Optimal sequencing of enzalutamide and abiraterone acetate plus prednisone in metastatic castration-resistant prostate cancer: a multicentre, randomised, open-label, phase 2, crossover trial

Daniel J Khalaf, Matti Annala*, Sinja Taavitsainen, Daygen L Finch, Conrad Oja, Joanna Vergidis, Muhammad Zulfiqar, Katherine Sunderland, Arun A Azad, Christian K Kollmannsberger, Bernhard J Eigl, Krista Noonan, Deepa Wadhwa, Andrew Attwell, Bruce Keith, Susan L Ellard, Lyly Le, Martin E Gleave, Alexander W Wyatt, Kim N Chi*

Lancet Oncol 2019; 20: 1730–39

Published Online November 11, 2019 https://doi.org/10.1016/S1470-2045(19)30688-6

See Comment page 1628

*Contributed equally

Division of Medical Oncology (D J Khalaf MD, C K Kollmannsberger MD, B J Eigl MD, Prof K N Chi MD); **and Division of Cancer Surveillance and Outcomes** (K Sunderland MPH), **BC Cancer, Vancouver, BC, Canada; Vancouver Prostate Centre, Vancouver, BC, Canada** (M Annala MSc, S Taavitsainen MSc, Prof M E Gleave MD, A W Wyatt DPhil, Prof K N Chi); **Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland** (M Annala, S Taavitsainen); **BC Cancer, Kelowna, BC, Canada** (D L Finch MD, D Wadhwa MD, S L Ellard MD); **BC Cancer, Surrey, BC, Canada** (C Oja MD, K Noonan MD, L Le MD); **BC Cancer, Victoria, BC, Canada** (J Vergidis MD, A Attwell MD); **BC Cancer, Abbotsford, BC, Canada** (M Zulfiqar MD, B Keith MD); **and Peter MacCallum Cancer Centre, Melbourne, VIC, Australia** (A A Azad MD)

Correspondence to: Dr Kim N Chi, Division of Medical Oncology, BC Cancer, Vancouver, BC V5Z 4E6, Canada **kchi@bccancer.bc.ca**

Summary

Background Abiraterone acetate plus prednisone and enzalutamide are both used for the treatment of metastatic castration-resistant prostate cancer. We aimed to determine the best sequence in which to use both drugs, as well as their second-line efficacy.

Methods In this multicentre, randomised, open-label, phase 2, crossover trial done in six cancer centres in British Columbia, Canada, we recruited patients aged 18 years or older with newly-diagnosed metastatic castration-resistant prostate cancer without neuroendocrine differentiation and Eastern Cooperative Oncology Group performance status 2 or less. Patients were randomly assigned (1:1) using a computer-generated random number table to receive either abiraterone acetate 1000 mg orally once daily plus prednisone 5 mg orally twice daily until PSA progression followed by crossover to enzalutamide 160 mg orally once daily (group A), or the opposite sequence (group B). Treatment was not masked to investigators or participants. Primary endpoints were time to second PSA progression and PSA response (≥30% decline from baseline) on second-line therapy, analysed by intention-to-treat in all randomly assigned patients and in patients who crossed over, respectively. The trial is registered with ClinicalTrials.gov, NCT02125357.

Findings Between Oct 21, 2014, and Dec 13, 2016, 202 patients were enrolled and randomly assigned to either group A (n=101) or group B (n=101). At the time of data cutoff, 73 (72%) patients in group A and 75 (74%) patients in group B had crossed over. Time to second PSA progression was longer in group A than in group B (median 19·3 months [95% CI 16·0–30·5] *vs* 15·2 months [95% CI 11·9–19·8] months; hazard ratio 0·66, 95% CI 0·45–0·97, p=0·036), at a median follow-up of 22·8 months (IQR 10·3–33·4). PSA responses to second-line therapy were seen in 26 (36%) of 73 patients for enzalutamide and three (4%) of 75 for abiraterone (χ^2 p<0·0001). The most common grade 3–4 adverse events throughout the trial were hypertension (27 [27%] of 101 patients in group A *vs* 18 [18%] of 101 patients in group B) and fatigue (six [10%] *vs* four [4%]). Serious adverse events were reported in 15 (15%) of 101 patients in group A and 20 (20%) of 101 patients in group B. There were no treatment-related deaths.

Interpretation Enzalutamide showed activity as a second-line novel androgen receptor pathway inhibitor, whereas abiraterone acetate did not, leading to a longer time to second PSA progression for the sequence of abiraterone followed by enzalutamide than with the opposite treatment sequence. Our data suggest that using a sequencing strategy of abiraterone acetate followed by enzalutamide provides the greatest clinical benefit.

Funding Canadian Cancer Society Research Institute, Prostate Cancer Canada, Movember Foundation, Prostate Cancer Foundation, Terry Fox New Frontiers Program, BC Cancer Foundation, Jane and Aatos Erkko Foundation, Janssen, and Astellas.

Introduction

Metastatic castration-resistant prostate cancer is characterised by disease progression despite suppression of gonadal androgens and results in an increasing symptom burden and ultimately death.[1] Discovery of androgen receptor-mediated signalling as a principal mechanism of metastatic castration-resistant prostate cancer progression led to the development of novel androgen receptor pathway inhibitors, of which abiraterone acetate (henceforth referred to as abiraterone) and enzalutamide are now widely used.[2] Abiraterone is an inhibitor of CYP17A1, an enzyme essential in the process of androgen synthesis, which can be upregulated in metastatic castration-resistant prostate cancer.[3] Enzalutamide is a potent androgen receptor inhibitor developed for its capacity to overcome androgen receptor

Research in context

Evidence before this study

We searched PubMed for studies published in English before May 1, 2019. We used the search terms "metastatic castration-resistant prostate cancer" AND "abiraterone" or "enzalutamide" AND "clinical trial". American Society Of Clinical Oncology Annual Meeting and The European Society for Medical Oncology Congress Proceedings were also searched using the same search strategy. We identified eight prospective trials of more than 100 patients assessing the effectiveness of abiraterone or enzalutamide for metastatic castration-resistant prostate cancer. The efficacy of abiraterone plus prednisone compared with prednisone plus placebo for metastatic castrate-resistant prostate cancer mCRPC was established in the landmark COU-AA-001 trial in the post-chemotherapy setting and COU-AA-002 trial in the pre-chemotherapy setting, with improved overall survival compared with prednisone alone. Similarly, enzalutamide improved overall survival compared with placebo in the same disease settings in the phase 3 AFFIRM and PREVAIL studies, and improved progression-free survival in the chemotherapy-naive setting compared with bicalutamide in two randomised phase 2 studies. In the randomised PLATO study, patients received enzalutamide plus abiraterone or placebo plus abiraterone at prostate-specific antigen (PSA) progression on enzalutamide; PSA response was low at 1% and 2% for each group, respectively. A prospective, single-arm trial of enzalutamide in 214 patients progressing after abiraterone showed that 27% had a PSA response and median time to PSA progression was 5·7 months. Recently, a randomised Alliance 031201 trial of combined enzalutamide plus abiraterone compared with abiraterone alone showed no difference in overall survival, but a modest improvement in radiographic progression free survival.

