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Prostate Cancer

Clinical Outcomes of Castration-resistant Prostate Cancer Treatments Administered as Third or Fourth Line Following Failure of Docetaxel and Other Second-line Treatment: Results of an Italian Multicentre Study

Orazio Caffo[a,*], *Ugo De Giorgi*[b], *Lucia Fratino*[c], *Daniele Alesini*[d], *Vittorina Zagonel*[e], *Gaetano Facchini*[f], *Donatello Gasparro*[g], *Cinzia Ortega*[h], *Marcello Tucci*[i], *Francesco Verderame*[j], *Enrico Campadelli*[k], *Giovanni Lo Re*[l], *Giuseppe Procopio*[m], *Roberto Sabbatini*[n], *Maddalena Donini*[o], *Franco Morelli*[p], *Donata Sartori*[q], *Paolo Zucali*[r], *Francesco Carrozza*[s], *Alessandro D'Angelo*[t], *Giovanni Vicario*[u], *Francesco Massari*[v], *Daniele Santini*[w], *Teodoro Sava*[x], *Caterina Messina*[y], *Giuseppe Fornarini*[z], *Leonardo La Torre*[aa], *Riccardo Ricotta*[bb], *Michele Aieta*[cc], *Claudia Mucciarini*[dd], *Fable Zustovich*[e], *Sveva Macrini*[ee], *Salvatore Luca Burgio*[b], *Sandra Santarossa*[c], *Carmine D'Aniello*[f], *Umberto Basso*[e], *Sara Tarasconi*[g], *Enrico Cortesi*[d], *Consuelo Buttigliero*[i], *Fiorella Ruatta*[h], *Antonello Veccia*[a], *Vincenza Conteduca*[b], *Francesca Maines*[a], *Enzo Galligioni*[a]

[a] *Medical Oncology Department, Santa Chiara Hospital, Trento, Italy;* [b] *Medical Oncology Department, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy;* [c] *Medical Oncology Department, National Cancer Institute, Aviano, Italy;* [d] *Department of Radiological, Oncological and Anatomopathological Sciences, La Sapienza, University of Rome, Rome, Italy;* [e] *Medical Oncology Unit 1, Istituto Oncologico Veneto IOV - IRCCS, Padua, Italy;* [f] *Division of Medical Oncology, Department of Uro-Gynaecological Oncology, Istituto Nazionale Tumori "Fondazione G. Pascale" - IRCCS, Naples, Italy;* [g] *Medical Oncology Department, General Hospital, Parma, Italy;* [h] *Medical Oncology I - Candiolo Cancer Institute - FPO, IRCCS, Candiolo, Italy;* [i] *Medical Oncology Department, University of Torino, San Luigi Hospital, Orbassano, Italy;* [j] *Medical Oncology Department, Villa Sofia Cervello Hospital, Palermo, Italy;* [k] *Medical Oncology Department, General Hospital, Lugo di Romagna, Italy;* [l] *Medical Oncology Department, Santa Maria degli Angeli Hospital, Pordenone, Italy;* [m] *Medical Oncology Department, Fondazione Istituto Nazionale Tumori, Milan, Italy;* [n] *Medical Oncology Division, Azienda Ospedaliero Universitaria, Policlinico di Modena, Modena, Italy;* [o] *Medical Oncology Department, General Hospital, Cremona, Italy;* [p] *Medical Oncology Department, Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy;* [q] *Medical Oncology Department, General Hospital, Mirano, Italy;* [r] *Department of Medical Oncology and Haematology, Humanitas Clinical and Research Center, Rozzano, Italy;* [s] *Medical Oncology Department, General Hospital, Faenza, Italy;* [t] *Medical Oncology Department, San Vincenzo Hospital, Taormina, Italy;* [u] *Division of Medical Oncology, San Giacomo Hospital, Castelfranco Veneto, Italy;* [v] *Medical Oncology, Azienda Ospedaliera Universitaria Integrata, University of Verona, Verona, Italy;* [w] *Medical Oncology Department, University Campus bio-Medico, Rome, Italy;* [x] *Medical Oncology Department, General Hospital, Verona, Italy;* [y] *Medical Oncology Department, Papa Giovanni XXIII Hospital, Bergamo, Italy;* [z] *Medical Oncology Department, IRCCS Azienda Ospedaliera Universitaria San Martino – IST Istituto Nazionale per la Ricerca sul Cancro, Genoa, Italy;* [aa] *Medical Oncology Department, General Hospital, Imola, Italy;* [bb] *Medical Oncology Department, Niguarda Cancer Centre, Ospedale Niguarda Ca' Granda, Milan, Italy;* [cc] *Medical Oncology Department, Referral Cancer Centre of Basilicata-IRCCS, Rionero in Vulture, Italy;* [dd] *Medical Oncology Department, General Hospital, Carpi, Italy;* [ee] *Medical Oncology Department, Santa Maria della Misericordia University Hospital, Udine, Italy*

