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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**

4

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21 **Conflict of Interest**

22 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
26 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
30 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
34 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
37 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),
38 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.

44

45 **Introduction:**

46 Androgen deprivation therapy (ADT) is the mainstay of therapy for metastatic prostate cancer (PC)
47 patients¹. Unfortunately, many patients eventually progress to the castrate-resistant prostate
48 cancer (CRPC) phase². Despite the therapeutic effects of new hormonal agents (NHAs) in CRPC, a
49 significant percentage of patients are primarily resistant or acquire resistance. About ~~1/3~~ 30% of
50 patients treated with abiraterone acetate (AA)⁵ and ~~20% of those treated with~~ Enzalutamide (E)⁸
51 develop a disease progression within three months from initiation. Considering the lack of head-
52 to-head studies comparing the different therapeutic agents, guiding the choice of the most
53 effective drug for each patient, there is an urgent need to identify prognostic factors of response
54 to NHAs. Several prognostic models have been developed to predict overall survival (OS)¹⁰⁻¹⁷ in
55 mCRPC patients. In particular, Halabi's model¹² included eight variables: Eastern Cooperative
56 Oncology Group Performance Status (ECOG PS), albumin, haemoglobin, prostate specific antigen
57 (PSA), Alkaline phosphatase (ALP), lactate dehydrogenase (LDH) level and opioids use¹³. Recently,
58 Armstrong et al (Annals 2018 e Eur Urol 2020), analyzing patients from PREVAIL trial, published an
59 internally validated prognostic model that stratifies men with mCRPC into three risk groups. This
60 model identified 11 key independent OS prognostic factors, and included a nomogram and a risk
61 group calculator for predicting 1-, 2-, and 3-yr OS for patients with mCRPC treated with enzalutamide
62 in the PREVAIL trial. Some clinical data indicate that the duration of ADT response influences
63 outcome of first-line NHAs therapy¹³⁻²¹ in mCRPC patients. Giacinti et al.¹⁸ showed that the
64 duration of ADT response did not affect progression-free survival (PFS) in 59 patients treated with
65 AA. Conversely, the studies by Lortolip¹⁹ and McKay²⁰ demonstrated that a duration of ADT
66 response less than 12 months worsened median overall response and OS in mCRPC patients and
67 the COU-AA02 trial showed an increased radiographic PFS in patients with longer prior exposure
68 to ADT within both treatment groups²¹. Nakabayashi et al²² 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 al²³ demonstrated that longer ADT duration correlated with better OS and greater PFS in a series of 64 patients treated with AA. Similarly, other small series²⁴⁻²⁶ 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-naïve and chemo-pretreated patients.

81

82 **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.

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

98 *Statistical analysis*

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

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

122

123 **Results**

124 Overall, data about ADT start and duration were available in 255 (82%) of 311 patients treated
125 with AA or E. Baseline characteristics of eligible patients are described in table 1.

126 In detail, 140 (54.9%) received AA and 115 patients (45.1%) received E. The median age was 73
127 years (range: 50-89 years). 118 patients (46.3%) had been treated with docetaxel before the
128 administration of NHA, while the remaining 137 (53.7%) were docetaxel-naïve. Use of AA and E
129 was significantly unbalanced between the 2 settings: namely, 61.4% of patients treated with AA
130 were pretreated with docetaxel, vs. 27.8% of patients treated with E. About 95% of patients had
131 ECOG PS 0 or 1 at baseline. Patients with visceral metastases were 32 (12.6%), and 74 (32.6%)
132 patients were assuming opioids to control pain. Median ADT duration response was 31.0 months
133 (0.36-250.1).

134 Table 2 shows patients baseline characteristics divided into three populations: 41 (16.1%) patients
135 in group 1(17 in docetaxel-naïve and 24 in post-Docetaxel setting), 106 (41.6%) patients in group
136 2(61 in docetaxel-naïve and 45 in post-Docetaxel setting) and 108 (42.4%) patients in group 3 (59
137 in docetaxel-naïve and 49 in post-Docetaxel setting). We found statistically significant differences
138 between the three groups in age ($p < 0.001$), opioids use ($p = 0.030$), baseline ALP ($p = 0.014$) and
139 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*

