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Optimal sequencing of enzalutamide and abiraterone plus prednisone in metastatic castration-resistant prostate cancer: a multi-centre, randomized, phase II trial

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Abstract

Background

Abiraterone + prednisone (abiraterone) and enzalutamide are both indicated for the treatment of metastatic castration-resistant prostate cancer (mCRPC). We aimed to determine the best sequence in which to utilize both agents as well as their second-line efficacy.

Methods

In this multicentre, randomized, open-label phase II crossover trial conducted across 6 cancer centres in British Columbia, Canada, patients ≥ 18 years with newly-diagnosed mCRPC without neuroendocrine differentiation and ECOG performance status ≤ 2 were randomized 1:1 using simple randomization to receive abiraterone 1000 mg orally daily plus prednisone 5 mg orally twice daily followed by enzalutamide 160 mg orally daily (arm A), or the opposite sequence (arm B). Primary endpoints were time to second PSA progression and PSA response rate (≥ 30% decline) on second-line therapy, analyzed by intention-to-treat in randomized patients and patients that crossed over, respectively. The trial is registered with ClinicalTrials.gov, number NCT02125357. The trial is completed and final analyses are reported here.

Findings

202 patients were randomized (101 to each arm) between October 21, 2014 and December 13, 2016. At the time of data cut-off 73 and 75 patients had crossed over in arm A and B, respectively. Time to second PSA progression was longer in arm A (median 19·3 vs 15·2 months, HR = 0·66, 95% CI 0·45 - 0·97, p = 0·036), at a median followup of 22·8 months (IQR 10·3 - 33·4). Second-line PSA response rates were 36% for enzalutamide and 4% for abiraterone (p < 0·0001). The most common grade 3-4 adverse events were hypertension (27 [27%] of 101 patients in arm A vs 18 [18%] of 101 in arm B) and fatigue (10 [10%] vs 4 [4%]). Serious adverse events were reported in 15 (15%) of 101 patients in arm A and 20 (20%) of 101 in arm B. There were no treatment related deaths.

Interpretation

Enzalutamide showed activity as a second-line novel androgen receptor pathway inhibitor while abiraterone did not, leading to superior time to second PSA progression for the sequence of abiraterone followed by enzalutamide. Our data suggests that employing a sequencing strategy of abiraterone followed by enzalutamide provides the greatest clinical benefit.

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Introduction

Metastatic castration-resistant prostate cancer (mCRPC) is characterized by disease progression despite suppression of gonadal androgens and results in an increasing symptom burden and ultimately death.[1] Discovery of androgen receptor (AR) mediated signalling as a principal mechanism of mCRPC progression led to the development of novel AR pathway inhibitors (ARPI) of which abiraterone acetate (henceforth abiraterone) and enzalutamide are now widely used in mCRPC.[2] Abiraterone is an inhibitor of CYP17A1, an enzyme critical in the process of androgen synthesis, which can be upregulated in mCRPC.[3] Enzalutamide is a potent AR inhibitor developed for its capacity to overcome AR overexpression, an adaptive mechanism implicated in the development of mCRPC.[4] Importantly, both agents are active clinically having shown improvements in overall survival and other important endpoints in large randomized phase III trials.[5]

Because these agents have never been compared head-to-head and have shown a similar degree of activity, either drug may be used as first-line treatment for mCRPC.[5] In chemotherapy-naïve patients, abiraterone + prednisone showed a survival benefit versus placebo + prednisone with a hazard ratio (HR) of 0·81 (95% CI 0·70 - 0·93) while in a separate phase III trial, enzalutamide improved overall survival compared with placebo (HR = 0·77, 95% CI 0·67 - 0·88).[6,7] Both treatments also achieved marked improvements in time to PSA progression, with hazard ratios of 0·49 (95% CI 0·42 - 0·57) and 0·17 (95% CI 0·15 - 0·20) in favor of abiraterone + prednisone and enzalutamide, respectively. Time to radiographic progression, frequency of skeletal-related events, and quality of life were also improved.[7–10]

It remains uncertain whether patients benefit from treatment with the alternate ARPI at progression since available data have consistently shown varying degrees of cross-resistance. Rates of 50% PSA response for enzalutamide in patients previously treated with abiraterone + prednisone have varied between 18 - 40% [11] whereas those associated with abiraterone +

prednisone in patients previously treated with enzalutamide have not exceeded 10% in single institution retrospective case series.[12,13] In line with these results, data from the phase III PLATO study showed a PSA response rate of 1% for abiraterone + prednisone in patients progressing on enzalutamide.[14] There is currently limited prospective data examining a strategy of the sequential use of both treatments and it remains unclear whether the order in which they are used impacts efficacy.

We conducted a randomized phase II crossover trial comparing the sequence of abiraterone + prednisone followed by enzalutamide at PSA progression versus the opposite sequence of enzalutamide followed by abiraterone + prednisone. Initial results for first-line therapy and genomic correlations from deep-targeted circulating tumor DNA sequencing were previously reported.[15] Herein, we report final study results for the comparison of treatment sequences, second-line therapy, and updated results for first-line therapy.

Methods

Study design

This was an open-label randomized phase II crossover trial conducted in 6 centers in British Columbia, Canada. Patients with newly-diagnosed mCRPC were randomly assigned 1:1 to receive abiraterone + prednisone followed by enzalutamide (arm A), or the opposite sequence of enzalutamide followed by abiraterone + prednisone (arm B). The study received ethical approval from the University of British Columbia - British Columbia Cancer Agency Research Ethics Board and was designed and conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. All patients provided written informed consent.

Participants

Eligible patients were ≥ 18 years old and had histologically-proven prostatic adenocarcinoma without evidence of neuroendocrine differentiation, with metastatic disease on CT scan, MRI and/or bone scan and a rising PSA (PSA progression per PCWG2 criteria) with castrate levels of testosterone (≤ 1·7 nmol/L) with ongoing medical castration or previous bilateral orchiectomy. Patients were required to maintain LHRH agonist/antagonist therapy for the duration of study treatment if not surgically castrated. Prior use of CYP17A1 inhibitors, enzalutamide, or experimental AR inhibitors was prohibited, while prior use of docetaxel for castration-sensitive disease was allowed. Eligible patients were required to have adequate organ function, defined as absolute neutrophil count ≥ 1.5 x 10^9 per liter, platelet count ≥ 100 x 10^9 per liter, hemoglobin ≥ 80 g/l, creatinine clearance ≥ 30 ml/min, serum potassium > lower limit of normal range, total bilirubin ≤ 1.5 x upper limit of normal, and alanine aminotransferase and aspartate aminotransferase ≤ 5 x upper limit of normal. Exclusion criteria included contraindications to abiraterone and enzalutamide per the manufacturer's label, Eastern Cooperative Oncology Group (ECOG) performance status > 2, brain metastases, active epidural disease, severe concurrent illness or co-morbid disease, active concurrent malignancy, history of seizures or cerebrovascular events, major surgery within 4 weeks of starting study treatment,

gastrointestinal disorders affecting absorption, and life expectancy < 6 months. The presence of visceral metastasis and pain requiring opioid analgesia were allowed.

