NLR), alkaline phosphatase levels, and PSA levels. Factors related to PSA kinetics associated with longer OS were PSA response >50%, early PSA response (>30% decline at four weeks), PSA decline >50% at week 12, PSA nadir <24.2ng/mL, time to PSA nadir >140 days, the combination of PSA nadir and time to PSA nadir, and low end-of-treatment PSA levels. The multivariate analysis identified ECOG PS (HR 37.46; p<0.001), NLR (HR 3.7; p<0.001), early PSA response (HR 1.22; p=0.002), and time to PSA nadir (HR 0.39; p=0.002) as independent prognostic markers.

Conclusion: Our results indicate an association between PSA kinetics, especially early PSA response, and outcome to AA after progression to docetaxel. Taken together with other factors, lack of an early PSA response could identify patients who are unlikely to benefit from AA and who could be closely monitored with a view to offering alternative therapies.

Keywords: castration-resistant prostate cancer, abiraterone, PSA kinetics, survival, early PSA response.

Introduction

The treatment armamentarium of metastatic castration-resistant prostate cancer (mCRPC) has increased in recent years with the FDA/EMA approval of hormonal therapies like abiraterone acetate (AA) and enzalutamide, cytotoxic therapies like cabazitaxel,1 and bone-targeted therapies like Radium-223.2,3 Given the increase in
treatment options for mCRPC, the selection of optimal therapeutic regimens is crucial for obtaining the maximum survival benefit. Predictive biomarkers of response can help in the selection of an effective treatment while avoiding unnecessary toxicities and excess costs associated with a potentially ineffective drug.

AA is a prodrug of abiraterone and is a selective, irreversible inhibitor of the androgen biosynthesis enzyme CYP17, which is involved in androgen production in the testes, adrenal glands and prostate tumor tissue. AA in combination with prednisone has demonstrated an increase in overall survival (OS) in patients with mCRPC and is approved for patients who progress during or after docetaxel-based chemotherapy, in chemotherapy-naïve patients, and in metastatic castration-sensitive patients. However, approximately one-third of treated patients show primary resistance to AA, highlighting the need for early identification of these patients in order to offer them an alternative therapy before progression-related clinical deterioration renders them ineligible for subsequent therapy, including chemotherapy.

Several studies have suggested a relationship between decrease in prostate-specific antigen (PSA) levels and survival, mainly in chemotherapy treated mCRPC patients. However, the role of PSA decline as a surrogate marker of survival in patients treated with hormonal therapies has not been clearly established. Biosynthesis of extragonadal androgens may contribute to progression in mCRPC, which still depends on androgen receptor signals, and a relationship between PSA kinetics and response to AA has been suggested, indicating that PSA kinetics may be a useful predictive biomarker of response.

In order to shed further light on the potential association of baseline patient characteristics and PSA kinetics with OS, we have performed a retrospective study of 104 mCRPC patients treated with AA after progression to docetaxel.

**Patients and Methods**

**Study Design and Patient Population**

This was a retrospective observational study that included 104 mCRPC patients treated at three centers of the Catalan Institute of Oncology (University Hospital of Germans Trias i Pujol, Badalona; Bellvitge University Hospital, l’Hospitalet de Llobregat; and University Hospital of Girona Doctor Josep Trueta, Girona) from August 2011 to October 2014. All patients had histologically confirmed prostate adenocarcinoma with evidence of metastatic disease and all had been previously treated with docetaxel. Patients received AA 1000mg orally once daily plus prednisone 5mg twice daily. Each treatment cycle was 28 days. Treatment was continued until disease progression according to the Prostate Cancer Working Group 2 (PCWG2) criteria, death, or unacceptable toxicity.

During treatment with AA, patients were assessed every four weeks. Clinical visits included a physical examination and routine laboratory analyses, including PSA levels, albumin, alkaline phosphatase (ALP) levels, neutrophil and lymphocyte counts, and hemoglobin levels. Thoracic-abdominopelvic computed tomography (CT) and/or a bone scan were performed before starting AA therapy and during the treatment period in accordance with the protocols of each center.

