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Prognostic role of the duration of response to androgen deprivation therapy in patients with metastatic castration resistant prostate cancer treated with enzalutamide or abiraterone acetate

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- 1 Prognostic role of the duration of response to androgen deprivation
- 2 therapy in patients with metastatic castration resistant prostate cancer
- **3 treated with Enzalutamide or Abiraterone Acetate**
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# 21 Conflict of Interest

- This research did not receive any specific grant from funding agencies in the public, commercial, or
- 23 not-for-profit sectors.

- 24 **Abstract**:
- 25 **Background:** Our retrospective study aims to evaluate the prognostic role of duration of response
- to androgen deprivation therapy (ADT) in metastatic castration resistant prostate cancer (mCRPC)
- 27 patients treated with enzalutamide (E) or (AA).
- 28 Materials and Methods: Patients were divided in 3 groups according to ADT response (group 1
- 29 [G1]:<12 months; group 2 [G2]: 12-36 months; group 3 [G3]: >36 months). Outcome measures
- were progression-free survival (PFS) and overall survival (OS).
- 31 **Results:** Patients with longer ADT response had better OS (median 17.3 months G1, 19.9 months
- 32 G2, 31.6 months G3; HR G3 vs G1 0.41, 95%CI 0.25-0.64; p= 0.001) and better PFS (median 5.9 m
- 33 G1, 8.8 months G2, 11.7 months G3; HR G3 vs G1 0.41, 95%CI 0.41-0.27; p<0,001). In docetaxel
- naive patients, median OS was 18.8 in G1, 35.2 in G2 and not reached in G3 (HR G3 vs G1 0.33,
- 35 95%CI 0.14-0.78; p = 0.038), median PFS was 7 months G1, 9.3 months G2 and 20 months G3 (HR
- 36 G3 vs G1 0.31, 95%CI 0.15-0.62; p = 0.003). In post-docetaxel patients median OS was 13.1 months
- in G1, 17.2 months in G2 and 21.4 months in G3 (HR G3 vs G1 0.52, 95%CI 0.29-0.94; p = 0.082),
- while median PFS was 5.2 months in G1, 6.8 months in G2 and 8.3 months in G3 ( HR G3 vs G1
- 39 0.54, 95%CI 0.32-0.91; p = 0.067).
- 40 **Conclusions:** Duration of ADT response is an independent prognostic factor of outcome with AA or
- 41 E.

- 42 **Keywords:** castration resistant prostate cancer; androgen deprivation therapy; abiraterone
- 43 acetate; enzalutamide; prognosis.

## Introduction:

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Androgen deprivation therapy (ADT) is the mainstay of therapy for metastatic prostate cancer (PC) patients<sup>1</sup>. Unfortunately, many patients eventually progress to the castrate-resistant prostate cancer (CRPC) phase<sup>2</sup>. Despite the therapeutic effects of new hormonal agents (NHAs) in CRPC, a significant percentage of patients are primarily resistant or acquire resistance. About  $\frac{1}{3}$  30% of patients treated with abiraterone acetate (AA)<sup>5</sup> and <del>20% of those treated with</del> Enzalutamide (E)<sup>8</sup> develop a disease progression within three months from initiation. Considering the lack of headto-head studies comparing the different therapeutic agents, guiding the choice of the most effective drug for each patient, there is an urgent need to identify prognostic factors of response to NHAs. Several prognostic models have been developed to predict overall survival (OS)<sup>10-17</sup> in mCRPC patients. In particular, Halabi's model<sup>12</sup> included eight variables: Eastern Cooperative Oncology Group Performance Status (ECOG PS), albumin, haemoglobin, prostate specific antigen (PSA), Alkaline phosphatase (ALP), lactate dehydrogenase (LDH) level and opioids use<sup>13</sup>. Recently, Armstrong at al (Annals 2018 e Eur Ur 2020), analyzing patients from PREVAIL trial, published an internally validated prognostic model that stratifies men with mCRPC into three risk groups. This model identified 11 key independent OS prognostic factors, and included a nomogram and a risk group calculator for predicting 1-, 2-, and 3-yr for patients with mCRPC treated with enzalutamide in the PREVAIL trial. Some clinical data indicate that the duration of ADT response influences outcome of first-line NHAs therapy<sup>13-21</sup> in mCRPC patients. Giacinti et al.<sup>18</sup> showed that the duration of ADT response did not affect progression-free survival (PFS) in 59 patients treated with AA. Conversely, the studies by Loriot<sup>19</sup> and McKay<sup>20</sup> demonstrated that a duration of ADT response less than 12 months worsened median overall response and OS in mCRPC patients and the COU-AA02 trial showed an increased radiographic PFS in patients with longer prior exposure to ADT within both treatment groups<sup>21</sup>. Nakabayashi et al<sup>22</sup> showed that those who had received

