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Postprogression Survival of Patients with Metastatic Hormone-sensitive Prostate Cancer who Received Darolutamide or Placebo in Combination with Docetaxel and Androgen Deprivation Therapy: Post Hoc Analysis of the Phase 3 ARASENS Trial

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Abstract

Background and objective: Darolutamide + docetaxel + androgen-deprivation therapy (ADT) significantly improved overall survival (OS) and delayed time to disease progression versus docetaxel + ADT in ARASENS (NCT02799602). We report data on subsequent antineoplastic therapies received and associated OS after discontinuation of the study treatment.

Methods: Patients were randomized 1:1 to darolutamide 600 mg orally twice daily or placebo, both with docetaxel + ADT. After treatment discontinuation, patients entered follow-up periods during which information on subsequent therapies and survival was collected. Postprogression OS was estimated using the Kaplan-Meier method as the time from initiation of first subsequent therapy to death and was compared in multivariable Cox regression analyses.

Key findings and limitations: Of the 1305 patients treated, 315/651 who received darolutamide and 495/654 who received placebo entered follow-up, and 57% and 76% of these patients, respectively, received subsequent therapy. In the darolutamide group, first subsequent therapy was either an androgen receptor pathway inhibitor (ARPI; 63%) or a taxane (29%), and corresponding postprogression median OS was similar (13 vs 11 mo; hazard ratio [HR] 1.25, 95% confidence interval [CI] 0.50–3.09). In the placebo group, first subsequent therapy was an ARPI in 78% and a taxane in 19% of cases, with worse OS for the taxane versus ARPI subgroup (14 vs 23 mo; HR 3.18, 95% CI 1.56–6.50). The main limitation of these analyses is their post hoc nature.

Conclusions and clinical implications: For ARPI-naïve patients who did not receive darolutamide in ARASENS, postprogression survival was longer with subsequent ARPI versus

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taxane treatment, but OS remained shorter in comparison to the darolutamide group. Decisions on postprogression therapy should consider disease volume and drugs with different mechanisms of action.

ADVANCING PRACTICE

What does this study add?

For patients with metastatic hormone-sensitive prostate cancer, darolutamide in combination with docetaxel + androgen deprivation therapy (ADT) improved survival and delayed progression to metastatic castration-resistant prostate cancer in comparison to placebo + docetaxel + ADT in the ARASENS trial. This post hoc analysis evaluated overall survival for patients who received subsequent antineoplastic therapy after discontinuing the study treatment. For patients who initially received darolutamide + docetaxel + ADT, there were minimal differences in survival by type of subsequent therapy. For patients who initially received placebo + docetaxel + ADT, an androgen receptor pathway inhibitor (ARPI) as subsequent therapy was associated with longer survival in comparison to subsequent taxane chemotherapy. This finding highlights the effectiveness of ARPIs in patients with metastatic prostate cancer and supports the earlier use of darolutamide as upfront treatment intensification along with docetaxel + ADT.

Clinical Relevance

The ARASENS trial established the concept of triplet therapy for patients with metastatic hormone-sensitive prostate cancer, demonstrating that adding darolutamide to docetaxel and ADT significantly improved survival compared to docetaxel and ADT alone. However, the optimal approach to managing disease progression following this intensified treatment regimen remains uncertain. This post hoc analysis provides valuable insights into oncological outcomes after disease progression and study treatment discontinuation. Notably, patients who did not receive darolutamide initially derived greater survival benefits from subsequent treatment with an ARPI than from additional chemotherapy. In contrast, among patients who had previously received darolutamide, the survival outcomes were similar regardless of whether they received an ARPI or chemotherapy after progression. Importantly, the findings confirm that the early inclusion of darolutamide in the treatment regimen delivers substantial survival benefits, further reinforcing the rationale for adopting triplet therapy in this patient population. Associate Editor: Gianluca Gianarini, MD

Patient Summary

The ARASENS trial showed that the addition of darolutamide (a second-generation hormone therapy [2GHT]) to chemotherapy and standard HT increased survival for patients with prostate cancer and the time for which their cancer responded to HT. When the cancer started to grow again, there was no great difference in survival time between 2GHT and chemotherapy as further treatment for patients who had already received darolutamide. However, for patients who had not received darolutamide, further treatment with 2GHT led to longer survival.

1. Introduction

The treatment landscape for metastatic hormone-sensitive prostate cancer (mHSPC) has evolved over recent years on the basis of results from randomized clinical trials [1–7]. Current treatment guidelines for mHSPC recommend combining androgen deprivation therapy (ADT) with a second-generation androgen receptor pathway inhibitor (ARPI; eg, abiraterone, apalutamide, enzalutamide) or a triple combination of ADT + docetaxel and either abiraterone or darolutamide [8–10].