The following baseline variables were recorded and patients classified accordingly: age (<74 vs ≥74 years), Eastern Cooperative Oncology Group (ECOG) performance status (PS) (0 vs 1 vs 2), number of previous lines of chemotherapy (1 vs ≥2), metastatic sites (bone only vs lymph node only vs bone and lymph nodes vs visceral), Gleason score (≤7 vs 8–10), neutrophil-to-lymphocyte ratio (NLR) (≤4 vs >4), hemoglobin levels (<10 gr/dl vs ≥10 gr/dl), ALP levels (<upper limit of normality [ULN] vs >ULN), PSA levels (classified by terciles), PSA doubling time (PSADT) (≤3 months vs >3 months), interval between starting androgen deprivation therapy and starting AA (≤20 months vs >20 months), interval between stopping docetaxel therapy and starting AA (≤3 months vs >3 months), and type of progression (PSA progression vs radiographic progression vs clinical deterioration). PSADT was calculated with the Memorial Sloan Kettering online calculator. NLR was the ratio of the absolute neutrophil count divided by the absolute lymphocyte count.

The following data regarding PSA kinetics were recorded during AA treatment: PSA response (>50% vs <50%); early PSA response, defined as the percentage of PSA decline at week 4 (decline ≥30% vs decline <30% or increase <20% vs increase >20%); PSA response at week 12 (>50% vs <50%); PSA nadir (≥2.4 ng/mL vs <2.4 ng/mL); time to PSA nadir; and end-of-treatment (EOT) PSA levels, defined as the levels at the last PSA assessment during AA treatment (classified by terciles).

**Statistical Analyses**

Data were recorded with Microsoft Excel 2007 and statistical analyses were carried out using R v3.6.0. We built
a multivariate model starting with all untransformed variables after excluding those exceeding 15% of individuals (for which there were insufficient numbers of observations). Data were imported from Excel into R with the readxl R package. Prior to analysis, data wrangling and cleaning was performed with the tidyverse suite of packages (including dplyr, purr, lubridate, stringr, and broom). Descriptive statistics including missing data were collected and visualized with the skimr and rms R packages. Data were described in terms of ranges, medians, frequencies, and percentages. OS was defined as the time from the start of AA treatment to death from any cause. Data were censored at the time of patient death. Optimal cut-off points for possible categorical transformations were identified with the survminer R package. A univariate analysis was performed to determine the association of different factors with OS and Kaplan Meier plots were generated using the survival R package. Due to limitations in sample size, not all variables identified as significant in the univariate analysis could be included in the multivariate analysis. After imputing missing data with the Hmisc R package, a variable selection strategy was followed based on elastic net Cox proportional hazards model fitting via penalized maximum likelihood, using the glmnet R package. This was followed by AIC maximization stepwise backward variable elimination towards model reduction. All models generated on imputed data were tested against intact data. An internal cross-validation was performed by bootstrapping with 200 iterations. Imputation, Cox modeling, stepwise model selection and model validation, were done using the rms R package. Recursive tree partitioning was explored using the party R package. Significance was set at p≤0.05.

**Results**

**Patient Characteristics and Treatment**

The main patient characteristics are detailed in Table 1. Median age was 74 years (range, 49–86), 82% of patients had ECOG PS 0–1, and 51.9% had a Gleason score ≥8. Bone metastases were present in 49% of the patients, while 11.6% had only lymph node metastases and 9.7% had visceral metastases. All patients had previously been treated with docetaxel and 32% had received two or more prior chemotherapy regimens.