[*] Corresponding author. Medical Oncology Department, Santa Chiara Hospital, Largo Medaglie d'Oro, 38100 Trento, Italy. Tel. +39 0461 902478; Fax: +39 0461 903364.
E-mail address: orazio.caffo@apss.tn.it (O. Caffo).

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Abstract

Background: The availability of new agents (NAs) active in patients with metastatic castration-resistant prostate cancer (mCRPC) progressing after docetaxel treatment (abiraterone acetate, cabazitaxel, and enzalutamide) has led to the possibility of using them sequentially to obtain a cumulative survival benefit.
Objective: To provide clinical outcome data relating to a large cohort of mCRPC patients who received a third-line NA after the failure of docetaxel and another NA.
Design, setting, and participants: We retrospectively reviewed the clinical records of patients who had received at least two successive NAs after the failure of docetaxel.
Outcome measurements and statistical analysis: The independent prognostic value of a series of pretreatment covariates on the primary outcome measure of overall survival was assessed using Cox regression analysis.
Results and limitations: We assessed 260 patients who received one third-line NA between January 2012 and December 2013, including 38 who received a further NA as fourth-line therapy. The median progression-free and overall survival from the start of third-line therapy was, respectively, 4 mo and 11 mo, with no significant differences between the NAs. Performance status, and haemoglobin and alkaline phosphatase levels were the only independent prognostic factors. The limitations of the study are mainly due its retrospective nature and the small number of patients treated with some of the sequences.
Conclusions: We were unable to demonstrate a difference in the clinical outcomes of third-line NAs regardless of previous NA therapy.
Patient summary: It is debated which sequence of treatments to adopt after docetaxel. Our data do not support the superiority of any of the three new agents in third-line treatment, regardless of the previously administered new agent.

1. Introduction

Docetaxel became the reference first-line treatment for metastatic castration-resistant prostate cancer (mCRPC) in 2004 [1], but it has only recently been demonstrated that new agents (NAs) such as cabazitaxel (CAB), abiraterone acetate (AA), and enzalutamide (ENZ) are active in mCRPC patients who have received first-line docetaxel [2–4].

The availability of agents that are active in various oncologic fields led to the possibility of using them sequentially in the hope of obtaining a cumulative survival benefit and, although it is not yet supported by clinical trial data, this has also been tried in the third- or fourth-line treatment of mCRPC in everyday clinical practice. The dramatic reduction in the funds available for health-care expenses means that it is becoming increasingly important to obtain clinical data concerning the efficacy and safety of the sequential use of NAs in mCRPC patients. The literature, however, has so far only provided retrospective analyses of small cohorts of patients receiving one specific third-line NA after another NA is administered as second line therapy [5–14], and no published study has assessed all of the NAs used as third-line therapy.

The aim of this retrospective study was to provide an estimate on the clinical outcomes relating to a large cohort of patients with mCRPC who received a third-line NA after the failure of docetaxel and another NA.

2. Patients and methods

CAB, AA, and ENZ initially became available in Italy for use after docetaxel failure in the form of compassionate-use programmes (CUPs); subsequently, CAB and AA were reimbursed by the National Health Service. We retrospectively reviewed the records of patients who started a third-line NA after the failure of first-line docetaxel and NA second-line treatment in ethics committee-approved observational studies of patients in CUPs or everyday clinical practice.

The inclusion criteria were previous treatment with a first-line docetaxel-based chemotherapy for mCRPC, and subsequent sequential therapy with at least two NAs. The NA-based treatment consisted of oral AA 1000 mg once daily or intravenous CAB 25 mg/m^2 every 3 wk plus prednisone 10 mg daily, or oral ENZ 160 mg once daily. The treatments were continued until the occurrence of disease progression, as defined by the Prostate Cancer Working Group 2 (PCWG2) criteria [15], death, or unacceptable toxicity. During treatment, prostate-specific antigen (PSA) levels were assessed monthly and radiographic evaluations were made every 3 or 4 mo, or in the presence of PSA progression.