With ARPIs ± chemotherapy now used in earlier stages of mHSPC, it is unclear what survival benefit can be expected from these agents when disease progresses to metastatic castration-resistant prostate cancer (mCRPC). Clinical trials of first-line therapies for mCRPC, including docetaxel (TAX 327 [11]), enzalutamide (PREVAIL [12]), abiraterone acetate (COU-AA-302 [13]), and radium-223 (ALSYMPCA [14]), were conducted before these therapies were available for mHSPC, and therefore may not reflect outcomes for patients who received these treatments for mHSPC. Potential cross-resistance between ARPIs could reduce treatment efficacy when they are used in sequence [15].

The ARASENS trial demonstrated the efficacy and safety of darolutamide versus placebo in combination with docetaxel and ADT in patients with mHSPC [7]. The risk of death was significantly reduced by 32.5% with darolutamide versus placebo even though 76% of patients in the placebo group received subsequent life-prolonging systemic antineoplastic therapy. Progression to mCRPC and time to initiation of subsequent systemic antineoplastic therapy were also significantly delayed with darolutamide. Health-related quality of life (HRQoL) was maintained in patients receiving darolutamide [7,16]. Given these

benefits, patients receiving darolutamide + docetaxel + ADT versus docetaxel + ADT spent a longer time in the mHSPC stage, which is associated with better HRQoL in comparison to mCRPC [17]. Here we report an exploratory post hoc analysis of subsequent antineoplastic therapies received after discontinuation of study treatment in ARASENS and the associated postprogression survival, taking into consideration specific covariates at study baseline and at the start of subsequent therapy.

2. Patients and methods

2.1. Study design and patients

For patients with mHSPC, the international, randomized, double-blind, placebo-controlled, phase 3 ARASENS trial (NCT02799602) evaluated darolutamide versus placebo, both plus docetaxel and ADT. The primary results have been published [7] and the methods are summarized here.

Eligible adult patients had confirmed metastatic prostate cancer on conventional imaging and Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, and were candidates for docetaxel and ADT in the investigator's opinion. Patients were excluded if they had only regional lymph node metastases or had received ADT more than 12 weeks (wk) before randomization, or second-generation ARPIs, chemotherapy, or immunotherapy before randomization.

All patients received ADT or underwent orchiectomy within 12 wk before randomization. Patients were randomized 1:1 to receive darolutamide 600 mg orally twice daily or matched placebo, and randomization was stratified by metastatic stage and by alkaline phosphatase level. Docetaxel (75 mg/m^2 for six cycles) was initiated within 6 wk after randomization.

Patients received study treatment until disease progression, a change in antineoplastic therapy, unacceptable toxicity, patient or physician decision, death, or non-adherence. Disease progression to mCRPC was defined as prostate-specific antigen (PSA) progression with serum testosterone <0.5 ng/ml, or radiologic progression of soft-tissue, visceral, or bone lesions. High-volume disease was defined according to CHAARTED criteria [18] as the presence of visceral metastases or at least four bone lesions with at least one beyond the vertebral bodies and pelvis.

Study treatment was unblinded only for an unexpected serious adverse reaction, and not for subsequent treatment decisions.

2.2. Assessments

After treatment discontinuation, patients entered active and long-term survival follow-up periods, during which prospective assessments occurred approximately every 12 wk. The two outcomes of this post hoc analysis were the number of patients who received subsequent life-prolonging systemic antineoplastic therapies (abiraterone acetate, apalutamide, enzalutamide, cabazitaxel, docetaxel, radium-223, sipuleucel-T, or lutetium-177 vipivotide tetraxetan) during follow-up, and survival outcomes for these patients. Study-site physicians in consultation with patients/caregivers made the decision to initiate subsequent therapy. Patients were not included in the analysis of subsequent therapy if they reached the study end without initiating subsequent therapy, terminated the study at the end of treatment without follow-up information, or discontinued follow-up without receiving subsequent therapy.

2.3. Statistical analyses

Subgroups were defined by the most common subsequent therapies, either an ARPI (abiraterone or enzalutamide) or taxane chemotherapy (cabazitaxel or docetaxel), to provide sufficient patient numbers. Demographics and baseline disease characteristics are reported descriptively for these subgroups. Reasons for and time to first subsequent therapies are summarized with differences and Wald confidence intervals (CIs). Postprogression survival was defined as time from the start of the first subsequent therapy to death, with median values and 95% CIs computed using Kaplan-Meier estimates. Cox regression analyses of overall survival (OS) were conducted from the start of subsequent therapy by treatment group taking into consideration prognostic factors (eg, age, ECOG PS, race, Gleason score, metastatic burden), reasons for and timing of subsequent therapy, and subsequent therapy received.