ADT more than 24 months received secondary next-generation hormonal therapy for a median duration of 40.0 months, whereas men who had developed resistance to ADT in less than 24 months had a median therapy duration of 18.4 months (P < .0001). Li et al<sup>23</sup> demonstrated that longer ADT duration correlated with better OS and greater PFS in a series of 64 patients treated with AA. Similarly, other small series <sup>24-26</sup> demonstrated that the duration of primary ADT could represent a predictive factor of response to AA or E. Moreover, it is well defined as AR play a main role in CRPC. NHAs interfere with AR pathway inhibiting the PC androgens synthesis (31,32) or preventing AR translocation (33). Considering these mechanisms, PC that are less dependent on AR signalling might be expected to have shorter ADT response duration, as an index of hormone responsiveness of disease, and worse outcomes with subsequent AR-targeted therapy. The aim of this work is to evaluate the role of ADT response duration as prognostic factor in patients with mCRPC treated with NHAs, both in chemo-naive and chemo-pretreated patients.

#### Materials and methods

83 Population

All mCRPC patients treated at the Division of Medical Oncology at San Luigi Gonzaga Hospital in Orbassano (Turin) between January 2010 and December 2018 who received AA or E were evaluated for eligibility for this retrospective study. If patients received both AA and E, only data of the first NHA treatment were considered in this analysis. CRPC was defined as disease progression despite ADT and may present as either a continuous rise in serum PSA levels with serum testosterone <50 ng/dL with/without the progression of pre-existing disease and/or the appearance of new metastases. All patients were treated with continuous ADT (LHRH agonist or antagonist). ADT response duration was defined as the time from the start of the ADT until the onset of the CRPC.

The baseline data collected were: treatment setting (docetaxel-naïve or docetaxel-pretreated), new generation hormonal drug (AA or E), age, ECOG PS, PSA, hemoglobin, albumin, ALP, LDH, analgesic opioids use, presence of visceral metastases. We collected outcome and follow-up data including best biochemical (PSA) response, date of disease progression, type of disease progression (clinical, instrumental, or biochemical), and date of death or date of last follow-up visit.

98 Statistical analysis

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For this analysis, patients were categorized in three groups according to ADT duration of response: group 1 (progression within 12 months), group 2 (progression between 12 and 36 months) and group 3 (progression after 36 months). Descriptive statistics for the patient groups were reported as percentages for categorical variables, and as median and range for continuous variables. We used  $\chi^2$ -test or Fisher exact test (as appropriate) for categorical variables and Wilcoxon-Mann-Whitney test for continuous variables to compare baseline characteristics among prognostic groups. The outcome measures were PFS and OS. PFS was defined as the time from the date of NHA treatment beginning to the date of clinical, biochemical and/or instrumental progression, or the date of death for patients who died without known progression, or the last date of follow-up for patients alive without progression. OS was defined as the time from the date of NHA treatment beginning to the date of death, or the last date of follow-up for alive or lost patients. The Kaplan-Meier method was used to calculate PFS and OS; the log rank test was used to compare the outcome among groups. The comparison among the groups was carried out in the overall population (patients treated with AA or E, in the Docetaxel-naïve setting or Docetaxel-pretreated); in the subgroups of patients treated with AA or E in the Docetaxel-naïve setting; in the subgroup of patients treated with AA or E pre-treated with Docetaxel. To assess the prognostic role of ADT duration, univariable and multivariable analysis were conducted, using the Cox regression model. To perform multivariable analysis, we considered all parameters validated in Halabi's nomogram,

presence or absence of visceral metastases, new-generation hormonal drug (AA or E) and treatment settings (Docetaxel-naive or Docetaxel-pretreated). All statistical tests were 2-tailed and P values < .05 were considered statistically significant. Subgroup analyses were exploratory and no correction for multiple testing was performed. Analyses were done with IBM SPSS for Windows, Version 25.0.

