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CADTH PCODR CLINICAL GUIDANCE REPORT

Clinical Report

ENZALUTAMIDE (XTANDI)

(Astellas Pharma Canada, Inc.)

Indication: In combination with androgen-deprivation therapy for the treatment of patients with metastatic castration sensitive prostate cancer.

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Abbreviations

ACE-27	Adult Comorbidity Evaluation-27
ADT	androgen-deprivation therapy
AE	adverse event
ANZUP	Australia and New Zealand Urogenital and Prostate Cancer
BPI-SF	Brief Pain Inventory-Short Form
CI	confidence interval
CrI	credible interval
CSPC	castration-sensitive prostate cancer
CT	Computed Tomography
ECOG	Eastern Cooperative Oncology Group
QLQ-C30	European Organization for Research and Treatment of Cancer quality of life questionnaire
EQ-5D-5L	EuroQoL 5-Dimensions, 5-Levels
FACT-P	Functional Assessment of Cancer Therapy-Prostate
GnRH	gonadotropin-releasing hormone
HR	hazard ratio
HRQoL	health-related quality of life
ICR	Independent Central Review
IQR	interquartile range
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	intention-to-treat
LHRH	luteinizing hormone-releasing hormone
mCSPC	metastatic castration sensitive prostate cancer
mHSPC	metastatic hormone sensitive prostate cancer
MID	minimally important difference
MRI	magnetic resonance imaging
NA	not applicable
NMA	network meta-analysis
NR	not reached
NSAA	non-steroidal anti-androgen

ORR	objective response rate
OS	overall survival
PCWG2	Prostate Cancer Working Group 2
PSA	prostate-specific antigen
QLQ-PR25	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Prostate 25
rPFS	Radiographic progression-free survival
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumors
SLR	systematic literature review
SSE	symptomatic skeletal related events
TEAE	treatment-emergent adverse events
Tid	three times a day

1 Guidance In Brief

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding enzalutamide (Xtandi) for metastatic castration sensitive prostate cancer. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature conducted by the Clinical Guidance Panel (CGP) and the CADTH Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from Registered Clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input, a summary of submitted Provincial Advisory Group Input, and a summary of submitted Registered Clinician Input, and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The purpose of this review is to evaluate the efficacy and safety of enzalutamide (Xtandi) in combination with androgen deprivation therapy (ADT) compared with ADT alone or ADT plus a non-steroidal anti-androgen (NSAA) in men with metastatic castrate sensitive prostate cancer (mCSPC).

Enzalutamide is a next-generation androgen receptor inhibitor that binds to the ligand-binding domain of the androgen receptor, which prevents the synthesis of androgens; a mechanism that is distinct from the first-generation anti-androgens. Enzalutamide has been issued marketing authorization without conditions for the treatment of patients with mCSPC. Note that the Health Canada indication aligns with the CADTH reimbursement criteria.

The recommended dose of enzalutamide (Xtandi) is 160 mg (four 40 mg capsules) administered orally once daily (with or without food). The product monograph states that enzalutamide is for use in patients who are maintaining treatment with a gonadotropin-releasing hormone (GnRH) analogue or who have had previously undergone surgical castration. Patients started on enzalutamide who are receiving a GnRH analogue should continue to receive a GnRH analogue.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The CADTH systematic review included two randomized controlled trials (RCTs) (ARCHES and ENZAMET) that assessed the efficacy and safety of enzalutamide for patients with mCSPC.

Trial Characteristics

ARCHES Trial

The ARCHES trial is an ongoing, multinational, randomized, double-blind, placebo-controlled, phase III trial that assesses the safety and efficacy of enzalutamide as compared to placebo in 1,150 men with metastatic hormone sensitive prostate cancer (mHSPC) regardless of prior docetaxel use or disease volume.[1] The trial was conducted in 202 centres within North and Latin America, Europe and Asia.[1] The majority of patients were recruited from Europe (59.6%).[1] It was sponsored by Astellas Pharma and Pfizer.[1]

Patients were included in the trial if they met the following criteria: adult men with pathologically confirmed prostate adenocarcinoma without neuroendocrine differentiation, signet-cell or small-cell features (according to local regulation); metastatic prostate cancer documented by positive bone scan or metastatic lesions on CT (computed tomography) or magnetic resonance imaging (MRI) scan; able to maintain ADT (androgen deprivation therapy) with an LHRHA (Luteinizing Hormone Releasing Hormone Analogue) agonist or antagonist during study treatment or have a history of bilateral orchiectomy after day 1 of randomization; and an Eastern Cooperative

Oncology Group (ECOG) performance status of 0 or 1. Patients who had prior disease progression while receiving ADT and/or docetaxel were excluded from the trial.

Patients were randomized on a 1:1 ratio to receive either enzalutamide (160 mg/day) with ADT or placebo with ADT. Randomization was stratified by disease volume (low vs high) and prior docetaxel chemotherapy for prostate cancer (no cycles, one to five cycles, or six cycles). During the double-blind treatment phase, at baseline, radiographic imaging assessments were performed using CT or MRI and bone scans, and subsequent imaging was performed at week 13 and every 12 weeks thereafter.[1] All radiographic assessments were confirmed by an Independent Central Review (ICR). Patients received their assigned therapy until unacceptable toxicity, radiographic progression, starting a new therapy for the treatment of prostate cancer or they met other discontinuation criteria.[1]

The primary endpoint was radiographic progress-free survival (rPFS) as assessed by ICR. Secondary outcomes included: overall survival (OS), time to first symptomatic skeletal related events (SSE), time to castration resistance, time to deterioration of quality of life (QoL), time to deterioration in urinary symptoms, time to start of new antineoplastic therapy, time to prostate specific antigen (PSA) progression, PSA undetectable rate (< 0.2 ng/mL), objective response rate (ORR) and time to pain progression. Exploratory outcomes were combined response (soft tissue lesions and bone lesions), PSA reduction, health-related quality of life (HRQoL) and safety.[1] The database cut-off for the ARCHES trial was 14-Oct-2018 and this represents a median follow-up time of 14.4 months.[1]

The ARCHES trial was designed to provide sufficient power for rPFS and OS. The required sample size for the trial was 1,100 patients. Two hundred and sixty-two rPFS events (i.e., radiographic progression at any time or death from any cause within 24 weeks after study drug discontinuation, whichever occurred first) were required to provide 90% power to detect a hazard ratio (HR) of 0.67 (30 months with enzalutamide vs. 20 months with placebo), using a log-rank test and two-sided significance α of 0.05.[1] For OS, 342 deaths were required to provide 80% power to detect a HR of 0.73 (55 months with enzalutamide vs. 40 months with placebo) for OS, using a log-rank test and two sided significance level α of 0.04.[1]

Overall, the baseline characteristics were well balanced.[1] The median age in the trial was 70 years (enzalutamide: 70.0 [range: 46 to 92] vs placebo: 70.0 [range: 42 to 92]) and a large proportion of patients had a Gleason score of ≥8 (enzalutamide: 67.2% vs placebo: 64.8%).[1] More than half of all the patients in the trial had a high volume of disease (enzalutamide: 61.7% vs placebo: 64.8%).[1] The majority of patients did not receive prior docetaxel (enzalutamide: 82.1% vs placebo: 82.3%) but they had previous use of ADT for ≤ 3 months (enzalutamide: 72.1% vs placebo: 68.4%).[1] The majority of patients in the trial had bone only (44.6% for all) or bone and soft tissue (39.8%) metastasis based on ICR.[2] The amount of bone lesions based on ICR varied for all patients in the trial (1 bone lesion: 13.3%; 2 to 4 bones lesions: 25.5%; 5 to 9: 17.5%; 10 to 19: 19.6%; and ≥ 20 [including too numerous to count]: 8.6%).[2]

A total of 1,150 patients were randomized to receive either enzalutamide (N = 574) or placebo (N = 576).[1] Two patients in the enzalutamide group and two in the placebo group did not receive their assigned therapies.[1] At the 14-Oct-2018 data cut-off, 76.1% of patients (N = 437) were still receiving enzalutamide and 57.6% of patients were still receiving placebo (N= 332).[1] In the enzalutamide group, 23.5% of patients discontinued their assigned treatment (N = 135) while 42.0% of patients discontinued treatment with placebo (N=242).[1] The most common reasons for discontinuation in the enzalutamide and placebo groups were progressive disease (11.3% vs. 29.7%).[1]

ENZAMET Trial

The ENZAMET trial is an ongoing, multinational, open-label, randomized phase III trial that assesses the safety and efficacy of enzalutamide as compared to standard care in 1,125 men with mHSPC.[3] The trial was conducted in 83 sites within Australia, Canada, Ireland, New Zealand, the United Kingdom and the United States.[3] The majority of patients were recruited from Australia.[3] The trial was led by the Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP) and the National Health and Medical Research Council (NHMRC) Clinical Trials Centre, University of Sydney. Regional sponsorship was provided by Cancer Trials Ireland, the Canadian Cancer Trials Group and the Dana–Farber Cancer Institute, as well as Astellas Pharma.

Patients were included in the trial if they met the following criteria: adult men with prostatic adenocarcinoma with metastases on CT, bone scanning with technetium-99, or both; and an ECOG performance status of 0 to 2. Patients were eligible for the trial if they had testosterone suppression that was initiated up to 12 weeks before randomization, or if they had previous adjuvant testosterone

suppression for up to 24 months that was completed at least 12 months earlier.[3] In addition, patients who started docetaxel prior to study entry were still eligible if they were tolerating full doses of docetaxel (75mg/m^2) with ADT, met all the eligibility criteria for the trial while receiving docetaxel and had no more than two cycles prior to randomization.[3] The first dose of docetaxel should be given at least four weeks after starting enzalutamide, and no more than six weeks after randomization.[3]

Prior to randomization, treating clinicians and patients decided if early treatment with docetaxel would be undertaken.[3] Similar decisions were made about the use of concomitant "anti-resorptive" therapy, which was used to delay skeletal related events (SREs) when initiating ADT (i.e., denosumab, zoledronic acid or any other therapy at doses proven to prevent SREs).[3]

Patients were centrally randomized on a 1:1 ratio to receive either enzalutamide (160 mg/day) with ADT or NSAA with ADT. The type of NSAA that was chosen was at the discretion of the treating clinician, and it could include: bicalutamide (50 mg/d), nilutamide (150mg/d) or flutamide (250mg/three times a day [tid]).[3] Randomization was stratified by disease volume (low vs high), study site, anti-resorptive therapy (yes vs no), comorbidities according to the Adult Comorbidity Evaluation-27 (ACE-27) (0 to 1 vs 2 to 3) and early planned use of docetaxel (yes vs no).[3]

During the open-label treatment phase, assessments occurred at baseline, day 29, week 12 and then every 12 weeks until clinical progression.[3] Patients received imaging with a CT scan or MRI and whole body bone scan a baseline and at evidence of PSA clinical progression, whichever occurred first.[3] Patients received their assigned therapy until unacceptable toxicity or clinical progression.[3] Clinical progression was defined as progression on imaging (Prostate Cancer Clinical Trials Working Group 2 [PCWG2] criteria for bone lesions and RECIST 1.1 for soft tissue lesions), development of symptoms attributable to cancer progression or initiation of other anticancer treatment for prostate cancer.[3] Patients who discontinued their assigned therapies could receive a subsequent therapy at the discretion of the treating clinician.[3]

The primary endpoint was OS. Secondary outcomes were PSA PFS and clinical PFS. Exploratory outcomes were HRQoL and safety. The database cut-off for the ENZAMET trial was 28-Feb-2019 and this represents a median follow-up of 34.4 months.[3]

Four hundred and seventy deaths were required to provide 80% power to detect a HR of 0.75, assuming a 3-year survival rate of 65% in the NSAA group, and using a log-rank test and two-sided significance level α of 0.05.[3]

Overall, the baseline characteristics were well balanced.[3] The median age in the trial was 69 years (enzalutamide: 69.2 [interquartile range (IQR) 63.2 to 74.5] vs NSAA: 69.0 [IQR: 63.6 to 74.5]) and a large proportion of patients had a Gleason score of 8 to 10 (enzalutamide: 60% and NSAA: 57%).[3] Eleven percent of patients in the enzalutamide group and 12% in the NSAA group had visceral metastases. More than half of all the patients in the trial had a high volume of disease (enzalutamide: 52% and NSAA: 53%).[3] Almost 10% of patients in the enzalutamide group (10.3%) and 9.8% in the NSAA group received bone anti-resorptive therapy and the majority of patients had 0 to 1 ACE-27 stratum (enzalutamide: 74.6% and NSAA:75.0%).[3] The majority of patients had previous LHRHA therapy (enzalutamide: 73% vs NSAA: 74%) and antiandrogen therapy (enzalutamide: 51% vs NSAA: 56%).[3] [redacted].[4] (*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

A total of 1,125 patients were randomized to receive either enzalutamide (N = 563) or NSAA plus ADT (N = 562).[3] Four patients in the NSAA group did not receive their assigned therapies.[3] At the database cut-off, 64.3% of patients (N = 362) were still receiving enzalutamide and 35.9% of patients were still receiving NSAA (N= 202).[3] In the enzalutamide group, 35.7% of patients discontinued their assigned treatment (N = 201) while 63.3% of patients discontinued treatment with NSAA (N=356).[3] The most common reason for discontinuation in the enzalutamide and NSAA groups was clinical progressive disease determined by radiographic imaging (enzalutamide: 43.8% vs NSAA: 40.4%).[3]

Limitations

ARCHES TRIAL

Overall, the ARCHES Trial was a well-designed RCT and there were no major concerns with the conduct of the trial. The randomization method and sample size were adequate, and a stratified randomization procedure was used based on known prognostic factors to minimize potential imbalances between the study groups that might lead to biased results. The study was double-blinded to minimize bias in the assessment of study outcomes and the efficacy analysis was conducted according to the intention-to-treat (ITT) principal. The study protocol was approved by institutional review boards or independent ethics committees at each study center and the trial was conducted in accordance with Good Clinical Practice guidelines. However, there are a number of limitations and potential sources of bias, which include:

- With no active treatment in the control arm, there is a lack of direct comparison to other relevant agents, such as docetaxel, abiraterone acetate in combination with prednisone and apalutamide.
- At the time of the data analysis, OS data was immature (median OS was not reached in either group) making the actual degree of long- term benefit unknown. Follow-up for long-term survival is ongoing and planned when 342 events have occurred. In addition, future analyses of OS may be confounded because patients are allowed enter the open-label of the trial and receive enzalutamide.
- All subgroup analyses used a univariable analysis. Subgroup analyses on subjects with low or high volume of disease or prior docetaxel chemotherapy for prostate cancer were conducted without alpha spending assigned and without adjustment for multiplicity. All the subgroup analyses should be considered exploratory or hypothesis generating due to small sample sizes.
- Patient-reported and HRQoL outcomes were exploratory endpoints in the ARCHES trial and were not included in the statistical hierarchy or adjusted for multiplicity. Furthermore, selection bias over time should be considered when interpreting results of the HRQoL assessment, as the long-term responders tend to be the healthier patients. Overall, interpretation of HRQoL end points is limited. It should be noted that time to deterioration of urinary symptoms was included in the statistical hierarchy.