3. Results

3.1. Patients

Of 1305 patients included in ARASENS, 651 received darolutamide and 654 received placebo, both with docetaxel + ADT (Supplementary Fig. 1). At the primary data cutoff date (October 25, 2021), more patients in the darolutamide arm than in the placebo arm were still receiving treatment (46% vs 19%) [7]. As previously reported, fewer patients in the darolutamide arm than in the placebo arm experienced disease progression, with event-free probabilities at month 24 of 72% (95% CI 69–76%) and 41% (95% CI 37–45%), respectively. The median time to initiation of subsequent therapy was not reached in the darolutamide arm (event-free rate at 24 mo: 76%, 95% CI 73–79%), and was 25 mo in the placebo arm (event-free rate at 24 mo: 52%, 95% CI 48–56%).

3.2. Subsequent antineoplastic therapies after discontinuation of study treatment

After discontinuation of the study treatment, 315 patients from the darolutamide + docetaxel + ADT arm entered follow-up and 57% (n = 179) received subsequent antineoplastic therapies; 495 patients from the placebo + doce taxel + ADT arm entered follow-up and 76% (n = 374) received subsequent antineoplastic therapies (Fig. 1). The primary reasons for patients not receiving subsequent therapy were death and patient withdrawal. In the darolutamide group, the first subsequent therapy was an ARPI (63% of patients) or a taxane (29% of patients). In the placebo group, 78% of patients started first subsequent therapy with an ARPI (enzalutamide or abiraterone). Baseline characteristics were generally similar between the subsequent therapy subgroups in the darolutamide and placebo arms,

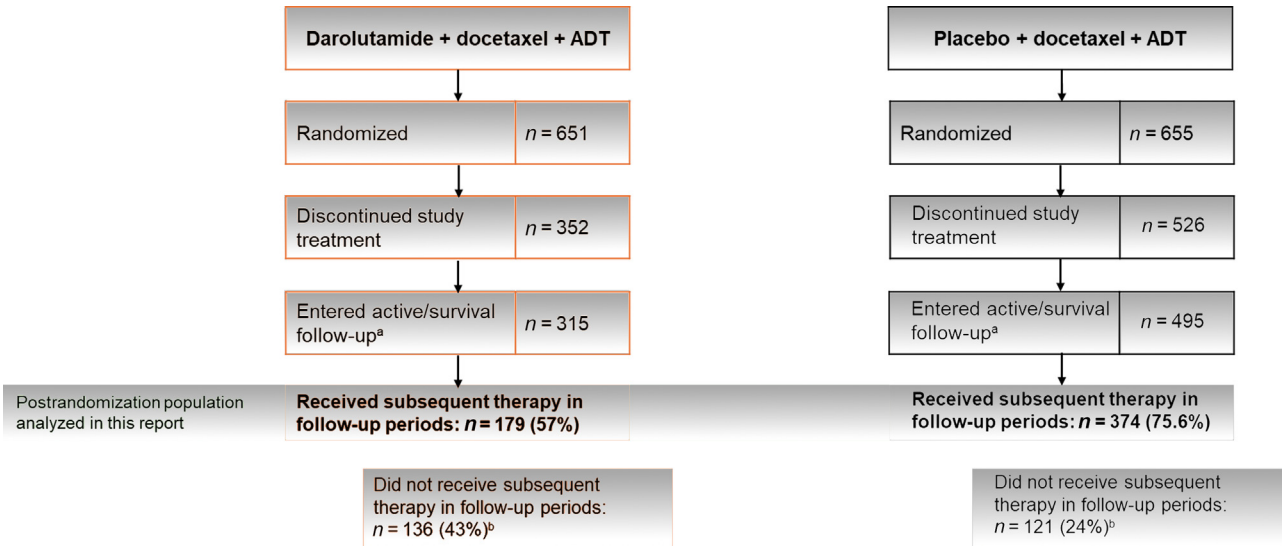

Fig. 1 – Patient disposition in the ARASENS study from treatment discontinuation through follow-up at the data cutoff date (October 25, 2021), defining the population who initiated subsequent therapy and analyzed in this report. ADT = androgen-deprivation therapy. [a]Not all patients who discontinued treatment entered active or survival follow-up. [b]The primary reasons for discontinuing follow-up were death and patient withdrawal.