2.1. Statistical analysis

Continuous variables are expressed as median values, and discrete variables as relative frequencies. For each line of treatment, we assessed the biochemical response rate (bRR; defined as a $\geq$50% reduction in PSA levels), the objective response rate (oRR; as determined by the physicians caring for the patients in accordance with PCWG2 criteria [15] and the Response Evaluation Criteria in Solid Tumors [16]), and overall survival (OS) and progression-free survival (PFS), calculated from the start date of each line of treatment. In particular, the primary outcome measure of OS was calculated as the time from the start date of third-line to death due any cause or the date on which the patient was last known to be alive. Patients lost to follow-up were treated as censored cases on the basis of the date they were last known to be alive.

Cox regression analysis was used to assess the independent prognostic value of a series of pretreatment covariates in terms of OS. Two outcome-oriented approaches were used to determine the cut-off points for continuous variables: We first examined plots of the martingale residuals against a single variable using the PROC LOESS option in SAS (SAS Institute Inc., Cary, NC, USA) and chose DIRECT SMOOTH with a smoothing parameter of two-thirds. Second, we applied

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Table 1 – Clinical outcomes of the different treatment lines

	Second line					Third line					Fourth line				
	Patients, no.	bRR, %	oRR, %	mPFS (IQR)	mOS (IQR)	Patients, no.	bRR, %	oRR, %	mPFS (IQR)	mOS (IQR)	Patients, no.	bRR, %	oRR, %	mPFS (IQR)	mOS (IQr)
All patients	260	38	14	6 (4–10)	21 (14-NA)	260	24	13	4 (3–8)	11 (6–24)	38	16	8	5 (3–12)	5 (4-11)
AA	143	31	14	7 (4–10)	20 (14–30)	80	24	15	5 (3–10)	15 (6–24)	11	18	9	5 (3–NA)	4 (4-NA)
CAB	89	47	17	7 (4–11)	26 (14–NA)	110	28	14	5 (3–9)	12 (6–20)	12	25	17	4 (3–12)	7 (5-NA)
ENZ	28	36	7	5 (3–6)	NR (14–NA)	70	20	10	4 (2–6)	10 (5–NA)	15	7	0	5 (3–7)	5 (2-7)

AA = abiraterone acetate; bRR = biochemical response rate; CAB = cabazitaxel; ENZ = enzalutamide; IQR = interquartile range; mPFS = median progression-free survival; mOS = median overall survival; NA = not applicable; oRR = objective response rate.

the Contal and O'Quigley method [17] based on the log-rank statistic, which provides *p* values corrected for examining multiple potential cut-off points. The cut-off points were determined using a SAS macro provided by Mandrekar et al [18,19].

We also evaluated whether the addition of a further NA after third-line treatment influenced OS by comparing survival from the end of third-line therapy in the patients who received a fourth line and those who did not, using a 3-mo landmark analysis to avoid the clear bias due to patients who died early after the end of their third-line treatment.

The statistical analyses were made using IBM SPSS Statistics v21.0 (IBM Corp, Armonk, NY, USA) and SAS v9.1 software (SAS Institute Inc., Cary, NC, USA).

3. Results

The data were collected from a consecutive series of 260 mCRPC patients who received one NA as third-line treatment after docetaxel and another NA in 31 Italian hospitals between January 2012 and December 2013. The third-line treatment consisted of AA in 80 patients (30.7%), CAB in 110 (42.3%), and ENZ in 70 (26.9%). Thirty-eight of the 260 patients also received a fourth-line NA (AA in 7 cases, CAB in 14, and ENZ in 17); two patients who responded to second-line CAB underwent a CAB rechallenge. Supplementary Table 1 shows the patients' main characteristics, and Figure 1 shows the NA sequences. There were no statistically significant differences in the characteristics of the patients in the AA, CAB, and ENZ groups at the start of the third-line treatment.

3.1. *Third-line clinical outcomes*

After a median follow-up of 6 mo (interquartile range: 4–11 mo), 49 of the 260 patients were still on third-line treatment in the absence of progression; the remaining 211 discontinued third-line treatment because of clinical progression (60.2%), radiological progression (59.7%), and/or