Procedures

Patients in arm A received abiraterone 1000 mg orally daily + prednisone 5 mg orally twice daily as first study treatment until confirmed PSA progression, wide-field radiation of symptomatic bone metastases, unacceptable treatment-related toxicity, or withdrawal of consent. They then crossed over to receive enzalutamide 160 mg orally daily until symptomatic or clinical progression, unacceptable treatment-related toxicity, or withdrawal of consent. Patients in arm B received the opposite sequence of enzalutamide followed by abiraterone + prednisone. If a patient no longer met the trial eligibility criteria at crossover, the patient was removed from the study. Dose modification for treatment-related adverse events was allowed at investigator discretion as per standard of care. PSA progression was defined as an increase of 2 ug/L and 25% from nadir confirmed by subsequent rising PSA ≥ 28 days later. For patients with no PSA decline, PSA progression was defined as an increase of 2 ug/L and 25% from baseline after ≥ 12 weeks of treatment. Adverse events were reported using Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Serum PSA was drawn at baseline and every 4 weeks on treatment. Serum alkaline phosphatase (ALP), lactate dehydrogenase (LDH), albumin, electrolytes, creatinine, and complete blood cell count were measured at the start of each study treatment. Imaging including CT scan of the chest, abdomen and pelvis and bone scan were performed at baseline and every 12 weeks, and additional imaging was performed if clinically indicated. At the time of crossover, serum PSA was repeated and imaging was performed within 4 weeks of crossover. Adverse events and concomitant medications were recorded every four weeks. Only adverse events ≥ grade 3, serious adverse events or adverse events of interest of any grade (fatigue, increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT),

hypertension, edema, hypokalemia, seizure) were recorded. After study completion, follow-up for determination of survival status was conducted every 3 months.

All PSA values entered in CRFs were reviewed by the central data monitor to ensure they were correctly entered from source laboratory reports. Progression events including radiographic progression and clinical progression reported by local study investigators were centrally reviewed by DK, KC, KS and MA against radiology reports and medical records to ensure the data were accurate and complete. Any discrepancies between reported events and clinical records were resolved via queries to local study investigators.

Randomization and masking

Patients enrolled by local study investigators were assigned 1:1 to arms A and B by the central study data monitor, using a simple randomization method and a computer-generated random number table. Arm assignments were not masked to investigators or participants.

Study outcomes

The first primary endpoint of the study was time to second PSA progression, defined as the time from start of first-line therapy to confirmed PSA progression on second-line therapy, or death from prostate cancer before crossover, whichever occurred first. If neither occurred, patients were right-censored at least treatment date. PSA progression was defined as an increase of 2 ug/L and 25% from nadir confirmed by subsequent rising PSA ≥ 28 days later. For patients with no PSA decline, PSA progression was defined as an increase of 2 ug/L and 25% from baseline after ≥ 12 weeks of treatment.[16] This primary endpoint was added to the trial protocol as an amendment on January 11, 2016 prior to completion of accrual and any data analysis.

The second primary endpoint was PSA response rate on second-line therapy. PSA response was defined as ≥ 30% PSA decline from baseline confirmed on repeat measurement ≥ 28 days

later. Patients that did not start second-line therapy were excluded from analysis. Patients that crossed over but had less than two subsequent PSA measurements were counted as having had no PSA decline.

Secondary endpoints included:

1) PSA response rate on first-line therapy, with PSA response defined as ≥ 30% PSA decline from baseline confirmed on repeat measurement ≥ 28 days later.
2) Time to PSA progression on first-line therapy, defined as time from start of therapy to confirmed PSA progression. Patients without PSA progression were right-censored at last treatment date.
3) Time to PSA progression on second-line therapy, defined as time from crossover to confirmed PSA progression. Patients without PSA progression were right-censored at last treatment date.
4) Overall survival, defined as time from start of first-line therapy to time of death from any cause, or last followup (censored).
5) Time on treatment for second-line therapy, defined as time from crossover to end of second-line treatment or death. Patients continuing second-line therapy were right-censored at last treatment date.
6) Time to clinical progression on second-line therapy, defined as time from crossover to clinical progression (including death from prostate cancer). Patients without clinical progression were right-censored at last treatment date.
7) Safety of second-line abiraterone and enzalutamide.
8) Change in Montreal Cognitive Assessment score on first-line and second-line therapy.
9) Correlation of cell-free DNA biomarkers with PSA response to first-line and second-line treatment.

Montreal Cognitive Assessment results for the trial participants have been reported previously[17]. Associations between cell-free DNA biomarkers and treatment response will be reported in a separate manuscript due to the quantity of genomic information and lack of a pre-specified analysis plan.

We chose not to analyze the pre-specified secondary endpoint of time to clinical progression on second-line treatment because full discretion was given to local study investigators to continue second-line treatment beyond PSA progression until it was felt there was no clinical benefit to continuation, per standard practice. Therefore the endpoint was felt to be subject to variability in individual physician decision-making.

Statistical analysis

For the first primary endpoint of time to second PSA progression, we determined that with an accrual of 100 patients to each arm and a pre-planned analysis after 140 events, our study would have 70% power to detect hazard ratio ≥ 1·519 between arms, using a two-sided α significance level of 0·05. For the second primary endpoint of PSA response to second-line therapy, we utilized a Simon's two stage design whereby a PSA response rate ≥ 30% in either arm would be of interest. We determined that at least 39 patients would have to receive second-line therapy in each arm for our study to have 90% power to show a 30% response rate in either arm with an alpha error of 0·1 and beta error of 0·1. Median followup times were calculated using the reverse Kaplan-Meier estimator.[18]