Table 1 – Patient demographics and disease characteristics at study baseline for subgroups stratified by first subsequent therapy[a]

Parameter	Abiraterone or enzalutamide		Cabazitaxel or docetaxel	
	Darolutamide + docetaxel + ADT (*n* = 112)	Placebo + docetaxel + ADT (*n* = 290)	Darolutamide + docetaxel + ADT (*n* = 52)	Placebo + docetaxel + ADT (*n* = 71)
Median age, yr (IQR)	68 (60–72)	67 (62–73)	66 (61–71)	65 (61–70)
Race, *n* (%)				
White	57 (51)	124 (43)	32 (62)	39 (55)
Asian	44 (39)	126 (43)	11 (21)	18 (25)
Black	3 (2.7)	12 (4.1)	3 (5.8)	7 (10)
Not reported	8 (7.1)	28 (9.7)	6 (12)	6 (8.5)
Region, *n* (%)				
North America	19 (17)	57 (20)	8 (15)	10 (14)
Asia Pacific	45 (40)	124 (43)	11 (21)	18 (25)
Rest of the world	48 (43)	109 (38)	33 (64)	43 (61)
ECOG performance status 1, *n* (%)	34 (30)	76 (26)	20 (39)	23 (32)
Gleason score ≥8 at initial diagnosis, *n* (%)	95 (85)	242 (83)	40 (77)	56 (79)
Stage M1 (de novo) at initial diagnosis, *n* (%)	103 (92)	266 (92)	46 (89)	61 (86)
Extent of metastatic disease, *n* (%)				
LNM only	1 (0.9)	8 (2.8)	0	1 (1.4)
BM ± LNM	95 (85)	234 (81)	38 (73)	54 (76)
VM ± LNM ± BM	16 (14)	48 (17)	14 (27)	16 (23)
High-volume disease, *n* (%)[b]	100 (89)	232 (80)	48 (92)	63 (89)
Median PSA, ng/ml (IQR)[c]	48 (6.7–266)	30 (5.9–116)	20 (5.4–87)	38 (7.3–202)
Alkaline phosphatase ≥ULN, *n* (%)[c]	84 (75)	172 (59)	36 (69)	41 (58)
Median TIST, mo (IQR)	18 (13–26)	17 (11–27)	20 (12–28)	14 (8.3–19)

ADT = androgen deprivation therapy; BM = bone metastases; ECOG = Eastern Cooperative Oncology Group; IQR = interquartile range; LNM = lymph node metastases (nonregional); PSA = prostate-specific antigen; TIST = time to initiation of subsequent antineoplastic therapy; ULN = upper limit of normal; VM = visceral metastases.

[a] Values may not add up to 100% because of missing information for some patients.

[b] High-volume disease was defined according to the CHAARTED criteria [18] as the presence of VM or at least four bone lesions, with at least one beyond the vertebral bodies and pelvis.

[c] Values were centrally assessed and samples were obtained while patients were receiving ADT.

except more patients in the taxane group had visceral disease (Table 1). In the placebo arm, 58% (295/508) of patients with high-volume disease and 45% (66/146) of patients with low-volume disease received an ARPI or taxane as first subsequent therapy. In the darolutamide arm, 30% (148/497) of patients with high-volume disease and only 10% (16/154) of patients with low-volume disease received an ARPI or taxane as first subsequent therapy. Information on all subsequent therapies by disease volume has been reported by Hussain et al [19].

The most common reason for initiating subsequent antineoplastic therapy was radiologic or clinical disease progression. Patients receiving subsequent treatment with ARPIs versus taxanes were more likely to have PSA progression,

with a 15% difference in both the darolutamide and placebo groups (Table 2). Radiologic or clinical progression remained the most frequent reason for reintroduction of taxane therapy in both groups (75% and 61%, respectively).

The mean (standard deviation) time to initiation of subsequent taxane therapy was 5.8 mo longer (0.03–12) for docetaxel than for cabazitaxel in the darolutamide group, and 1.3 mo longer (−3.6 to 6.1) for docetaxel than for cabazitaxel in the placebo group (Supplementary Table 1). The difference in mean time to subsequent therapy between abiraterone and enzalutamide was <1 mo in both the darolutamide group and the placebo group.

3.3. *Postprogression survival*

For patients who initially received darolutamide + docetaxel + ADT, the median postprogression OS was 13 (95% CI 10–17) mo after receiving an ARPI and 11 (95% CI 7.2–14) mo after receiving a taxane (Fig. 2A). Multivariable analysis showed that high-volume disease and a shorter time from the end of docetaxel use to initiation of subsequent therapy were associated with worse survival, but there were no differences in OS between ARPI and taxane therapy after progression (Supplementary Table 2). For patients who initially received placebo + docetaxel + ADT, median postprogression OS was 23 (95% CI 21–27) mo in the ARPI subgroup and 14 (95% CI 11–21) mo in the taxane subgroup (Fig. 2B). High-volume disease, a shorter time from docetaxel to subsequent therapy, and clinical or radiologic progression versus PSA progression were associated with shorter survival in the placebo group, while subsequent ARPI versus taxane therapy was associated with longer OS versus chemotherapy (Supplementary Table 2).