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#### Results

Overall, data about ADT start and duration were available in 255 (82%) of 311 patients treated with AA or E. Baseline characteristics of eligible patients are described in table 1. In detail, 140 (54.9%) received AA and 115 patients (45.1%) received E. The median age was 73 years (range: 50-89 years). 118 patients (46.3%) had been treated with docetaxel before the administration of NHA, while the remaining 137 (53.7%) were docetaxel-naïve. Use of AA and E was significantly unbalanced between the 2 settings: namely, 61.4% of patients treated with AA were pretreated with docetaxel, vs. 27.8% of patients treated with E. About 95% of patients had ECOG PS 0 or 1 at baseline. Patients with visceral metastases were 32 (12.6%), and 74 (32.6%) patients were assuming opioids to control pain. Median ADT duration response was 31.0 months (0.36-250.1).Table 2 shows patients baseline characteristics divided into three populations: 41 (16.1%) patients in group 1(17 in docetaxel-naïve and 24 in post-Docetaxel setting), 106 (41.6%) patients in group 2(61 in docetaxel-naïve and 45 in post-Docetaxel setting) and 108 (42.4%) patients in group 3 (59 in docetaxel-naïve and 49 in post-Docetaxel setting). We found statistically significant differences between the three groups in age (p <0.001), opioids use (p = 0.030), baseline ALP (p = 0.014) and baseline LDH (p = 0.006). The baseline differences in opioid use suggest that the groups might be 140 mismatched for other factors not measured. Namely, patients with longer ADT duration were 141 significantly older, with lower values of baseline ALP and LDH and were assuming less opioids. 142 Overall Survival Kaplan-Meier curves for OS according to duration of ADT response category are shown in figure 143 1a. Median OS was 17.3 months in group 1 (95%CI, 8.9 - 25.6), 19.9 months in group 2 (95%CI, 144 145 12.8 - 27.1) and 31.6 months in group 3 (95%CI, 19.3 – 43.9). Probability of being alive at 24 months was 31.3%, 45.3% and 56.4%, respectively. Hazard ratio (HR) for group 2 vs group 1 was 146 147 0.64 (95% CI, 0.40-1.02). HR for group 3 vs group 1 was 0.41 (95% CI, 0.25 – 0.66); Total p-value was 0.001. Kaplan-Meier curves for OS according to duration of ADT response category in patients 148 who received AA or E being docetaxel-naïve are shown in figure 2a. In this subgroup, median OS 149 150 was 18.8 months in group 1 (95%CI, 13.6 – 24.0), 35.2 months in group 2 (95%CI, 16.1 - 54.2) and was not reached in group 3. Probability of being alive at 24 months was 39.2%, 50.7% and 70.1%, 151 respectively. HR for group 2 vs group 1 was 0.57 (95%Cl, 0.26 – 1.28). HR for group 3 vs group 1 152 was 0.33 (95%CI, 0.14-0.78). Total p-value was 0.038. Kaplan-Meier curves for OS according to 153 154 duration of ADT response category in Docetaxel-pretreated patients are shown in figure 2b. In Docetaxel-pretreated patients, median OS for group 1 was 13.2 months (95%CI, 1.8 - 24.6); for 155 156 group 2 was 17.2 months (95%CI, 12.4 – 22.0) and for group 3 was 21.4 months (95%CI, 17.5 -25.2). Probability of being alive at 24 months was 26.7%, 40.0% and 44.2%, respectively. HR for 157 158 group 2 vs group 1 was 0.72 (95%Cl, 0.41 – 1.28). HR for group 3 vs group 1 was 0.52, (95%Cl, 0.29 - 0.94). Total p-value was 0.082. Kaplan-Meier curves for OS according to duration of ADT 159 response category in AA treated patients are shown in figure 4a. Among patients treated with AA, 160 161 median OS was 17.3 in group 1 (95%CI, 9.5 - 25.1), 16.3 in group 2 (95%CI, 14.3 - 18.2) and 25.5 in 162 group 3 (95%CI, 13.3 - 37.7). Probability of being alive at 24 months was 22.6%, 27.3% and 52.1%, 163 respectively. HR for group 2 vs group 1 was 0.71 (95% CI, 0.41-1.25). HR for population 3 vs