ENZAMET Trial

Overall, the ENZAMET trial was a well-designed RCT and there were no major concerns with the conduct of the trial. The randomization method and sample size were adequate, and a stratified randomization procedure was used based on known prognostic factors to minimize potential imbalances between the study groups that might lead to biased results. The efficacy analysis was conducted according to the ITT principal. The study protocol was approved by institutional review boards or independent ethics committees at each study center and the trial was conducted in accordance with Good Clinical Practice guidelines. However, there are some limitations and potential sources of bias, which include:

- The ENZAMET Trial used an open-label study design. This study design has the potential to bias outcomes, including: clinical or rPFS, patient reported outcomes and safety. However, bias was minimized by reviewing the imaging reports centrally. It was noted the images themselves were not reviewed centrally, which could increase the risk of detection bias.
- The database cut-off of 28-Feb-2019 represents an interim analysis of the ENZAMET trial. Although the effect of enzalutamide appears to be protective on OS as compared to NSAA, follow-up for long-term survival is ongoing and planned when 470 events have occurred.
- The subgroup analysis comparing the effect of disease burden and early use of docetaxel was conducted due to clinical interest. It should be noted that the trial was neither designed nor powered to reliably analyze the results in these subgroup analyses, and therefore, they should be interpreted with caution.
- To account for the type 1 error associated with all the planned adjusted and subgroup analyses, hypothesis tests were grouped into discrete families, and the p-value was evaluated within each family.[3] However, the effect of enzalutamide as compared to NSAA on PSA PFS and clinical PFS was not adjusted for multiple testing, and therefore, these results should be interpreted with caution.

- Patient-reported and HRQoL outcomes were exploratory endpoints in the ENZAMET trial and were not included in the adjustment for multiplicity. Furthermore, the effect of selection bias should be considered over time because the long-term responders tend to be the healthier patients. Overall, interpretation of HRQoL end points is limited.

Efficacy Outcomes

Efficacy results for the ARCHES and ENZAMET Trials are presented in Table 1.

ARCHES TRIAL

Radiographic Progression-Free Survival

rPFS as assessed by ICR was the primary outcome in the ARCHES trial. rPFS was calculated as the time from randomization to the first objective evidence of radiographic disease progression (rPD) as assessed by ICR or death up to 24 weeks after study drug discontinuation, whichever occurred first.[1] rPD was defined by RECIST 1.1 for soft tissue disease or the appearance of two or more new bone lesions on a bone scan. Deaths were due to any cause within 24 weeks (2 scan cycles) from study drug discontinuation.[1] The 24 week cut-off from study drug discontinuation was selected for deaths because it ensures a similar follow-up period as for monitoring of radiographic progression (i.e., two 12-week radiologic assessment cycles post-treatment discontinuation).[1]

At the 14-Oct-2018 data cut-off, 13.8% of patients in the enzalutamide group had radiographic progression and 2.1% died within 24 weeks of treatment discontinuation in the absence of radiographic progression (N=79 and N=12) relative to 32.6% and 2.3% of patients in the placebo group (N =188 and N=13).[1] The median rPFS was not reached in the enzalutamide group (95% CI, NR to NR) and it was 19.0 months (95% CI: 16.6 to 22.2 months) in the placebo group.[1] Enzalutamide was associated with a longer rPFS as compared to placebo (HR: 0.39, 95% CI: 0.30 to 0.50; p-value ≤0.0001).[1]

Armstrong et al (2019) performed prespecified subgroup analyses testing the effect of enzalutamide versus placebo on rPFS.[1] The estimates from the subgroups were consistent with the overall estimates of rPFS, including disease volume and prior docetaxel chemotherapy.[1] However, the subgroup analysis did not adjust for stratification factors or multiplicity and should be interpreted with caution.

Time to PSA Progression

Time to PSA progression was a key secondary outcome in the ARCHES trial. It was defined as the time from randomization to a 25% or greater increase in PSA and an absolute increase of ≥ 2 ng/mL above the nadir (i.e. lowest PSA value observed postbaseline or at baseline), which was confirmed by a second consecutive value at least three weeks later.[1] Only PSA assessments taken prior to the start of a new antineoplastic therapy were used.[1] The statistical analysis was similar to the primary analysis for rPFS; however, a prespecified 2-sided significance level of 0.01 was used for the analysis.[1] In the enzalutamide group, 7.8% of patients had PSA progression (N=45) relative to 32.8% of patients in the placebo group (N=189).[2] The median time to PSA progression was not reached for both treatment groups. Enzalutamide was associated with a significant improvement in time to PSA progression as compared to placebo (HR: 0.19, 95% CI: 0.13 to 0.26; p-value < 0.0001).[1]

Time to initiation of new antineoplastic therapy

Time to initiation of new antineoplastic therapy was a key secondary outcome and it was defined as the time from randomization to the initiation of antineoplastic therapy (including cytotoxic and hormonal therapies) subsequent to the study treatments.[1] The statistical analysis was similar to the primary analysis for rPFS; however, a prespecified 2-sided significance level of 0.01 was used for the analysis.[1] Eight percent of patients in the enzalutamide group initiated a new antineoplastic therapy (N=46) compared to 23.1% of patients in the placebo group (N=133).[2] The median time to initiating a new antineoplastic therapy was 30.2 months (95% CI: NR) for enzalutamide and was not reached for placebo.[1] Enzalutamide was associated with a significant improvement in time to initiation of new antineoplastic therapy as compared to placebo (HR: 0.28, 95% CI: 0.20 to 0.40; p-value < 0.0001).[1]

Rate of PSA Decline to < 0.2 ng/mL

Rate of PSA Decline to < 0.2 ng/mL was a key secondary outcome and it was defined as the proportion of patients with detectable (≥ 0.2 ng/mL) PSA at baseline, which become undetectable (< 0.2 ng/mL) during study treatment.[1] Only PSA assessments taken were

taken prior to the initiation of new antineoplastic therapy were analyzed.[1] Differences in response rates were compared using a stratified Cochran-Mantel-Haenszel score test with a significance level of 0.01.[1] Patients in the enzalutamide group had a higher PSA undetectable rate when compared to those in the placebo group (68.1% [N=348] vs 17.6% [N=89]; p <0.001).[1] The absolute difference between the two groups was 50.5% (95% CI: 45.3, 55.7; P < 0.0001).[2]

Objective Response Rate

ORR was a key secondary outcome and it was defined as the proportion of patients who had measurable disease at baseline and had a complete or partial response in their soft tissue as assessed by ICR using RECIST 1.1.[1] Differences in response rates were compared using a stratified Cochran-Mantel-Haenszel score test with a significance level of 0.01.[1] ORR was significantly higher for enzalutamide (ORR: 83.1% [N=147]) as compared to placebo (ORR: 63.7% [N=116]) (p-value for difference ≤ 0.001).[1]

Time to Deterioration of Urinary Symptoms

Time to deterioration of urinary symptoms was defined as the time from randomization to the first deterioration in urinary symptoms. This was classified as an increase in urinary symptoms scores, using the modified urinary symptoms scale derived from a selected subset of symptoms from the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) questionnaire module by ≥ 50% of the standard deviation observed in the modified urinary symptoms scale at baseline.[1] The statistical analysis was similar to the primary analysis for rPFS; however, a prespecified 2-sided significance level of 0.01 was used for the analysis.[1] Almost a third of patients in the enzalutamide and in the placebo groups experienced a deterioration of urinary symptoms (32.1% [N=184] vs 34.9% [N=201], respectively).[6] The median time to deterioration of urinary symptoms was not reached in the enzalutamide group and it was 16.8 months (95% CI: 14.06 to NR) in the placebo group.[2] There was no difference between the treatment groups for time to deterioration of urinary symptoms (HR: 0.88, 95% CI: 0.72 to 1.08; p-value = 0.2162).[1]

Overall Survival

OS was a secondary outcome in the ARCHES trial. It was defined as the time from randomization to death due to any cause.[1] The 14-Oct-2018 data cut-off represents an interim analysis for OS. The statistical analysis was similar to the primary analysis for rPFS. An O'Brien Fleming alpha spending function was used to determine the stopping boundaries for the interim analysis and control the two-sided α of 0.04.[1] At the data cut-off, only 24.6% (N=84) of the total 342 events that were required for the final OS analysis, and thus, the stopping boundary for OS at the interim analysis was 0.0000054, which would imply that the OS results may be immature.[2]

In the enzalutamide group, 6.8% of patients died (N=39) compared to 7.8% of patients in the placebo group (N=45).[2] The median OS was not reached for both treatment groups. There was no difference between the two treatment groups on the effect of OS (HR: 0.81, 95% CI: 0.53 to 1.25; p-value = 0.3361).[1] The results of OS are immature and should be interpreted with caution.

Time to First Symptomatic Skeletal Related Events

Time to first SSE was an exploratory outcome and it was defined as the time from randomization to the occurrence of a first SSE. SSE was measured as a radiation or surgery to bone, clinically apparent pathologic bone fracture, or spinal cord compression.[1] The statistical analysis was similar to the primary analysis for rPFS. In the enzalutamide group, 5.4% of patients had an SSE (N=31) while 9.7% of patients in the placebo group did (N=56).[2] The median time to first SSE was not reached for both treatment groups. Enzalutamide was associated with a significant improvement in time to first SSE as compared to placebo (HR: 0.52, 95% CI: 0.33 to 0.80; p-value = 0.0026).[1]

Time to Castration Resistance

Time to castration-resistance was an exploratory outcome and it was defined as the time from randomization to the first castration-resistant event, which was classified as radiographic disease progression, PSA progression, or SSE with castrate levels of testosterone [< 50 ng/dL], whichever occurs first.[1] The statistical analysis was similar to the primary analysis for rPFS. More patients in the placebo group had castration-resistance 44.6% (N=257) than in the enzalutamide group (15.7% [N=90]).[2] The median time to castration-resistance was 13.8 months in the placebo group and it was not reached for the enzalutamide group.[2] Enzalutamide was

associated with a significant improvement in time to castration-resistance as compared to placebo (HR: 0.28, 95% CI: 0.22 to 0.36; p-value < 0.001).[1]

Time to deterioration of QoL

Time to deterioration of QoL was an exploratory outcome and it was defined as the time from randomization to a 10-point reduction on the Functional Assessment of Cancer Therapy-Prostate(FACT-P) total score.[1] The statistical analysis was similar to the primary analysis for rPFS. Almost half of all patients in the enzalutamide and placebo groups had a 10-point reduction on the FACT-P total score (48.8% [N=280] vs 47.6% [N=274]).[2] The median time to deterioration of QoL was 11.3 months (95% CI: 11.0 to 13.8) in the enzalutamide group and it was 11.1 (95% CI: 8.5 to 13.8) in the placebo group.[1] There was no difference between the two treatment groups on the effect of time to deterioration of QoL (HR: 0.96, 95% CI: 0.81 to 1.14; p-value = 0.6548).[1]

Time to pain progression

Time to pain progression was an exploratory outcome and it was defined as the time from randomization to an increase of ≥ 30% on the pain severity score from baseline using the Brief Pain Inventory-Short Form (BPI-SF).[1] The statistical analysis was similar to the primary analysis for rPFS. More than half of all patients in the enzalutamide and placebo groups had an increase of ≥ 30% on the pain severity score (56.5% [N=324] vs 57.1% [N=329]).[2] The median time to pain progression was 8.3 months (95% CI: 8.3 to 10.9) in the enzalutamide group and it was 8.3 (95% CI: 5.7 to 8.4) in the placebo group.[2] There was no difference between the two treatment groups on the effect of time to pain progression (HR: 0.92, 95% CI: 0.78 to 1.07; p-value = 0.2715).[1]

ENZAMET Trial

Overall Survival

OS was the primary outcome in the trial and it was defined as time from randomization to death due to any cause.[3] Kaplan-Meier analyses were used to obtain the estimates of OS for each treatment group with corresponding 95% CIs. Differences in treatment effect were tested using an unstratified log-rank p-value. Unadjusted Cox proportional hazards models were used to estimate the HRs with their corresponding 95% CIs.

At the 28-Feb-2019 data cut-off, 18.1% of patients died (N=102) in the enzalutamide group compared to 25.4% of patients in the placebo group (N=143).[3] The median OS was not reached for both treatment groups. Treatment with enzalutamide was associated with a significant improvement in OS as compared to the NSAA group (HR: 0.67, 95% CI: 0.52 to 0.86; p-value = 0.002).[3] The survival rate at three-years was 80% (N=94) in the enzalutamide group and 72% (N=130) in the NSAA group.[3] The protective effect of enzalutamide on OS was observed in the pre-specified subgroups, which included: age, ECOG performance status, Gleason score at initial diagnosis, volume of disease, planned early use of docetaxel and ACE-27 scores. Overall, the subgroup analysis was consistent with the ITT results. However, after adjusting for multiply testing, there were no significant differences among the subgroups. The subgroups assessing the effect of disease burden and use of early docetaxel on enzalutamide and OS were identified as subgroups of clinical interest. There did not appear to be a significant difference between these subgroups; however, there were a small number of OS events.

Clinical PFS

Clinical PFS was a secondary outcome in the trial and it was defined as time from randomization to first evidence of disease progression or death from any cause, whichever occurs first, or the date of last known follow-up without clinical progression.[3] Clinical progression was defined as progression on imaging (Prostate Cancer Working Group 2 [PCWG2] criteria for bone lesions and RECIST 1.1 for soft tissue lesions), development of symptoms attributable to cancer progression or initiation of other anticancer treatment for prostate cancer.[3] The statistical analysis was similar to the primary analysis for OS. Overall, 29.1% of patients had progression or died (N=167) compared to 56.9% of patients in the placebo group (N=320).[3] [redacted].[7] (*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information*

Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).

Treatment with enzalutamide was associated with a significant improvement in clinical PFS as compared to the NSAA group (HR: 0.40, 95% CI: 0.33 to 0.49; p-value < 0.001).[3] The effect of enzalutamide on clinical PFS remained significant after adjusting for multiple testing.[3]

PSA PFS

PSA PFS was a secondary outcome in the trial and it was defined as the time from randomization to first evidence of PSA progression, clinical progression, or death from any cause, whichever occurs first, or the date of last PSA test without PSA progression.[3] PSA progression is classified as a rise in PSA by more than 25% AND more than 2ng/mL above the nadir (lowest PSA point), which was reconfirmed by performing a repeat PSA test at least 3 weeks later.[3] Clinical progression was defined as progression on imaging (PCWG2 criteria for bone lesions and RECIST 1.1 for soft tissue lesions), development of symptoms attributable to cancer progression or initiation of other anticancer treatment for prostate cancer.[3] The statistical analysis was similar to the primary analysis for OS. Overall, 30.9% of patients had progression or died (N=174) compared to 59.3% of patients in the placebo group (N=333).[3] The median PSA PFS was not reached for the enzalutamide group and it was [redacted] in the placebo group.[7] (*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).* Treatment with enzalutamide was associated with a significant improvement in PSA PFS as compared to the NSAA group (HR: 0.39, 95% CI: 0.33 to 0.47; p-value < 0.001).[3]

Health-Related Quality of Life

ARCHES Trial

In the ARCHES trial, HRQoL was measured using the BPI-SF, FACT-P, QLQ-PR25 and the EuroQoL 5-Dimensions, 5-Levels visual analog scale (EQ-5D-5L).[8,9] PRO instruments were measured at baseline, week 13, and every 12 weeks during the study until disease progression. Longitudinal changes from baseline to week 73 were assessed using mean scores and mixed-model repeated measures and were adjusted for baseline PRO score, volume of disease, and prior docetaxel therapy.