4. Discussion

Progression of prostate cancer to mCRPC carries a high human and economic burden, with poor HRQoL, particularly in patients with bone metastases and associated pain, a risk of fractures, and a potential need for treatment [20,21]. The Prostate Cancer Disease Specific Programme surveyed patients with mHSPC (n = 376) and mCRPC (n = 331) to determine the effects of disease on HRQoL, including pain [17]. Patients with mCRPC reported the lowest HRQoL scores and highest pain scores. Therefore, delaying progression to mCRPC is an important treatment goal for patients and their caregivers to maintain the highest possible HRQoL for the longest time.

In ARASENS, most patients had de novo metastatic disease. The group receiving darolutamide + docetaxel + ADT stayed on treatment without disease progression for more than 2 yr longer than the group receiving placebo + docetaxel + ADT. Median OS was not reached in the darolutamide group and was 48.9 mo in the placebo group [7]. Approximately 50% of patients in the placebo group received subsequent therapy independent of disease volume. This finding emphasizes that patients with de novo mHSPC are prone to poor disease outcomes, including progression to mCRPC, a decline in HRQoL, and a need for additional effective therapy. In the darolutamide group, only 10% of patients with low-volume disease and 30% with high-volume disease received subsequent therapy. The sustained effect of the darolutamide combination in patients with de novo mHSPC independent of disease volume shows the benefit of early treatment intensification in this patient population.

We analyzed subsequent therapy received after discontinuation of the study treatment and postprogression survival. It is important to remember that ARASENS was a placebo-controlled trial and unblinding of the study treatment was not allowed at the time of disease progression. Considering the limited toxicity and the absence of specific side effects with darolutamide, it was impossible for the investigator to guess what treatment the patient received during the trial.

Our findings regarding initiation and types of subsequent therapies received in ARASENS corroborate those reported in other clinical trials evaluating ARPI + ADT ± docetaxel combination therapy in patients with mHSPC. Consistently across the ARCHES, TITAN, and PEACE-1 studies, fewer

Table 2 – Reasons for starting subsequent antineoplastic therapy by randomized treatment group in ARASENS

Reason for subsequent therapy[a]	Darolutamide + DOC + ADT (n = 179)			Placebo + DOC + ADT (n = 374)		
	Patients, n (%)		Δ, %	Patients, n (%)		Δ, %
	ARPI[b] (n = 112)	Taxane[c] (n = 52)	(95% CI)	ARPI[b] (n = 290)	Taxane[c] (n = 71)	(95% CI)
Radiologic or clinical progression[d]	68 (61)	39 (75)	−14 (−29 to 0.6)	146 (50)	43 (61)	−10 (−23 to 2.5)
PSA progression[e]	34 (30)	8 (15)	15 (2.0–28)	116 (40)	18 (25)	15 (3.1–26)
Adverse event/laboratory toxicity	2 (1.8)	2 (3.8)	n/a	0	1 (1.4)	n/a

Δ = difference in reason for subsequent therapy, with Wald CI; ADT = androgen deprivation therapy; ARPI = androgen receptor pathway inhibitor; CI = confidence interval; DOC = docetaxel; n/a = not applicable; PSA = prostate-specific antigen.

[a] Other/unknown reasons were reported for 8 patients receiving an ARPI and 3 patients receiving a taxane in the darolutamide group, and for 28 patients receiving an ARPI and 9 patients receiving a taxane in the placebo group.

[b] First subsequent therapy with abiraterone or enzalutamide.

[c] First subsequent therapy with cabazitaxel or docetaxel.

[d] Radiologic progression was defined as bone, soft-tissue, or visceral lesions on conventional imaging; clinical progression was defined as symptomatic progressive disease or a change of antineoplastic therapy that was not defined by radiologic or PSA progression.

[e] PSA progression was defined as a relative PSA increase of ≥25% above the nadir and an absolute increase ≥2 ng/ml above the nadir ≥12 wk after randomization, confirmed by a second assessment ≥3 wk later, with serum testosterone <0.5 ng/ml.