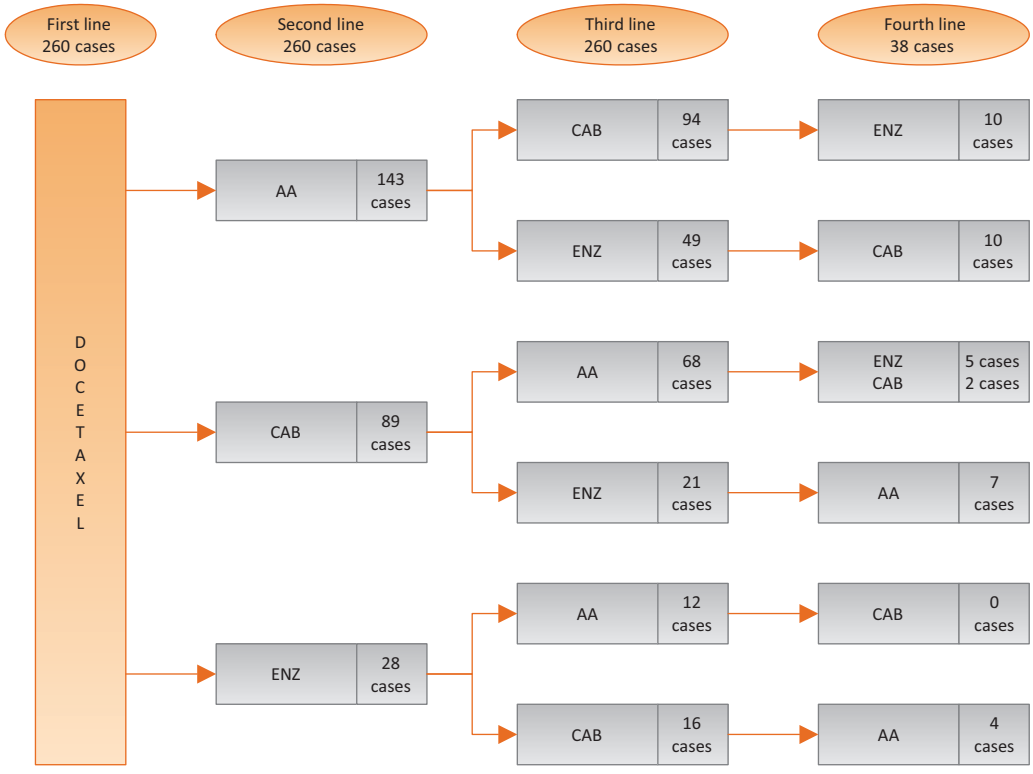

Fig. 1 – New agent–based treatments after docetaxel failure.
AA = abiraterone acetate; CAB = cabazitaxel; ENZ = enzalutamide.

biochemical progression (58.4%). After progression, 38 patients received a further NA as fourth-line treatment. At the time of analysis, 122 patients had died and 138 were still alive.

A ≥50% reduction in PSA levels was observed in 62 patients (bRR: 24%) and an objective response in 34 (oRR: 13%), with no statistically significant difference between the groups stratified on the basis of the drug received or the second- or third-line sequence (Supplementary Table 2).

Median PFS and OS from the start of third-line treatment were, respectively, 4 and 11 mo (once again with no significant difference between the drug or sequence groups) (Table 1, Supplementary Table 2).

The OS multivariate analysis (Table 2) showed statistically significant values for baseline performance status (PS) (patients with a PS of 2 had a worse prognosis: 6 vs 13 mo) (Supplementary Fig. 1), baseline haemoglobin levels (patients with haemoglobin levels ≤11 g/dl had a shorter OS: 7 vs 18 mo) (Supplementary Fig. 2), and baseline alkaline phosphatase levels (patients with alkaline phosphatase levels >278 IU/l had a shorter OS: 6 vs 13 mo) (Supplementary Fig. 3). By assessing the survival outcomes of all of the possible combinations of these factors, we identified three groups with different OS outcomes: patients with a PS of 2 associated with one or both of the other two factors (group 1; median OS: 5 mo), patients with only one of the prognostic factors or a combination of low haemoglobin and high alkaline phosphatase levels (group 2; median OS: 9 mo), and patients without any negative factors (group 3; median OS: 20 mo) (Fig. 2, Supplementary Table 3).

3.2. *Fourth-line clinical outcomes*

Among the 38 patients who received fourth-line treatment, bRR and oRR were, respectively, 16% and 8%, and the median PFS and OS were both 5 mo. The 3-mo landmark analysis of OS after third-line progression did not show any statistically significant difference between the patients who received a fourth-line treatment and those who did not (data not shown).

4. Discussion

To the best of our knowledge, this is the largest study of mCRPC patients receiving third-line NA treatment after the failure of docetaxel and another NA, and the first to provide data concerning the clinical outcomes of all three NA third-line treatments, and some concerning the administration of fourth-line NA treatment, of patients exposed to second- and third-line NAs.