164 population 1 was 0.38 (95% CI, 0.22-0.67). Total p-value was 0.001. Kaplan-Meier curves for OS according to duration of ADT response category in E treated patients are shown in figure 4b. In 165 patients treated with E, median OS for group 1 was 20.7 (95%CI, not estimable), for group 2 was 166 34.6 (95%CI, 23.6 - 45.6) and in group 3 was 41.1 (95%CI, 21.7 - 60.4). Probability of being alive at 167 24 months was 45.4%, 69.5% and 67.0%, respectively. HR for population 2 vs population 1 was 168 169 0.56 (95% CI, 0.24-1.30). HR for population 3 vs population1 was 0.37 (95% CI, 0.14-0.96). Total pvalue was 0.121. 170 The multivariable analysis (adjusted for baseline PSA, ALP, LDH, hemoglobin, albumin, ECOG PS, 171 use of opioids, presence of visceral disease) showed that basal PSA value (HR for higher vs lower 172 PSA 1.86, 95%CI 1.19 - 2.89, p=0.006), ECOG PS (HR for PS 1 vs 0 2.14; 95%CI 1.40 - 3.27), the 173 174 duration of the response to ADT (HR for group 2 vs 1 0.74, 95% CI 0.42 - 1.30; HR for group 3 vs 1 175 0.45, 95%Cl 0.26 - 0.79; p = 0.013) are independent variables associated with the OS (table 3). Progression free survival 176 Kaplan-Meier curves for PFS according to duration of ADT response category are shown in figure 177 178 1b. Median PFS was 6.0 months (95%CI, 5.0 – 6.9) in group 1, 8.8 months (95%CI, 7.21-10.34) in group 2 and 11.7 months (95%CI, 10.0 - 13.4) in group 3, respectively. Probability of being 179 180 progression-free at 12 months was 15.7%, 36.1%, 47.5%, respectively. HR for group 2 vs group 1 181 was 0.56 (95% CI, 0.37-0.85). HR for group 3 vs group 1 was 0.41 (95% CI, 0.27 – 0.62; total p-value 182 was < 0.001. In Docetaxel-naive patients (figure 3a), the median PFS for group 1 was 7.0 months (95%CI, 4.8-9.1), for group 2 was 9.3 months (95%CI, 7.0-11.7) and for group 3 was 20.0 months 183 (95%CI, 11.4-28.5). Probability of being progression-free at 12 months was 17.7%, 41.1% and 184 185 66.4%, respectively.HR for group 2 vs group 1 was 0.57 (95% CI, 0.30-1.11). HR for group 3 vs 186 group 1 was 0.31 (95% CI, 0.15 - 0.62); total p-value was 0.003. Kaplan-Meier curves for PFS 187 according to duration of ADT response category in Docetaxel-pretreated patients are shown in

figure 3b. In Docetaxel-pretreated patients, median PFS was 5.2 months in group 1 (95%CI, 3.2 -7.3); 6.8 months in group 2 (95%CI, 3.9-9.6) and 8.3 months in group 3 (95%CI, 5.7-10.9). HR for group 2 vs group 1 was 0.60 (95%Cl, 0.35 - 1.02). HR for group 3 vs group 1 was 0.54, (95%Cl, 0.32-0.91). Total p-value was 0.067. Kaplan-Meier curves for PFS according to duration of ADT response category in AA treated patients are shown in figure 5a. Among patients treated with AA, median PFS for group 1 was 5.9 (95%CI, 3.8 – 7.9), for group 2 was 8.2 (95%CI, 5.6 – 10.8) and for group 3 was 11.4 (95%CI, 8.6 - 14.1). Probability of being progression-free at 12 months was 10.1%, 31.6% and 44.9%, respectively. HR for group 2 vs group 1 was 0.50 (95% CI, 0.29-0.85). HR for group 3 vs group 1 was 0.35 (95% Cl, 0.21-0.60). Total p-value was 0.001. Kaplan-Meier curves for PFS according to duration of ADT response category in E treated patients are shown in figure 5b. In patients treated with E, median PFS for group 1 was 6.0 (95%CI, 4.5-7.4), for group 2 was 9.6 (95%CI, 4.9-14.3) and for group 3 was 17.6 (95%CI, 7.0-28.2). Probability of being progressionfree at 12 months was 24.3%, 41.2% and 53.5%, respectively. HR for group 2 vs group 1 was 0.65 (95% CI, 0.34-1.25). HR for group 3 vs group 1 was 0.40 (95% CI, 0.19-0.82). Total p-value was 0.041. The multivariable analysis (adjusted for the same variables used in OS analysis) demonstrated that setting (HR for post-decetaxel vs docetaxel-naïve 1.50, 95%CI 1.04-2.18, p=0.031), ECOG PS HR for PS1 vs PS0 1.51; 95%CI 1.05-2.15, p=0.025), baseline PSA (HR for higher vs lower PSA 1.50,95%CI 1.04-2.14) and duration of ADT response HR for group 2 vs group 1 0.54, 95%CI 0.33 - 0.89, HR for group 3 vs group 1 0.45, 95%CI 0.27 - 0.74, p=0.007) are independent variables associated with the PFS (table 3).