Added value of this study

Abiraterone and enzalutamide are among the most efficacious and well-tolerated drugs for metastatic castrate-resistant prostate cancer, and optimising the use of both drugs is an important research goal. To our knowledge, this was the first randomised, head-to-head comparison of abiraterone plus prednisone and enzalutamide. The trial also mandated crossover to the alternative drug at progression, to compare both treatment sequences, and the second-line activity of both drugs. Our trial is the first, to our knowledge, to show an advantage to using a sequencing strategy of both drugs: the treatment sequence of abiraterone plus prednisone followed by enzalutamide had a longer time to PSA progression than did the opposite sequence. Our findings are also the first randomised data showing activity of enzalutamide as a second-line treatment targeting the androgen receptor, and minimal activity of second-line abiraterone plus 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 first progression on abiraterone plus prednisone. Our results showed similar outcomes with first-line abiraterone plus prednisone and enzalutamide supporting the use of either drug in the first-line setting. Treatment with abiraterone plus prednisone followed by enzalutamide at first progression results in improved time to PSA progression and is the optimal sequencing strategy for these drugs.

overexpression, an adaptive mechanism implicated in the development of metastatic castration-resistant prostate cancer.[4]

Because these drugs have never been compared head to head and have shown similar activity, either drug can be used as first-line treatment for mCRPC.[5] In patients who were chemotherapy naive, abiraterone plus prednisone showed an overall survival benefit compared with placebo plus prednisone, with a hazard ratio (HR) of 0·81 (95% CI 0·70–0·93),[6] and in a separate phase 3 trial in similar patients,[7] enzalutamide improved overall survival compared with placebo (HR 0·77, 95% CI 0·67–0·88). Both treatments also achieved marked improvements in time to prostate-specific antigen (PSA) progression with a HR of 0·49 (95% CI 0·42–0·57) for abiraterone plus prednisone versus placebo plus prednisone and a HR of 0·17 (0·15–0·20) for enzalutamide versus placebo. Time to radiographic progression, frequency of skeletal-related events, and quality of life were also improved with both drugs.[7–10]

Whether patients treated with one androgen receptor pathway inhibitor benefit from treatment with the alternate drug at progression is uncertain because available data have consistently shown varying degrees of cross resistance. The proportion of patients with a 50% PSA response to enzalutamide in patients previously given abiraterone plus prednisone has varied between 18% and 40%,[11] whereas the proportion who respond with abiraterone plus prednisone after previous treatment with enzalutamide has not exceeded 10% in single-institution, retrospective case series.[12,13] In line with these results, only 1% of patients in the phase 3 PLATO study[14] showed a PSA response to abiraterone plus prednisone after progression on enzalutamide. There is currently a scarcity of prospective data examining optimal sequential use of both treatments and it remains unclear whether the order in which they are used affects activity.

We did a randomised, phase 2, crossover trial comparing enzalutamide at progression versus the opposite sequence of enzalutamide followed by abiraterone plus prednisone. Initial results for first-line therapy and genomic correlations from deep targeted circulating tumour DNA sequencing were previously reported.[15] We report final study results for the comparison of treatment sequences and second-line therapy, and updated results for first-line therapy.

Methods

Study design and participants

See Online for appendix

We did a randomised, open-label, phase 2, crossover trial in six centres in British Columbia, Canada (appendix p 7). Eligible patients were aged 18 years or older and had newly diagnosed, histologically proven prostatite adenocarcinoma without evidence of neuroendocrine differentiation, with metastatic disease on CT scan, MRI, or bone scan, and a rising PSA (PSA progression per Prostate Cancer Working Group 2 [PCWG2] criteria) with castrate concentrations of testosterone (≤1·7 nmol/L) with ongoing medical castration or previous bilateral orchiectomy. Patients were required to maintain luteinising hormone-releasing hormone (LHRH) agonist or antagonist therapy for the duration of study treatment if not surgically castrated. Previous use of CYP17A1 inhibitors (eg, abiraterone), enzalutamide, or experimental androgen receptor inhibitors was prohibited, whereas previous use of docetaxel for castration-sensitive disease was allowed. Eligible patients were required to have adequate organ function, defined as absolute neutrophil count $1·5\times10^9$ cells per L or higher, platelet count 100×10^9 per L or higher, haemoglobin 80 g/L or higher, creatinine clearance 30 mL/min or higher, serum potassium higher than lower limit of normal range, total bilirubin 1·5 times upper limit of normal or less, and alanine aminotransferase and aspartate aminotransferase five times upper limit of normal or less. Exclusion criteria included contraindications to abiraterone acetate and enzalutamide per the manufacturer's label, Eastern Cooperative Oncology Group (ECOG) performance status more than 2, brain metastases, active epidural disease, severe concurrent illness or comorbid 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 of less than 6 months. The presence of visceral metastasis and pain requiring opioid analgesia were allowed.

All patients provided written, informed consent. The study received ethical approval from the University of British Columbia and British Columbia Cancer Agency Research Ethics Board and was designed and done in accordance with Good Clinical Practice and the Declaration of Helsinki.

Randomisation and masking

Patients enrolled by local study investigators were randomly assigned (1:1) to receive abiraterone plus prednisone followed by enzalutamide (group A) or enzalutamide followed by abiraterone plus prednisone (group B) by the central study data monitor, using a simple randomisation method and a computer-generated random number table (Microsoft Excel 2010). Only the data monitor had access to the random number sequence. Investigators and participants were not masked to treatment assignment.