The BPI-SF item 3 (pain at its worst [in the last 24 hours]) and FACT-P total scores remained stable over time. In addition, the mean scores for pain severity and pain interference, as measured by the BPI-SF remained stable during the study. The authors also commented that there were no statistical differences from baseline to week 73 for the BPI-SF score, any of the any FACT-P subscales, or the EQ-5D-5L VAS.[8,9] However, there was a significant difference for the FACT-P personal well-being score, which favored placebo over enzalutamide (difference: –1.02 [95% CI: –1.90, –0.13]) but there was no clinically meaningful difference.[8,9]

ENZAMET Trial

In the ENZAMET trial, HRQoL was assessed using the European Organization for Research and Treatment of Cancer quality of life questionnaire (QLQ-C30), the QLQ-PR25 and the EQ-5D-5L instruments. Only data from the QLQ-C30 instrument will be reported. PRO instruments were measured at baseline, week 4 and 12, and every 12 weeks during the study until clinical progression.[10] Longitudinal changes from baseline to Year 3 were assessed using differences in least squares means with mixed model for repeated measures. There was no significant difference between the two treatment groups for the QLQ-C30 Global Health and the minimal important difference (MID) was not met.[7]

Safety Outcomes

ARCHES Trial

The safety set in the ARCHES trial consisted of patients who had received at least one dose of the study treatment.[1] There was a total of 1,146 patients in the safety set, with 572 patients in the enzalutamide group and 574 patients in the placebo group.[1] At the

14-Oct-2018 data cut-off, the median duration of therapy was 12.8 months (range: 0.2 to 26.6) in the enzalutamide group and 11.6 months (range: 0.2 to 24.6) in the placebo group.[1]

Overall, 7.2% of patients in the enzalutamide group and 5.2% in the placebo group discontinued their assigned therapies due to an AE.[1] Only 4.4% of patients in the enzalutamide group had an AE that led to a to dose reduction as compared to 1.9% of patients in the placebo group.[2]

Treatment-emergent adverse events (TEAEs) of any grade were reported in most patients in the trial (enzalutamide: 85.1% and ADT along: 85.9%). Grade 3 and 4 TEAEs were similar for both treatment groups (enzalutamide: 23.6% and 24.7%). Slightly more patients in the placebo group had a serious TEAE as compared to the enzalutamide group (19.5% vs 18.2%). In the enzalutamide group, 3.8% of patients had a drug-related SAE relative to 2.8% in the placebo group.[1]

Overall, 2.4% of patients in the enzalutamide group and 1.7% in the placebo group died.[1] None of the deaths in the enzalutamide group were related to the therapy as assessed by the investigator. However, one death in the placebo group (i.e., general physical health deterioration) was related to the therapy.[1]

ENZAMET Trial

The safety set in the ENZAMET trial consisted of patients who had received at least one dose of the study treatment.[3] There was a total of 1,121 patients in the safety set, with 563 patients in the enzalutamide group and 558 patients in the NSAA.[3] At the 28-Feb-2019 data cut-off, the median duration of therapy was 29.5 months (range: 0.1 to 58.4) in the enzalutamide group and 22.1 months (range: 0.0 to 58.6) in the NSAA group.[4]

More patients in the enzalutamide group discontinued study treatment due to an adverse event than the NSAA group (N=33 vs N=14). It was noted that six patients in the enzalutamide group discontinued due to a seizure while one patient discontinued enzalutamide because of clinical progression before the seizure event.[3]

More patients in the enzalutamide group had a grade ≥ 3 AE than the NSAA group (57.0% vs 43.0%).[3] The number of febrile neutropenia events was similar across the treatment groups (N enzalutamide: 37 and N NSAA: 32) and all but 2 of these events occurred during early docetaxel treatment (N=67 of N=69).[3] Seizures of any grade occurred in 7 patients in the enzalutamide group and no events occurred in the NSAA group.[3] In addition, fatigue was reported more often in the enzalutamide group than the NSAA group (N=465 and N=363). Clinically significant grade fatigue occurred more in the enzalutamide group (25%) compared to the NSAA group (14%).[3]

Patients treated with enzalutamide and early docetaxel were more likely to have grade 2 peripheral sensory neuropathy (9%) compared to the NSAA group (3%).[3] Among those who did not receive early docetaxel treatment, 2 of 312 (1%) in NSAA group had an event while there were no events in the enzalutamide group. Three patients treated with enzalutamide and early docetaxel had a grade 3 peripheral sensory neuropathy event compared to one patient in the NSAA group.

Overall, there were 385 serious AEs reported among 235 patients in the enzalutamide group and 297 serious AEs in 189 patients in the NSAA group.[3] It was reported that the rate of serious AEs during treatment exposure was similar across groups (0.34 per-year [95% CI, 0.29-0.40] in enzalutamide vs. 0.33 per-year [0.28-0.39] in NSAA).[3]

Table 1: Highlights of Key Outcomes for the ARCHES and ENZAMET Trials

	ARCHES	
	Enzalutamide Group (N=574)	Placebo Group (N= 576)
Primary Outcome		
rPFS, median (95% CI)	NR (NR, NR)	19.0 (16.6, 22.2)
HR (95%CI)	0.39 (0.30, 0.50)	
p-value	< 0.0001	
Key Secondary Outcomes		
Time to PSA progression, median (95% CI)	NR	NR
HR (95%CI)	0.19 (0.13, 0.26)	
p-value	< 0.0001	
Time to start of new antineoplastic therapy, median (95% CI)	30.2 (NR)	NR
HR (95%CI)	0.28 (0.20, 0.40)	
p-value	< 0.0001	
PSA undetectable rate (decline to < 0.2 ng/mL), number (%)	348 (68.1)	89 (17.6)
Difference in rate (95%CI)	50.5% (45.3, 55.7)	
p-value	< 0.0001	
ORR, number (%)	147 (83.1)	116 (63.7)
Difference in rate (95%CI)	19.3% (10.4, 28.2)	
p-value	< 0.0001	
Time to deterioration in urinary symptoms, median (95% CI)	NR (19.35, NR)	16.8 (14.06, NR)
HR (95%CI)	0.88 (0.72, 1.08)	
p-value	0.2162	
Overall Survival, median (95% CI)	NR	NR
HR (95%CI)	0.81 (0.53, 1.25)	
p-value	0.3361	

AE = adverse event, CI = confidence interval, HR = hazard ratio, HRQoL = health-related quality of life, NR = not reported, SD = standard deviation, TRAE = treatment-related adverse event, WDAE = withdrawal due to adverse event

*HR < 1 favours [group]

	ENZAMET	
	Group (N=563)	Group (N= 562)
Primary Outcome		
OS, median (95% CI)	NR	NR
HR (95%CI)	0.67 (0.52, 0.86)	
p-value	0.0018	
Secondary Outcomes		
Clinical PFS, median (95% CI)	NR	[redacted][7]
HR (95%CI)	0.40 (0.33, 0.49)	
p-value	< 0.001	
PSA PFS, median (95% CI)	NR	[redacted][7]

	ENZAMET
HR (95%CI)	0.39 (0.33, 0.47)
p-value	< 0.001
(*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*	

AE = adverse event, CI = confidence interval, HR = hazard ratio, HRQoL = health-related quality of life, NR = not reported, SD = standard deviation, TRAE = treatment-related adverse event, WDAE = withdrawal due to adverse event

*HR < 1 favours [group]

1.2.2 Additional Evidence

See Section 3, Section 4, and Section 5 for a complete summary of patient advocacy group input, Provincial Advisory Group (PAG) Input, and Registered Clinician Input, respectively.

Patient Advocacy Group Input

One patient group input was provided by the Canadian Cancer Society for the review of enzalutamide for the treatment of mCSPC. A 13-question survey was developed by the Canadian Cancer Society and disseminated by email to the Prostrate Cancer Canada network and prostate cancer support groups in Canada. The survey generated a total of 94 respondents, 56 of whom were prostrate cancer survivors, 32 were current prostate cancer patients and four were caregivers. One respondent identified themselves as "other" and another respondent preferred not to say. Out of the 94 respondents, 20 reported having mCSPC and six reported having experience with enzalutamide. The responses to the survey were collected from March 3 to March 7, 2020.

From a patient's perspective, the diagnosis of prostrate cancer has a significant physical and emotional impact on their lives. Some common symptoms and challenges of living with prostate cancer experienced by patients included sexual dysfunction, fatigue, anxiety/depression and bladder and/or bowel problems. Some previous treatments used by patients included surgery, chemotherapy, hormone therapy, second-line hormone therapy, radiation therapy, Radium-223, and active surveillance/monitoring. Six patients had experience with enzalutamide, the majority of whom reported that the drug had been effective in improving their cancer. All six patients reported that enzalutamide has lowered their prostrate specific antigen (PSA) level. The survey respondents were asked to indicate how important they think a drug like enzalutamide would be for patients with mCSPC. The majority of respondents responded that the drug would be an important treatment options for patients with mCSPC. Overall, patients with prostrate cancer value maintaining quality of life, access to new treatment options, a delay in need for chemotherapy or palliative care and a delay in the onset of symptoms, with a particular emphasis on controlling for side-effects that impact quality of life.

Provincial Advisory Group (PAG) Input

Input was obtained from **all nine** provinces (Ministries of Health and/or cancer agencies) and **one** federal drug plan participating in CADTH. PAG identified the following as factors that could impact the implementation:

Clinical factors:
- Eligible population and use in high-risk patients
- Sequencing with other therapies for prostate cancer

Economic factors:
- Add-on therapy to androgen deprivation therapy

Registered Clinician Input

A total of three clinician inputs were provided for the review of enzalutamide for mCSPC: one joint clinician input from Cancer Care Ontario (CCO) Genitourinary (GU) DAC, one individual clinician input from Sunnybrook Odette Cancer Centre in Ontario, and one individual clinician input from a clinician practicing in Ontario. According to the submitted input, current treatments for mCSPC include abiraterone plus prednisone for high risk/high volume patients (not currently funded in Ontario), docetaxel in rare cases, apalutamide (not currently funded in Ontario), and ADT plus chemotherapy for elderly and frail patients or those with comorbidities. Overall, the clinicians agreed that enzalutamide can generally be prescribed to all patient subgroups with mCSPC; however, there are certain subgroups of patients for whom enzalutamide would be preferred over other options, such as patients who don't qualify for docetaxel and/or abiraterone, patients with node-predominant mCSPC, and patients who have hypertension. All three clinician groups had

experience with prescribing enzalutamide, which is also commonly prescribed to patients with metastatic castration resistant prostate cancer (mCRPC). The clinicians reported that the majority of patients prefer enzalutamide over docetaxel and/or chemotherapy due to less toxicity. No major contraindications to enzalutamide were mentioned by the clinicians. The clinicians stated that the choice between enzalutamide and other androgen receptors is usually based on comorbidities, contraindications, patient preferences and toxicity profiles. For sequencing and priority of treatments, the clinicians advised that enzalutamide would be used in the first line setting. Other options upon progression would be docetaxel chemotherapy, radium-223 (for bone-limited metastatic disease), or investigational therapies through clinical trial participation. An unmet need for mCSPC patients was asserted by one clinician due to limited access to other oral androgen receptor antagonists.

Summary of Supplemental Questions

In the absence of head-to-head trial data for enzalutamide compared to other relevant treatments for men with mCSPC, the Sponsor submitted an NMA comparing enzalutamide with other relevant treatments for this patient population. In conclusion, enzalutamide + ADT showed statistically significant benefit versus placebo + ADT for the OS and rPFS outcomes in the total mCSPC population. Enzalutamide + ADT was also compared with NSAA + ADT for the OS outcome and this difference in benefit was statistically significant. When compared against docetaxel + ADT, enzalutamide + ADT was statistically significantly better for the rPFS outcome and demonstrated a trend (but was not statistically significant) towards a HR improvement for the OS outcome. When compared with the two remaining regimens (i.e., abiraterone + prednisone + ADT and apalutamide + ADT), enzalutamide + ADT demonstrated numerically improved HRs (which were not statistically significant) for both the rPFS and OS outcomes.

[redacted].[38] (*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Several limitations of the study must be considered. There was a lack of clarity on exclusion criteria of the trials and the screening process and no list of excluded studies was included. Furthermore, it was unclear if the authors initially reviewed subgroups from studies that included patients with low volume and high volume. This would be problematic in the NMA if the initial randomization in the individual studies was not stratified by disease burden (e.g., randomization is not maintained in the subgroup analysis in the individual study, thereby creating a methodological issue in the NMA).

Although the Sponsor explored the effects of clinical and methodological heterogeneity, there was still a presence of heterogeneity among the studies with respect to ECOG scores, high and low volume proportions, previous local [redacted][38] (*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)* but this does not indicate whether clinical heterogeneity is still present. [redacted].(*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)*. Based on the review teams assessment of the NMA, the ADT groups were also varied between the studies (e.g. medical vs chemical castration), and some of the ADT protocols in the studies were not clearly reported (e.g. reporting solely “ADT” with no further details). There were also inconsistencies between included studies on outcome definitions. Although the Sponsor defined their outcome definitions, the definitions for these outcomes were not always consistent in the included studies. This is apparent in the inclusion/exclusion of certain studies based on PFS definitions. Additionally, there was heterogeneity in study design as a mix of open-label and double-blind trials were included.

Secondly, the standard Bayesian MNA methods assume the proportionality of hazards, which was used for the OS and rPFS outcomes. This assumption was tested and found to apply for the majority of cases.

[redacted].[38] (*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Currently approved treatment for Canadian men with mHPSC include ADT, chemotherapy (e.g., docetaxel) or chemotherapy plus ADT; the NMA included additional treatments (e.g., abiraterone and apalutamide), that are currently not publicly available in Canada but accessible via patient access programs. Additionally, some outcomes were not included that would have been relevant to the populations (e.g. HRQoL and safety data).

Comparison with Other Literature

The CADTH Clinical Guidance Panel and the CADTH Methods Team did not identify other relevant literature providing supporting information for this review.

1.2.3 Factors Related to Generalizability of the Evidence

Table 2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

Table 2: Assessment of generalizability of evidence for enzalutamide in combination with ADT

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td>Population</td><td>ECOG Performance Status</td><td>ARCHES: Patients were included in the trial if they had an ECOG performance status of 0 or 1.
<table>
<tr><th>ECOG PS</th><th>Enzalutamide + ADT N = 574</th><th>Placebo + ADT N =576</th></tr>
<tr><td>0</td><td>448 (78.0)</td><td>443 (76.9)</td></tr>
<tr><td>1</td><td>125 (21.8)</td><td>133 (23.1)</td></tr>
</table>
ENAZMET: Patients were included in the trial if they had an ECOG performance status of 0 to 2.
<table>
<tr><th>ECOG PS</th><th>Enzalutamide + ADT N = 563</th><th>NSAA + ADT N =562</th></tr>
<tr><td>0</td><td>405 (71.9)</td><td>405 (72.1)</td></tr>
<tr><td>1</td><td>150 (26.6)</td><td>151</td></tr>
</table></td><td>Are the results of both trials generalizable to patients with and ECOG performance status of ≥ 2?</td><td>The CGP agreed that the benefit for patients with an ECOG status of 2 or greater cannot be formally concluded from the ARCHES and ENZAMET trials.