PSA response rates for first and second-line therapy were compared between arms using the X^2 test. Hazard ratios and P-values for time to event outcomes were estimated using univariate Cox regression. Multivariate Cox regression incorporating patient age (the only baseline characteristic that differed significantly between arms) was used to confirm findings. For all secondary and exploratory endpoints, we utilized a significance threshold of $\alpha < 0{\cdot}05$ (two-

sided). All endpoints were analyzed using the intention-to-treat principle: endpoints relating to first-line or combined treatment were evaluated in all randomized patients, while endpoints relating to second-line treatment were evaluated in patients that crossed over.
A larger proportion of patients than expected developed radiographic and/or clinical progression rather than PSA progression. Therefore, final analysis was conducted when 140 second-line progression events of any kind had occurred, rather than 140 second-line PSA progression events (without protocol amendment). There were no planned interim analyses. Preliminary results for first-line PSA response rate (secondary endpoint) and first-line time to any progression (post-hoc exploratory endpoint) have been reported earlier.[15]

Post-hoc exploratory analyses included:

1) Time to progression on first-line therapy, defined as the time from start of therapy to confirmed PSA progression, radiographic progression (PCWG2 criteria), clinical progression, or death from prostate cancer, whichever occurred first. If no events occurred, patient was right-censored at last treatment date.
2) Time to progression on second-line therapy, defined as the time from crossover to confirmed PSA progression, radiographic progression (PCWG2 criteria), clinical progression, or death from prostate cancer, whichever occurred first. If no events occurred, patient was right-censored at last treatment date.
3) Time to second progression, defined as the time from start of first-line therapy to confirmed PSA progression on second-line therapy, radiographic progression (PCWG2 criteria) on second-line therapy, clinical progression on second-line therapy, or death from prostate cancer, whichever occurred first. If no events occurred, patient was right-censored at last treatment date.
4) Comparison of second-line PSA response rate between arms using Pearson's chi-squared test.

5) Clinical correlates of time to PSA progression and PSA response rate in patients receiving second-line enzalutamide.
6) Comparison of crossover clinical characteristics between arms.
7) Sensitivity analysis of time to second PSA progression, excluding patients with delayed crossovers.
8) Comparison of time from progression to crossover between arms.
9) Subgroup analysis to determine whether second-line enzalutamide was superior in all patient subgroups.

The safety populations for first- and second-line adverse events comprised all patients who received at least one dose of assigned first-line and second-line therapy, respectively. In comparisons of crossover clinical characteristics between arms, continuous-valued characteristics were compared using the rank-sum test, and boolean characteristics were compared using Fisher's exact test.

This trial is registered with ClinicalTrials.gov, number NCT02125357. The full trial protocol document is available at https://clinicaltrials.gov/ProvidedDocs/57/NCT02125357/Prot_SAP_000.pdf.

All Cox regression analyses, associated confidence intervals, and Kaplan-Meier curves were calculated using R (version 3.6.0) with the "survival" package (version 2.44.1.1). Confidence intervals for PSA response rates, Pearson's chi-squared tests, rank-sum tests, and Fisher's exact tests were calculated using Julia (version 1.1.0) with the "HypothesisTests" package (version 0.8.0).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. KC, DK, MA and KS had access to the raw patient data.

Results

Patients were enrolled between October 21, 2014 and December 13, 2016. The median follow-up at time of data cut-off (May 31, 2018) was 30·7 months, and final accrual was 101 patients to each arm. Patient clinical characteristics at the start of first-line therapy and at crossover are shown in Table 1. At crossover, lactate dehydrogenase (LDH) levels were higher in the abiraterone-first arm (median 0·85 vs 0·74 units relative to ULN, p = 0.0008). At the time of data cut-off, 73 patients from arm A had crossed over to receive enzalutamide and 75 patients from arm B had crossed over to receive abiraterone + prednisone. 17 patients in arm A and 17 patients in arm B discontinued therapy without crossing over (Figure 1). No patients were lost to followup before crossover. A large proportion of patients had delayed crossover, defined as initiation to second-line therapy > 2 weeks from the date of confirmed progression: 43 patients in arm A and 48 patients in arm B. However, the median time from progression to crossover was relatively short and did not differ significantly between arms (1·8 vs 1·7 months, p = 0·46, post-hoc analysis).

At the time of data cut-off, 148 patients had crossed over to start second-line therapy, and 142 patients had progressed on second-line therapy or had died of prostate cancer before crossover. This triggered pre-planned analysis of the two primary endpoints. The first primary endpoint, time from start of first-line therapy to PSA progression on second-line therapy was superior for the abiraterone-first arm (median 19·3 vs 15·2 months, HR = 0·66, 95% CI 0·45 - 0·97, p = 0·036) (Figure 2A). With a median followup of 22·8 months (IQR 10·3 - 33·4), there were 106 events (93 second-line PSA progression, 13 prostate cancer deaths before crossover) for this endpoint in the analyzed intention-to-treat population (101 patients in each arm).Time from start of first-line therapy to progression of any kind on second-line therapy (an exploratory endpoint) was also superior for the abiraterone-first arm (median 16·0 vs 12·8 months, HR = 0·69, 95% CI 0·50 - 0·96, p = 0·029) (Appendix p 1). With a median followup of 27·4 months (IQR 21·0 - 35·2), there were 142 events (93 second-line PSA progression, 36 radiographic or

clinical progression, 13 prostate cancer deaths before crossover) for this endpoint in the analyzed intention-to-treat population (101 patients in each arm). To address the issue of delayed crossovers, we performed a post-hoc sensitivity analysis excluding patients who crossed over more than 2 weeks after confirmed PSA progression. Results were consistent with the primary analysis: the abiraterone-first arm had longer time from start of first-line therapy to second PSA progression (median 28·4 months vs 14·2 months, HR = 0·65, 95% CI 0·36 - 1·17, p = 0·15).

The difference between the arms was confirmed by the second primary endpoint: PSA responses to second-line therapy were seen in 26 (36%) of 73 patients in the abiraterone-first arm and 3 (4%) of 75 patients in the enzalutamide-first arm. The pre-specified efficacy threshold of 30% response rate was thereby only reached in the abiraterone-first arm. As a post-hoc analysis, we also confirmed that second-line PSA response rates in the two arms were significantly different (p < 0·0001) (Figure 2C).

Between trial start and data cutoff, there were 48 deaths in the abiraterone-first arm and 58 in the enzalutamide-first arm (median overall survival 28·8 vs 24·7 months, HR = 0·79, 95% CI 0·54 - 1·16, p = 0·23, secondary endpoint) (Figure 3). Median followup for overall survival was 30.7 months (IQR 25·1 - 36·2). For the 25 patients that died on study, causes of death were prostate cancer (16 patients), cerebral hemorrhage (2 patients), cardiac issues (1 patient), infection (1 patient), metastatic melanoma (1 patient), urosepsis (1 patient), bacteremia (1 patient), complications from surgery for colon cancer (1 patient), and esophageal carcinoma (1 patient). There were no treatment-related deaths.