Procedures

Patients in group A received abiraterone 1000 mg orally once daily plus prednisone 5 mg orally twice daily as first study treatment until confirmed PSA progression, wide-field radiotherapy of symptomatic bone metastases, unacceptable treatment-related toxicity, or withdrawal of consent. They then crossed over to receive enzalutamide 160 mg orally once daily until symptomatic or clinical progression, unacceptable treatment-related toxicity, or withdrawal of consent. Patients in group B received the opposite sequence of enzalutamide followed by abiraterone plus 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 response was defined as 30% or higher PSA decline from baseline confirmed on repeat measurement at least 28 days later. PSA progression was defined as an increase of 2 µg/L and 25% from nadir confirmed by subsequent

	Baseline		Crossover	
	Group A (n=101)	Group B (n=101)	Group A (n=73)	Group B (n=75)
Age (years)	72·9 (51·3–93·3)	77·6 (49·3–94·1)	73·8 (51·5–92·7)	78·0 (49·8–93·2)
PSA (ng/mL)	35·0 (2·2–2817·0)	37·0 (1·7–1060·0)	16·0 (0·8–991·0)	12·0 (0·20–1604·0)
Alkaline phosphatase, relative to ULN	0·82 (0·29–12·50)	0·75 (0·30–47·80)	0·88 (0·31–6·87)	0·75 (0·31–4·67)
Lactate dehydrogenase, relative to ULN	0·79 (0·37–4·00)	0·80 (0·31–12·90)	0·85 (0·22–4·69)	0·74 (0·38–2·46)
Haemoglobin (g/L)	130 (89–155)	130 (89–165)	132 (87–152)	129 (79–157)
ECOG performance status 0–1	89 (88%)	79 (78%)	62 (85%)	57 (76%)
Previous docetaxel for castration-sensitive disease	5 (5%)	6 (6%)	..	..
Bone metastases	85 (84%)	82 (81%)	61 (84%)	65 (87%)
Lung metastases	8 (8%)	9 (9%)	6 (8%)	7 (9%)
Liver metastases	5 (5%)	7 (7%)	4 (5%)	7 (9%)

Data are median (range), or n (%). Group A=abiraterone plus prednisone followed by enzalutamide. Group B=enzalutamide followed by abiraterone plus prednisone. PSA=prostate-specific antigen. ULN=upper limit of normal. ECOG=Eastern Cooperative Oncology Group.

Table 1: **Patient clinical characteristics at baseline and at crossover**

rising PSA at least 28 days later. For patients with no PSA decline, PSA progression was defined as an increase of 2 µg/L and 25% from baseline after 12 weeks or more of treatment.[16] Adverse events were reported using Common Terminology Criteria for Adverse Events (CTCAE; version 4·0).

Serum PSA was taken at baseline and every 4 weeks on treatment. Serum alkaline phosphatase, lactate dehydrogenase, 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, was done at baseline and every 12 weeks, and additional imaging was done if clinically indicated. At the time of crossover, serum PSA testing was repeated and imaging was done within 4 weeks of crossover. Adverse events and concomitant medications were recorded every 4 weeks. Only adverse events grade 3 or higher, and serious adverse events or adverse events of interest of any grade (fatigue, increased aspartate aminotransferase, increased alanine aminotransferase, hypertension, oedema, hypokalaemia, and seizure) were recorded. After study completion, follow-up for determination of survival status was done every 3 months.

All PSA values entered in case report forms 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, that were reported by local study investigators were centrally reviewed by DJK, KNC, KS, and MA against radiology reports and medical records to ensure that the data were accurate and complete. Any discrepancies between reported events and clinical records were resolved via queries to local study investigators.

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. This primary endpoint was added to the trial protocol as an amendment on Jan 11, 2016, before completion of accrual and any data analysis. The second primary endpoint was the proportion of patients with PSA response on second-line therapy.

Secondary endpoints were proportion of patients with PSA response on first-line therapy; time to PSA progression on first-line therapy, defined as time from start of therapy to confirmed PSA progression; time to PSA progression on second-line therapy, defined as time from crossover to confirmed PSA progression; overall survival, defined as time from start of first-line therapy to time of death from any cause, or last follow-up (censored); time on treatment for second-line therapy, defined as time from crossover to end of second-line treatment or death; time to clinical progression on second-line therapy, defined as time from crossover to clinical progression, including death from prostate cancer; safety of second-line abiraterone and enzalutamide; change in Montreal Cognitive Assessment score on first-line and second-line therapy; and correlation of cell-free DNA biomarkers with PSA response after 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