| Characteristic                          | N (%) |
|----------------------------------------|-------|
| Age                                    |       |
| < 74 y                                 | 54 (51.9) |
| ≥ 74 y                                 | 50 (48.1) |
| Median age, years (range)              | 74 (49–86) |
| ECOG PS                                |       |
| 0                                      | 19 (18.2) |
| 1                                      | 67 (64.5) |
| 2                                      | 18 (17.3) |
| Gleason score                          |       |
| < 8                                    | 35 (33.7) |
| ≥ 8                                    | 54 (51.9) |
| Not available                          | 15 (14.4) |
| Location of metastases                 |       |
| Lymph node only                        | 12 (11.6) |
| Bone only                              | 51 (49) |
| Bone and lymph node                    | 30 (28.8) |
| Visceral                               | 10 (9.7) |
| Not available                          | 1 (0.9) |
| Previous lines of chemotherapy         |       |
| 1                                      | 70 (67.3) |
| ≥2                                     | 34 (32.7) |
| NLR                                    |       |
| < 4                                    | 25 (24.03) |
| ≥4                                     | 75 (72.11) |
| Hemoglobin levels                      |       |
| <10 g/dL                               | 84 (80.7) |
| ≥10 g/dL                               | 20 (19.3) |
| Median (range)                         | 14.9 (7.5–130) |
| ALP levels                             |       |
| ≤ULN                                   | 58 (55.8) |
| >ULN                                   | 40 (38.4) |
| Not available                          | 6 (5.8) |
| Median (range)                         | 183.07 (0.98–1127) |
| PSA levels by terciles                 |       |
| Low                                    | 39 (37.5) |
| Intermediate                           | 42 (40.4) |
| High                                   | 22 (21.2) |
| Not available                          | 1 (0.9) |
| Median ng/mL (range)                   | 284.6 (0.5–6947) |

**Abbreviations:** ECOG PS, Eastern Cooperative Oncology Group performance status; NLR, neutrophil-to-lymphocyte ratio; ALP, alkaline phosphatase; PSA, prostate-specific antigen.

Median duration of treatment was 7.85 months (range, 1–52 months). At the time of this analysis, 96 patients (92%) had died. Median OS was 16.4 months (95% confidence interval [CI] 12.2–20.6) for all patients (Figure 1A) and 1-year and 2-year survival rates were 66% and 33%, respectively. Median progression-free survival was 7.8 months (95% CI 5.9–9.6) (Figure 1B).
Prognostic Impact of PSA Kinetics

Table 3 shows the univariate analysis of OS according to factors related to PSA kinetics. PSA response >50% (p<0.001), early PSA response ≥30% (p=0.01; Figure 3), PSA response >50% at week 12 (p<0.001), PSA nadir <2.4ng/mL (p<0.001), time to PSA nadir >140 days (p<0.001), and low EOT PSA levels (p<0.001) were associated with longer OS. In addition, we observed a combinatorial effect for PSA nadir plus time to PSA nadir, where patients with lower PSA nadir and longer time to PSA nadir had the longest OS (hazard ratio [HR] 0.57; 95% CI 1.43–1.75; p< 0.001) (Figure 4).

The multivariate analysis identified ECOG PS (HR 37.46; p<0.001), NLR (HR 3.7; p<0.001), early PSA response (HR 1.22; p=0.002), and time to PSA nadir (HR 0.39; p=0.002), as independent markers of OS (Table 4). Based on these findings, we generated a decision tree for survival analysis in mCRPC, which indicated that baseline ECOG PS and NLR combined could predict OS (Figure 5).

Discussion

Several treatment options are now available for mCRPC. Novel hormonal therapies, including AA, have demonstrated activity in patients previously treated with docetaxel, but other therapies, such as cabazitaxel or radium-223, can be useful in patients refractory to hormonal therapies. Primary resistance to AA in pre-docetaxel mCRPC patients is near 20%, and the identification of patients with primary resistance may help avoid ineffective treatments. In the present study, we have examined the impact on OS of several baseline characteristics and parameters related to PSA kinetics in patients with mCRPC treated with AA. The multivariate analysis identified two baseline characteristics (ECOG PS and NLR) and two variables associated with PSA kinetics (early PSA response and time to PSA nadir) as independent markers of OS.