Despite their sequential use, it was postulated that they may be subject to mechanisms of cross-resistance, as the androgen receptor machinery remains the ultimate target of all NAs [20–22], and previous exposure to one could affect the activity of another [23].

Table 3 shows that a number of published retrospective studies have described generally small series of patients who received a specific sequence of two NAs after the failure of docetaxel [5–14], most of which suggested that the third-line activity of NAs is less than that observed in the pivotal second-line trial. This was confirmed by our findings and is not surprising, because it can be expected that longer survival and the presence of more advanced disease will progressively reduce disease control. This assumption was indirectly confirmed by the comparison of the characteristics of our patients at the start of their third-line treatment with those observed at the start of the second line: Pain was more frequent ($p < 0.001$), and they had lower median haemoglobin levels ($p = 0.009$), and higher median levels of alkaline phosphatase ($p = 0.02$), lactate dehydrogenase ($p = 0.006$), and PSA ($p = 0.005$). The differences in these parameters, which are usually considered as having prognostic value, suggest more advanced disease and may explain the reduction in activity.

Table 2 – Cox proportional hazards analysis of third-line overall survival by variable of interest

	p value	Exp(B)	95% CI of exp(B)	
			Lower	Upper
Age (≤72 vs >72 yr)	0.453	1.170	0.777	1.762
Gleason score (≤7 vs >7)	0.147	0.744	0.499	1.109
Previous hormonal lines, no. (≤2 vs >2)	0.474	0.857	0.562	1.307
Time from diagnosis to mCRPC (≤51 vs >51 mo)	0.834	1.059	0.621	1.805
Hormone therapy before mCRPC (≤32 vs >32 mo)	0.910	1.031	0.606	1.753
Docetaxel lines, no. (1 vs >1)	0.463	1.229	0.708	2.133
Time from docetaxel to second-line therapy (≤11 vs >11 mo)	0.353	1.221	0.801	1.859
ECOG performance status (0–1 vs 2)	0.001	0.475	0.300	0.751
Pain (no vs yes)	0.332	0.811	0.532	1.238
Visceral disease pain (no vs yes)	0.174	0.729	0.463	1.149
Haemoglobin (≤11 vs >11 g/dl)	0.000	2.135	1.431	3.186
Alkaline phosphatase (≤278 vs >278 IU/l)	0.004	0.522	0.336	0.811
Lactate dehydrogenase (≤406 vs >406 IU/l)	0.527	0.867	0.557	1.349
Prostate-specific antigen (≤329 vs >329 IU/l)	0.173	0.738	0.476	1.143
Second-line PFS (≤5 vs >5 mo)	0.231	1.275	0.857	1.898

ECOG = Eastern Cooperative Oncology Group; Exp = exponential; CI = confidence interval; mCRPC = metastatic castration-resistant prostate cancer; PFS = progression-free survival.

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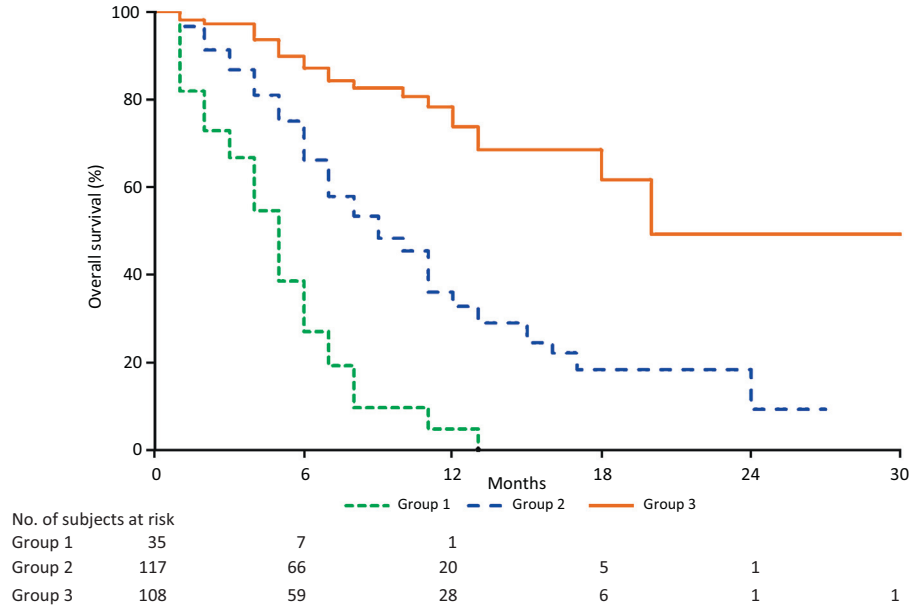

Fig. 2 – Overall survival from start of third-line treatment, by prognostic group (median values: group 1: 5 mo; group 2: 9 mo; group 3: 20 mo; log-rank $p < 0.001$).