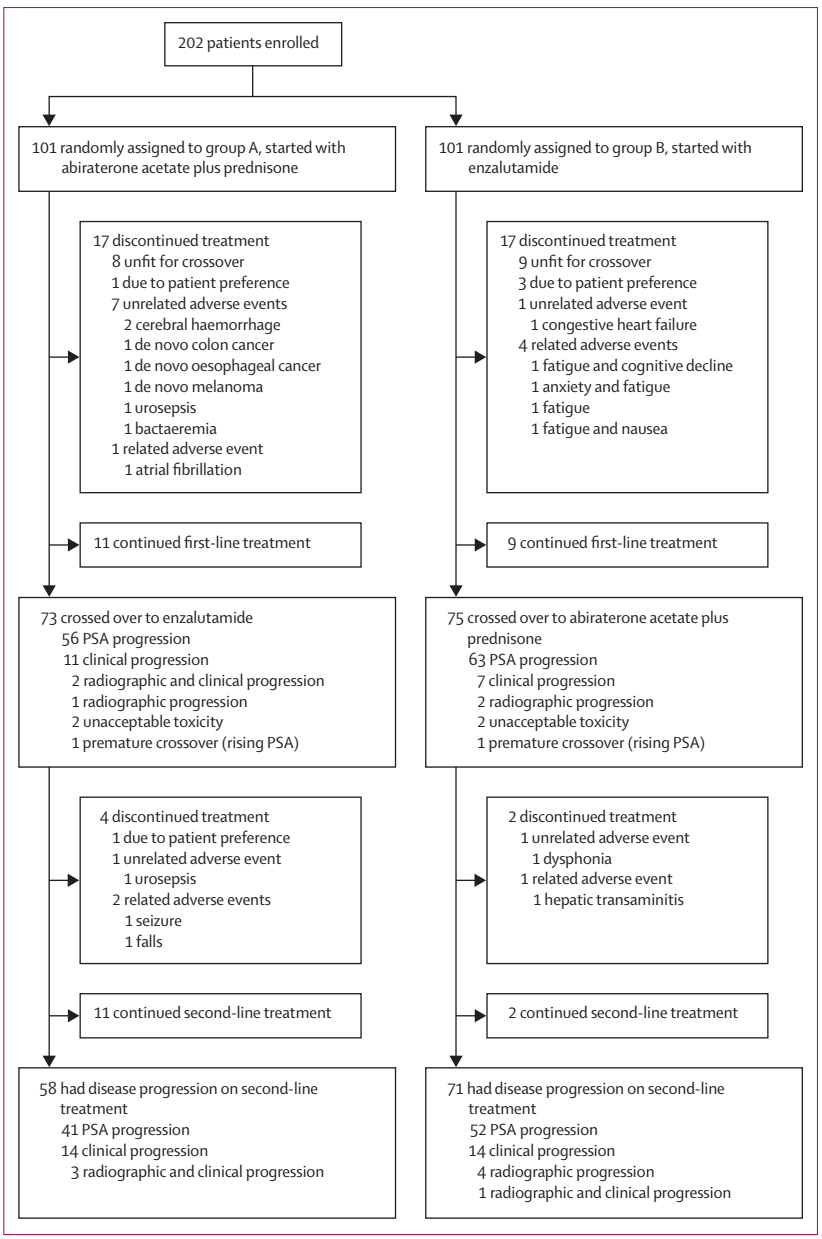

Figure 1: **Trial profile**
PSA=prostate-specific antigen.

because of the quantity of genomic information and absence of a prespecified analysis plan.

We chose not to analyse the prespecified 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 group and a preplanned analysis after 140 events, our study would have 70% power to detect a HR of 1·519 or more between groups, using a two-sided α level of 0·05. For the second primary endpoint of PSA response to second-line therapy, we used a Simon's two stage design in which a PSA response of 30% or higher in either group would be of interest. We determined that at least 39 patients would have to receive second-line therapy in each group to have 90% power to show a 30% response in either group with an α error of 0·1 and β error of 0·1. Median follow-up times were calculated using the reverse Kaplan-Meier estimator.[18]

For all time-to-event analyses, if no event occurred, the patient was right-censored at last treatment date. Patients who crossed over but had fewer than two subsequent PSA measurements were counted as having had no PSA decline. PSA response for first-line therapy was compared between groups using the Pearson's χ^2 test. HRs and p values for time to event outcomes were estimated using univariate Cox regression. For all secondary and exploratory endpoints, we used a significance threshold of α less than 0·05 (two-sided). All endpoints were analysed using the intention-to-treat principle: endpoints relating to first-line or combined treatment were evaluated in all randomly assigned patients, whereas endpoints relating to second-line treatment were evaluated in patients who crossed over.

A larger proportion of patients than expected developed radiographic or clinical progression rather than PSA progression. Therefore, the final analysis was done when 140 second-line progression events of any kind occurred, rather than 140 second-line PSA progression events (without protocol amendment). There were no planned interim analyses.

We did nine post-hoc analyses: 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; 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; time to second progression, defined as the time from start of first-line therapy to confirmed PSA progression, radiographic progression (PCWG2 criteria), or clinical progression on second-line therapy, or death from prostate cancer, whichever occurred first; comparison of second-line PSA responses between groups using Pearson's χ^2 test; clinical correlates of time to PSA progression and PSA response in patients receiving second-line enzalutamide; comparison of crossover clinical characteristics between groups; sensitivity analysis of time to second PSA progression (primary endpoint), excluding patients with delayed crossovers; comparison between groups of time from first progression of any kind to crossover; and subgroup analysis to determine whether second-line enzalutamide was better than second-line abiraterone in all patient subgroups. Preliminary results for first-line PSA response (secondary endpoint) and time to any

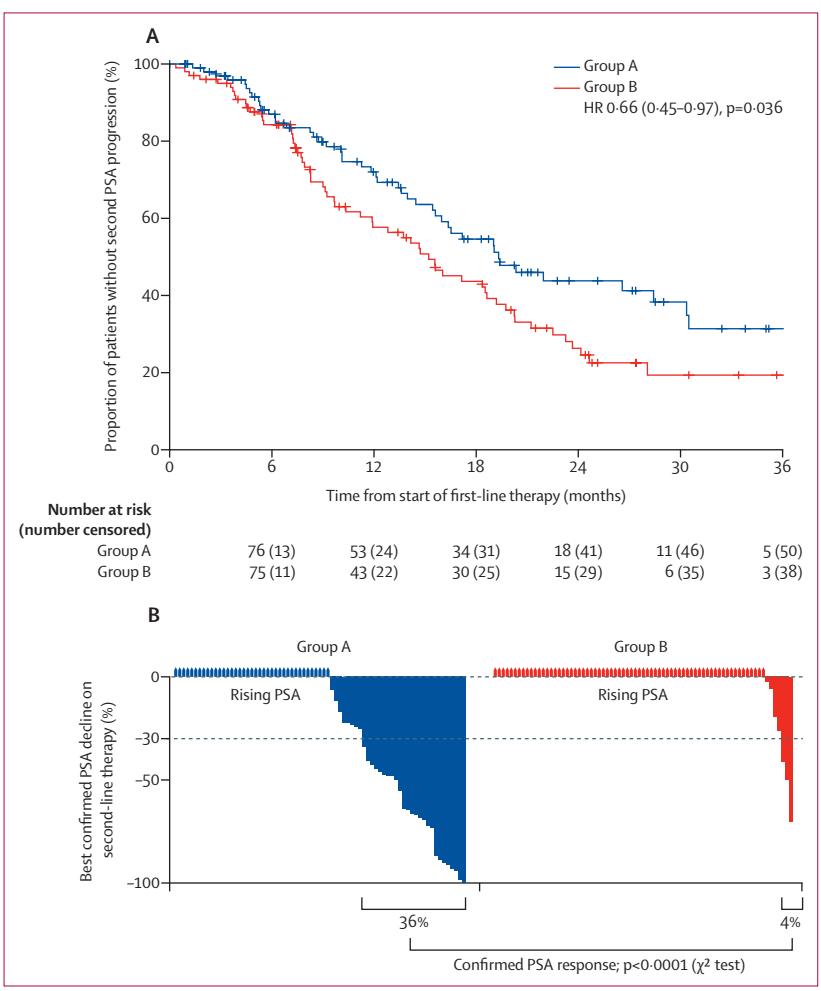

Figure 2: **Time from start of first-line therapy to second PSA progression (A) and best confirmed PSA decline during second-line therapy (B)**

HR and p values are based on Cox regression. PSA response was defined as confirmed 30% PSA decline (dotted line). PSA=prostate-specific antigen. HR=hazard ratio. Group A=abiraterone plus prednisone followed by enzalutamide. Group B=enzalutamide followed by abiraterone plus prednisone.

progression on first-line treatment (post-hoc exploratory endpoint) have been reported previously.[15]

The safety populations for first-line 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 groups, continuous-valued characteristics were compared using the rank-sum test, and Boolean characteristics were compared using Fisher's exact test.