However, the CGP noted that it would be reasonable in some situations where it is believed the disease is impacting on performance status to offer enzalutamide plus ADT, based on clinical experience and the manageable side-effect profile of this oral drug.</td></tr>
</table>

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td></td><td></td><td>(26.9)</td></tr>
<tr><td>2</td><td>8 (1.4)</td><td>6 (1.1)</td></tr>
</table>
</td><td></td><td></td></tr>
<tr><td></td><td>High-risk factors</td><td>
ARCHES:
<table>
<tr><th></th><th>Enzalutamide + ADT N = 574</th><th>Placebo + ADT N =576</th></tr>
<tr><td>Gleason score of at least 8</td><td>67.2%</td><td>64.8%</td></tr>
<tr><td>High-volume disease</td><td>61.7%</td><td>64.8%</td></tr>
</table>
ENZAMET:
<table>
<tr><th>ECOG PS</th><th>Enzalutamide + ADT N = 563</th><th>NSAA + ADT N =562</th></tr>
<tr><td>Gleason score of 8 to 10</td><td>60%</td><td>57%</td></tr>
<tr><td>Visceral metastases</td><td>11%</td><td>12%</td></tr>
<tr><td>High-volume disease</td><td>52%</td><td>53%</td></tr>
</table>
</td><td>Are the results of both trials generalizable to patients with high risk factors?</td><td>The CGP supported generalizing trial results to patients who have high risk factors.
The CGP felt that based on the evidence (ARCHES and ENZAMET trials) it is reasonable to expect that enzalutamide plus ADT will be equally beneficial in high- and low-risk/volume patients.</td></tr>
<tr><td></td><td>Location of metastatic disease</td><td>ARCHES: Patients were included in the trial if they had:
• Metastatic prostate cancer documented by positive bone scan (for bone disease) or metastatic lesions on CT or MRI scan (for soft tissue). Subjects whose disease spread is limited to regional pelvic lymph nodes are not eligible.

ENZAMET: Patients were included in the trial if they had:
• Metastatic adenocarcinoma of the prostate defined by:
Documented histopathology or cytopathology of prostate adenocarcinoma from a biopsy of a metastatic site
OR
Documented histopathology of prostate adenocarcinoma from a TRUS biopsy, radical</td><td>Are the results of both trials generalizable to patients with node-predominant disease?</td><td>The CGP supports generalizing the results of the trials to metastatic disease regardless of the location of the metastases (i.e., bone, lymph nodes or other locations).

As patients with non-metastatic CSPC were excluded from the trial, there are no data to support the generalizability of treatment benefit with enzalutamide plus ADT in this patient population.

However, with newer imaging modalities, eg. PSMA PET, the definition of metastatic disease may change (vs. conventional imaging) and</td></tr>
</table>

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
		prostatectomy, or TURP and metastatic disease consistent with prostate cancer. OR Metastatic disease typical of prostate cancer (i.e. involving bone or pelvic lymph nodes or para-aortic lymph nodes) AND a serum concentration of PSA that is rising and >20ng/mL		enzalutamide plus ADT would be reasonable in this context.
	Prior treatments	**ARCHES**: Patients were included in the trial if they had: • Prior ADT given for < 39 months in duration and > 9 months before randomization as neoadjuvant/adjuvant therapy **ENZAMET**: Patients were included in the trial if they had: Prior ADT for prostate cancer (including bilateral orchidectomy), in the adjuvant setting, where the completion of adjuvant hormonal therapy was more than 12 months prior to randomization AND the total duration of hormonal treatment did not exceed 24 months. For depot preparations, hormonal therapy is deemed to have started with the first dose and to have been completed when the next dose would otherwise have been due, e.g. 12 weeks after the last dose of depot goserelin 10.8 mg	Are the trials' results generalizable to patients who have received ADT in the adjuvant setting where the time since completion of adjuvant hormonal therapy is 12 or more months ago?	Regarding patients who have received prior adjuvant ADT, the CGP considered it acceptable to provide these patients with enzalutamide as long as treatment with ADT had been completed more than one year from the timing of initiating enzalutamide.
		ARCHES: Patients were included in the trial if they had: • Up to 3 months of ADT with LHRH agonists or antagonists or orchiectomy with or without concurrent antiandrogens prior to day 1, with no radiographic evidence of disease progression or rising PSA levels prior to day 1 • Up to 6 months of ADT with LHRH agonists or antagonists or orchiectomy with or without concurrent antiandrogens prior to day 1 if subject was treated with docetaxel, with no radiographic evidence of disease progression or rising PSA levels prior to day 1 **ENZAMET**: Patients were included in the trial if they had: Prior ADT for prostate cancer (including bilateral orchidectomy),	Are the trials' results generalizable to patients who have started ADT 12 or more weeks ago? What would be the maximum duration of prior ADT before adding enzalutamide in practice?	Regarding patients who have started ADT, the CGP felt that up to 6 months is the maximum duration of prior ADT before adding enzalutamide in practice. The CGP noted that there is insufficient evidence to generalize the trial results to patients who have started ADT more than 6 months ago.

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
		started less than 12 weeks prior to randomization AND PSA is stable or falling. The 12 weeks starts from whichever of the following occurs earliest: first dose of oral antiandrogen, LHRHA, or surgical castration		
		ARCHES: Patients were included in the trial if they had: • Up to 6 cycles of docetaxel therapy with final treatment administration completed within 2 months of day 1 and no evidence of disease progression during or after the completion of docetaxel therapy; • Up to 6 months of ADT with LHRH agonists or antagonists or orchiectomy with or without concurrent antiandrogens prior to day 1 if subject was treated with docetaxel, with no radiographic evidence of disease progression or rising PSA levels prior to day 1. **ENZAMET**: Patients were included in the trial if they had: • Already commenced docetaxel prior to study entry, were tolerating full doses of docetaxel (75mg/m2) with ADT, met all eligibility criteria for the trial while receiving docetaxel, and had had no more than 2 cycles prior to randomization. For patients who had not already started chemotherapy, the first dose of docetaxel should be given at least 4 weeks after starting enzalutamide/NSAA, and no more than 6 weeks after randomization. The use of early docetaxel was at the discretion of the treating physician and patient and the decision had to be prior to randomization.	Are the trials' results generalizable to patients who have received more than 2 cycles of docetaxel prior to initiation of enzalutamide?	There is currently insufficient evidence to generalize the results reported for enzalutamide plus ADT to patients who have received more than 2 cycles of prior docetaxel therapy. Regarding patients who have received more than 2 cycles of prior docetaxel therapy, the CGP felt that, beyond ADT, enzalutamide should not be routinely combined with or sequenced right after docetaxel therapy. However, if a patient on docetaxel would show intolerance to docetaxel, the CGP felt that it would be reasonable to switch that patient to enzalutamide plus ADT.
		ARCHES: Patients were included in the trial if they had: • One course of palliative radiation or surgical therapy to treat symptoms of metastatic disease if it was administered at least 4 weeks prior to day 1	Are the results of the trial generalizable to patients who have had at least one course of radiation therapy or surgical intervention for	The CGP supported generalizing trial results to patients who have had at least 1 course of radiation therapy or surgical intervention for metastatic prostate cancer.

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
		ENAZMET: Patients were included in the trial if they had: • A surgical castration as prior therapy for prostate cancer less than 12 weeks prior to randomization and stable or falling PSA levels	their metastatic disease?	
Intervention	Treatment Intent	The intent of treatment in clinical trials for mCSPC is palliative.	Are the results of the treatment generalizable to an alternative treatment intent? (i.e., if the trial is palliative in intent, could the therapy also be used in the adjuvant setting or vice versa?)	The CGP agreed that the goal of therapy for mCSPC is palliative. The results cannot be generalized to any other treatment intent.
	First-generation non-steroidal antiandrogens	**ARCHES:** Patients received placebo with ADT (i.e., LHRH agonist or antagonist or bilateral orchiectomy). **ENZAMET:** Patients received nonsteroidal antiandrogen (NSAA) (i.e. bicalutamide, nilutamide or flutamide) with an LHRH analogue or surgical castration.	Are the results of the trials generalizable to the Canadian clinical practice, where first-generation antiandrogens are infrequently used.	The CGP supported generalizing trial results to patients who do not routinely receive first-generation antiandrogens with an LHRH or surgical castration. The CGP noted that there is currently insufficient evidence to determine if first-generation non-steroidal antiandrogens in combination with ADT have clinically meaningful benefit.
Comparator	Standard of care	**ARCHES:** Patients received placebo with ADT (i.e., LHRH agonist or antagonist or bilateral orchiectomy). **ENZAMET:** Patients received NSAA (i.e. bicalutamide, nilutamide or flutamide) with an LHRH analogue or surgical castration. Patients were also permitted to receive up to 6 cycles of concomitant docetaxel (75 mg/m^2). The decision to use early docetaxel was made prior to randomization by the treating clinician. Continue next time: look at midostaurin The review team has identified the following relevant comparators for enzalutamide plus ADT: • The standard of care is docetaxel plus androgen deprivation therapy	If the comparator is non-standard, are the results of the trial applicable in the Canadian setting?	There is a lack of direct evidence indicating the preferred treatment between enzalutamide + ADT and other ARAT therapies or chemotherapy. NMAs support similar survival benefit of enzalutamide compared to abiraterone or apalutamide and suggest less high-grade toxicity with ARATs than with docetaxel. However, the CGP agreed with the CADTH Methods Team, that due to several limitations identified in the NMAs caution must be used in interpreting the comparative efficacy and safety estimates. Given the

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
		(ADT) for higher burden disease or ADT alone for those unable to tolerate chemotherapy (i.e., docetaxel). • Available through patient access programs are: (1) apalutamide plus ADT [received a final conditional positive pERC recommendation in April 2020] and abiraterone plus prednisone plus ADT [though at the time of this publication, the abiraterone Initial Recommendation is suspended]. In order to assess the comparative efficacy of enzalutamide compared with currently used therapies, the CADTH Methods Team reviewed one sponsor submitted network-meta analysis (NMA) and two published NMAs. Refer to section 7 for more details.		absence of direct comparison, there is no robust evidence to ascertain which of the agents (i.e., enzalutamide, other ARATs or docetaxel) has superior efficacy. Therefore, the CGP concluded that patient values and preferences, co-morbidities, individual toxicity profiles, and treatment availability (provincial reimbursement) should guide treatment selection. Regarding patients with low volume/low risk or high volume/high risk mCSPC, the CGP were of the opinion that treatment choice would be at the discretion of the treating clinician and would depend on considerations of all clinical variables and discussion with the patient.
Outcomes	Appropriateness of primary and secondary outcomes	**ARCHES:** Primary endpoint: Radiographic progress-free survival (rPFS) as assessed by ICR. Secondary outcomes: Overall survival (OS), time to first symptomatic skeletal related events (SSE), time to castration resistance, time to deterioration of quality of life (QoL), time to deterioration in urinary symptoms, time to start of new antineoplastic therapy, time to prostate specific antigen (PSA) progression, PSA undetectable rate (< 0.2 ng/mL), objective response rate (ORR) and time to pain progression. **ENZAMET:** Primary endpoint: OS. Secondary outcomes: PSA PFS and clinical PFS.	Were the primary and secondary outcomes appropriate for the trial design?	The primary outcome of OS is a clinically meaningful endpoint at both the patient and upstream healthcare system levels. The composite evidence of ARCHES and ENZAMET should be taken together to support enzalutamide as a life-prolonging therapy in this mCSPC setting. The primary endpoint of rPFS assessed by ICR in the ARCHES trial was appropriate for the trial design. Studies are currently underway to determine if rPFS is a surrogate endpoint for survival in this setting.
	Prostate specific membrane antigen (PSMA) positron emission tomography (PET) detected metastases	**ARCHES**: Patients were included in the trial if they had hormone-sensitive metastatic disease, either de novo or after recurrence after prior local therapy, that was documented by a positive bone scan, or metastatic lesions on computed tomography or magnetic resonance imaging.	Are the trial results generalizable to patients with only PSMA-PET detected metastases?	Currently these patients would be considered to have “M0 CSPC” and benefit is unclear. In the absence of metastases on conventional imaging the CGP did feel results could be generalized to this group. It should be noted that PSMA PET is currently not approved or

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
		ENAZMET: Patients were included in the trial if they had prostatic adenocarcinoma with metastases that was documented by computed tomography, bone scanning with technetium-99, or both.		funded in Canada but does represent an important new imaging modality currently available through trials and will impact disease management in the very near future. It is generally felt that it is a more sensitive test than standard CT.
Setting	Trial centres	**ARCHES**: [redacted][6] **EZAMET**: [redacted][4]	Do the trial results apply to patients from Canadian centres? Are there any known differences in practice patterns between the countries listed and Canada?	The CGP agreed that trial results were applicable to Canadian patients.
	Concomitant use of docetaxel	**ARCHES:** Patients were included in the trial if they had: • Up to 6 cycles of docetaxel therapy with final treatment administration completed within 2 months of day 1 and no evidence of disease progression during or after the completion of docetaxel therapy; **ENZAMET**: Patients were included in the trial if they had: • Already commenced docetaxel prior to study entry, were tolerating full doses of docetaxel (75mg/m2) with ADT, met all eligibility criteria for the trial while receiving docetaxel, and had had no more than 2 cycles prior to randomization. For patients who had not already started chemotherapy, the first dose of docetaxel should be given at least 4 weeks after starting enzalutamide/NSAA, and no more than 6 weeks after randomization. The use of early docetaxel was at the discretion of the treating physician and patient and the decision had to be prior to randomization.	Are the trial results generalizable to patients in Canadian clinical practice, who do not routinely receive concomitant docetaxel?	The CGP agreed that the results of the ENZAMET trial can be generalized to the Canadian context, where concomitant docetaxel therapy is not routinely offered. The majority of patients in ENZAMET were not receiving concomitant docetaxel and thus the OS benefits seen overall and in this group are applicable to typical Canadian practice, where both enzalutamide and docetaxel would not be routinely administered concomitantly in this setting.

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
(*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*				
Abbreviations ECOG = Eastern Cooperative Oncology Group; PS = performance status; RT = radiation therapy				

1.2.4 Interpretation

Burden of Illness and Need

As prostate cancer is the third leading cause of cancer-related death in men in Canada, the burden of illness is relatively high. Most men succumbing to prostate cancer will develop metastases during their disease course, and many will present with mCSPC. A precise number of men presenting with mCSPC eligible for enzalutamide treatment is not directly available but, based on a cancer death rate of 4,100 per year, this could represent 2,000-3,000 patients per year in Canada. The detection of men with mCSPC may also increase in future if diagnostic prostate specific membrane antigen-positron emission tomography (PSMA-PET) scanning is widely adopted as it has been in other jurisdictions.

Need

After 75 years of treatment limited to different methods of gonadal androgen deprivation, new treatments options reported over the past five years for men with newly diagnosed mCSPC represent a significant medical advance. In men with “high burden” mCSPC in the CHAARTED trial, chemotherapy with six cycles of docetaxel improved median overall survival nearly 1.5 years compared to ADT alone.[11] CGP regarded this improvement in median OS as noteworthy and clinically very meaningful.

Evidence from indirect treatment (see section 7 in this report for more details) comparisons report similar OS benefits with docetaxel, abiraterone/prednisone, apalutamide, and enzalutamide in men with mCSPC (for more details refer to section 7 of this document). However, network meta-analyses suggest less high-grade toxicity with ARATs than with docetaxel. There is a lack of direct evidence indicating the preferred treatment between enzalutamide + ADT and other ARAT therapies or chemotherapy. The CGP agreed with the CADTH Methods Team that due to several limitations identified in the NMAs caution must be used in interpreting the comparative efficacy and safety estimates. Given the absence of direct comparison, there is no robust evidence to ascertain which of the agents (i.e., enzalutamide, other ARATs, or docetaxel) has superior efficacy. Therefore, the CGP concluded that patient values and preferences, co-morbidities, individual toxicity profiles, and treatment availability (provincial reimbursement) should guide treatment selection.