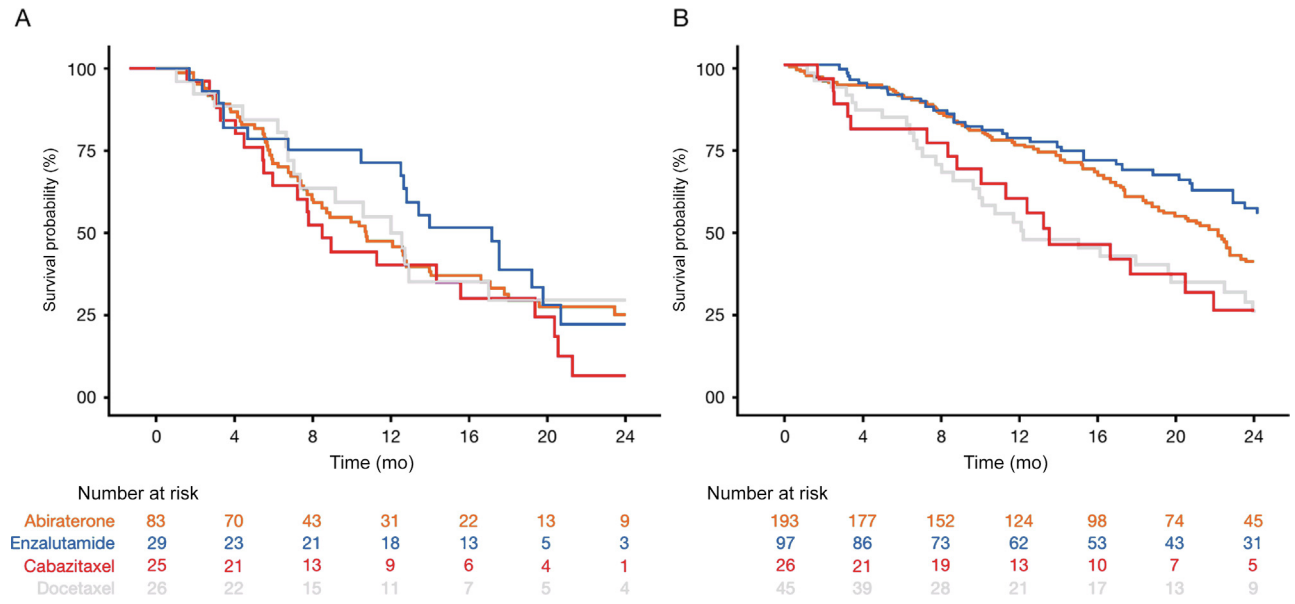

Fig. 2 – Postprogression survival stratified by first subsequent therapy (abiraterone, dark green; enzalutamide, light green; cabazitaxel, dark purple; docetaxel, light purple) in the (A) darolutamide + docetaxel + androgen deprivation therapy (ADT) and (B) placebo + docetaxel + ADT arms. Ten patients in the darolutamide arm and eight in the placebo arm received radium-223 as subsequent therapy, and five patients in each treatment arm received apalutamide, sipuleucel-T, lutetium-177 vipivotide tetraxetan, or combinations as their first subsequent therapy without an androgen receptor pathway inhibitor, chemotherapy, or radium-223.

patients who had received intensified treatment with an ARPI started subsequent therapy in comparison to patients who had received placebo [1–3]. The most common subsequent therapies in these trials were docetaxel, cabazitaxel, abiraterone, and enzalutamide.

Following publication of results from PREVAIL and COU-AA-302, abiraterone and enzalutamide became standards of care for patients whose disease progressed on ADT, independent of prior docetaxel therapy [12,22,23]. Docetaxel rechallenge was not supported by high-level evidence, and cabazitaxel seems to be preferred over an ARPI only in patients with more aggressive disease [22,24]. For patients who initially received placebo in ARASENS, postprogression survival after receiving an ARPI was 23 mo, which is consistent with data from enzalutamide and abiraterone trials. OS for patients who received enzalutamide was 36 mo in an updated analysis of PREVAIL (pre-docetaxel) [25] and 18 mo in AFFIRM (post-docetaxel) [26]. OS for patients who received abiraterone was 35 mo in the final analysis of COU-AA-302 (pre-docetaxel) [13] and 15 mo in COU-AA-301 (post-docetaxel) [27]. In ARASENS, postprogression survival after receipt of a second taxane was shorter at 11 mo. In the TROPIC cabazitaxel registration trial, median OS was 15 mo [28], similar to that observed in AFFIRM and COU-AA-301. We hypothesize that physicians selected patients with poorer prognosis to receive a taxane, consistent with the APCCC recommendation [22].

For patients who initially received darolutamide, postprogression survival with ARPI therapy was shorter at 13 mo, suggesting cross-resistance between ARPIs. The CARD trial randomized patients previously treated with docetaxel and abiraterone or enzalutamide to receive cabazitaxel or the ARPI that they did not receive previously [29]. Median OS was better with cabazitaxel (14 mo) than with an ARPI (11 mo), with a hazard ratio for death of 0.64 (95% CI 0.46–0.89; $p = 0.008$). These results are similar to the postprogression survival in the ARASENS darolutamide group of 11 mo for patients who received subsequent taxane therapy and 13 mo for those who received a different ARPI.