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, Pearson's χ^2 test 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). This trial is registered with ClinicalTrials.gov, NCT02125357.

Role of the funding source

The funder 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.

Results

Between Oct 21, 2014, and Dec 13, 2016, 202 patients were enrolled, of whom 101 were assigned to each group. The median follow-up at time of data cutoff (May 31, 2018) was 30·7 months (IQR 25·1–36·2). Patient clinical characteristics at the start of first-line therapy and at crossover are shown in table 1. At crossover, median lactate dehydrogenase levels were higher in group A than in group B (p=0·0008; post-hoc analysis). At the time of data cutoff, 73 (72%) patients from group A had crossed over to receive enzalutamide and 75 (74%) patients from group B had crossed over to receive abiraterone plus prednisone. 17 (17%) patients in group A and 17 (17%) patients in group B discontinued therapy without crossing over (figure 1). No patients were lost to follow-up before crossover. A large proportion of patients had delayed crossover (56 [79%] patients in group A and 57 [79%] patients in group B), defined as initiation of second-line therapy more than 2 weeks from the date of confirmed progression. However, times from progression to crossover did not differ significantly between groups (median 39 [IQR 28–85] days *vs* 36 [29–86] days, p=0·60, post-hoc analysis).

At the time of data cutoff, 148 (73%) of 202 patients had crossed over to start second-line therapy, and 142 patients had disease progression 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 to second PSA progression, was longer in group A than in group B (median 19·3 months [95% CI 16·0–30·5] *vs* 15·2 months [11·9–19·8]; HR 0·66, 95% CI 0·45–0·97, p=0·036; figure 2A). With a median follow-up of 22·8 months (IQR 10·3–33·4), there were 106 events (93 second-line PSA progression events and 13 prostate cancer deaths) before crossover. The difference between the groups was confirmed by the second primary endpoint: PSA responses to second-line therapy were seen in 26 (36%) of 73 patients in group A and three (4%) of 75 patients in group B (figure 2B). The prespecified efficacy threshold of 30% of patients having a response was therefore only reached in group A. As a post-hoc analysis, we also confirmed that second-line PSA response was significantly different in the two groups (p<0·0001).

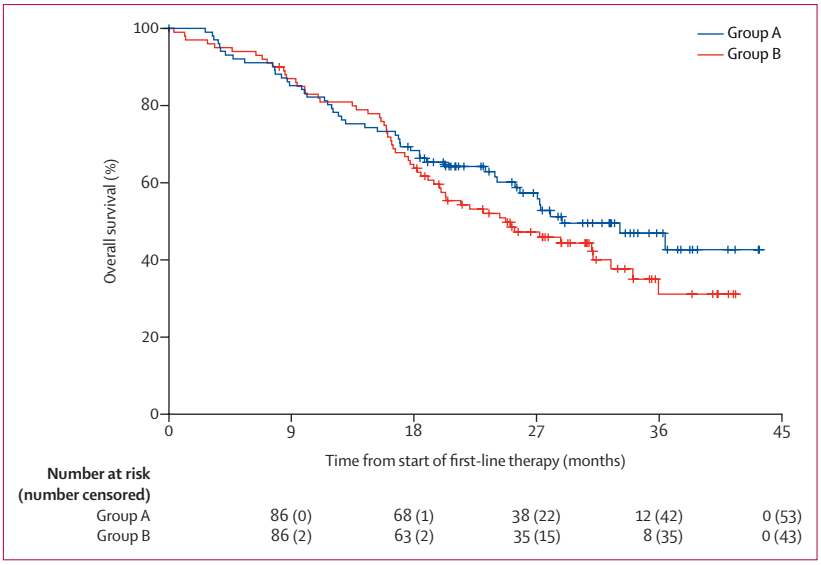

***Figure 3*: Overall survival**
Group A=abiraterone plus prednisone followed by enzalutamide. Group B=enzalutamide followed by abiraterone plus prednisone.

Between trial start and data cutoff, there were 48 deaths in group A and 58 in group B (median overall survival 28·8 months [95% CI 25·4–not reached] *vs* 24·7 months [18·8–34·0]; HR 0·79, 95% CI 0·54–1·16, p=0·23; figure 3). Median follow-up for overall survival was 30·7 months (IQR 25·1–36·2). For the 25 patients who died on study (other deaths occurred after the patient had already left the trial, and causes of death were not cataloged for these patients), causes of death were prostate cancer (16 patients), cerebral haemorrhage (two), cardiac issues (one), infection (one), metastatic melanoma (one), urosepsis (one), bactaeremia (one), complications from surgery for colon cancer (one), and esophageal carcinoma (one). There were no treatment-related deaths.

In the patient population that crossed over to second-line therapy, second-line enzalutamide was better than second-line abiraterone for both time to PSA progression on second-line therapy (median 3·5 months [95% CI 2·9 –8·7] *vs* 1·7 months [1·6–2·5]; HR 0·42, 95% CI 0·28–0·65, p<0·0001; figure 4A) and time on second-line