Regarding patients with low volume/low risk or high volume/high risk mCSPC, the CGP were of the opinion that treatment choice would be at the discretion of the treating clinician and would depend on considerations of all clinical variables and discussion with the patient. As there is insufficient evidence to guide this decision, there is inter-clinician variability in the identification of the optimal patient. Selection criteria may include prolonged prior ADT therapy, lower disease burden and whether or not patients had de novo metastatic disease.

Effectiveness

ARCHES

The ARCHES trial was a multinational, double-blind, randomized, placebo-controlled, phase III trial testing the addition of enzalutamide to standard androgen deprivation therapy (ADT). Eligible patients had an Eastern Cooperative Oncology performance score of 0 or 1, pathologically confirmed prostate adenocarcinoma and either de novo metastatic disease or metastatic disease which was recurrent after prior local therapy. Metastatic disease was documented by a positive bone scan or metastatic lesions were seen on computed tomography or magnetic resonance imaging. Prior ADT and up to six cycles of prior docetaxel chemotherapy were permitted.

The ARCHES trial randomized 1,150 metastatic castration sensitive prostate cancer (mCSPC) patients to either enzalutamide (160 mg/day) plus ADT or placebo plus ADT. The primary endpoint was radiological progression-free survival (rPFS), defined as the time from randomization to the first objective evidence of radiographic disease progression or death.

The combination of enzalutamide + ADT improved rPFS compared to placebo + ADT (HR 0.39; 95% CI 0.30–0.50; p= 0.001; median not reached vs. 19.0 months). Due to the immaturity of the study and the median duration of OS, median OS was not reached in either arm and no survival differences were observed between the two arms. Overall 18% (205) men received at least one dose of docetaxel prior to randomization; subgroup analysis showed that rPFS benefit was seen in both chemotherapy-treated and chemotherapy-naive patients. As well, although 37% (423 patients) of men were low-volume based on CHAARTED criteria, benefit in rPFS with enzalutamide-treated patients was seen regardless of volume of disease.

Median treatment duration was 12.8 months (range, 0.2 to 26.6 months) in the enzalutamide plus ADT group and 11.6 months (range, 0.2 to 24.6 months) in the placebo plus ADT group. Grade 3 or greater AEs, serious AEs, and AEs leading to treatment discontinuation were reported in similar proportions of patients in both treatment groups. There were no unexpected AEs; of the 14 AEs (2.4%) leading to death in the enzalutamide plus ADT group and 10 (1.7%) in the placebo plus ADT group, none were assessed by the investigator to be related to treatment in the enzalutamide plus ADT group, whereas one event (general physical health deterioration) was assessed by the investigator to be related in the placebo plus ADT group. There was no significant difference between treatment groups in risk of deterioration of urinary symptoms or QoL, suggesting there was no negative impact on PROs due to the addition of enzalutamide to ADT

The ARCHES trial therefore confirmed that the addition of enzalutamide to ADT for men with mHSPC provided clinically meaningful improvements across key efficacy endpoints while maintaining the high level of quality of life reported at baseline. This was also one of the first trials to allow the use of docetaxel chemotherapy up front, and benefit was seen regardless of prior docetaxel use.

ENZAMET

The ENZAMET trial was a multinational, open-label, randomized phase 3 trial aimed to determine the effects of adding enzalutamide to ADT on overall survival in men with metastatic, hormone-sensitive prostate cancer. Eligible patients had an Eastern Cooperative Oncology Group (ECOG) performance score of 0-2, pathologically confirmed prostate adenocarcinoma and either de novo metastatic disease or metastatic disease which was recurrent after prior local therapy. Metastatic disease was documented by a positive bone scan or computed tomography. Prior ADT and up to six cycles of prior docetaxel chemotherapy were permitted.

ENZAMET randomized 1125 men with mCSPC to receive ADT and enzalutamide daily (160 mg) or a non-steroidal antiandrogen (NSAA: bicalutamide, nilutamide, or flutamide), with a primary end-point of OS. Secondary objectives were to determine the effects on progression-free survival as determined by the prostate-specific antigen (PSA) level, clinical progression-free survival (based on imaging, symptoms, signs, or changes in therapy), and adverse events.

Enzamet showed there was an OS benefit of adding enzalutamide to ADT compared to NSAA (HR 0.67; 95% CI 0.52–0.86; p=0.002). The median OS was not reached for both treatment groups. Kaplan-Meier estimates of OS at three years were 80% in the enzalutamide group and 72% in the NSAA arm. For PSA progression-free survival, there were 174 events in the enzalutamide group and 333 events in the standard-care group (rate of event-free survival at 3 years, 67% and 37% respectively; hazard ratio, 0.39; 95% CI, 0.33 to 0.47; P<0.001). For clinical progression-free survival, there were 167 events in the enzalutamide group and 320 events in the standard-care group (rate of event-free survival at 3 years, 68% and 41%, respectively; hazard ratio, 0.40; 95% CI, 0.33 to 0.49; P<0.001)

Unlike the ARCHES trial, the concurrent use of docetaxel was permitted and the decision to treat with chemotherapy was at the discretion of the investigator. Use of chemotherapy was well-balanced between the two arms (45% enzalutamide and 44% NSAA planned for early docetaxel use). In a subgroup analysis, the benefits of enzalutamide on OS appeared only in the group without planned early docetaxel use (early docetaxel: HR 0.9; 95% CI 0.62–1.31; no early docetaxel: HR 0.53; 95% CI 0.37-0.75). Although the authors state that the study is underpowered and data is too immature to specifically answer whether combination docetaxel and enzalutamide is beneficial in metastatic hormone sensitive prostate cancer, these results demonstrate that this combination should not be used.

The ENZAMET trial therefore showed that in men with metastatic hormone-sensitive prostate cancer receiving ADT, the addition of enzalutamide resulted in longer overall survival, PSA progression-free survival, and clinical progression-free survival within 3 years than the use of standard nonsteroidal antiandrogen therapy.

Safety

ARCHES/ENZAMET

Overall enzalutamide was well tolerated, and no new toxicities were encountered in the trial. Adding early enzalutamide to ADT was associated with a higher frequency of toxic effects, especially peripheral neuropathy associated with the concomitant use of docetaxel. Patients who were treated with enzalutamide reported more fatigue and more often discontinued therapy before disease progression. Even though the risk of seizure was low, enzalutamide should be used with care in patients with a history of seizures and/ or in patients who are on drugs which can lower the seizure threshold. Overall, slightly more fractures were observed in patients receiving enzalutamide, which may be due to osteopenia/osteoporosis from androgen deprivation therapy. Increased osteopenia is a known side effect of antiandrogen therapy and has similarly been observed with all second-generation hormonal agents. This can potentially be ameliorated with the use of bone protective therapies such as calcium, vitamin D, bisphosphonates, and/or denosumab. Exploratory data collected on patient reported outcomes suggested that enzalutamide + ADT did not show a negative effect on quality of life compared with ADT + placebo or NSAA + ADT.

1.3 Conclusions

The Clinical Guidance Panel concluded that there is a net overall clinical benefit to enzalutamide + ADT compared with ADT + placebo (ARCHES)/ ADT + NSAA (ENZAMET) in the treatment of mCSPC. This conclusion is based on evidence from two high-quality RCTs that demonstrated a clinically meaningful and statistically significant benefit in rPFS (ARCHES, ENZAMET),and overall survival (ENZAMET), similar and acceptable adverse event profiles compared with placebo in men treated with ADT, and lack of decline in HRQoL. The CGP agreed that rPFS and OS are clinically meaningful endpoints for this incurable disease. Extending the period patients remain in the castration-sensitive setting is important as the transition from mCSPC to mCRPC is a clinically relevant event that is associated with a higher burden of symptoms, decrease in quality of life, and death.

In making this recommendation, the Clinical Guidance Panel considered:

- In most jurisdictions in Canada, docetaxel is publicly funded for mCSPC. The toxicity of docetaxel is increased in men with mCSPC compared to CRPC, probably for pharmacological reasons.[12,13] So additional non-cytotoxic options providing similar benefits with less toxicity risk are recognized as an unmet need by clinicians and patients.
- Unfortunately, there are little published data directly comparing these options. Network meta-analyses support the contention of similar OS benefit with less toxicity risk with ARATs compared to docetaxel but a preferred ARAT drug is not identified. Based on current available data, abiraterone/prednisone, apalutamide, or enzalutamide all remain potential options and alternatives to docetaxel in this population.
- As these treatments have been shown on average to improve OS, all men with newly diagnosed mCSPC should be evaluated for treatments in addition to ADT. However, what is the most appropriate treatment for an individual patient will depend on patient preference, patient factors affecting generalizability of trial results, and access to treatment. As men with prostate cancer are generally older, more likely to have comorbidities, and may have mCSPC very sensitive to treatment with ADT alone, generalizability of clinical trial data to real world patients should be done thoughtfully.
- Finally, despite inclusion of mCSPC patients receiving docetaxel in the ARCHES and ENZAMET trials, there is no high-level evidence supporting combination or sequencing of the options potentially available for mCSPC.

Table 3: CADTH Clinical Guidance Panel (CGP) Response to Provincial Advisory Group Implementation Questions

PAG Implementation Questions	CGP Response
Currently Funded Treatments	
The standard of care for newly diagnosed metastatic castration (hormone)-sensitive prostate cancer (mCSPC) is docetaxel plus androgen deprivation therapy (ADT) for patients with high burden disease or ADT alone for those unable to tolerate chemotherapy (i.e., docetaxel).	
• PAG noted that in the ENZAMET trial, the comparator group received a testosterone-lowering agent or surgical castration and a first-generation nonsteroidal antiandrogen (bicalutamide, nilutamide, or flutamide). Patients in the enzalutamide arm also received testosterone-lowering agent or surgical castration but did not receive another first-generation antiandrogen. PAG noted that first-generation antiandrogens are not used frequently in Canadian practice.	• The CGP supported generalizing trial results to patients who do not routinely receive first-generation antiandrogens with an LHRH or surgical castration. The CGP noted that there is currently insufficient evidence to determine if first-generation non-steroidal antiandrogens in combination with ADT have clinically meaningful benefit.
• PAG is seeking information on comparative efficacy of enzalutamide plus ADT versus apalutamide plus ADT, abiraterone plus ADT, and docetaxel plus ADT.	• Currently, only indirect comparisons can be made between enzalutamide plus ADT, apalutamide plus ADT, abiraterone plus prednisone and ADT, and docetaxel plus ADT as no trial to date has directly compared these drugs. Refer to Sections 7 for summaries and critical appraisals of a Sponsor-submitted and published network-meta analyses. The CGP noted that network-meta analyses suggest similar overall survival benefit of enzalutamide compared to docetaxel, abiraterone or apalutamide and suggest less high-grade toxicity with ARATs than with docetaxel. However, the CGP agreed with the CADTH Methods Team, that due to several limitations identified in the network-meta analyses caution must be used in interpreting the comparative efficacy and safety estimates. Given the absence of direct comparison, there is no robust evidence to ascertain which of the agents (i.e., enzalutamide, other androgen receptor-targeted agents, or docetaxel) has superior efficacy. Therefore, the CGP concluded that patient values and preferences, co-morbidities, individual toxicity profiles, and treatment availability (provincial reimbursement) should guide treatment selection.
Eligible Patient Population	
PAG is seeking guidance on whether the following patients would be eligible for treatment with enzalutamide plus ADT:	
• Patients having experienced at least one course of radiation therapy or surgery to treat symptoms related to metastatic disease	• The trials' results are generalizable to patients who have had at least 1 course of radiation therapy or surgical intervention for metastatic prostate cancer.
• Patients with an ECOG performance status score greater than 2	• The CGP agreed that the benefit for patients with an ECOG status of 2 or greater cannot be formally concluded from the ARCHES and ENZAMET trials. However, the CGP noted that it would be reasonable in some situations where it is believed the disease is impacting on performance status to offer enzalutamide plus ADT,

PAG Implementation Questions	CGP Response
	based on clinical experience and the manageable side-effect profile of this oral drug.
• Patients having started ADT (12 or more weeks ago). What would be the maximum duration of prior ADT before adding enzalutamide in practice?	• Regarding patients who have started ADT, the CGP felt that up to 6 months is the maximum duration of prior ADT before adding enzalutamide in practice. The CGP noted that there is insufficient evidence to generalize the trial results to patients who have started ADT more than 6 months ago.
• Patients having received more than 2 cycles of docetaxel.	• Despite the fact that ARCHES allowed sequential docetaxel and enzalutamide; and ENZAMET allowed concurrent docetaxel and enzalutamide, there is no adequate data to support this approach in the Canadian context. Enzalutamide should not be routinely combined with or sequenced right after docetaxel therapy. However, if a patient on docetaxel would show intolerance to docetaxel, the CGP felt that it would be reasonable to switch that patient to enzalutamide plus ADT.
• Patients having received ADT in the adjuvant setting where the time since completion of adjuvant hormonal therapy is 12 or more months	• Regarding patients who have received prior adjuvant ADT, the CGP considered it acceptable to provide these patients with enzalutamide so long as treatment with ADT had been completed more than one year from the timing of initiating enzalutamide.
• Patients with non-metastatic CSPC	• As patients with non-metastatic CSPC were excluded from the trial, there are no data to support the generalizability of treatment benefit with enzalutamide plus ADT in this patient population.
• Patients intolerant to one of the alternative drugs	• The CGP noted that there is currently no evidence on switching patients who are intolerant to an alternative dug to enzalutamide plus ADT. However, the CGP noted that switching therapies in this context would appear reasonable and beneficial to patients who generally do better with than without treatment.
• Patients with high-risk factors	• The CGP supported generalizing trial results to patients who have high risk factors. The CGP felt that based on the evidence (ARCHES and ENZAMET trials) it is reasonable to expect that enzalutamide plus ADT will be equally beneficial in high- and low-risk/volume patients.
Is there any evidence or recommendations to support using ADT + enzalutamide only in specific high-risk subgroups rather than all patients with mCSPC? Since abiraterone has evidence for use in high-risk mCSPC, are there specific high-risk patient populations where abiraterone versus enzalutamide would be preferred due to clinical reasons?	The CGP noted that in the absence of evidence to guide this decision, there is inter-clinician variability in the identification of the optimal patient. Selection criteria may include prolonged prior ADT therapy, lower disease burden and whether or not patients had de novo metastatic disease.
If recommended for reimbursement, PAG noted that patients currently treated with ADT and with or without docetaxel for greater than 12 weeks would need to be	The CGP agrees that patients currently treated with ADT alone or with docetaxel for up to six months and who have not progressed would need to be addressed on a time-limited basis. However, patients who