In the patient population that crossed over to second-line therapy, second-line enzalutamide was superior for the following endpoints: time to PSA progression on second-line therapy (median 3·5 vs 1·7 months, HR = 0·42, 95% CI 0·28 - 0·65, p < 0·0001, secondary endpoint),

time on treatment on second-line therapy (median 4·6 vs 3·6 months, HR = 0·66, 95% CI 0·46 - 0·94, p = 0·023, secondary endpoint), and time to progression on second-line therapy (median 2·7 vs 1·7 months, HR = 0·43, 95% CI 0·20 - 0·61, p < 0·0001, exploratory endpoint) (Figure 4A, Appendix p 2-3). Median followup durations for these endpoints were 3·9 (IQR 2·1 - 16·0), 19·4 (IQR 13·6 - 25·7), and 16·5 (IQR 11·7 - 17·9) months, respectively. As a post-hoc analysis, we explored whether second-line enzalutamide was superior in all patient subgroups (Appendix p 4), and whether any clinical factors were prognostic for second-line enzalutamide response The only clinical factor associated with shorter time to PSA progression on second-line enzalutamide therapy was time to PSA progression < 3 months on first-line therapy (Table 2).

For first-line therapy, PSA responses were seen in 69 (68%) of 101 patients treated with abiraterone + prednisone and 83 (82%) of 101 patients treated with enzalutamide, indicating a difference between the arms (p = 0·023, secondary endpoint) (Figure 4B). However, there was no significant difference between first-line abiraterone and first-line enzalutamide in terms of time to PSA progression (median 11·2 vs 10·2 months, HR = 0·95, 95% CI 0·66 - 1·36, p = 0·78, secondary endpoint) or time to any progression (median 7·9 vs 7·3 months, HR = 0·95, 95% CI 0·70 - 1·29, p = 0·74, exploratory endpoint) (Figure 4C, Appendix p 5). Median followup durations for these endpoints were 21·6 (IQR 6·7 - 28·5) and 27·2 (IQR 20·2 - 37·3) months, respectively. Both endpoints were calculated for the intention-to-treat population.

Adverse events of interest of all grades are shown in Appendix p 6. Their incidence and severity were consistent with the known toxicity profile of both drugs. The most common grade 3-4 adverse events for first-line therapy were hypertension (23 [23%] of 101 patients for abiraterone vs 13 [13%] of 101 patients for enzalutamide), fatigue (6 [6%] vs 2 [2%]), increased ALT (6 [6%] vs 1 [1%]), fracture (3 [3%] vs 4 [4%]), increased AST (5 [5%] vs 1 [1%]), and back pain (3 [3%] vs 3 [3%]). The most common grade 3-4 adverse events for second-line therapy were hypertension (13 [18%] of 73 patients for enzalutamide vs 11 [15%] of 75 patients for abiraterone), fatigue (4 [5%] vs 2 [3%]), back pain (2 [3%] vs 3 [4%]), and extremity pain (3 [4%] vs 1 [1%]). Serious adverse events were reported in 15 (15%) of 101 patients in arm A and 20 (20%) of 101 patients in arm B. There were no treatment-related serious adverse events or deaths.

For first-line therapy, 6 (6%) of 101 patients required a dose reduction for abiraterone vs 18 (18%) of 101 for enzalutamide. For second-line therapy, 14 (19%) of 73 patients required a dose reduction for enzalutamide vs 4 (5%) of 75 for abiraterone. One patient in arm A (atrial fibrillation) and four patients in arm B (fatigue + cognitive impairment; fatigue + anxiety; fatigue; fatigue + nausea) discontinued first-line therapy and did not cross over because of treatment-

related adverse events. Two patients in arm A (seizure; falls) and one patient in arm B (hepatic transaminitis) discontinued second-line therapy before progression due to treatment-related adverse events (Figure 1).

Discussion

In this randomized phase II crossover trial we found that second-line activity of abiraterone following progression on enzalutamide was minimal, whereas enzalutamide retained clinical activity following progression on abiraterone with a median time to PSA progression of 3.5 months. Accordingly, time to second PSA progression was superior for the sequence of abiraterone followed by enzalutamide, and this was driven by the second-line activity of enzalutamide. To our knowledge, these were the first prospective data estimating the degree of cross-resistance for both sequences as well as the first randomized prospective comparison of both treatment sequences in their entirety. Finally, to our knowledge, this was the first randomized head-to-head comparative assessment of the efficacy of both agents in the first-line setting for mCRPC, demonstrating no difference between them for time to PSA progression, despite a higher PSA response rate for enzalutamide.

Overall, our findings demonstrate that alternating ARPI at progression can be beneficial when abiraterone + prednisone is used first. However, given the modest response to second-line enzalutamide, other available and appropriate therapies should also be considered for patients progressing after first-line ARPI, such as taxane chemotherapy and radium-223. We are investigating the optimal sequencing of taxane and ARPI therapy in two ongoing clinical trials (NCT02254785 and NCT04015622).

The need for high quality evidence to inform sequencing is set to expand as the treatment paradigm for advanced prostate cancer continues to shift towards intensified treatment in earlier disease states. Recently, both abiraterone + prednisone and enzalutamide have received new indications, specifically in metastatic castration-sensitive disease for abiraterone + prednisone and in non-metastatic castration-resistant disease for enzalutamide.[19,20] Our data are the first to show an advantage in sequencing ARPI and provide a robust assessment of cross-resistance

between both agents and thus can help to inform the choice of subsequent treatment following failure of ARPI in earlier treatment settings.

It is notable that our results for first-line therapy closely mirror those from the COU-AA-302 and PREVAIL trials of abiraterone + prednisone and enzalutamide in which the rates of 50% PSA response were 62 % and 78% (compared with 65% and 80% in our study) and median times to PSA progression were 11·1 and 11·2 months (compared with 11·2 and 10·2 months in our study).[8,21] However, a higher proportion of patients in our study than expected developed progression within 12 weeks on first-line therapy (25% on abiraterone + prednisone and 22% on enzalutamide), or declined rapidly precluding crossover (5% and 7%), reflective of more aggressive disease status and the inclusive nature of this study population. In addition, overall survival was worse in our trial compared with the abiraterone + prednisone arm from the COU-AA-002 trial (34·7 months) and enzalutamide from PREVAIL (35·3 months).[6,7] The use of pragmatic selection criteria which allowed enrollment of patients with poor prognostic factors including visceral metastasis, pain requiring opioid analgesia or ECOG performance status of 2, and a relatively advanced median study sample age may account for these outcomes, but also allows for potentially greater generalizability.