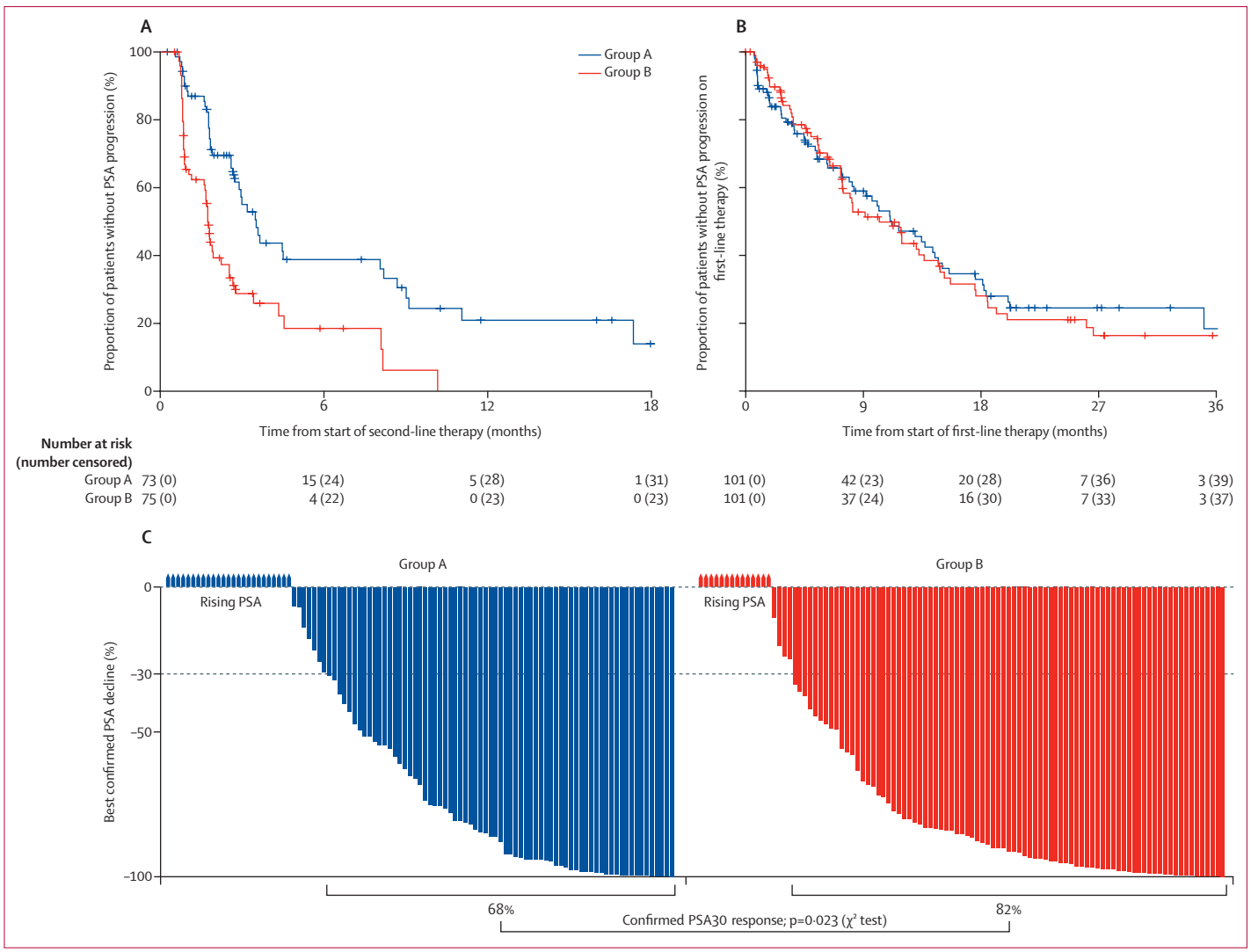

Figure 4: **Time to PSA progression during second-line therapy (A), time to PSA progression during first-line therapy (B), and best confirmed PSA decline during first-line therapy (C)**
PSA response was defined as confirmed 30% PSA decline (dotted line). PSA=prostate-specific antigen.

treatment (median 4·6 months [95% CI 3·7–7·4] *vs* 3·6 months [2·9–5·4]; HR 0·66, 95% CI 0·46–0·94, p=0·023; p 2). Median follow-up for these endpoints was 3·9 months (IQR 2·1–16·0) and 19·4 months (13·6–25·7), respectively.

For first-line therapy, PSA responses were seen in 69 (68%) of 101 patients given abiraterone plus prednisone and 83 (82%) of 101 patients given enzalutamide (χ^2 p=0·023; 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 months [95% CI 8·3–15·0] *vs* 10·2 months [7·5–14·7]; HR 0·95, 95% CI 0·66–1·36, p=0·78; figure 4C). Median follow-up was 21·6 months (IQR 6·7–28·5).

Incidence and severity of adverse events of interest were consistent with the known toxicity profile of both drugs (p 6). The most common grade 3–4 adverse events throughout the trial were hypertension (27 [27%] of 101 patients in group A *vs* 18 [18%] of 101 patients in group B) and fatigue (six [10%] *vs* four [4%]). The most common grade 3–4 adverse events for first-line therapy were hypertension (23 [23%] of 101 patients given abiraterone *vs* 13 [13%] of 101 patients given enzalutamide), fatigue (six [6%] *vs* two [2%]), increased alanine aminotransferase (six [6%] *vs* one [1%]), fracture (three [3%] *vs* four [4%]), increased aspartate aminotransferase (five [5%] *vs* one [1%]), and back pain (three [3%] *vs* three [3%]). The most common grade 3–4 adverse events for second-line therapy were hypertension (13 [18%] of 73 patients given enzalutamide *vs* 11 [15%] of 75 patients given abiraterone), fatigue (four [5%] *vs* two [3%]), back pain (two [3%] *vs* three [4%]), and extremity pain (three [4%] *vs* one [1%];

p 7–9). Serious adverse events were reported in 15 (15%) of 101 patients in group A and 20 (20%) of 101 patients in group B. There were no treatment-related serious adverse events.

For first-line therapy, six (6%) of 101 patients required a dose reduction for abiraterone compared with 18 (18%) of 101 for enzalutamide. For second-line therapy, 14 (19%) of 73 patients required a dose reduction for enzalutamide compared with four (5%) of 75 for abiraterone. Five patients discontinued first-line therapy and did not cross over because of treatment-related adverse events (atrial fibrillation [one in group A], fatigue [one in group B], fatigue and cognitive impairment [one in group B], fatigue and anxiety [one in group B], and fatigue and nausea [one in group B]). Some patients discontinued second-line therapy before disease progression due to the following treatment-related adverse events: seizure and falls (two patients in group A) and hepatic transaminitis (one in group B; figure 1).

Time from start of first-line therapy to progression of any kind on second-line therapy (post-hoc endpoint) was longer in group A than in group B (median 15·0 months [95% CI 12·2–19·3] *vs* 10·3 months [8·3–14·7]; HR 0·69, 95% CI 0·50–0·96, p=0·029; p 1). With a median follow-up of 27·4 months (IQR 21·0–35·2), there were 142 events (93 second-line PSA progression events, 36 radiographic or clinical progression events, and 13 prostate cancer deaths before crossover). To address the issue of delayed crossovers, we did a post-hoc sensitivity analysis excluding patients who crossed over more than 2 weeks after confirmed progression. Results were consistent with the primary analysis: group A had a longer time from start of first-line therapy to second PSA progression than did group B; however, there was no statistical difference between the groups (median not reached [95% CI 16·5–not reached] *vs* 19·2 [11·2 to not reached]; HR 0·60, 95% CI 0·29–1·21, p=0·15).