Our retrospective analysis suffers from the main methodological limitations of its predecessors in assessing treatment outcomes: Activity measures such as the oRR and PFS can be greatly influenced by different policies of imaging frequency, which may shorten or lengthen PFS or fail to detect a radiologic response or progression, or by interpretation bias because objective responses are determined by individual physicians. Furthermore, although the bRR may better reflect mCRPC treatment activity in everyday clinical practice because PSA levels are routinely assessed, its value as a surrogate parameter is questionable. Consequently, OS remains the most reliable measure of clinical outcome and represented the main target of our analysis.

We found that OS from the start of third-line treatment was similar regardless of the NA used, and that it was not affected by the previously administered NA. The sequences involving the two hormonal NAs seemed to lead to less activity in the third line than that of the sequences in which CAB was administered before or after a hormonal NA, although the difference was not statistically significant (Supplementary Table 2). Our data, therefore, do not support the superiority of any of the three NAs in third-line treatment, regardless of the previously administered NA.

Although our data on the use of NAs in fourth-line treatment come from a small number of patients, they do not seem to support the routine use of NAs after a third-line failure, as their activity was highly limited.

Although based on retrospective data, our analysis did provide some interesting suggestions about the selection of patients for third-line NA treatment that are particularly relevant to the current debate concerning the economic sustainability of new drugs. The availability of a number of agents that are active on the same disease introduces the possibility of their sequential use, but they are expensive and, at a time of restricted resources, their use can only be justified if they offer a clear clinical benefit.

The evidence concerning the third- or fourth-line use of NAs in the treatment of mCRPC is very limited. As our results

Table 3 – Published papers on new-agent sequencing

Sequence	Authors	Patients, no.	Median age, yr	bRR	oRR	Median third-line PFS	Median third-line OS
AA → ENZ	Bianchini et al [5]	39	70	12.8	4.3	2.8	NR
	Schrader et al [8]	35	70	28.6	2.9	4.0	7.1
	Schmid et al [9]	35	72	10	2.8	3.1	7.5
	Badrising et al [10]	61	69	21	NR	3.0	7.9
	Thomsen et al [11]	24	72	17	NR	NR	4.8
	Thomson et al [12]	23	76	39.1	NR	2.8	8.5
ENZ → AA	Noonan et al [7]	30	70	3	11	3.85	12.5
	Loriot et al [6]	38	71	8	8	2.7	7.2
ABI → CABA	Al Nakouzi et al [14]	79	69	35.4	NR	4.4	15.8
AA/ENZ → CAB	Pezaro et al [13]	41	68.9	39	9	4.6	15.8

AA = abiraterone acetate; bRR = biochemical response rate; CAB = cabazitaxel; ENZ = enzalutamide NR = not reported; oRR = objective response rate; OS = overall survival; PFS = progression-free survival.

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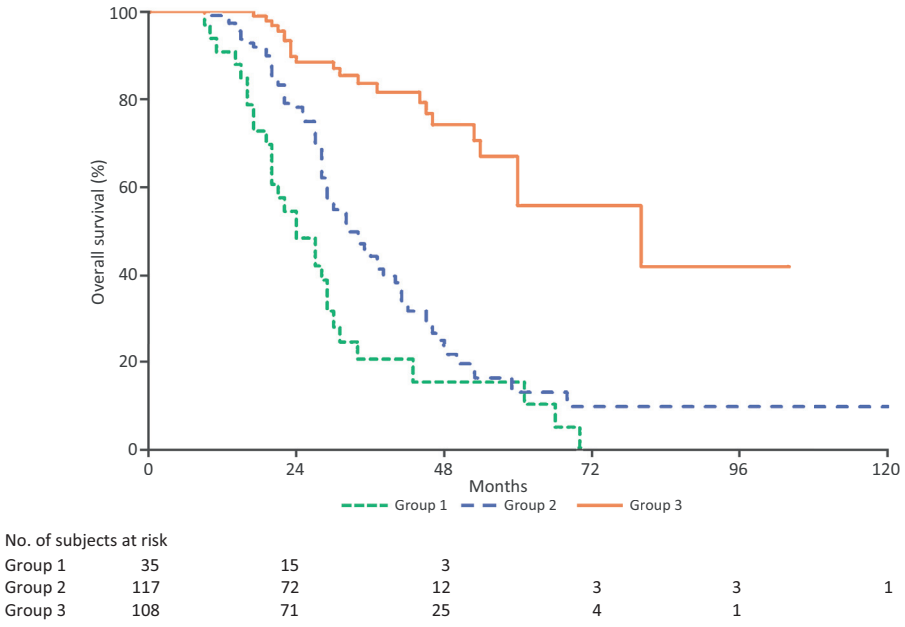