Our results for second-line therapy are also consistent with those reported in the literature. The activity of abiraterone + prednisone following enzalutamide was minimal in the PLATO trial, as well as in other retrospective reports.[12–14] A prospective single-arm study of enzalutamide in patients having received abiraterone + prednisone for at least 24 weeks found a PSA response rate of 27% and time to PSA progression of 5·7 months [22] while a large number of retrospective studies have shown similar modest benefit.[11] In contrast, our prospective, comparative and randomized study provides robust data assessing the second-line activity of both agents, and for evaluating an optimal sequencing strategy. These results support a role for enzalutamide as a second-line ARPI, but not for abiraterone + prednisone.

Mechanistically, there are acquired changes in the AR-axis which are characteristic of both ARPI and may explain the higher second-line response rate with enzalutamide. Mutations involving the ligand-binding domain of the AR emerge during the course of AR-axis inhibition and may allow activation by alternate ligands.[2] Well-described examples associated with abiraterone + prednisone resistance include the L702H mutation which allows AR activation by glucocorticoids [2,23], and the T878A mutation which confers agonist activity to progesterone, a hormone increased by treatment with abiraterone.[24] Enzalutamide still retains AR inhibitory activity against both these mutations. Alternatively, resistance mechanisms common to both drugs include amplification of the AR gene which emerges under selective pressure induced by androgen-deprivation therapy and has been observed in > 50% of mCRPC cases.[25–27] The AR-axis may also re-activate through mechanisms no longer amenable to ligand inhibition, including AR splice variants lacking a ligand-binding domain, or bypass signalling through alternate steroid receptors such as the glucocorticoid receptor.[2]

We acknowledge limitations to our study which should be taken into consideration in the interpretation of our results. The overall sample size was relatively small and there were a number of patients that did not cross over to second-line therapy, which may have limited our power to detect differences in outcomes. The imbalance in age between arms and the open-label nature of the study are further limitations. Results for secondary endpoints should be considered exploratory as we examined multiple secondary endpoints without α corrections for multiple testing.

In conclusion, our study demonstrated that abiraterone and enzalutamide share similar first-line activity for mCRPC. Enzalutamide retains clinical activity as a second-line agent following abiraterone, in contrast to abiraterone which retains no second-line activity following

enzalutamide. Our findings demonstrate that the treatment sequence of abiraterone followed by enzalutamide is preferred and may result in improved clinical benefit.

Contributors

KNC, AWW and AAA conceived and designed the trial. KNC, MEG, DF, JV, MZ, CKK, BJE, DJK, CO, AAA, KN, DW, AA, BK, SLE and LL acquired the data. MA, DJK, ST, KS and KNC compiled and analyzed the data. DJK, MA, KNC and AWW prepared the manuscript. All authors reviewed and approved the final version of the manuscript.

Declaration of interests

DJK reports reports personal fees from Bayer, outside the submitted work; MA reports grants from Jane and Aatos Erkko Foundation, during the conduct of the study; ST reports grants from Jane and Aatos Erkko Foundation, during the conduct of the study; DLF reports personal fees from Janssen, personal fees from Astellas, personal fees from Bayer, outside the submitted work; JV reports non-financial support from Bayer, personal fees from Pfizer, personal fees and non-financial support from Astellas, non-financial support from Merck, personal fees from Pfizer, personal fees and non-financial support from BMS, personal fees from Janssen, personal fees from Bayer, personal fees from BMS, outside the submitted work; AAA reports personal fees from Janssen, grants, personal fees, non-financial support and other from Astellas, personal fees from Novartis, grants and non-financial support from Merck Serono, personal fees from Tolmar, personal fees, non-financial support and other from Amgen, personal fees and other from Pfizer, personal fees from Bayer, personal fees and other from Telix Pharmaceuticals, personal fees and other from Bristol-Myers Squibb, personal fees and other from Sanofi, personal fees from Noxopharm, outside the submitted work; CKK reports personal fees from Janssen, personal fees from Astellas, personal fees from Pfizer, personal fees from Ipsen, personal fees from Eisai, personal fees from Roche, personal fees from Merck, personal fees from BMS, outside the submitted work; BJE reports personal fees from AstraZeneca, personal fees from Roche, personal fees from Janssen, personal fees from Merck, outside the submitted

work; AA reports personal fees from Astellas, outside the submitted work; SLE reports reports other from Janssen, outside the submitted work; MEG reports a patent OGX-011, OGX-427 issued; AWW reports grants and personal fees from Janssen, outside the submitted work; KNC reports grants from Janssen and grants from Astellas during the conduct of the study; grants and personal fees from Janssen, grants and personal fees from Astellas, grants and personal fees from Sanofi, grants and personal fees from AstraZeneca, grants and personal fees from Bayer, grants and personal fees from Pfizer, grants and personal fees from Roche, outside the submitted work. All other authors declare no competing interests.

Data sharing

The full study protocol document is available for download through ClinicalTrials.gov, number NCT02125357. De-identified patient-level data will be made available to qualified researchers upon request, after signing of a data transfer agreement with BC Cancer. Requests for data sharing (including a research proposal) should be made to the corresponding author.

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Tables

Table 1. Patient clinical characteristics at baseline and crossover. ULN = upper limit of normal, PSA = prostate specific antigen, ECOG = Eastern Cooperative Oncology Group.

Characteristic	At Baseline		At Crossover	
At Baseline	**Arm A (n = 101)**	**Arm B (n = 101)**	**Arm A (n = 73)**	**Arm B (n = 75)**
Median age (range)	72·9 (51·3 - 93·3)	77·6 (49·3 - 94·1)	73·8 (51·5 - 92·7)	78·0 (49·8 - 93·2)
Median PSA, ng/mL (range)	35·0 (2·2 - 2817)	37·0 (1·7 - 1060)	16·0 (0·8 - 991)	12·0 (0·2 - 1604)
Median alkaline phosphatase, relative to ULN (range)	0·82 (0·29 - 12·5)	0·75 (0·30 - 47·8)	0·88 (0·31 - 6·87)	0·75 (0·31 - 4·67)
Median lactate dehydrogenase, relative to ULN (range)	0·79 (0·37 - 4·0)	0·80 (0·31 - 12·9)	0·85 (0·22 - 4·69)	0·74 (0·38 - 2·46)
Median hemoglobin, g/L (range)	130 (89 - 155)	130 (89 - 165)	132 (87 - 152)	129 (79 - 157)
ECOG performance status 0 - 1	89 (88·1%)	79 (78·2%)	62 (84·9%)	57 (76·0%)
Prior docetaxel for castration-sensitive disease	5 (5.0%)	6 (5.9%)	-	-
Bone metastases	85 (84·2%)	82 (81·2%)	61 (83·6%)	65 (86·7%)
Lung metastases	8 (7·9%)	9 (8·9%)	6 (8·2%)	7 (9·3%)
Liver metastases	5 (5·0%)	7 (6·9%)	4 (5·5%)	7 (9·3%)

Table 2. Univariate analysis of clinical factors associated with time to PSA progression and PSA response rate during second-line enzalutamide treatment. ULN = upper limit of normal; PSA = prostate specific antigen; ECOG = Eastern Cooperative Oncology Group.