PAG Implementation Questions	CGP Response
addressed on a time-limited basis.	have been treated for mCSPC with ADT alone or with docetaxel for more than six months and who have not progressed should not be considered eligible for enzalutamide. The rational for this derives in part from the fact that composite data from ARAT trials in this setting would allow ARAT commencement within 6 months of ADT initiation as inclusion for those studies.
Implementation Factors	
The recommended dose of enzalutamide is 160 mg (four 40 mg capsules) as a single oral daily dose. It can be taken with or without food. Enzalutamide would be taken with additional androgen deprivation agents; pill burden may be an issue.	The CGP agreed that oral therapy is favourable to alternative treatment options that may require more inconvenient routes of administration (e.g. injection) and can result in additional costs such as travel and chair time). The CGP stated that patients have not particularly complained about the administration of the pills for enzalutamide in their practice and are generally accepting of this dosing. However, enzalutamide is administered until disease progression or unacceptable toxicity whereas docetaxel chemotherapy is administered for 6 cycles only.
As enzalutamide is an add-on therapy, additional pharmacy resources for dispensing and monitoring of side effects (e.g., drug-drug interactions, high blood pressure, and liver function test elevations) would be needed. Nevertheless, additional clinic visits may be needed to monitor adverse events, which differ between drug classes.	Enzalutamide is a drug that has been around for a long time, and treating physicians are well versed in administering it. The additional resources would be minimal, especially considering the benefits seen with its use. It is likely that post-treatment monitoring is similar for both groups of patients. There may be small increase for patients on active therapy with enzalutamide which could slightly impact out-patient clinic utilization.
PAG noted that the ENZAMET trial defined progression either by a PSA increase or radiographically. A clear definition of progression would be needed to identify discontinuation criteria.	Commonly clinicians will seek confirmation of progression in all possible areas, i.e., PSA progression, clinical progression (i.e., well-being of patient), and radiographic progression. PSA progression and radiographic progression tend to align with each other. However, if a patient has PSA progression alone (no radiographic progression or development of symptoms attributable to cancer progress) then a patient may continue treatment.
Early/prior docetaxel use (ENZAMET: early docetaxel up to two cycles prior to randomization; ARCHES: prior docetaxel up to 6 cycles with final treatment administration completed within 2 months of day 1) was permitted. PAG is seeking clarity on docetaxel dosage, timing, and optimal target population.	In patients with mCSPC, there are two main approaches: ADT and 6 cycles of docetaxel or ADT and an androgen receptor targeted agent (abiraterone, apalutamide or enzalutamide). Despite the fact that ARCHES allowed sequential docetaxel and enzalutamide; and ENZAMET allowed concurrent docetaxel and enzalutamide, there is no adequate data to support this approach in the Canadian context. In Canadian clinical practice, we would not routinely consider starting a patient with mCSPC on 6 cycles of docetaxel chemotherapy and adding another drug (such as abiraterone plus prednisone, apalutamide or enzalutamide) either during or right after completion of docetaxel chemotherapy treatment, as there is no available evidence to support this concomitant approach. If a patient after completion of docetaxel chemotherapy is found to have developed metastatic castration resistant prostate cancer, then that patient will be managed according to the treatment options available for the metastatic castration resistant setting.
If androgen deprivation therapy is started in the metastatic hormone sensitive setting with an LHRH agonist, does the LHRH agonist continue for this phase	The CGP agreed that the LHRH agonist continues to be administered indefinitely with current treatment and with all treatments the patients would receive upon progression in the mCRPC setting.

PAG Implementation Questions	CGP Response
of treatment and onwards with all treatments the patient would receive upon progression in the mCRPC setting	
Sequencing and Priority of Treatment	
PAG is seeking guidance on the appropriate place in therapy of enzalutamide plus ADT and overall sequencing of all treatments available for non-metastatic, metastatic, castration-resistant, and castration-sensitive prostate cancer settings. • PAG would like to understand the role of docetaxel after progression on enzalutamide + ADT.	• If patients progress on enzalutamide plus ADT they fall into the category of mCRPC. Docetaxel plus ADT is an appropriate treatment option in the mCRPC setting.
• PAG is seeking information on the appropriate treatments following progression on enzalutamide plus ADT, particularly for castration-resistant disease (e.g., abiraterone + prednisone).	• The CGP was unable to make an informed recommendation on the optimal sequencing of treatments for castration-resistant prostate cancer after treatment with enzalutamide plus ADT in the castration-sensitive setting, noting that there is insufficient evidence to inform this clinical situation. If a patient is found to have developed castration resistant prostate cancer, then that patient will be managed according to the treatment options available for the metastatic castration resistant setting.
• Given apalutamide exhibits a similar mechanism of action, PAG would like to know if sequencing of the two antiandrogens should be allowed.	• CGP noted that in the absence of sufficient evidence, generally there is the sense among clinicians that alternating the mechanisms of action of therapies in managing this disease is preferable to using the same mechanisms of action sequentially (e.g., hormone therapy followed by chemotherapy would be preferred over hormone therapy followed by hormone therapy). Accordingly, patients progressing on ADT + enzalutamide, are usually offered chemotherapy at the time of progression.

PAG = Provincial Advisory Group, CGP = Clinical Guidance Panel; metastatic castration resistant prostate cancer (mCRPC)

2 Background Clinical Information

This section was prepared by the CADTH Genitourinary Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

2.1 Description of the Condition

Prostate cancer is the most common cancer diagnosed in Canadian men (excluding non-melanoma skin cancers) and third leading cause of cancer related death with 4,100 deaths expected in 2017.[14]

2.2 Accepted Clinical Practice

Treatment for Recurrent and Metastatic Castration-Sensitive Prostate Cancer:

Despite local ablative treatment, some men with localized prostate cancer develop recurrent disease as evidenced by a biochemical recurrence (elevation in PSA) with or without signs of metastases. In addition, some men may present with de novo metastatic disease. For nearly three-quarters of a century medical or surgical castration (ADT) has been first-line therapy for recurrent or metastatic prostate cancer. ADT suppresses gonadal androgen production and usually consists of treatment with either an LHRH

antagonist or agonist, or bilateral orchiectomy. The addition of a non-steroidal antiandrogen to ADT has been shown to modestly improve OS in meta-analysis of randomized trials.[15] Nearly all patients with mCSPC initially respond to ADT but all will eventually progress to castration-resistant prostate cancer (CRPC).

Previous trials in men with mHSPC combining ADT with other treatments such as docetaxel chemotherapy[16] or the selective androgen biosynthesis inhibitor abiraterone[17] have demonstrated significant clinical benefits, including significantly improved overall survival (OS). Currently ADT plus docetaxel is one option for mHSPC, that tends to be used more often in fit patients and those with high volume disease. Abiraterone plus ADT in combination with prednisone is another option, which is approved[18] on the basis of the LATITUDE trial (ClinicalTrials.gov identifier: NCT01715285),[19] which exclusively enrolled men with high-risk mHSPC. It is currently under review at CADTH for mCSPC (though at the time of this writing, the abiraterone Initial Recommendation is suspended). It is currently available via patient access programs in Canada. Apalutamide plus ADT is also approved in this setting based on the TITAN trial (ClinicalTrials.gov identifier: NCT02489318).[20]Apalutamide plus ADT has received a conditional positive final pERC recommendation in April 2020. It is currently not yet a publicly funded treatment option.

The focus of this report will be on Enzalutamide which was evaluated in two key trials ARCHES (NCT02677896)[1] and ENZAMET (NCT02446405).[3] The efficacy and safety of enzalutamide, a potent androgen-receptor (AR) inhibitor, has been demonstrated across the spectrum of castration-resistant prostate cancer (CRPC) by several, large-scale, randomized, controlled clinical trials.[3,21] In addition, a phase II, open-label, single-arm study investigating enzalutamide monotherapy in patients with hormone-naïve prostate cancer[22] demonstrated long-term reductions in prostate-specific antigen (PSA) levels, with minimal changes in overall bone mineral density and global health status.

As discussed earlier, in addition to enzalutamide, several other systemic therapies added to standard ADT have been reported to benefit men with mCSPC including docetaxel, abiraterone/prednisone, and apalutamide.[23-25] Aside from patient-specific factors, it is unclear which approach provides optimal clinical value. ADT should be continued with all these therapies, and all increase the risk of adverse effects compared to ADT alone. Most of these treatments also have high level evidence and regulatory approval supporting their use in the CRPC setting, so questions remain about the optimal sequencing of these therapies across the natural history of metastatic prostate cancer.

Enzalutamide is approved across the spectrum of prostate cancer, from non-metastatic prostate cancer to metastatic castration resistant prostate cancer (before or after docetaxel chemotherapy). mCSPC may be identified by newer imaging modalities like PSMA-PET imaging in some men who otherwise only have a rising PSA as a sign of CSPC, and although data in this population is not yet available, it is reasonable to consider offering enzalutamide in patients with metastatic disease identified on the basis of newer imaging modalities.

3 Summary of Patient Advocacy Group Input

One patient group input was provided by the Canadian Cancer Society for the review of enzalutamide for the treatment of metastatic castration sensitive prostate cancer (mCSPC). A 13-question survey was developed by the Canadian Cancer Society and disseminated by email to the Prostrate Cancer Canada network and prostate cancer support groups in Canada. The survey generated a total of 94 respondents, 56 of whom were prostrate cancer survivors, 32 were current prostate cancer patients and four were caregivers. One respondent identified themselves as “other” and another respondent preferred not to say. Out of the 94 respondents, 20 reported having mCSPC and six reported having experience with enzalutamide. The responses to the survey were collected from March 3 to March 7, 2020.

From a patient’s perspective, the diagnosis of prostrate cancer has a significant physical and emotional impact on their lives. Some common symptoms and challenges of living with prostate cancer experienced by patients included sexual dysfunction, fatigue, anxiety/depression and bladder and/or bowel problems. Some previous treatments used by patients included surgery, chemotherapy, hormone therapy, second-line hormone therapy, radiation therapy, Radium-223, and active surveillance/monitoring. Six patients had experience with enzalutamide, the majority of whom reported that the drug had been effective in improving their cancer. All six patients reported that enzalutamide has lowered their prostrate specific antigen (PSA) level. The survey respondents were asked to indicate how important they think a drug like enzalutamide would be for patients with mCSPC. The majority of respondents responded that the drug would be an important treatment options for patients with mCSPC. Overall, patients with prostrate cancer value maintaining quality of life, access to new treatment options, a delay in need for chemotherapy or palliative care and a delay in the onset of symptoms, with a particular emphasis on controlling for side-effects that impact quality of life. Few patients also noted that cost-effectiveness would be of value for new treatments.

Of note, quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that are reported have also been reproduced as is according to the submission, without modification. Please see below for a summary of specific input received from the patient groups.

3.1 Condition and Current Therapy Information

3.1.1 Patients Experiences

Respondents of the survey were asked to indicate what symptoms and challenges they had experienced because of prostrate cancer that had affected their day-to-day living and quality of life. The top five symptoms/challenges reported by respondents were: bladder and or bowel problems (n=46, 48.94%); fatigue (n=35, 37.23%); living with uncertainty (n=35, 37.23%); anxiety, and panic attacks and/or depression (n=28, 29.79%). Other side symptoms/challenges reported by respondents included: weakness (n=11; 11.07%); low white blood cells and increased risk of infections (n=5, 5.32%); pain (n=5; 5.32%) and weight loss/loss of appetite (n=4, 4.26%).

Respondents were asked to indicate which side-effects of prostate cancer treatments are the most important for them to control. This question was asked in respect to any prostate cancer treatment and not the drug-in-review specifically. The most common side effects reported by respondents were: sexual dysfunction (n=57, 60.64%); fatigue (n=24; 25.53%); anxiety, panic attacks and/or depression (n=17, 18.09%). Other side effects reported by the respondents to be the most important to control were: weight gain (n=16, 17.02%); loss of muscle mass (n=14, 14.89%); high blood pressure (n=8, 8.51%); hot flashes (n=8, 8.51%); weakness (n=8, 8.51%); diabetes (n=5, 5.32%); diarrhea (n=4, 4.62%); low white blood cells/ risk of infection (n=6, 6.38%); pain (n=3, 3.19%); nausea (n=1, 1.06%); weight loss/ loss of appetite (n=1, 1.06%). No respondent reported anemia. Six respondents responded that they do not know and one preferred not to say.

The Canadian Cancer Society specifically noted the significant impact of a prostate cancer diagnosis on the mental health of patients. The following are some comments provided by the survey respondents:

"I believe it is extremely important to receive feedback from frontline patients regarding their treatment experience. I think prostate treatments have is a significant mental health impact on men and their quality of life that is under-reported and there are minimal post-treatment resources available to them. Thank you for the opportunity to participate in this survey."

"I had no symptoms, but yet my cancer was in the final stage before escaping the prostate. I'm 33-months NED and recovering well from surgery. Although if there were one thing I could do differently, it would be to join a support group as soon as I was diagnosed, even before doing research and making a decision. I didn't realize at the time I was in shock from hearing the word "cancer," and that's not a good time to make a treatment decision."

3.1.2 Patients' Experiences with Current Therapy

Respondents were asked to identify what treatments they have used for prostate cancer. The most common treatment was surgery (n=50, 53.19%), followed by radiation therapy (n=42, 44.68%), hormone therapy/ADT (n=32, 34.04%), active surveillance/monitoring (n=25, 25.53%), second line hormone therapy (n=12, 12.77%), and radium – 233 (n=4, 4.26%). There were 8 (8.51%) respondents who chose the "other" option in the survey questionnaire and identified the following treatments: Flomax & terazosin, HIFU, pelvic floor physiotherapy and cryotherapy.

The Canadian Cancer Society commented that patients had not experienced any difficulty in accessing enzalutamide since it was funded in all provinces and territories. The Canadian Cancer Society emphasized that the drug should continue to be available in all provinces/ territories for the new indication under review to ensure continued access for all patients.

3.1.3 Impact on Caregivers

No input was provided regarding caregiver experiences.

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for New Therapies

Respondents were asked to report the most important issues that they expect a new drug for metastatic prostrate cancer to address. The following four issues were reported in order of importance: maintaining quality of life, providing access to a new treatments option, delay the need for chemotherapy or palliative care and delay the onset of symptoms with a particular emphasis on controlling for side-effects that impact quality of life. Additionally, the Canadian Cancer Society noted that two respondents mentioned the cost-effectiveness of a drug to be an important consideration when evaluating new treatments for prostrate cancer.

Respondents of the survey were provided with a list of eight side-effects and asked to indicate which of the side-effects would make them reconsider taking enzalutamide. Over a half of the respondents (n=51) stated that they did not know which side effects would make them reconsider taking enzalutamide; and 11 respondents (11.70%) responded that no adverse effect would stop them from taking enzalutamide. The respondents reported that they would consider the following side effects fatigue (n=12, 12.77%), high blood pressure (n=12, 12.77%); diarrhea (n=10, 10.64%), pain (n=9. 9.57%), hot flashes (n=8, 8.51%), and loss of appetite (n=4, 4.26%). Fifteen patients responded "other" and identified incontinence, weight gain and muscle loss as side-effects that would make them reconsider taking enzalutamide.

The Canadian Cancer Society commented that the survey responses may indicate that there is a lack of clear trade-offs for side effects associated with enzalutamide. The Canadian Cancer Society also commented that these numbers *"may also suggest that respondents may not be aware of the trade-offs they would be willing to make with second-line hormone therapies until they are faced with making the decision".*

3.2.2 Patient Experiences to Date

Six respondents who reported experience with enzalutamide. When asked about the effectiveness of the drug in treating mCSPC, three respondents noted that the drug was very *effective (my cancer has improved significantly)*; two reported that it was somewhat *effective (my cancer has improved slightly);* and one respondent noted that the drug was somewhat *ineffective (my cancer has worsened slightly).*

The six respondents were asked to describe the positive and negative effects that they had experienced with enzalutamide. All six respondents indicated lower PSA levels as a positive effect. Specifically, one respondent noted that his/her PSA levels were lowered for about six months. One respondent commented the following:

- *"Have only been taking Xtandi for month and half....PSA has dropped considerably, however this may be in part due to radiation .on large spot on my hip.....two weeks prior to starting Xtandi"*

The following comments were provided by the respondents about the negative effects of enzalutamide:

- *"Diarrhea"*
- *"Weight gain, increased fatigue, more depressed"*
- *"Fatigue and cognitive skills"*
- *"Hot flashes, muscle loss, tiredness, loss of appetite"*
- *"Almost eliminates my testosterone takes lots of my energy away"*

When the survey respondents were asked *"How important do you think a drug like enzalutamide (Xtandi) is for men with metastatic prostate cancer? Enzalutamide is an oral drug that delays the progression of metastatic prostrate cancer",* 59% of the respondents responded '*very important*'," 37% responded '*somewhat important'* and 4% responded '*I don't know*'.