After a median follow-up of 16·5 months (IQR 11·7–17·9), post-hoc analysis showed that time to progression on second-line therapy for patients who crossed over was longer for those who received second-line enzalutamide than second-line abiraterone (median 2·7 months [95% CI 2·4–3·5] *vs* 1·7 months [95% CI 1·0–1·8]; HR 0·43, 95% CI 0·20–0·61, p<0·0001; p 3). As a post-hoc analysis, we explored whether second-line enzalutamide was better in all patient subgroups (p 4), and whether any clinical factors were prognostic for second-line enzalutamide response (table 2). After a median follow-up of 27·2 months (IQR 20·2–37·3) months, post-hoc analysis of time to any progression on first-line therapy showed no difference between groups A and B (7·9 months [95% CI 5·5–11·0] *vs* 7·3 months [95% CI 5·7–9·1]; HR 0·95, 95% CI 0·70–1·29, p=0·74; p 5).

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

Data are n/N (%), unless otherwise stated. PSA=prostate-specific antigen. HR=hazard ratio. ULN=upper limit of normal. ECOG=Eastern Cooperative Oncology Group. Group A=abiraterone plus prednisone followed by enzalutamide. *Reference for HR.

Table 2: **Post-hoc univariate analysis of clinical factors associated with time from crossover to second PSA progression and PSA response in Group A**

Discussion

In this randomised, open-label, phase 2, crossover trial we found that time to second PSA progression was better for the sequence of abiraterone followed by enzalutamide (group A) than for enzalutamide followed by abiraterone (group B; median 19·3 months *vs* 15·2 months). This seemed to be driven by the second-line activity of enzalutamide, which was greater than that of abiraterone (median time to PSA progression on second-line therapy in patients who crossed over: 3·5 months *vs* 1·7 months). To our knowledge, these are the first prospective data estimating the degree of cross-resistance for both sequences, as well as the first randomised comparison of both treatment sequences in their entirety. Finally, to our knowledge, this study was the first randomised, head-to-head comparative assessment of the efficacy of both drugs in the first-line setting for metastatic castration-resistant prostate cancer, showing no difference in time to first-line PSA progression, despite a higher amount of patients having a PSA response when given enzalutamide.

Overall, our findings show that alternating androgen receptor pathway inhibitors at progression can be beneficial when abiraterone plus prednisone is used first. However, because of the modest response to second-line enzalutamide, other available and appropriate therapies should also be considered for patients progressing after first-line androgen receptor pathway inhibitors, such as taxane chemotherapy and radium-223. We are

investigating the optimal sequencing of taxane and androgen receptor pathway inhibitor 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 framework for advanced prostate cancer continues to shift towards intensified treatment in earlier disease states. Recently, both abiraterone plus prednisone and enzalutamide have received new indications, specifically in metastatic castration-sensitive disease for abiraterone plus prednisone and in non-metastatic castration-resistant disease for enzalutamide.[19,20] Our data are, to our knowledge, the first to show an advantage in sequencing androgen receptor pathway inhibitors and provide a robust assessment of cross-resistance between both drugs, and thus can help to inform the choice of subsequent treatment following failure of androgen receptor pathway inhibitors in earlier treatment settings.

It is notable that our results for first-line therapy closely mirror those from the COU-AA-302[21] trial and PREVAIL[8] trial of abiraterone plus prednisone and enzalutamide, in which a PSA response (defined as greater than 50% PSA reduction in these trials) was seen in 62% of patients for abiraterone and 78% of patients for enzalutamide (compared with 65% and 80% in our study) and median times to PSA progression were 11·1 months and 11·2 months (compared with 11·2 months and 10·2 months in our study). However, a higher number of patients than expected declined rapidly precluding crossover in our study (eight patient for group A and nine for group B), reflective of more aggressive disease status and the inclusive nature of this study population. Additionally, median overall survival was worse in our trial (28·8 months for first-line abiraterone and 24·7 months for group B compared with group A 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 enrolment 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 might account for these outcomes, but also allows for potentially greater generalisability.

Our results for second-line therapy are consistent with those reported in the literature. The activity of abiraterone plus 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 who received abiraterone plus prednisone for at least 24 weeks found that 27% of patients had a PSA response with a time to PSA progression of 5·7 months,[22] and a large number of retrospective studies have shown similar modest benefit.[11] By contrast, our randomised, comparative study provides robust data for assessing the second-line activity of both drugs, and for evaluating an optimal sequencing strategy. These results support a role for enzalutamide as a second-line androgen receptor pathway inhibitor, but not for abiraterone plus prednisone.

Mechanistically, acquired changes in the androgen receptor signalling axis might explain why patients given enzalutamide had a higher second-line response. Mutations involving the ligand-binding domain of the androgen receptor emerge during the course of androgen receptor signalling axis inhibition and could allow activation by alternate ligands.[2] Well-described examples associated with abiraterone plus prednisone resistance include the *L702H* mutation, which allows androgen receptor activation by glucocorticoids,[2,23] and the *T878A* mutation, which confers agonist activity to progesterone, a hormone that is increased by treatment with abiraterone.[24] Enzalutamide still retains androgen receptor inhibitory activity against both these mutations. Alternatively, resistance mechanisms common to both drugs include amplification of the androgen receptor gene, which emerges under selective pressure induced by androgen-deprivation therapy and has been observed in more than 50% of metastatic castration-resistant prostate cancer cases.[25–27] The androgen receptor signalling axis could also reactivate through mechanisms no longer amenable to ligand inhibition, including androgen receptor splice variants that do not have 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 some patients who did not cross over to second-line therapy, which might have limited our power to detect differences in outcomes. The imbalance in age between groups and the open-label nature of the study are further limitations. Results for secondary endpoints should be considered exploratory because we examined multiple secondary endpoints without α corrections for multiple testing.

In conclusion, our study showed that abiraterone and enzalutamide have similar first-line activity for metastatic castration-resistant prostate cancer. Enzalutamide retains clinical activity as a second-line drug following abiraterone, whereas abiraterone retains no second-line activity following enzalutamide. Our findings show that the treatment sequence of abiraterone followed by enzalutamide is preferred and can result in improved clinical benefit.