			Time to PSA progression on second-line therapy		PSA response on second-line therapy
Clinical factor	**Category**	**Patients**	**Hazard ratio (95% CI)**	**P-value**	**Number of responders (%)**
First-line time to confirmed PSA progression	≥ 3 months (ref) < 3 months	53 16	2·92 (1·45 - 5·86)	0·003	21 (40%) 3 (19%)
Confirmed first-line PSA response	Yes (ref) No	51 22	1·85 (0·97 - 3·53)	0·063	20 (39%) 6 (27%)
PSA at crossover	< 16 ng/mL (ref) ≥ 16 ng/mL	36 37	1·55 (0·83 - 2·88)	0·166	13 (36%) 13 (35%)
Hemoglobin at crossover	≥ 130 g/L (ref) < 130 g/L	39 34	1·49 (0·80 - 2·78)	0·207	15 (38%) 11 (32%)
Lactate dehydrogenase at crossover	< 1 x ULN (ref) ≥ 1 x ULN	58 14	0·95 (0·40 - 2·27)	0·906	20 (34%) 5 (36%)
Alkaline phosphatase at crossover	< 1 x ULN (ref) ≥ 1 x ULN	44 28	1·25 (0·65 - 2·41)	0·511	17 (39%) 8 (29%)
ECOG performance status at crossover	< 2 (ref) ≥ 2	62 10	0·71 (0·25 - 2·00)	0·512	23 (37%) 3 (30%)

Figures

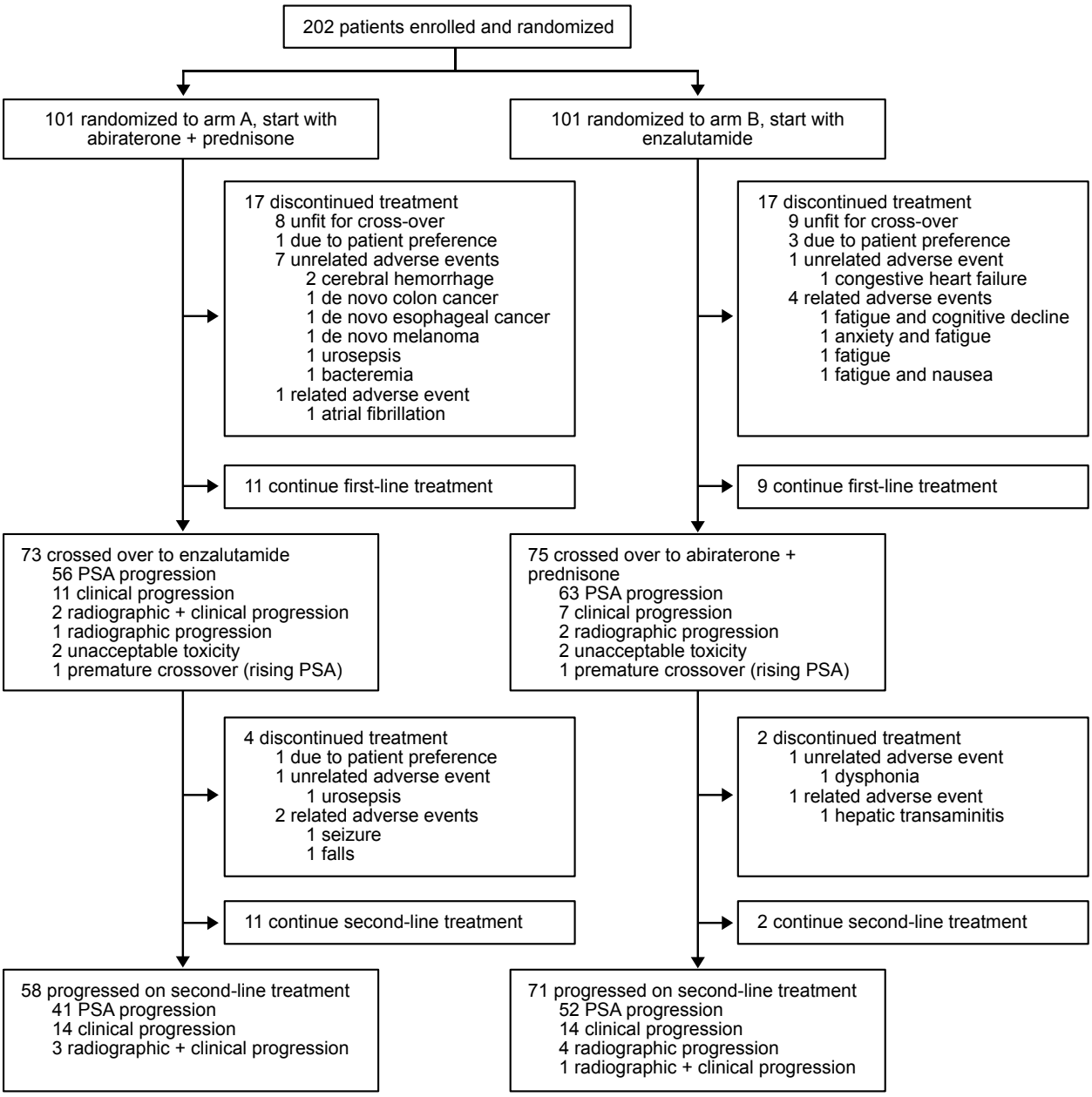

Figure 1. Trial profile.