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#### Discussion

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Our analysis showed that a longer duration of response to ADT is associated with better outcomes in CRPC patients receiving NHAs (E or AA). The subgroup analyses showed consistent effect for docetaxel-naïve group and for both E and AA groups. We demonstrated a significant difference between the three groups divided according to the duration of ADT response: the group who responded longer to ADT (> 36 months ) showed a better prognosis in terms of both OS and PFS. In recent years, life expectancy of mCRPC patients has considerably increased, due to the introduction of new drugs t including NHAs (AA5,6 and E7,8), chemotherapy (Docetaxel3 and Cabazitaxel<sup>4</sup>) and Radium-223<sup>9</sup>. A critical challenge remains the lack of prognostic and predictive biomarkers able to guide therapeutic choices and to assist clinicians in patient risk stratification. Some prognostic models have been proposed and are used in clinical practice<sup>10-17</sup>. In particular, according to the updated version of Halabi's model<sup>13</sup> the independent variables correlating with survival in CRPC patients are: opioid use, LDH levels, site of disease, ECOG PS, haemoglobin, ALP and PSA levels. Recently, Armstrong at colleagues (xx e xx) conducted a final 5-yr survival analysis of PREVAIL trial in men with chemotherapy-naïve mCRPC from the enzalutamide and placebo arms. They developed and validated a prognostic model for overall survival identifying 3 risk groups for predicting 1-, 2-, and 3-years survival probabilities. According thise model the independent variables correlating with OS in chemotherapy-naïve mCRPC are: number of bone metastases, pattern of spread (no liver metastases versus any liver metastases), baseline pain, NLR value, harmoglobin, albumin, ALP, LDH and PSA levels. Nowadays, it is well established that the shift from castration sensitive PC to CRPC is due to the activation of both androgen receptor (AR)-dependent pathways and mechanisms not dependent on AR signaling<sup>27</sup>. In the former case, there is an adaptation of neoplastic cells to a microenvironment with low levels of androgens by overexpression of enzymes able to produce androgens<sup>28</sup>, AR overexpression<sup>29</sup>, AR gene mutation<sup>2</sup> and expression of AR variant of splicing<sup>30</sup>. NHAs interfere with AR pathway and mechanisms of resistance to ADT: AA acetate acts as a potent

inhibitor of the PC androgens synthesis<sup>31,32</sup>, while E binds and inhibits AR translocation inside the nucleus<sup>33</sup>. Considering these mechanisms, ADT response duration can be considered as an index of hormone responsiveness of disease and there is a strong rationale to study its role as a prognostic factor during NHAs. In addition to the primary analysis, in our multivariable analysis we evaluated all the variables of Halabi's model. The value of baseline PSA and ECOG PS were independent variables for OS, while chemotherapy setting, baseline PSA and ECOG PS were independent variables for PFS. The limited sample size did not allow to show a statistical significance for the other factors included in Halabi's nomogram, but our results confirmed the most recent literature data concerning the prognostic role of the duration of response to ADT<sup>18-26</sup>. While the available literature evaluated patients mostly treated with AA, our study included patients treated with AA or E in similar percentages (54.9% and 45.1% respectively), although unbalanced between the docetaxel-naïve and post-docetaxel settings. In the subgroup analysis, a significant difference in OS between the three groups was demonstrated only in patients treated with AA, whereas for E there was not a significant difference in survival probability. However, the subgroup analysis was conducted with exploratory intent and was not adequately powered for each subgroup. Furthermore, we found a statistically significant difference in PFS among groups of patients with different ADT duration both in AA and E subgroups, supporting the prognostic role of ADT duration relevancy both for AA and E. The analysis of Hung et al.<sup>26</sup> conducted in 80 patients, compared the outcomes of AA and E after ADT but no differences were detected. Considering the aforementioned limitations, although we cannot exclude a similar effect in patients treated with E, the results of our study suggests that the outcome of patients treated with AA is significantly better in patients with a response to ADT longer than 12 months, compared to patients with a shorter duration of response. This result can be explained due to the specific mechanism of action