Our patients were treated off-study, yet OS was within the range of that reported in the COU-AA-302 trial, despite the fact that a higher percentage of our patients had PS 2 (17% vs 10%). In the COU-AA-301 trial, ECOC PS >1, presence of liver metastases, time between starting androgen deprivation therapy and starting AA >36 months, low serum albumin, and high serum ALP and LDH levels were associated with a poorer outcome to AA. Our findings regarding ECOG PS, time between

Baseline Characteristics and OS

In the univariate analysis, the following baseline characteristics were associated with longer OS: ECOG PS <2 (p<0.001) (Figure 2A); only lymph node metastases (p=0.04); interval between starting androgen deprivation therapy and starting AA ≥20 months (p=0.006); interval between stopping docetaxel and starting AA ≥3 months (p=0.04); NLR <4 (p<0.001) (Figure 2B); ALP levels ≤ULN (p=0.03); and low/intermediate PSA levels (p<0.001). No other significant association between baseline characteristics and OS was observed (Table 2).
starting androgen deprivation therapy and starting AA, and ALP levels were in line with these results. In addition, however, we found that low NLR, low baseline PSA levels, the absence of bone metastases, and high hemoglobin levels were also associated with longer OS.

NLR is a marker of inflammation and immune status related to carcinogenesis, and its role as a potential prognostic and predictive marker has been evaluated in many solid tumors, including mCRPC. In a study carried out at the Princess Margaret Cancer Centre, NLR ≥5 was significantly associated with PSA response and survival in 116 patients with mCRPC treated with AA, 53% of whom had previously been treated with docetaxel. NLR has also been identified as a prognostic marker in patients with mCRPC treated with second-line chemotherapy. Furthermore, a persistent NLR <3 during treatment with enzalutamide was associated with greater treatment efficacy in patients with mCRPC. Taken together with these previous results, our finding in the present study that a high NLR was related to shorter OS suggests that NLR is a promising prognostic marker and leads us to postulate that NLR in combination with ECOG PS can be a useful prognostic marker in patients with mCRPC. Whereas in patients with PS 0 and PS 2, survival is well defined, in the intermediate group of patients with PS 1, NLR can be useful in selecting which patients are likely to benefit from AA, especially as NLR assessment can easily be incorporated into routine clinical practice.

In contrast, age and Gleason score were not associated with OS. In fact, AA has demonstrated activity in mCRPC regardless of patient age, and several studies have found that Gleason score may well lose prognostic impact in heavily pretreated mCRPC patients. Additionally, the number of prior chemotherapy lines was not associated with OS. More than 50% of our patients who had received a second line of chemotherapy before AA were treated with docetaxel, in accordance with common practice at that time, and the interval between ending docetaxel and starting AA was more highly associated with OS than the number of previous lines.

The prognosis of mCRPC patients ranges from a few months to several years and is influenced by multiple factors. Several studies have identified predictive biomarkers of resistance to hormonal therapies. For example, Wnt pathway genes have been associated with resistance to AA and baseline circulating tumor cell counts have also shown promise as prognostic markers. Our findings on PSA kinetics can further refine these biomarker-based data and can be used in routine clinical practice to identify patients likely to be resistant to AA.