Fig. 3 – Overall survival from start of docetaxel by prognostic group (median values: group 1: 24 mo; group 2: 32 mo; group 3: 80 mo; log-rank $p < 0.001$).

suggest that the outcomes of all third-line NAs are similar, the main question is not which NA or which sequence to adopt, but whether it is possible to identify the patients who are more likely to receive a clinical benefit from third-line treatment. The addition of a second-line NA to first-line docetaxel led to longer OS in the pivotal trials of AA and CAB, which, respectively, indicated an expected median cumulative survival of 32.6 mo and 29 mo in the absence of subsequent NA treatment [24,25]. It is striking that our group 1 and 2 patients with negative prognostic profiles had a median OS of 24 mo and 32 mo, respectively, after their first docetaxel dose (similar to the cumulative survival found in the pivotal trials), whereas those with a better prognostic profile (group 3) had a median OS of 80 mo (Fig. 3). This suggests that in presence of features of more advanced disease (in our experience, some baseline characteristics such as worse PS, low haemoglobin levels, and high alkaline phosphatase levels), third-line NA may have low probability of disease control and should be used cautiously. It is worth noting that although limited by the small number of patients and based on everyday clinical practice outside of clinical trials, all the variables selected in our analysis were included in the prognostic model recently developed for patients treated with cabazitaxel after docetaxel [26].

The limitations of this study are mainly due its retrospective nature, the fact that the data were obtained from highly selected patients able to receive third-line treatment, and the small number of patients treated with some of the sequences (for example, ENZ was received by very few patients because it was not available in everyday clinical practice but only provided in CUPs). Consequently, our results do not allow any definite conclusion to be drawn concerning the similar activity of third-line NAs or the possibility of identifying groups with a different prognosis on the basis of the recognised factors; therefore, they need to be confirmed by prospective analyses of larger mCRPC populations.

5. Conclusions

Although retrospective, our study provides data from a sufficiently large number of patients treated with at least two successive NAs after docetaxel that suggest some clues for selecting patients who should receive further treatment after second-line treatment, even though these require confirmation in larger prospective studies. This is not only important in the light of the current debate concerning the economic sustainability of oncologic treatments, but also because the question of the sequential use of NAs will become even more pressing as they begin to be used to treat chemotherapy-naïve patients.

Author contributions: Orazio Caffo had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Caffo.
Acquisition of data: Caffo, De Giorgi, Fratino, Alesini, Zagonel, Facchini, Gasparro, Ortega, Tucci, Verderame, Campadelli, Lo Re, Procopio, Sabbatini, Donini, Morelli, Sartori, Zucali, Carrozza, D'Angelo, Vicario, Massari, Santini, Sava, Messina, Fornarini, La Torre, Ricotta, Aieta, Mucciarini, Zustovich, Macrini, Burgio, Santarossa, D'Aniello, Basso, Tarasconi, Cortesi, Buttigliero, Ruatta, Veccia, Conteduca, Maines.
Analysis and interpretation of data: Caffo, Galligioni.
Drafting of the manuscript: Caffo.
Critical revision of the manuscript for important intellectual content: Caffo, De Giorgi, Fratino, Alesini, Zagonel, Facchini, Gasparro, Ortega, Tucci, Verderame, Campadelli, Lo Re, Procopio, Sabbatini, Donini, Morelli, Sartori, Zucali, Carrozza, D'Angelo, Vicario, Massari, Santini, Sava, Messina, Fornarini, La Torre, Ricotta, Aieta, Mucciarini, Zustovich,

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eururo.2014.10.014.