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of AA, that acts as CYP17A1 inhibitor and also as an AR antagonist<sup>34</sup>. D4-AA, one of the most important metabolite of AA, is a strong AR antagonist with an activity comparable to E<sup>23</sup>. The wider action of AA on AR pathway signalling compared with E could prove the most important activity of AA in a disease with higher hormone responsiveness. However, the retrospective nature, the absence of a validation dataset and the relatively limited number of patients in our study only allow us to generate hypotheses for future studies. Additionally, we compared PFS and OS of patients chemotherapy pretreated and chemotherapynaive. Li and colleagues<sup>23</sup> and Davies and colleagues' <sup>24</sup> populations included only patients pretreated with Docetaxel. Both studies showed a significant role of a longer duration of response to ADT as a predictive factor of response to NHAs. We found a statistically significant benefit in OS and PFS in the subgroup of patients who achieved a greater duration of response to ADT and received NHAs in the docetaxel naïve setting, while the difference did not reach statistical significance in docetaxel pre-treated patients. The limited statistical power of the subgroup analysis could be the simplest explanation of this difference. However, another explanation could be the influence of Docetaxel on AR. Preclinical data showed that taxanes may impair AR activity by interfering with AR signaling pathway, blocking the polymerization of microtubules and AR nuclear translocation therefore reducing AR-induced gene expression<sup>35,36</sup>. Evidence from two clinical studies showed that Docetaxel in mCPRC patients causes a down regulation of AR expression<sup>37,38</sup> possibly influencing the outcome of subsequent NHAs therapy. In conclusion, we showed that the duration of response to androgen-deprivation therapy is an independent prognostic factor for better OS and PFS in CRPC patients treated with NHAs. This can be an important starting point for other studies planned to identify patients with a greater risk of primary resistance to NHAs therapies. This is a crucial challenge for the future, in order to choose

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the most effective therapy for each patient and consequently to improve survival and reduce
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#### 289 **References**

- 1. Huggins C, Hodges CV. Studies on prostatic cancer. I. The effect of castration, of estrogen and
- androgen injection on serum phosphatases in metastatic carcinoma of the prostate. CA Cancer
- 292 J Clin 1972; 22:232-40.. doi: 10.3322/canjclin.22.4.232.
- 293 2. Tucci M, Scagliotti GV, Vignani F. Metastatic castration-resistant prostate: time for innovation.
- 294 Future Oncology 2015;11(1):91-106. doi: 10.2217/fon.14.145.
- 295 3. Berthold DR, Pond GR, Soban F, et al. Docetaxel plus prednisone or mitoxantrone plus
- 296 prednisone for advanced prostate cancer: updated survival in the TAX 327 study. J Clin Oncol
- 297 2008; 26:242-5.doi: 10.1200/JCO.2007.12.4008.
- 4. de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for
- 299 metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a
- randomised open-label trial. Lancet 2010; 376:1147-54.doi: 10.1016/S0140-6736(10)61389-X.
- 301 5. Fizazi K, Scher HI, Molina A, et al: Abiraterone acetate for treatment of metastatic castration-
- resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised,
- double-blind, placebo-controlled phase 3 study. Lancet Oncol 2012; 13:983-92.doi:
- 304 10.1016/S1470-2045(12)70379-0.
- 305 6. Ryan CJ, Smith MR, Fizazi K, et al. Abiraterone acetate plus prednisone versus placebo plus
- prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer
- 307 (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled
- 308 phase 3 study. Lancet Oncol 2015; 16:152-60.doi: 10.1016/S1470-2045(14)71205-7.
- 309 7. Beer TM, Armstrong AJ, Rathkopf D, et al. Enzalutamide in Men with Chemotherapy-naive
- 310 Metastatic Castration-resistant Prostate Cancer: Extended Analysis of the Phase 3 PREVAIL
- 311 Study. Eur Urol 2017; 71:151-154.doi: 10.1016/j.eururo.2016.07.032.
- 312 8. Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after
- 313 chemotherapy. N Engl J Med 2017; 367:1187-97. doi: 10.1056/NEJMoa1207506.
- 9. Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic
- prostate cancer. N Engl J Med 2013; 369:213-23.doi: 10.1056/NEJMoa1213755.
- 10. Berry W. R., Laszlo J, Cox E., et al. Prognostic factors in metastatic and hormonally unresponsive
- carcinoma of the prostate. Cancer 1979;44(2):763–775.
- 318 11. Kantoff W.P. et al. Hydrocortisone with or without mitoxantrone in men with hormone-
- refractory prostate cancer: Results of the cancer and leukemia group B 9182 study. J. Clin.
- 320 Oncol.1999;17(8):2506-2513. doi:10.1200/JCO.1999.17.8.2506.