PSA nadir and time to PSA nadir were also associated with OS in our study. Previous studies have also reported the impact of these factors on OS, in both chemotherapy- and hormonotherapy-treated patients. Along these same lines, our univariate analysis revealed an association.
| Characteristic                              | Median OS (Months) | 95% CI         | p-value* |
|--------------------------------------------|--------------------|----------------|----------|
| **ECOG PS**                                |                    |                |          |
| 0                                          | 27.72              | 19.55–36.36    | <0.001   |
| 1                                          | 19.33              | 14.83–24.33    |          |
| 2                                          | 6.02               | 5.29–11.9      |          |
| **Age**                                    |                    |                |          |
| < 74 years                                 | 20.28              | 15.39–27.75    | 0.531    |
| ≥ 74 years                                 | 13.68              | 11.21–21.21    |          |
| **Previous lines of chemotherapy**         |                    |                |          |
| 1                                          | 17.56              | 13.58–24.33    | 0.497    |
| ≥2                                         | 15.99              | 13.64–22.92    |          |
| **Location of metastases**                 |                    |                |          |
| Lymph node only                            | 34.41              | 22.92–NR       | 0.043    |
| Bone only                                  | 14.83              | 13.48–21.44    |          |
| Bone and lymph node                        | 18.08              | 12.16–25.02    |          |
| Visceral                                   | 8.02               | 4.41–NR        |          |
| **Gleason score**                          |                    |                |          |
| <8                                         | 14.83              | 11.9–21.53     | 0.503    |
| ≥8                                         | 17.56              | 13.58–23.01    |          |
| **Time between starting androgen deprivation therapy and starting AA** |        |                |          |
| <20 months                                 | 9.37               | 8.02–NR        | 0.006    |
| ≥20 months                                 | 16.9               | 14.4–21.99     |          |
| **Time between stopping docetaxel and starting AA** |        |                |          |
| <3 months                                  | 12.26              | 7.17–21.21     | 0.04     |
| ≥3 months                                  | 18.08              | 14.4–21.99     |          |
| **NLR**                                    |                    |                |          |
| <4                                         | 21.21              | 16.47–27.02    | <0.001   |
| ≥4                                         | 12.99              | 8.02–16.27     |          |
| **Hemoglobin levels**                      |                    |                |          |
| <10 g/dL                                   | 11.56              | 9.21–21.21     | 0.063    |
| ≥10 g/dL                                   | 19                 | 14.66–24.33    |          |
| **ALP levels**                             |                    |                |          |
| ≤ULN                                       | 16.9               | 14.1–26.43     | 0.025    |
| >ULN                                       | 13.64              | 11.9–22.06     |          |
| **PSA levels by terciles**                 |                    |                |          |
| Low (<54 ng/mL)                            | 21.35              | 13.64–39.32    | <0.001   |
| Intermediate (54–293 ng/mL)                | 21.21              | 16.47–28.41    |          |
| High (>293 ng/mL)                          | 11.9               | 8.91–17.56     |          |

Note: *Significant p-values are shown in bold.

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; NLR, neutrophil-to-lymphocyte ratio; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; ULN, upper limit of normal; PSA, prostate-specific antigen; NR, not reached.
able to predict 30% PSA decline. Based on our findings in the present study, we propose a decision tree for survival analysis based on the variables of ECOG PS and NLR, both of which are easily collected from all patients. We plan to test the validity of our proposal in future studies.

### Table 3 Univariate Analysis of Overall Survival (OS) According to Prostate-Specific Antigen (PSA) Kinetics

| Parameter | N (%) | Median OS (Months) | 95% CI | p-value |
|-----------|-------|--------------------|--------|---------|
| PSA response >50% | | | | |
| No | 52 (50) | 12.36 | 9.21–16.47 | <0.001 |
| Yes | 52 (50) | 22.06 | 18.08–28.41 | |
| Early PSA response (at week 4)* | | | | |
| ≥30% decrease | 45 (43.3) | 21.53 | 18.08–28.41 | |
| <30% decrease or <20% increase | 18 (17.3) | 14.25 | 8.12–28.34 | |
| >20% increase | 33 (31.7) | 13.48 | 8.91–20.28 | 0.012 |
| PSA response at week 12* | | | | |
| >50% | 36 (34.6) | 25.35 | 20.38–28.67 | <0.001 |
| <50% | 15 (14.4) | 12.97 | 9.47–16.47 | |
| PSA nadir* | | | | |
| ≥2.4 ng/mL | 69 (66.3) | 14.66 | 12.16–19.33 | <0.001 |
| <2.4 ng/mL | 17 (16.3) | 30.87 | 21.99-NR | |
| Time to PSA nadir* | | | | |
| ≤140 days | 53 (51) | 13.64 | 10.65–16.47 | <0.001 |
| >140 days | 22 (21.1) | 28.34 | 22.06–46.82 | |
| EOT PSA* | | | | |
| Low (≤54 ng/mL) | 39 (37.5) | 25.35 | 20.71–29.49 | <0.001 |
| Intermediate (54–293 ng/mL) | 42 (40.4) | 16.68 | 13.68–24.33 | |
| High (>293 ng/mL) | 22 (21.2) | 10.08 | 7.2–16.27 | |