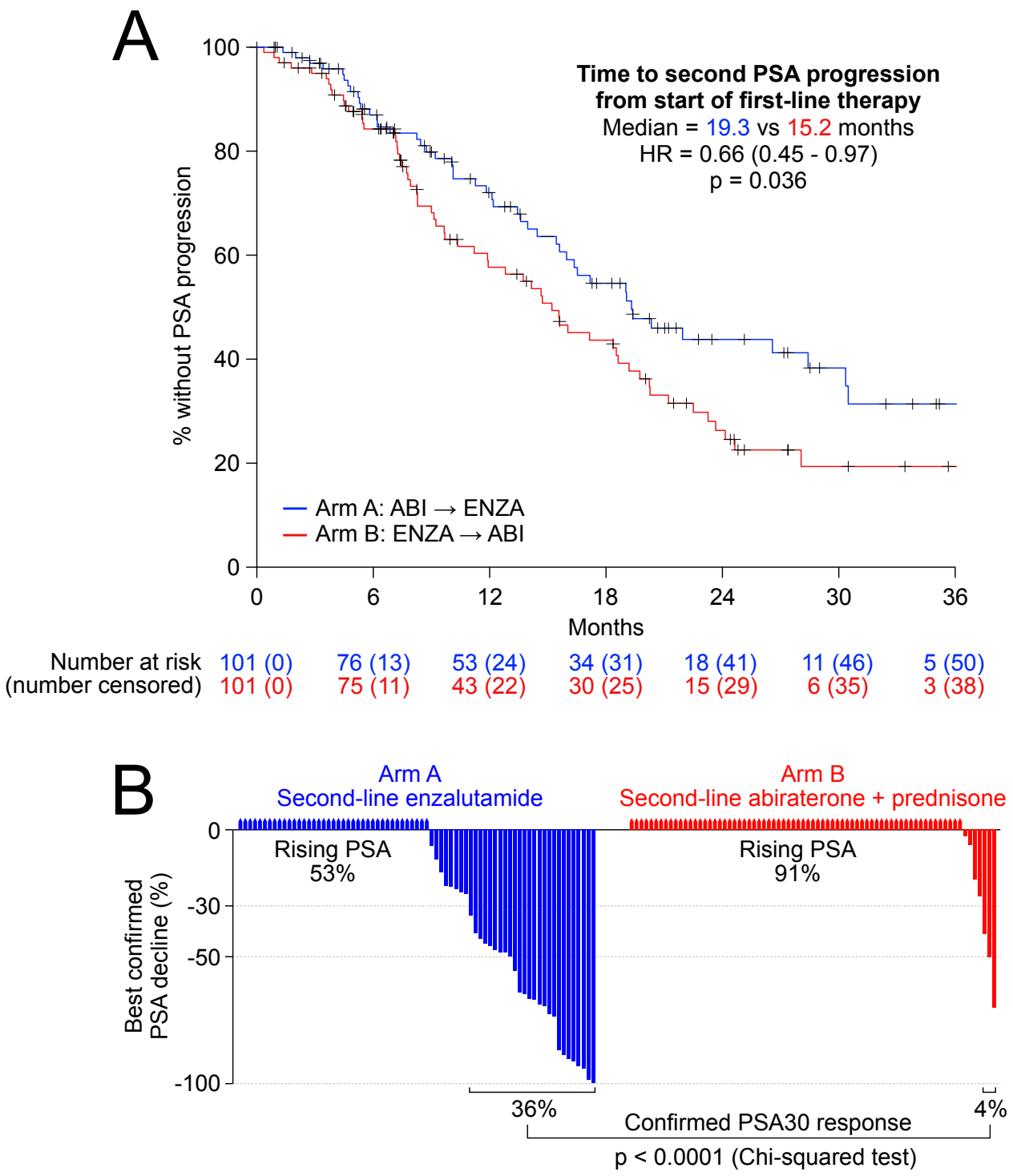

Figure 2. Time from start of first-line therapy to second PSA progression (A), and PSA response rate during second-line therapy (B). Hazard ratios (HR) and p-values are based on Cox regression. Hazard ratio 95% confidence interval is shown in parentheses.

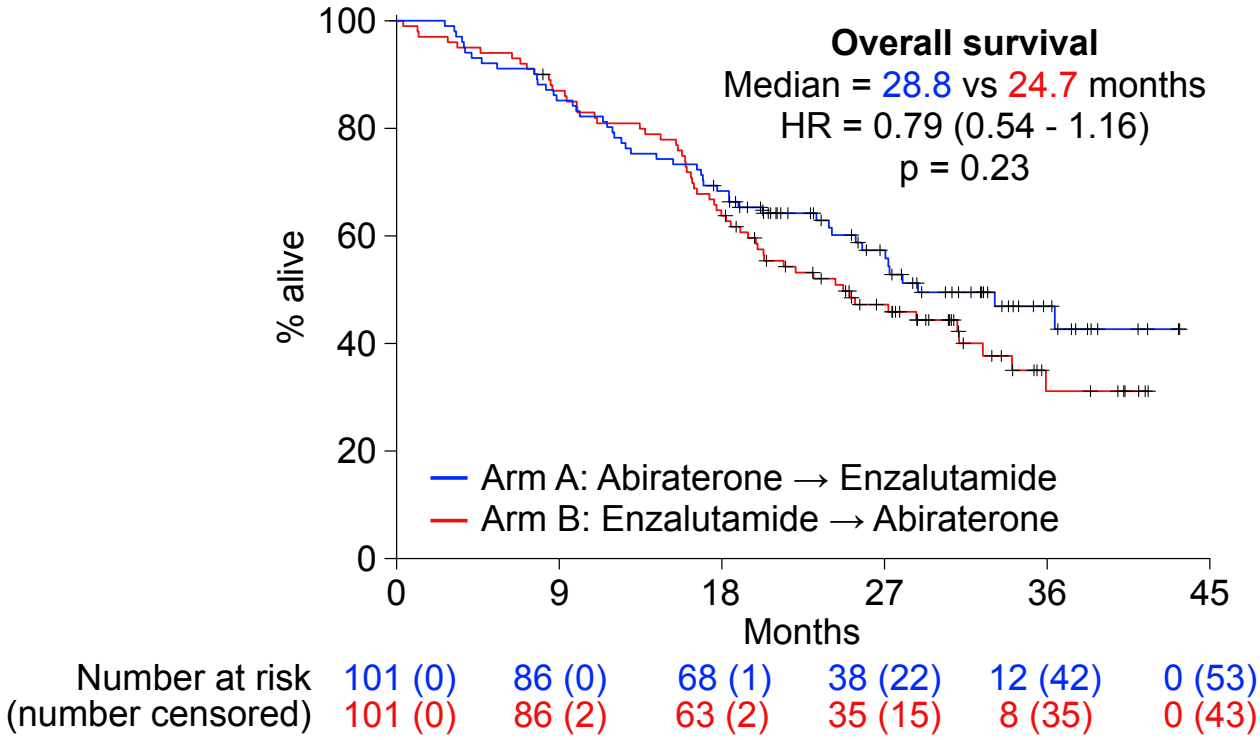

Figure 3. Overall survival. Hazard ratio (HR) and p-value are based on Cox regression. Hazard ratio 95% confidence interval is shown in parentheses.