- 321 12. Halabi S. et al. Prognostic model for predicting survival in men with hormone-refractory
- metastatic prostate cancer. J. Clin. Oncol.2003;21(7):1232–1237.
- 323 13. Halabi S. et al. Updated prognostic model for predicting overall survival in first-line
- 324 chemotherapy for patients with metastatic castration-resistant prostate cancer.J . Clin.
- 325 Oncol.2014; 32(7):671–677. doi:10.1200/JCO.2013.52.3696.
- 326 14. Smaletz O, Scher HI, Small EJ, et al. Nomogram for overall survival of patients with progressive
- metastatic prostate cancer after castration. J Clin Oncol. 2002;20(19):3972-3982.
- 328 doi:10.1200/JCO.2002.11.021.
- 329 15. Armstrong AJ, Garrett-Mayer ES, Yang YC, et al. A contemporary prognostic nomogram for
- men with hormone-refractory metastatic prostate cancer: a TAX327 study analysis. Clin Cancer
- Res. 2007;13(21):6396-6403. doi:10.1158/1078-0432.CCR-07-1036.
- 332 16. Armstrong AJ, Garrett-Mayer E, de Wit R, et al. Prediction of survival following first-line
- chemotherapy in men with castration-resistant metastatic prostate cancer. Clin Cancer Res.
- 334 2010;16(1):203-211. doi:10.1158/1078-0432.CCR-09-2514.
- 17. Halabi S, Lin CY, Small EJ, et al. Prognostic model predicting metastatic castration-resistant
- prostate cancer survival in men treated with second-line chemotherapy. J Natl Cancer Inst.
- 337 2013;105(22):1729-1737. doi:10.1093/jnci/djt280.
- 18. Giacinti S. et al. Duration of response to first androgen deprivation therapy, time to castration
- resistance prostate cancer, and outcome of metastatic castration resistance prostate cancer
- patients treated with abiraterone acetate. Anticancer. Drugs 2017;28(1):110–115. doi:
- 341 10.1097/CAD.0000000000000434.
- 342 19. Loriot Y. et al. Prior long response to androgen deprivation predicts response to next-
- generation androgen receptor axis targeted drugs in castration resistant prostate cancer.Eur. J.
- 344 Cancer 2015;51(14):1946–1952. doi: 10.1016/j.ejca.2015.06.128.
- 20. McKay R.R, Werner L, Fiorillo M, et al. Predictors of duration of abiraterone acetate in men
- with castration-resistant prostate cancer. Prostate Cancer Prostatic Dis. 2016;19(4):398-405.
- 347 doi:10.1038/pcan.2016.31.
- 348 21. Oudard S, Kheoh TS, Yu M. et al.Impact of prior endocrine therapy on radiographic
- progression-free survival (rPFS) in patients (pts) with chemotherapy-naive metastatic
- castration-resistant prostate cancer (mCRPC): Results from COU-AA-302. J Clin Oncol 2017;
- 351 32:4 suppl, 14-14. doi: 10.1016/j.eururo.2015.10.021.