143 Kaplan-Meier curves for OS according to duration of ADT response category are shown in figure
144 1a. Median OS was 17.3 months in group 1 (95%CI, 8.9 - 25.6), 19.9 months in group 2 (95%CI,
145 12.8 - 27.1) and 31.6 months in group 3 (95%CI, 19.3 – 43.9). Probability of being alive at 24
146 months was 31.3%, 45.3% and 56.4%, respectively. Hazard ratio (HR) for group 2 vs group 1 was
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
148 was 0.001. Kaplan-Meier curves for OS according to duration of ADT response category in patients
149 who received AA or E being docetaxel-naïve are shown in figure 2a. In this subgroup, median OS
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
151 was not reached in group 3. Probability of being alive at 24 months was 39.2%, 50.7% and 70.1%,
152 respectively. HR for group 2 vs group 1 was 0.57 (95%CI, 0.26 – 1.28). HR for group 3 vs group 1
153 was 0.33 (95%CI, 0.14-0.78). Total p-value was 0.038. Kaplan-Meier curves for OS according to
154 duration of ADT response category in Docetaxel-pretreated patients are shown in figure 2b. In
155 Docetaxel-pretreated patients, median OS for group 1 was 13.2 months (95%CI, 1.8 - 24.6); for
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 -
157 25.2). Probability of being alive at 24 months was 26.7%, 40.0% and 44.2%, respectively. HR for
158 group 2 vs group 1 was 0.72 (95%CI, 0.41 – 1.28). HR for group 3 vs group 1 was 0.52, (95%CI, 0.29
159 – 0.94). Total p-value was 0.082. Kaplan-Meier curves for OS according to duration of ADT
160 response category in AA treated patients are shown in figure 4a. Among patients treated with AA,
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
165 according to duration of ADT response category in E treated patients are shown in figure 4b. In
166 patients treated with E, median OS for group 1 was 20.7 (95%CI, not estimable), for group 2 was
167 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
168 24 months was 45.4%, 69.5% and 67.0%, respectively. HR for population 2 vs population 1 was
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 p-
170 value was 0.121.

171 The multivariable analysis (adjusted for baseline PSA, ALP, LDH, hemoglobin, albumin, ECOG PS,
172 use of opioids, presence of visceral disease) showed that basal PSA value (HR for higher vs lower
173 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
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%CI 0.26 - 0.79; p = 0.013) are independent variables associated with the OS (table 3).

176 *Progression free survival*

177 Kaplan-Meier curves for PFS according to duration of ADT response category are shown in figure
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
179 group 2 and 11.7 months (95%CI, 10.0 - 13.4) in group 3, respectively. Probability of being
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-naïve patients (figure 3a), the median PFS for group 1 was 7.0 months
183 (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
184 (95%CI, 11.4-28.5). Probability of being progression-free at 12 months was 17.7%, 41.1% and
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

188 figure 3b. In Docetaxel-pretreated patients, median PFS was 5.2 months in group 1 (95%CI, 3.2 -
189 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
190 group 2 vs group 1 was 0.60 (95%CI, 0.35 – 1.02). HR for group 3 vs group 1 was 0.54, (95%CI,
191 0.32–0.91). Total p-value was 0.067. Kaplan-Meier curves for PFS according to duration of ADT
192 response category in AA treated patients are shown in figure 5a. Among patients treated with AA,
193 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
194 group 3 was 11.4 (95%CI, 8.6 – 14.1). Probability of being progression-free at 12 months was
195 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
196 for group 3 vs group 1 was 0.35 (95% CI, 0.21-0.60). Total p-value was 0.001. Kaplan-Meier curves
197 for PFS according to duration of ADT response category in E treated patients are shown in figure
198 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
199 (95%CI, 4.9–14.3) and for group 3 was 17.6 (95%CI, 7.0–28.2). Probability of being progression-
200 free at 12 months was 24.3%, 41.2% and 53.5%, respectively. HR for group 2 vs group 1 was 0.65
201 (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
202 0.041.

203 The multivariable analysis (adjusted for the same variables used in OS analysis) demonstrated that
204 setting (HR for post-docetaxel vs docetaxel-naïve 1.50, 95%CI 1.04-2.18, p=0.031), ECOG PS HR for
205 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
206 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
207 group 3 vs group 1 0.45, 95%CI 0.27 - 0.74, p=0.007) are independent variables associated with the
208 PFS (table 3).

209

210 Discussion

211 Our analysis showed that a longer duration of response to ADT is associated with better outcomes
212 in CRPC patients receiving NHAs (E or AA). The subgroup analyses showed consistent effect for
213 docetaxel-naïve group and for both E and AA groups. We demonstrated a significant difference
214 between the three groups divided according to the duration of ADT response: the group who
215 responded longer to ADT (> 36 months) showed a better prognosis in terms of both OS and PFS.
216 In recent years, life expectancy of mCRPC patients has considerably increased, due to the
217 introduction of new drugs including NHAs (AA^{5,6} and E^{7,8}), chemotherapy (Docetaxel³ and
218 Cabazitaxel⁴) and Radium-223⁹. A critical challenge remains the lack of prognostic and predictive
219 biomarkers able to guide therapeutic choices and to assist clinicians in patient risk stratification.
220 Some prognostic models have been proposed and are used in clinical practice¹⁰⁻¹⁷. In particular,
221 according to the updated version of Halabi's model¹³ the independent variables correlating with
222 survival in CRPC patients are: opioid use, LDH levels, site of disease, ECOG PS, haemoglobin, ALP
223 and PSA levels. Recently, Armstrong and colleagues (xx e xx) conducted a final 5-yr survival analysis of
224 PREVAIL trial in men with chemotherapy-naïve mCRPC from the enzalutamide and placebo arms. They
225 developed and validated a prognostic model for overall survival identifying 3 risk groups for predicting 1-, 2-
226 , and 3-years survival probabilities. According this model the independent variables correlating with OS in
227 chemotherapy-naïve mCRPC are: number of bone metastases, pattern of spread (no liver metastases
228 versus any liver metastases), baseline pain, NLR value, haemoglobin, albumin, ALP, LDH and PSA levels.
229 Nowadays, it is well established that the shift from castration sensitive PC to CRPC is due to the
230 activation of both androgen receptor (AR)-dependent pathways and mechanisms not dependent
231 on AR signaling²⁷. In the former case, there is an adaptation of neoplastic cells to a
232 microenvironment with low levels of androgens by overexpression of enzymes able to produce
233 androgens²⁸, AR overexpression²⁹, AR gene mutation² and expression of AR variant of splicing³⁰.
234 NHAs interfere with AR pathway and mechanisms of resistance to ADT: AA acetate acts as a potent