3.3 Companion Diagnostic Testing

The Canadian Cancer Society reported the Prostate Specific Antigen (PSA) as the companion diagnostic test for enzalutamide. This patient group stated that PSA test helps to monitor the effectiveness of prostate cancer treatments. They also commented that patients are usually in favour of the test because it is a non-invasive blood test. The costs of the tests are covered for patients that have been diagnosed with prostate cancer or suspected of having it. However, the test is not covered in Ontario and British Columbia for asymptomatic patients who want to be screened for prostate cancer. The Canadian Cancer Society stated in their input that patients in these provinces have to pay out-of-pocket for the test for prostate cancer screening, and that many patients are not in favour of paying out-of-pocket for this test.

3.4 Additional Information

None identified.

4 Summary of Provincial Advisory Group (PAG) Input

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.cadth.ca/pcodr). PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from **all nine** provinces (Ministries of Health and/or cancer agencies) and **one** federal drug plan participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:
- Eligible population and use in high-risk patients
- Sequencing with other therapies for prostate cancer

Economic factors:
- Add-on therapy to androgen deprivation therapy

Please see below for more details.

4.1 Currently Funded Treatments

The standard of care for newly diagnosed metastatic castration (hormone)-sensitive prostate cancer (mCSPC) is docetaxel plus androgen deprivation therapy (ADT) for high-risk patients or ADT alone for those unable to tolerate chemotherapy (i.e., docetaxel). PAG noted that in the ENZAMET trial, "ADT alone" comprised a testosterone-lowering agent or surgical castration and a first-generation nonsteroidal antiandrogen (bicalutamide, nilutamide, or flutamide). Patients in the enzalutamide arm also received testosterone-lowering agent or surgical castration but did not receive another first-generation antiandrogen. PAG noted that first-generation antiandrogens are not used frequently in Canadian practice.
Apalutamide and abiraterone + prednisone, both combined with ADT, are under review by CADTH for the same indication. PAG is seeking information on comparative efficacy of enzalutamide plus ADT versus apalutamide plus ADT, abiraterone plus ADT, and docetaxel plus ADT.

4.2 Eligible Patient Population

The reimbursement request is for patients with metastatic hormone-sensitive prostate cancer. PAG is seeking guidance on whether the following patients would be eligible for treatment with enzalutamide plus ADT:
- Patients having experienced least one course of radiation therapy or surgery to treat symptoms related to metastatic disease
- Patients with an ECOG performance status score greater than 2
- Patients having started ADT (12 or more weeks ago)
- Patients having received more than 2 cycles of docetaxel
- Patients having received ADT in the adjuvant setting where the time since completion of adjuvant hormonal therapy is 12 or more months
- Patients with non-metastatic CSPC
- Patients intolerant to one of the alternative drugs
- Patients with high-risk factors

If recommended for reimbursement, PAG noted that patients currently treated with ADT and with or without docetaxel for greater than 12 weeks would need to be addressed on a time-limited basis. PAG is seeking guidance on the maximum duration of ADT that can be given before addition of enzalutamide.

There is a potential for indication creep to the non-metastatic setting; PAG noted this would be considered out of scope for this review.

Implementation Factors

The recommended dose of enzalutamide is 160 mg (four 40 mg capsules) as a single oral daily dose. It can be taken with or without food. Enzalutamide would be taken with additional androgen deprivation agents; pill burden may be an issue. On the other hand, the

ability to fine-tune dosage of enzalutamide by adjusting the number of capsules would help minimize drug wastage. Once daily dosage is considered an enabler to implementation.

As enzalutamide is already funded for mCRPC, there is a familiarity with the dispensing, administration and monitoring of the drug. This would be an enabler. Enzalutamide is a relatively well tolerated oral therapy not requiring clinic visits for administration. However, as enzalutamide is an add-on therapy, additional pharmacy resources for dispensing and monitoring of side effects (e.g., drug-drug interactions, high blood pressure, and liver function test elevations) would be needed. Nevertheless, additional clinic visits may be needed to monitor adverse events, which differ between drug classes.

PAG noted that the ENZAMET trial defined progression either by a PSA increase or clinically (radiography-based). A clear definition of progression would be needed to identify discontinuation criteria. Additionally, early/prior docetaxel use (ENZAMET: early docetaxel up to two cycles prior to randomization; ARCHES: prior docetaxel up to 6 cycles with final treatment administration completed within 2 months of day 1) was permitted. PAG is seeking clarity on docetaxel dosage, timing, and optimal target population.

PAG noted that patients with mCSPC are seen by radiation oncologists/urologists as well as medical oncologists for those receiving docetaxel. PAG indicated that a large patient population exists, resulting in a significant budget impact. PAG further remarked that enzalutamide is a convenient oral treatment that can be administered at the patient's home and chemotherapy chair time is not required. However, in some jurisdictions, oral medications are not funded in the same mechanism as intravenous cancer medications. This may limit accessibility of treatment for patients in these jurisdictions as they would first require an application to their pharmacare program and these programs can be associated with co-payments and deductibles, which may cause financial burden on patients and their families. The other coverage options in those jurisdictions which fund oral and intravenous cancer medications differently are: private insurance coverage or full out-of-pocket expenses.

4.4 Sequencing and Priority of Treatments

PAG is seeking guidance on the appropriate place in therapy of enzalutamide plus ADT and overall sequencing of all treatments available for non-metastatic, metastatic, castration-resistant, and castration-sensitive prostate cancer settings. In view of the three androgen receptor-targeted agents currently under review by CADTH for mCSPC, PAG is seeking advice on the selection of the preferred therapy (abiraterone, apalutamide, enzalutamide) in this population.

PAG is seeking clarity on the eligibility criteria for treatment of patients with docetaxel+ADT before adding enzalutamide. In the same vein, PAG would like to understand the role of docetaxel after progression on enzalutamide + ADT.

PAG is seeking information on the appropriate treatments following progression on enzalutamide plus ADT, particularly for castration-resistant disease (e.g., abiraterone+prednisone). Furthermore, given apalutamide exhibits a similar mechanism of action, PAG would like to know if sequencing of the two antiandrogens should be allowed.

4.5 Companion Diagnostic Testing

None identified.

4.6 Additional Information

None.

5 Summary of Registered Clinician Input

A total of three clinician inputs were provided for the review of enzalutamide for mCSPC: one joint clinician input from Cancer Care Ontario (CCO) Genitourinary (GU) DAC, one individual clinician input from Sunnybrook Odette Cancer Centre in Ontario, and one individual clinician input from a clinician practicing in Ontario. According to the submitted input, current treatments for mCSPC include abiraterone plus prednisone for high risk/high volume patients (not currently funded in Ontario), docetaxel in rare cases, apalutamide (not currently funded in Ontario), and ADT plus chemotherapy for elderly and frail patients or those with comorbidities. Overall, the clinicians agreed that enzalutamide can generally be prescribed to all patient subgroups with mCSPC; however, there are certain subgroups of patients for whom enzalutamide would be preferred over other options, such as patients who don't qualify for docetaxel and/or abiraterone, patients with node-predominant mCSPC, and patients who have hypertension. All three clinician groups had experience with prescribing enzalutamide, which is also commonly prescribed to patients with mCRPC. The clinicians reported that the majority of patients prefer enzalutamide over docetaxel and/or chemotherapy due to less toxicity. No major contraindications to enzalutamide were mentioned by the clinicians. The clinicians stated that the choice between enzalutamide and other androgen receptors is usually based on comorbidities, contraindications, patient preferences and toxicity profiles. For sequencing and priority of treatments, the clinicians advised that enzalutamide would be used in the first line setting. Other options upon progression would be docetaxel chemotherapy, radium-223 (for bone-limited metastatic disease), or investigational therapies through clinical trial participation. An unmet need for mCSPC patients was asserted by one clinician due to limited access to other oral androgen receptor antagonists.

Please see below for details from the clinician input(s).

5.1 Current Treatment(s)

Two clinicians noted abiraterone and prednisone combination as an additional treatment for high risk/high volume patients, which is only available through private insurance and/or compassionate care programs. These two clinicians also mentioned docetaxel as an option, one of whom noted that it is rarely used due to increased toxicity. One clinician also mentioned that apalutamide is commonly used, as it is available through compassionate care programs. The clinician stated that the use of ADT plus chemotherapy is limited to patients who are elderly and frail, and those with a limited lifespan due to comorbidities.

One clinician noted that the treatments listed under the provincial funding algorithm are currently funded in Ontario for high volume mCSPC patients only, not high-risk patients as noted in the current funding algorithm.

5.2 Eligible Patient Population

5.2.1 IMPLEMENTATION QUESTION: Is there any evidence or recommendations to support using ADT + enzalutamide only in specific high-risk subgroups rather than all patients with mCSPC? Since abiraterone has evidence for use in high-risk mCSPC, are there specific high-risk patient populations where abiraterone vs. enzalutamide would be preferred due to clinical reasons?

One of the clinicians noted that the choice between abiraterone and enzalutamide is made on an individual basis in consultation with a physician based on the patient's side-effects, comorbidities and contraindications.

Another clinician noted that although there is some overlap in the indication for enzalutamide for mCSPC compared to docetaxel and abiraterone, published studies suggest using enzalutamide for patients that do not qualify for docetaxel (i.e., high volume mCSPC) or abiraterone (i.e., high-risk mCSPC). Specifically, enzalutamide would be prescribed for patients with node-predominant mCSPC, which cannot be high-volume or high-risk because nodes are not part of the high versus low volume and high vs low risk classification.

Another clinician commented that the population in the funding request aligns with the need identified in clinical practice and there exists an unmet need for mCSPC patients due to limited access to other oral androgen receptor antagonists. The clinician agreed that the inclusion and exclusion criteria of the clinical trial can be applied in practice; however, some patients with an ECOG performance of 3 may also be candidates for enzalutamide if the decline in the their ECOG performance status is related to cancer and they are otherwise in good health. Currently, there is no evidence to restrict the use of enzalutamide + ADT to specific high-risk subgroups of patients with mCSPC. The clinician advised that, in rare cases, enzalutamide can cause central nervous system (CNS) toxicity and therefore may not be used for patients with severe fatigue or previous CNS disease. Furthermore, enzalutamide would be preferred in patients with hypertension (a potential side-effect of abiraterone), liver dysfunction, or poorly controlled diabetes. The clinician also stated that patient preference can help guide the decision between enzalutamide and abiraterone.

5.3 Relevance to Clinical Practice

All three clinician inputs stated that they have experience using enzalutamide in their clinical practice. The clinicians from CCO and Sunnybrook Cancer Centre noted that enzalutamide is commonly also prescribed to mCRPC patients since clinical studies do not show a difference in treatment tolerance between ADT+ enzalutamide for mCRPC and ADT+ enzalutamide for mCSPC. The clinician from Sunnybrook Odette Cancer Centre mentioned that alternatives to enzalutamide would be prescribed to patients with an increased risk of dementia or seizures. The individual clinician from Ontario noted that because enzalutamide has similar long-term outcomes as docetaxel/chemotherapy, but with less toxicity, the majority of patients prefer enzalutamide, especially elderly patients with comorbidities who are quite often not candidates for chemotherapy. The clinicians from CCO and the individual clinician from Ontario noted that there are currently no strict contraindications for enzalutamide. Additionally, the individual clinician from Ontario noted that factors such as patient preferences for pill sizes (enzalutamide is in the form of a large pill) or CNS toxicity may help patients decide among androgen receptors.

5.4 Sequencing and Priority of Treatments with New Drug Under Review

It was advised in all three clinician inputs that enzalutamide would be used in the first line setting for men with prostate cancer. One of the clinicians stated that enzalutamide would be used in conjunction with androgen deprivation therapy (such as LHRH agonists or antagonists). The clinicians noted that if a patient with mCSPC received enzalutamide in the first-line setting, they would not receive it in the mCRPC setting as they will be resistant. Two of the clinician inputs listed the following options upon progression on enzalutamide for mCSPC for mCSPC: docetaxel chemotherapy, radium-223 (for bone-limited metastatic disease) or clinical trial participation.

5.4.1 Under what circumstances would any of the androgen receptor targeted agents (abiraterone, apalutamide, enzalutamide) be preferred in the mCSPC setting?

The individual clinician from Ontario responded that all three options (abiraterone, apalutamide, enzalutamide) would be preferred over chemotherapy. The clinician added that currently there are no head-to-head trials that would specify the circumstances in which any of the androgen receptor targeted agents would be preferred in the mCSPC setting. Clinicians providing input stated that comorbidities, contraindications, patient preferences, and drug toxicity profiles would guide decision making. For example, patients with significant pre-existing fatigue and/or seizure disorders would best benefit from abiraterone, whereas patients with brittle diabetes would best benefit from apalutamide or enzalutamide. One clinician additionally commented that this would be the same in the mCRPC setting. The clinician from Sunny Brook Cancer Centre stated that abiraterone would be prescribed for high-risk mCSPC patients, as per the LATITUDE trial eligibility criteria, and apalutamide would be preferred for mCSPC patients with at least one bone metastases. Furthermore, enzalutamide would be used for patients with mCSPC patients without any restrictions.

5.4.2 Please consider the overall sequencing of all treatments available for non-metastatic, metastatic, castration-resistant, and castration-sensitive prostate cancer settings. In particular, please delineate sequencing of therapies, including antiandrogens and docetaxel, following treatment with enzalutamide plus ADT in the mCSPC setting and progression to mCRPC.

The joint clinician input from CCO stated that mCSPC patients who progress on treatment with enzalutamide plus ADT, usually receive chemotherapy (docetaxel followed by cabazitaxel), radium-223 (if bone predominant disease) and sometimes olaparib (if approved and funded for men with a DNA damage response (DDR) abnormality, such as BRCA2).

The individual clinician from Ontario stated that after progression on enzalutamide + ADT, the typical treatment outside of clinical trials would be Radium-223 followed by docetaxel. Patients with bone-limited disease would be prescribed docetaxel followed by Radium-223. On subsequent progression, patients would be prescribed cabazitaxel followed by other androgen receptor antagonists that are not previously used for the patient.

The clinician from Sunny Brook Cancer Centre re-stated that for men progressing on enzalutamide for mCSPC (i.e, patients who castration-and enzalutamide resistant) would receive either docetaxel chemotherapy, Ra223. This clinician further asserted that, based on the available evidence, all Canadian patients with advanced prostrate cancer should be able to access at least one of the following: abiraterone, apalutamide, enzalutamide and darolutamide.

5.4.3 If androgen deprivation therapy is started in the metastatic hormone sensitive setting with an LHRH agonist, does the LHRH agonist continue for this phase of treatment and onwards with all treatments the patient would receive upon progression in the mCRPC setting?

All three clinician inputs stated that if androgen deprivation therapy is started in the metastatic hormone sensitive setting with an LHRH agonist, the LHRH agonist would continue for this phase of treatment and onwards with all treatments the patient would receive upon progression in the mCRPC setting.

5.5 Companion Diagnostic Testing

None identified.