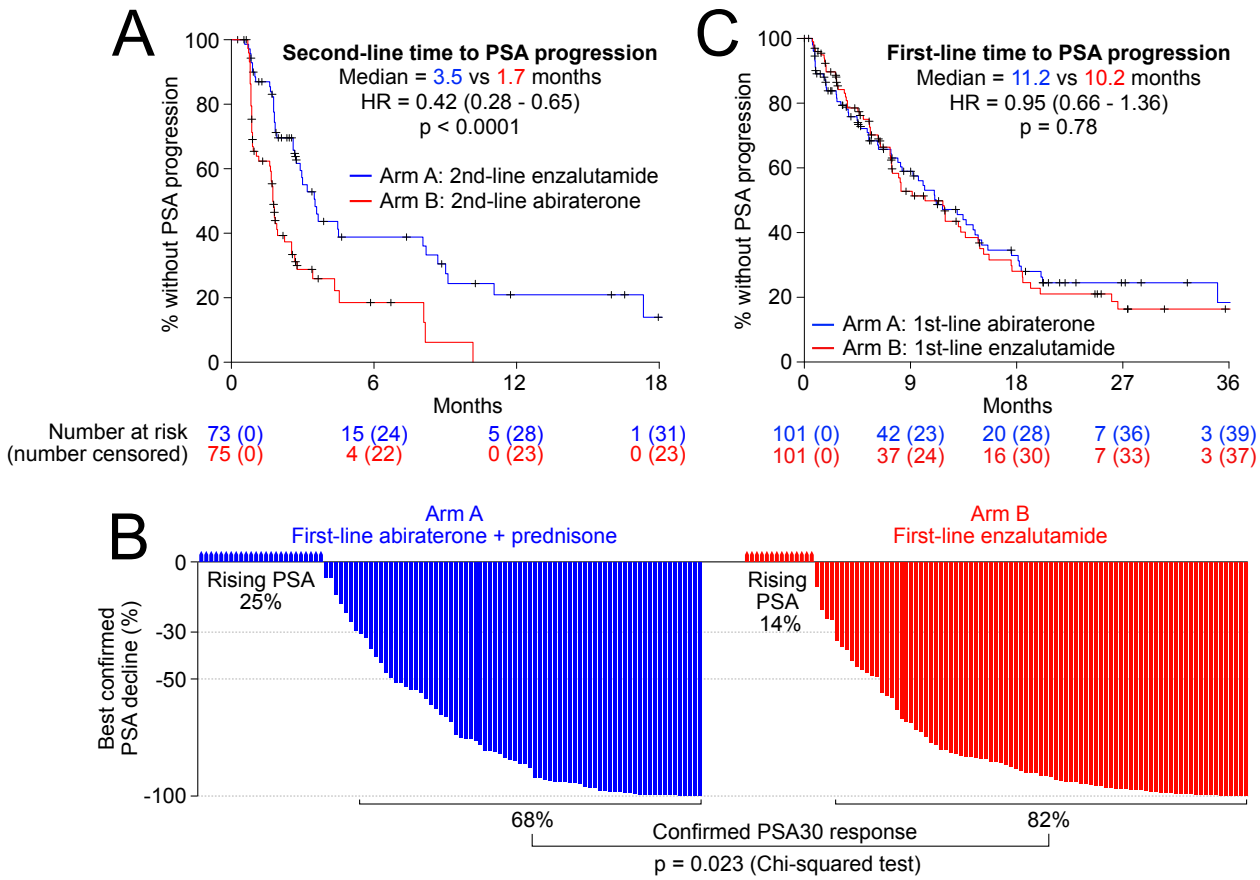

Figure 4. Time to PSA progression during second-line therapy (A). PSA response rate for first-line therapy (B). Time to PSA progression during first-line therapy (C). Hazard ratios (HR) and p-values are based on Cox regression. Hazard ratio 95% confidence interval is shown in parentheses.

Research in context

Evidence before this study

We searched PubMed for studies published before May 1st 2019. We used the search strategy "metastatic castration-resistant prostate cancer" AND "abiraterone" or "enzalutamide" AND "clinical trial". ASCO Annual Meeting and ESMO Congress Proceedings were also searched using the same search strategy. We identified 8 prospective trials of more than 100 patients assessing the effectiveness of abiraterone and/or enzalutamide for mCRPC. The efficacy of abiraterone + prednisone for mCRPC was established in the landmark COU-AA-001 and COU-AA-002 trials in the post-chemotherapy and pre-chemotherapy settings, respectively, with improved overall survival versus prednisone alone. Similarly, enzalutamide improved overall survival versus placebo in the same disease settings in the phase III AFFIRM and PREVAIL studies, and improved progression-free survival in the chemotherapy-naïve setting versus bicalutamide in two randomized phase II studies. In the randomized PLATO study, patients received enzalutamide + abiraterone or placebo + abiraterone at PSA progression on enzalutamide; PSA response rates were low at 1% and 2% for each arm, respectively. A prospective single-arm trial of enzalutamide in 214 patients progressing after abiraterone showed a PSA response rate of 27% and median time to PSA progression of 5.7 months. Recently, a randomized trial of combined enzalutamide + abiraterone vs abiraterone alone demonstrated no difference in overall survival, but a modest improvement in rPFS.

Added value of the study

Abiraterone and enzalutamide are among the most efficacious and well-tolerated agents for mCRPC and optimizing the use of both agents is an important research goal. This was the first prospective randomized head-to-head comparison of abiraterone + prednisone vs enzalutamide. The trial also mandated cross-over to the alternate agent at progression, in order to compare both treatment sequences as well as the second-line activity for both agents. This

trial was the first to show an advantage to utilizing a sequencing strategy of both agents: the treatment sequence of abiraterone + prednisone followed by enzalutamide had a longer time to PSA progression compared with the opposite sequence. This is also the first randomized prospective data demonstrating activity of enzalutamide as a second-line androgen-receptor targeting treatment, in contrast with the minimal activity of second-line abiraterone + prednisone.

Implications of all the available evidence

Our results confirm that second-line enzalutamide is active and should be considered an appropriate treatment option at progression on abiraterone + prednisone. Our results demonstrated similar outcomes with first-line abiraterone + prednisone and enzalutamide supporting the use of either agent in this setting. Treatment with abiraterone + prednisone followed by enzalutamide at PSA progression results in improved time to PSA progression and is the optimal sequencing strategy for these agents.