235 inhibitor of the PC androgens synthesis^{31,32}, while E binds and inhibits AR translocation inside the
236 nucleus³³. Considering these mechanisms, ADT response duration can be considered as an index of
237 hormone responsiveness of disease and there is a strong rationale to study its role as a prognostic
238 factor during NHAs.

239 In addition to the primary analysis, in our multivariable analysis we evaluated all the variables of
240 Halabi's model. The value of baseline PSA and ECOG PS were independent variables for OS, while
241 chemotherapy setting, baseline PSA and ECOG PS were independent variables for PFS. The limited
242 sample size did not allow to show a statistical significance for the other factors included in Halabi's
243 nomogram, but our results confirmed the most recent literature data concerning the prognostic
244 role of the duration of response to ADT¹⁸⁻²⁶.

245 While the available literature evaluated patients mostly treated with AA, our study included
246 patients treated with AA or E in similar percentages (54.9% and 45.1% respectively), although
247 unbalanced between the docetaxel-naïve and post-docetaxel settings. In the subgroup analysis, a
248 significant difference in OS between the three groups was demonstrated only in patients treated
249 with AA, whereas for E there was not a significant difference in survival probability. However, the
250 subgroup analysis was conducted with exploratory intent and was not adequately powered for
251 each subgroup. Furthermore, we found a statistically significant difference in PFS among groups of
252 patients with different ADT duration both in AA and E subgroups, supporting the prognostic role of
253 ADT duration relevancy both for AA and E. The analysis of Hung et al.²⁶ conducted in 80 patients,
254 compared the outcomes of AA and E after ADT but no differences were detected. Considering the
255 aforementioned limitations, although we cannot exclude a similar effect in patients treated with E,
256 the results of our study suggests that the outcome of patients treated with AA is significantly
257 better in patients with a response to ADT longer than 12 months, compared to patients with a
258 shorter duration of response. This result can be explained due to the specific mechanism of action

259 of AA, that acts as CYP17A1 inhibitor and also as an AR antagonist³⁴. D4-AA, one of the most
260 important metabolite of AA, is a strong AR antagonist with an activity comparable to E²³. The
261 wider action of AA on AR pathway signalling compared with E could prove the most important
262 activity of AA in a disease with higher hormone responsiveness. However, the retrospective
263 nature, the absence of a validation dataset and the relatively limited number of patients in our
264 study only allow us to generate hypotheses for future studies.

265 Additionally, we compared PFS and OS of patients chemotherapy pretreated and chemotherapy-
266 naive. Li and colleagues²³ and Davies and colleagues' ²⁴ populations included only patients pre-
267 treated with Docetaxel. Both studies showed a significant role of a longer duration of response to
268 ADT as a predictive factor of response to NHAs. We found a statistically significant benefit in OS
269 and PFS in the subgroup of patients who achieved a greater duration of response to ADT and
270 received NHAs in the docetaxel naïve setting, while the difference did not reach statistical
271 significance in docetaxel pre-treated patients. The limited statistical power of the subgroup
272 analysis could be the simplest explanation of this difference. However, another explanation could
273 be the influence of Docetaxel on AR. Preclinical data showed that taxanes may impair AR activity
274 by interfering with AR signaling pathway, blocking the polymerization of microtubules and AR
275 nuclear translocation therefore reducing AR-induced gene expression^{35,36}. Evidence from two
276 clinical studies showed that Docetaxel in mCPRC patients causes a down regulation of AR
277 expression^{37,38} possibly influencing the outcome of subsequent NHAs therapy.

278 In conclusion, we showed that the duration of response to androgen-deprivation therapy is an
279 independent prognostic factor for better OS and PFS in CRPC patients treated with NHAs. This can
280 be an important starting point for other studies planned to identify patients with a greater risk of
281 primary resistance to NHAs therapies. This is a crucial challenge for the future, in order to choose

282 the most effective therapy for each patient and consequently to improve survival and reduce
283 health care costs.

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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
405 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
407 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
409 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
411 category in patients treated with abiraterone (panel A) and in patients treated with enzalutamide
412 (panel B).