Two covariates, high-volume disease and a shorter time from the end of docetaxel to subsequent therapy, were associated with worse survival in both subsequent therapy cohorts, consistent with literature showing that these factors are prognostic for more aggressive mHSPC [30,31]. In the placebo arm, survival was better for patients who started subsequent therapy at PSA progression than for those who started at clinical or radiologic progression. Whether this is an effect of early treatment initiation or different disease biology leading to different types of progression remains uncertain. There is limited clinical trial information to guide subsequent treatment selection on disease progression for patients with mHSPC who initially receive intensified therapy. Our analysis revealed that for ARPI-naïve patients, the first ARPI exposure provided longer postprogression survival than subsequent taxane therapy did. For those who initially received intensified ARPI therapy, subsequent ARPI treatment was not associated with worse survival than subsequent taxane therapy; however, survival times in the subsequent treatment period were shorter than those during initial ARPI therapy. Results from a phase 2 crossover study and subsequent meta-analysis support alternation of ARPIs in patients with mCRPC on the basis of a longer time to second PSA progression (but no significant difference in OS) with the sequence abiraterone → enzalutamide versus enzalutamide → abiraterone [32–34]. Given the modest response to second-line APRI therapy, treatment selection should also include other therapies available.

This report of postprogression survival in ARASENS is limited by its exploratory, post hoc nature for a subgroup of patients who entered follow-up and received subsequent therapy. Baseline disease characteristics and covariates at initiation of subsequent therapy were considered in multivariable analyses; however, other confounders may affect the results. In addition, some recently approved treatments, including lutetium-177 vipivotide tetraxetan and poly-ADP ribose polymerase inhibitors, were not available at the time of ARASENS. Despite the remarkable progress made in this field, there is still a need for new drugs with different mechanisms of action to further improve outcomes for patients with advanced prostate cancer.

5. Conclusions

For ARPI-naïve patients who received chemotherapy for mHSPC in ARASENS, subsequent ARPI therapy versus chemotherapy was associated with better postprogression survival, particularly for patients with PSA progression. For patients who received early treatment intensification with darolutamide + ADT + docetaxel, subsequent ARPI therapy was associated with similar OS to that with subsequent chemotherapy. Postprogression survival was shorter for patients with high-volume disease and those with a shorter time to subsequent therapy. Further assessment of subsequent treatments in patients who progress after initial treatment of mHSPC is needed.

Author contributions: Marc-Oliver Grimm 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: Grimm, Smith, Hussain, Saad, Fizazi, Verholen, Tombal.
Acquisition of data: Grimm, Smith, Hussain, Saad, Fizazi, Tombal.
Analysis and interpretation of data: All authors.
Drafting of the manuscript: All authors.
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Supplementary data