Contributors

KNC, AWW, and AAA conceived and designed the trial. KNC, MEG, DLF, 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 analysed the data. DJK, MA, KNC, and AWW prepared the manuscript. KNC, DJK, MA, and KS had access to the raw patient data. All authors reviewed and approved the final version of the manuscript.

Declaration of interests

DJK 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, Astellas, and Bayer, outside the submitted work. JV reports non-financial support from Bayer; personal fees from Pfizer, Janssen, Bayer, Bristol-Myers Squibb, and Astellas; and non-financial support from Astellas, Merck, and Bristol-Myers Squibb, outside the submitted work. AAA reports personal fees from Janssen, Novartis, Astellas, Amgen, Pfizer, Bayer, Telix, Bristol-Myers Squibb, Sanofi, Noxopharm, and Tolmar; grants from Astellas and Merck Serono; and non-financial support from Astellas, Amgen, and Merck Serono. CKK reports personal fees from Janssen, Astellas, Pfizer, Ipsen, Eisai, Roche, Merck, and Bristol-Myers Squibb, outside the submitted work. BJE reports personal fees from AstraZeneca, Roche, Janssen, and Merck, outside the submitted work. AA reports personal fees from Astellas, outside the submitted work. SLE reports Janssen stock ownership, 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 Astellas during the conduct of the study; grants from Janssen, Astellas, Sanofi, AstraZeneca, Bayer, Pfizer, and Roche; and personal fees from Janssen, Astellas, Sanofi, AstraZeneca, Bayer, Pfizer, and 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.

Acknowledgments

This study was funded by the Canadian Cancer Society Research Institute, Prostate Cancer Canada, Movember Foundation, Prostate Cancer Foundation, Terry Fox New Frontiers Program, BC Cancer Foundation, Jane and Aatos Erkko Foundation, Janssen, and Astellas.

References

1 Penson DF, Litwin MS. The physical burden of prostate cancer. *Urol Clin North Am* 2003; **30:** 305–13.

2 Watson PA, Arora VK, Sawyers CL. Emerging mechanisms of resistance to androgen receptor inhibitors in prostate cancer. *Nat Rev Cancer* 2015; **15:** 701–11.

3 Attard G, Belldegrun AS, de Bono JS. Selective blockade of androgenic steroid synthesis by novel lyase inhibitors as a therapeutic strategy for treating metastatic prostate cancer. *BJU Int* 2005; **96:** 1241–6.

4 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.

5 Virgo KS, Basch E, Loblaw DA, et al. Second-line hormonal therapy for men with chemotherapy-naive, castration-resistant prostate cancer: American Society of Clinical Oncology provisional clinical opinion. *J Clin Oncol* 2017; **35:** 1952–64.

6 Ryan CJ, Smith MR, Fizazi K, et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol* 2015; **16:** 152–60.

7 Beer TM, Armstrong AJ, Rathkopf D, et al. Enzalutamide in men with chemotherapy-naive metastatic castration-resistant prostate cancer: extended analysis of the phase 3 PREVAIL study. *Eur Urol* 2017; **71:** 151–14.

8 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.

9 Loriot Y, Miller K, Sternberg CN, et al. Effect of enzalutamide on health-related quality of life, pain, and skeletal-related events in asymptomatic and minimally symptomatic, chemotherapy-naive patients with metastatic castration-resistant prostate cancer (PREVAIL): results from a randomised, phase 3 trial. *Lancet Oncol* 2015; **16:** 509–21.

10 Logothetis CJ, Basch E, Molina A, et al. Effect of abiraterone acetate and prednisone compared with placebo and prednisone on pain control and skeletal-related events in patients with metastatic castration-resistant prostate cancer: exploratory analysis of data from the COU-AA-301 randomised trial. *Lancet Oncol* 2012; **13:** 1210–17.

11 Chi K, Hotte SJ, Joshua AM, et al. Treatment of mCRPC in the AR-axis-targeted therapy-resistant state. *Ann Oncol* 2015; **26:** 2044–56.

12 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.

13 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.

14 Attard G, Borre M, Gurney H, et al. Abiraterone alone or in combination with enzalutamide in metastatic castration-resistant prostate cancer with rising prostate-specific antigen during enzalutamide treatment. *J Clin Oncol* 2018; **36:** 2639–46.

15 Annala M, Vandekerkhove G, Khalaf D, et al. Circulating tumor DNA genomics correlate with resistance to abiraterone and enzalutamide in prostate cancer. *Cancer Discov* 2018; **8:** 444–57.

16 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.

17 Khalaf DJ, Sunderland K, Eigl BJ, et al. Health-related quality of life for abiraterone plus prednisone versus enzalutamide in patients with metastatic castration-resistant prostate cancer: results from a phase II randomized trial. *Eur Urol* 2019; **75:** 940–47.

18 Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. *Control Clin Trials* 1996; **17:** 343–46.

19 Fizazi K, Tran N, Fein L, *et al*. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. *N Engl J Med* 2017; **377:** 352–60.

20 Hussain M, Fizazi K, Saad F, et al. Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer. *N Engl J Med* 2018; **378:** 2465–74.

21 Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med* 2014; **371:** 424–33.

22 de Bono JS, Chowdhury S, Feyerabend S, et al. Antitumour activity and safety of enzalutamide in patients with metastatic castration-resistant prostate cancer previously treated with abiraterone acetate plus prednisone for ≥24 weeks in Europe. *Eur Urol* 2018; **74:** 37–45.

23 Lorente D, Mateo J, Zafeiriou Z, et al. Switching and withdrawing hormonal agents for castration-resistant prostate cancer. *Nat Rev Urol* 2015; **12:** 37–47.

24 Chen EJ, Sowalsky AG, Gao S, et al. Abiraterone treatment in castration-resistant prostate cancer selects for progesterone responsive mutant androgen receptors. *Clin Cancer Res* 2015; **21:** 1273–80.

25 Robinson D, Van Allen EM, Wu Y-M, et al. Integrative clinical genomics of advanced prostate cancer. *Cell* 2015; **162:** 454.

26 Romanel A, Gasi Tandefelt D, Conteduca V, et al. Plasma AR and abiraterone-resistant prostate cancer. *Sci Transl Med* 2015; **7:** 312re10.

27 Azad AA, Volik SV, Wyatt AW, et al. Androgen receptor gene aberrations in circulating cell-free DNA: biomarkers of therapeutic resistance in castration-resistant prostate cancer. *Clin Cancer Res* 2015; **21:** 2315–24.