**Note:** Details of PSA kinetics were not available for all patients.

**Abbreviations:** EOT, end of treatment; NR, not reached.

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**Figure 3** Overall survival according to early PSA response (at week 4).

**Figure 4** Overall survival according to PSA nadir plus time to PSA nadir.
As with all retrospective studies, our results must be interpreted with caution and should be validated in prospective studies including a larger number of patients. Our study has several limitations, such as the limited number of patients included and a number of patients with some missing data. Despite these limitations, however, our findings indicate that NLR can be a useful baseline marker to predict outcome in patients with mCRPC treated with AA and that early PSA response to AA may be a useful marker of treatment efficacy. While an early change in PSA is generally not a sufficient reason for modifying treatment in clinical trials, we propose to closely monitor patients with an early PSA increase during AA treatment, as well as taking into account other prognostic and predictive markers, when deciding on next treatment options.

**Patient Consent**

For this type of study, formal consent is not required.

**Data Sharing Statement**

Supporting data for this study is freely available upon request to the corresponding author.

**Ethics Approval**

This study was approved by the Ethics Committees of the Catalan Institute of Oncology at University Hospital of Germans Trias i Pujol (PI 16-183). This approval covers all three centers of the Catalan Institute of Oncology. The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All patient data were anonymized and

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**Table 4 Multivariate Analysis of Overall Survival**

| Variable                        | Hazard Ratio (95% CI) | p-value |
|---------------------------------|-----------------------|---------|
| **Baseline Characteristics**    |                       |         |
| **ECOG PS**                     |                       |         |
| 0                               | 1.00 (Ref)            |         |
| 1                               | 3.30 (1.54–7.09)      | 0.002   |
| 2                               | 37.46 (10.77–130.21)  | <0.001  |
| **NLR**                         |                       |         |
| <4                              | 1.00 (Ref)            |         |
| ≥4                              | 3.70 (1.77–7.74)      | <0.001  |
| **PSA Kinetics**                |                       |         |
| **Early PSA response (at week 4)** |                   |         |
| Response                        | 1.00 (Ref)            |         |
| No response                     | 1.22 (1.07–1.38)      | 0.002   |
| **Time to PSA nadir**           |                       |         |
| ≤140 days                       | 1.00 (Ref)            |         |
| ≥140 days                       | 0.39 (0.21–0.73)      | 0.002   |

**Abbreviations:** NLR, neutrophil-to-lymphocyte ratio; PSA, prostate-specific antigen.

As with all retrospective studies, our results must be interpreted with caution and should be validated in prospective studies including a larger number of patients. Our study has several limitations, such as the limited number of patients included and a number of patients with some missing data. Despite these limitations, however, our findings indicate that NLR can be a useful baseline marker to predict outcome in patients with mCRPC treated with AA and that early PSA response to AA may be a useful marker of treatment efficacy. While an early change in PSA is generally not a sufficient reason for modifying treatment in clinical trials, we propose to closely monitor patients with an early PSA increase during AA treatment, as well as taking into account other prognostic and predictive markers, when deciding on next treatment options.

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**Figure 5 Decision tree for survival of prostate cancer patients, showing ECOG PS and NLR at the beginning of abiraterone acetate treatment.**
codified to ensure adequate compliance with the Spanish Data Protection Law 15/1999 and Royal Decree-Law 5/2018 of 27 July on urgent measures for the adaptation of Spanish law to European Union regulations on data protection. All data are stored in the Medical Oncology Service of the ICO-Badalona, Germans Trias i Pujol University Hospital.

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**Disclosure**

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