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References

[1] Armstrong AJ, Azad AA, Iguchi T, et al. Improved survival with enzalutamide in patients with metastatic hormone-sensitive prostate cancer. J Clin Oncol 2022;40:1616–22.
[2] Chi KN, Chowdhury S, Bjartell A, et al. Apalutamide in patients with metastatic castration-sensitive prostate cancer: final survival analysis of the randomized, double-blind, phase III TITAN study. J Clin Oncol 2021;39:2294–303.
[3] Fizazi K, Foulon S, Carles J, et al. Abiraterone plus prednisone added to androgen deprivation therapy and docetaxel in de novo metastatic castration-sensitive prostate cancer (PEACE-1): a multicentre, open-label, randomised, phase 3 study with a 2 × 2 factorial design. Lancet 2022;399:1695–707.
[4] Fizazi K, Tran N, Fein L, et al. Abiraterone acetate plus prednisone in patients with newly diagnosed high-risk metastatic castration-sensitive prostate cancer (LATITUDE): final overall survival analysis of a randomised, double-blind, phase 3 trial. Lancet Oncol 2019;20:686–700.
[5] James ND, Spears MR, Sydes MR. Abiraterone in metastatic prostate cancer. N Engl J Med 2017;377:1696–7.
[6] Kyriakopoulos CE, Chen YH, Carducci MA, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer: long-term survival analysis of the randomized phase III E3805 CHAARTED trial. J Clin Oncol 2018;36:1080–7.
[7] Smith MR, Hussain M, Saad F, et al. Darolutamide and survival in metastatic, hormone-sensitive prostate cancer. N Engl J Med 2022;386:1132–42.
[8] Cornford P, Tilki D, van den Bergh RCN, et al. EAU-EANM-ESTRO-ESUR-ISUP-SIOG guidelines on prostate cancer. Arnhem, The Netherlands: European Association of Urology; 2024.
[9] Fizazi K, Gillessen S, ESMO Guidelines Committee. Updated treatment recommendations for prostate cancer from the ESMO Clinical Practice Guideline considering treatment intensification and use of novel systemic agents. Ann Oncol 2023;34:557–63.
[10] Lowrance W, Dreicer R, Jarrard DF, et al. Updates to advanced prostate cancer: AUA/SUO Guideline (2023). J Urol 2023;209:1082–90.
[11] Berthold DR, Pond GR, Soban F, de Wit R, Eisenberger M, Tannock IF. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer: updated survival in the TAX 327 study. J Clin Oncol 2008;26:242–5.
[12] Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med 2014;371:424–33.
[13] 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 (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol 2015;16:152–60.
[14] 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.
[15] Cattrini C, Espana R, Mennitto A, et al. Optimal sequencing and predictive biomarkers in patients with advanced prostate cancer. Cancers 2021;13:4522.
[16] Fizazi K, Smith MR, Hussain M, et al. 1360MO Quality of life and patient-relevant endpoints with darolutamide in the phase III ARASENS study. Ann Oncol 2022;33(Suppl 2):S1162.
[17] Boye M, Ribbans A, Leith A, Clayton E, Butcher J, Rybowski S. Real-world health-related quality of life and caregiver need in patients with metastatic hormone-sensitive and metastatic castration-resistant prostate cancer. J Clin Oncol 2022;40(6 Suppl):54.
[18] Sweeney CJ, Chen YH, Carducci M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. N Engl J Med 2015;373:737–46.
[19] Hussain M, Tombal B, Saad F, et al. Darolutamide plus androgen-deprivation therapy and docetaxel in metastatic hormone-sensitive prostate cancer by disease volume and risk subgroups in the phase III ARASENS trial. J Clin Oncol 2023;41:3595–607.
[20] Kretschmer A, van den Bergh RCN, Martini A, et al. Assessment of health-related quality of life in patients with advanced prostate cancer-current state and future perspectives. Cancers 2021;14:147.
[21] Leaning D, Kaur G, Morgans AK, Ghouse R, Mirante O, Chowdhury S. Treatment landscape and burden of disease in metastatic castration-resistant prostate cancer: systematic and structured literature reviews. Front Oncol 2023;13:1240864.
[22] Gillessen S, Bossi A, Davis ID, et al. Management of patients with advanced prostate cancer-metastatic and/or castration-resistant prostate cancer: report of the Advanced Prostate Cancer Consensus Conference (APCCC) 2022. Eur J Cancer 2023;185:178–215.
[23] Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med 2013;368:138–48.
[24] Gillessen S, Armstrong A, Attard G, et al. Management of patients with advanced prostate cancer: report from the Advanced Prostate Cancer Consensus Conference 2021. Eur Urol 2022;82:115–41.
[25] Armstrong AJ, Lin P, Tombal B, et al. Five-year survival prediction and safety outcomes with enzalutamide in men with chemotherapy-naive metastatic castration-resistant prostate cancer from the PREVAIL trial. Eur Urol 2020;78:347–57.
[26] 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.
[27] 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.
[28] 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.
[29] de Wit R, de Bono J, Sternberg CN, et al. Cabazitaxel versus abiraterone or enzalutamide in metastatic prostate cancer. N Engl J Med 2019;381:2506–18.
[30] Francini E, Gray KP, Xie W, et al. Time of metastatic disease presentation and volume of disease are prognostic for metastatic hormone sensitive prostate cancer (mHSPC). Prostate 2018;78:889–95.
[31] Tewari AK, Gillessen S, Sweeney CJ. Metastatic prostate cancer: in search of more granularity. J Clin Oncol 2021;39:2968–9.
[32] Khalaf DJ, Annala M, Taavitsainen S, et al. Optimal sequencing of enzalutamide and abiraterone acetate plus prednisone in metastatic castration-resistant prostate cancer: a multicentre, randomised, open-label, phase 2, crossover trial. Lancet Oncol 2019;20:1730–9.
[33] Maughan BL, Antonarakis ES. Does sequencing order of antiandrogens in prostate cancer matter? Nat Rev Urol 2020;17:197–8.
[34] Mori K, Miura N, Mostafaei H, et al. Sequential therapy of abiraterone and enzalutamide in castration-resistant prostate cancer: a systematic review and meta-analysis. Prostate Cancer Prostat Dis 2020;23:539–48.