References

[1] Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004;351:1502–12.
[2] De Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet 2010;376:1147–54.
[3] De Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 2011;364:1995–2005.
[4] Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012;367:1187–97.
[5] Bianchini D, Lorente D, Rodriguez-Vida A, et al. Antitumour activity of enzalutamide (MDV3100) in patients with metastatic castration-resistant prostate cancer (CRPC) pre-treated with docetaxel and abiraterone. Eur J Cancer 2014;50:78–84.
[6] Loriot Y, Bianchini D, Ileana E, et al. Antitumour activity of abiraterone acetate against metastatic castration-resistant prostate cancer progressing after docetaxel and enzalutamide (MDV3100). Ann Oncol 2013;24:1807–12.
[7] Noonan KL, North S, Bitting RL, Armstrong AJ, Ellard SL, Chi KN. Clinical activity of abiraterone acetate in patients with metastatic castration-resistant prostate cancer progressing after enzalutamide. Ann Oncol 2013;24:1802–7.
[8] Schrader AJ, Boegemann M, Ohlmann CH, et al. Enzalutamide in castration-resistant prostate cancer patients progressing after docetaxel and abiraterone. Eur Urol 2014;65:30–6.
[9] Schmid SC, Geith A, Boker A, et al. Enzalutamide after docetaxel and abiraterone therapy in metastatic castration-resistant prostate cancer. Adv Ther 2014;31:234–41.
[10] Badrising S, van der Noort V, van Oort IM, et al. Clinical activity and tolerability of enzalutamide (MDV3100) in patients with metastatic, castration-resistant prostate cancer who progress after docetaxel and abiraterone treatment. Cancer 2014;120:968–75.
[11] Thomsen FB, Roder MA, Rathenborg P, Brasso K, Borre M, Iversen P. Enzalutamide treatment in patients with metastatic castration-resistant prostate cancer progressing after chemotherapy and abiraterone acetate. Scand J Urol 2014;48:268–75.
[12] Thomson D, Charnley N, Parikh O. Enzalutamide after failure of docetaxel and abiraterone in metastatic castrate-resistant prostate cancer. Eur J Cancer 2014;50:1040–1.
[13] Pezaro CJ, Omlin AG, Altavilla A, et al. Activity of cabazitaxel in castration-resistant prostate cancer progressing after docetaxel and next-generation endocrine agents. Eur Urol 2014;66:459–65.
[14] Al Nakouzi N, Le Moulec S, Albigès L, et al. Cabazitaxel remains active in patients progressing after docetaxel followed by novel androgen receptor pathway targeted therapies. Eur Urol. In press. http://dx.doi.org/10.1016/j.eururo.2014.04.015
[15] Scher HI, Halabi S, Tannock I, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol 2008;26:1148–59.
[16] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–47.
[17] Contal C, O'Quigley J. An application of changepoint methods in studying the effect of age on survival in breast cancer. Comput Statist Data Anal 1999;30:253–70.
[18] Mandrekar J, Mandrekar S, Cha S. Cutpoint determination methods in survival analysis using SAS®. Presented at: SAS Users Group 28; March 30–April 2, 2003; Seattle, WA, USA.
[19] Williams C, Mandrekar J, Mandrekar S, et al. Finding optimal cutpoints for continuous covariates with binary and time-to-event outcomes. Mayo Foundation Technical Report Series, No. 79. Rochester, MN: Department of Health Sciences Research, Mayo Clinic; 2006.
[20] Efstathiou E, Titus M, Tsavachidou D, et al. Effects of abiraterone acetate on androgen signaling in castrate-resistant prostate cancer in bone. J Clin Oncol 2012;30:637–43.
[21] Tran C, Ouk S, Clegg NJ, et al. Development of a second-generation antiandrogen for treatment of advanced prostate cancer. Science 2009;324:787–90.
[22] Zhu ML, Horbinski CM, Garzotto M, Qian DZ, Beer TM, Kyprianou N. Tubulin-targeting chemotherapy impairs androgen receptor activity in prostate cancer. Cancer Res 2010;70:7992–8002.
[23] Van Soest RJ, van Royen ME, de Morree ES, et al. Cross-resistance between taxanes and new hormonal agents abiraterone and enzalutamide may affect drug sequence choices in metastatic castration-resistant prostate cancer. Eur J Cancer 2013;49:3821–30.
[24] Sartor AO, Oudard S, Ozguroglu M, et al. Survival benefit from first docetaxel treatment for cabazitaxel plus prednisone compared with mitoxantrone plus prednisone in patients with metastatic castration-resistant prostate cancer (mCRPC) enrolled in the TROPIC trial [abstract 4525]. J Clin Oncol 2011;29.
[25] Chi KN, Scher HI, Molina A, et al. Exploratory analysis of survival benefit and prior docetaxel (D) treatment in COU-AA-301, a phase III study of abiraterone acetate (AA) plus prednisone (P) in metastatic castration-resistant prostate cancer (mCRPC) [abstract 15]. J Clin Oncol 2012;30(Suppl 5).
[26] 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 2013;105:1729–37.

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