- 352 22. Nakabayashi M, Werner L, Oh WK, Regan MM, Kantoff PW, Taplin ME. Secondary hormonal
- therapy in men with castration-resistant prostate cancer. Clin Genitourin Cancer. 2011;9(2):95-
- 354 103. doi:10.1016/j.clgc.2011.06.006.
- 23. Li JR, Chiu KY, Wang SS, et al. Effectiveness of Deferred Combined Androgen Blockade Therapy
- Predicts Efficacy in Abiraterone Acetate Treated Metastatic Castration-Resistant Prostate
- Cancer Patients after Docetaxel. Front Pharmacol. 2017;8:836. Published 2017 Nov 22.
- 358 doi:10.3389/fphar.2017.00836.
- 359 24. Davies RS, Smith C, Button MR, et al. What Predicts Minimal Response to Abiraterone in
- Metastatic Castrate-resistant Prostate Cancer?. Anticancer Res. 2015;35(10):5615-5621.
- 361 25. Afshar M, Al-Alloosh F, Pirrie S, et al. Predictive factors for response to abiraterone in
- metastatic castration refractory prostate cancer. Anticancer Res. 2015;35(2):1057-1063.
- 26. Hung J, Taylor AR, Divine GW, et al. The Effect of Time to Castration Resistance on Outcomes
- 364 With Abiraterone and Enzalutamide in Metastatic Prostate Cancer. Clin Genitourin Cancer.
- 365 2016;14(5):381-388. doi:10.1016/j.clgc.2016.03.021.
- 366 27. Buttigliero et al. Understanding and Overcoming the Mechanisms of Primary and Acquired
- Resistance to Abiraterone and in Castration Resistant Prostate. Cancer Treat Rev.
- 368 2015;41(10):884-92. doi: 10.1016/j.ctrv.2015.08.002.
- 28. Chen CD, Welsbie DS, Tran C, et al. Molecular determinants of resistance to antiandrogen
- 370 therapy. Nat Med. 2004;10:33–9. doi:10.1038/nm972.
- 371 29. Stanbrough M, Bubley GJ, Ross K, et al. Increased expression of genes converting adrenal
- androgens to testosterone in androgen-independent. Cancer Res. 2006;66:2815–25. doi:
- 373 10.1158/0008-5472.CAN-05-4000.
- 374 30. Hu R, Dunn TA, Wei S, et al. Ligand-independent androgen receptor variants derived from
- 375 splicing of cryptic exons signify hormone-refractory prostate cancer. Cancer Res.
- 376 2009;69(1):16-22. doi:10.1158/0008-5472.CAN-08-2764.
- 31. Mostaghel EA, Page ST, Lin DW, et al. Intraprostatic androgens and androgen-regulated gene
- expression persist after testosterone suppression: therapeutic implications for castration-
- resistant prostate cancer. Cancer Res. 2007;67(10):5033-5041. doi:10.1158/0008-5472.CAN-
- 380 06-3332.
- 32. Locke JA, Guns ES, Lubik AA, et al. Androgen levels increase by intratumoral de novo
- steroidogenesis during progression of castration-resistant prostate cancer. Cancer Res.
- 383 2008;68(15):6407-6415. doi:10.1158/0008-5472.CAN-07-5997.

- 384 33. Heemers HV, Tindall DJ. Androgen receptor (AR) coregulators: a diversity of functions
- converging on and regulating the AR transcriptional complex. Endocr Rev. 2007;28(7):778-808.
- 386 doi:10.1210/er.2007-0019.
- 34. Yin L, Hu Q. CYP17 inhibitors-, C17,20-lyase inhibitors and multi-targeting agents. Nat Rev Urol.
- 388 2014 Jan;11(1):32-42. doi: 10.1038/nrurol.2013.274. Epub 2013 Nov 26.
- 389 35. Darshan MS, Loftus MS, Thadani-Mulero M, et al. Taxane-induced blockade to nuclear
- accumulation of the androgen receptor predicts clinical responses in metastatic prostate
- 391 cancer. Cancer Res. 2011;71(18):6019-6029. doi:10.1158/0008-5472.CAN-11-1417.
- 36. Thadani-Mulero M, Nanus DM, Giannakakou P. Androgen receptor on the move: boarding the
- microtubule expressway to the nucleus. Cancer Res. 2012;72(18):4611-4615.
- 394 doi:10.1158/0008-5472.CAN-12-0783.
- 37. Jiang J, Huang H. Targeting the Androgen Receptor by Taxol in Castration-Resistant Prostate
- 396 Cancer. Mol Cell Pharmacol. 2010;2(1):1-5.
- 38. Mezynski J, Pezaro C, Bianchini D, et al. Antitumour activity of docetaxel following treatment
- with the CYP17A1 inhibitor abiraterone: clinical evidence for cross-resistance?. Ann Oncol.
- 399 2012;23(11):2943-2947. doi:10.1093/annonc/mds119.
- 401 Legends to figures

- 402 Figure 1. Kaplan-Meier curves for overall survival (panel A) and for progression-free survival (panel
- 403 B) according to duration of ADT response category in the whole cohort of patients.
- 404 Figure 2. Kaplan-Meier curves for overall survival according to duration of ADT response category
- in docetaxel-naïve setting (panel A) and docetaxel-pretreated setting (panel B).
- 406 Figure 3 Kaplan-Meier curves for progression-free survival according to duration of ADT response
- category in docetaxel-naïve setting (panel A) and docetaxel-pretreated setting (panel B).
- 408 Figure 4. Kaplan-Meier curves for overall survival according to duration of ADT response category
- in patients treated with abiraterone (panel A) and in patients treated with enzalutamide (panel B).
- 410 **Figure 5.** Kaplan-Meier curves for progression-free survival according to duration of ADT response
- category in patients treated with abiraterone (panel A) and in patients treated with enzalutamide
- 412 (panel B).