5.6 Implementation Questions

5.6.1 What would be the maximum duration of prior ADT before adding enzalutamide in practice?

It was stated in the CCO clinician input that the maximum duration of prior ADT before adding enzalutamide would ideally be less than six months. Most patients should be evaluated before their second LHRH injection which is usually within three to four months; however, some patients may not be able to start androgen receptor axis-targeted agents such as enzalutamide within six months due to delays in referral and/or evaluations. The clinician input stressed that these patients could still benefit from enzalutamide therapy. The clinician from Sunnybrook Cancer Centre stated that, according to the ARCHES and ENZAMET trials, three months would be the maximum duration of prior ADT before adding enzalutamide. However, the clinician added that the TITAN trial supports six months, and because enzalutamide and apalutamide are similar drugs, the clinician concluded that six months seemed more reasonable.

The individual clinician from Ontario also agreed that three months would be reasonable. Patients who might have a had an expected poor prognosis and may have been started on ADT alone, can experience significant improvements in their health and performance status with the addition of enzalutamide, which makes the drug valuable to these patients.

5.7 Additional Information

None identified.

6 Systematic Review

6.1 Objectives

The purpose of this review is to evaluate the efficacy and safety of enzalutamide in combination with androgen deprivation therapy (ADT) compared with ADT alone or ADT plus a non-steroidal anti-androgen (NSAA) in men with metastatic castrate sensitive prostate cancer (mCSPC).

Supplemental Questions most relevant to the CADTH review and to the Provincial Advisory Group were identified while developing the review protocol and are outlined in section 7.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP and the CADTH Methods Team. Studies were chosen for inclusion in the review based on the criteria in the Table 4 below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold. The literature search strategy and detailed methodology used by the CADTH Methods Team are provided in Appendix A.

Table 4: Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published or unpublished RCTs In the absence of RCT data, fully published clinical trials investigating the safety and efficacy of enzalutamide should be included.	Patients with mCSPC Subgroups: • Age (<65 years vs ≥ 65 years) • Ethnicity (White vs Black vs Asian vs Hispanic or Latino vs Other) • ECOG performance status (0 vs ≥ 1) • Baseline Gleason score (< 8 or ≥ 8) • Volume of disease (low vs high) • Prior docetaxel therapy (yes vs no) • Previous use of ADT or orchiectomy (yes vs no) • Visceral metastases (yes vs no)	Enzalutamide	ADT Docetaxel + ADT Abiraterone + prednisone + ADT Apalutamide + ADT	Primary • OS • PFS • HRQoL Secondary • ORR • Time to PSA progression • Time to first use of new antineoplastic therapy • Time to first SSE • Time to castration resistance • PSA response rates Safety • AEs • SAEs • WDAEs • Dose adjustment, interruption and/or discontinuation • Time to discontinuation

Abbreviations: ADT = Androgen deprivation therapy; AE=adverse events; ECOG = Eastern Cooperative Oncology Group; HRQoL=Health related quality of life; mCSPC = metastatic castration sensitive prostate cancer; OS = overall survival; PFS = progression-free survival; PSA = prostate-specific antigen; RCT=randomized controlled trial; SAE=serious adverse events; SSE = symptomatic skeletal related events; WDAE=withdrawals due to adverse events

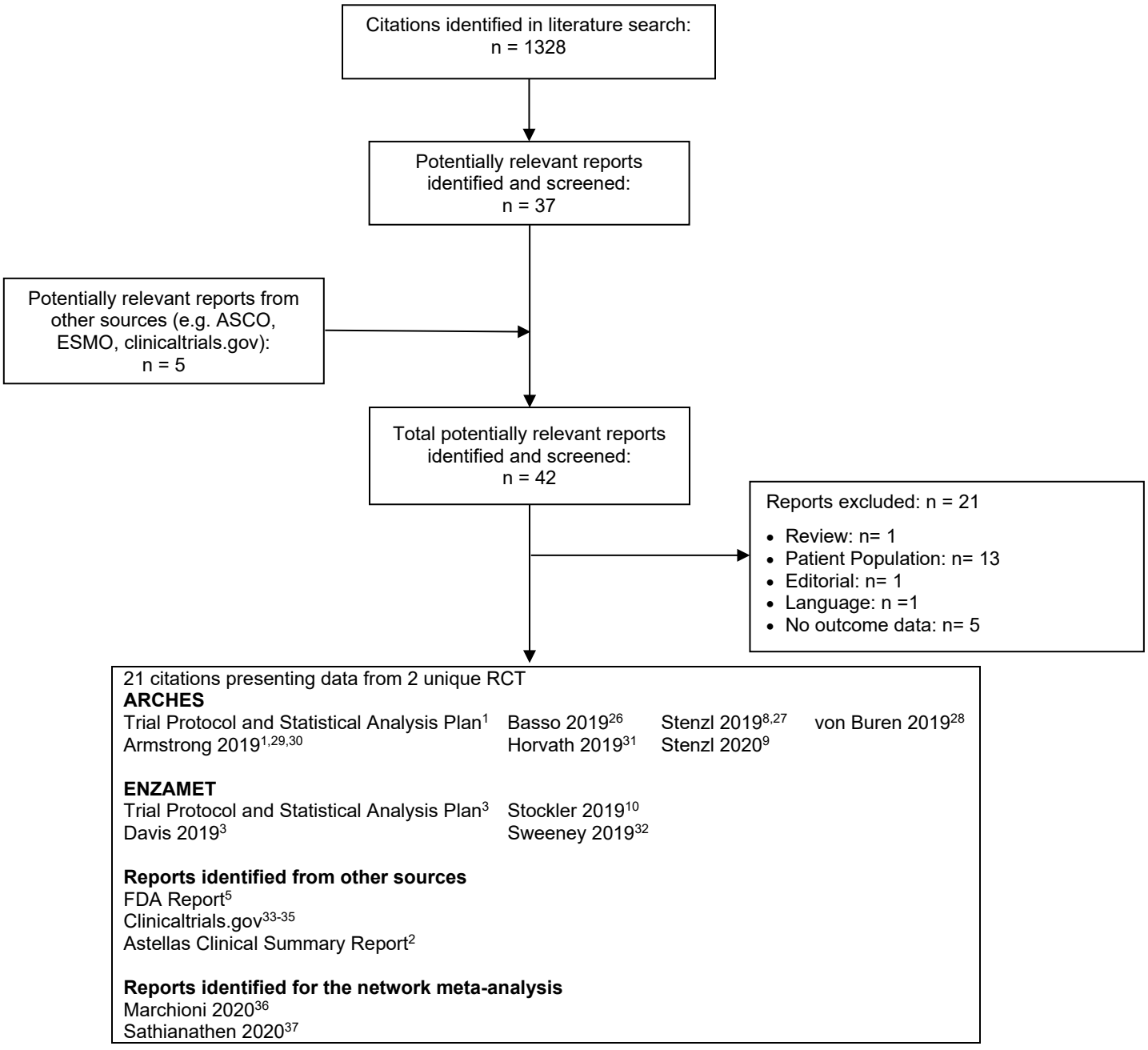
** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

6.3 Results

6.3.1 Literature Search Results

Of the 1,328 potentially relevant reports identified, two trials, reported in 24 citations, were included in the CADTH systematic review (Figure 1: Flow Diagram for Study Selection). 21 reports were excluded because 13 had a different patient population, five did not include outcome data, two were either a review or an editorial and one was not in English. Additional reports related to the trials were obtained from the Sponsor.

Figure 1: Flow Diagram for Study Selection



Note: Additional data related to studies Sponsor Clinical Summary Report[38], Clinical Study Reports[4,6], Indirect Treatment Comparison[38] and Checkpoint Responses[7] were also obtained through requests to the Sponsor by CADTH

6.3.2 Summary of Included Studies

The CADTH systematic review included two RCTs (ARCHES and ENZAMET) that assessed the efficacy and safety of enzalutamide for patients with mCSPC.

6.3.2.1 Detailed Trial Characteristics

The summary of the trials and select quality characteristics are presented in Table 4 and Table 5.

Table 4: Summary of trial characteristics of the included studies

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Study ARCHES Trial[1] (NCT02677896) **Characteristics** Randomized, double-blind, placebo-controlled phase III trial with an open-label extension phase Randomized N= 1,150 Treated N= 1,146 **Number of centres and number of countries** 202 centres in North and Latin America, Europe, and Asia **Patient Enrolment Dates** 21-Mar-2016 to 12-Jan-2018 **Data cut-off** 14-Oct-2018 **Final Analysis Date** May-2021 **Funding** Astellas	Key Inclusion Criteria: 1. Adult (defined according to local regulation) males with pathologically confirmed prostate adenocarcinoma, without neuroendocrine differentiation, signet-cell, or small-cell features. 2. Metastatic prostate cancer documented by positive bone scan (for bone disease) or metastatic lesions on CT or MRI scan (for soft tissue). 3. Must maintain ADT with an LHRH agonist or antagonist during study treatment or have a history of bilateral orchiectomy after day 1 of randomization. 4. ECOG performance status of 0 or 1. Key Exclusion Criteria: 1. Received any prior pharmacotherapy, radiation therapy or surgery for metastatic prostate cancer (the following exceptions are permitted): A. Up to 3 months of ADT with LHRH agonists or antagonists or orchiectomy with or without concurrent antiandrogens prior to day 1, with no radiographic evidence of disease progression or rising PSA levels prior to day 1; B. 1 course of palliative radiation or surgical therapy to treat symptoms resulting from metastatic disease if it was administered at least 4 weeks prior to day 1; C. Up to 6 cycles of docetaxel therapy with final treatment administration completed within 2 months of day 1 and no evidence of disease progression during or after the completion of docetaxel therapy; D. Up to 6 months of ADT with LHRH agonists or antagonists or orchiectomy with or without concurrent antiandrogens prior to day 1 if subject was treated with docetaxel, with no radiographic evidence of disease progression or rising PSA levels prior to day 1; E. Prior ADT given for < 39 months in duration and > 9 months before randomization as neoadjuvant/ adjuvant therapy.	Enzalutamide (160 mg/day) + ADT vs Placebo + ADT	Primary: rPFS based on ICR Secondary: OS Time to SSE Time to castration resistance Time to deterioration of QoL Time to deterioration in urinary symptoms Time to start of new antineoplastic therapy Time to PSA progression PSA undetectable rate ORR Time to pain progression Tertiary: PSA decline Safety Outcomes HRQoL

	2. Received treatment with 5-α reductase inhibitors, estrogens, cyprotoerone acetate or androgens within 4 weeks prior to day 1. 3. Received treatment with systemic glucocorticoids greater than the equivalent of 10 mg per day of prednisone within 4 weeks prior to day 1, intended for the treatment of prostate cancer. 4. Received prior aminoglutethimide, ketoconazole, abiraterone acetate or enzalutamide for the treatment of prostate cancer or participation in a clinical study of an investigational agent that inhibits the AR or androgen synthesis. 5. Known or suspected brain metastasis or active leptomeningeal disease. 6. History of seizure or any condition that may predispose to seizure.		

Abbreviations: ADT = Androgen Deprivation Therapy; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; ICR = Independent Central Review; LHRH = luteinizing hormone-releasing hormone; MRI = magnetic resonance imaging; ORR = Objective Response Rate; PCWG2 = Prostate Cancer Clinical Trials Working Group 2; PSA = Prostate Specific Antigen; rPFS = Radiographic Progression-Free Survival; SSE = symptomatic skeletal related events;

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Study ENZAMET Trial[3] (NCT02446405) **Characteristics** Randomized, open-label phase III trial Randomized N= 1,125 Treated N= 1,121 **Number of centres and number of countries** 83 centres in Australia, Canada, Ireland, New Zealand, United Kingdom and USA **Patient Enrolment Dates** Mar-2014 to Mar-2017 **Data cut-off** 28-Feb-2019 **Final Analysis Date** Dec-2020 **Funding** ANZUP, NHMRC Clinical Trials Centre, University of Sydney and Astellas	<u>Key Inclusion Criteria:</u> 1. Male aged 18 or older with metastatic adenocarcinoma of the prostate defined by: A. Documented histopathology or cytopathology of prostate adenocarcinoma from a biopsy of a metastatic site; OR B. Documented histopathology of prostate adenocarcinoma from a TRUS biopsy, radical prostatectomy, or TURP and metastatic disease consistent with prostate cancer; OR C. Metastatic disease typical of prostate cancer (i.e. involving bone or pelvic lymph nodes or para-aortic lymph nodes) AND a serum concentration of PSA that is rising and >20ng/mL. 2. Target or non-target lesions according to RECIST 1.1. 3. Adequate bone marrow, liver and renal function 4. ECOG performance status of 0 to 2. 5. Testosterone suppression that was initiated up to 12 weeks before randomization, or if they had previous adjuvant testosterone suppression for up to 24 months that was completed at least 12 months earlier. <u>Key Exclusion Criteria:</u> 1. Prostate cancer with significant sarcomatoid or spindle cell or neuroendocrine small cell components 2. History of seizure or any condition that may predispose to seizure, loss of consciousness or transient ischemic attack within 12 months of	Enzalutamide (160 mg/day) + LHRHA or Surgical Castration Vs NSAA + LHRHA or Surgical Castration	<u>Primary:</u> OS <u>Secondary:</u> PSA PFS Clinical PFS <u>Tertiary:</u> HRQoL Safety Outcomes

	randomization, significant CVD within the last 3 months. 3. Life expectancy of less than 12 months. 4. History of another malignancy within 5 years prior to randomization, except for either non-melanomatous carcinoma of the skin or, adequately treated, non-muscle-invasive urothelial carcinoma of the bladder. 5. Prior ADT for prostate cancer (including bilateral orchidectomy), except in the following settings: A. Started less than 12 weeks prior to randomization AND PSA is stable or falling. The 12 weeks starts from whichever of the following occurs earliest: first dose of oral antiandrogen, LHRHA, or surgical castration. B. In the adjuvant setting, where the completion of adjuvant hormonal therapy was more than 12 months prior to randomization AND the total duration of hormonal treatment did not exceed 24 months. 6. Prior cytotoxic chemotherapy for prostate cancer, but up to 2 cycles of docetaxel chemotherapy for metastatic disease is permitted.		

Abbreviations: ADT = Androgen Deprivation Therapy; CT = computed tomography; CVD = cardiovascular disease; ECOG = Eastern Cooperative Oncology Group; ICR = Independent Central Review; LHRHA = Luteinizing Hormone Releasing Hormone Analogue; MRI = magnetic resonance imaging; NSAA = Non-steroidal anti androgen; ORR = Objective Response Rate; PCWG2 = Prostate Cancer Clinical Trials Working Group 2; PSA = Prostate Specific Antigen; rPFS = Radiographic Progression-Free Survival; RECIST = Response Evaluation Criteria in Solid Tumours

Table 5: Select quality characteristics of included studies that assessed the efficacy and safety of enzalutamide in combination with ADT for patients with mCSPC

Study	ARCHES
Treatment vs. Comparator	Enzalutamide with ADT vs placebo with ADT
Primary outcomes	rPFS based on ICR
Required sample size	1,100 participants were required to be included in the study. 262 rPFS events were required to provide 90% power to detect a HR of 0.67 (30 months with enzalutamide vs. 20 months with placebo), using a log-rank test and two-sided significance α of 0.05.[1] For OS, 342 deaths were required to provide 80% power to detect a HR of 0.73 (55 months with enzalutamide vs. 40 months with placebo) for OS, using a log-rank test and two sided significance level α of 0.04.[1]
Sample size	1,150
Randomization method	Randomization was stratified by disease volume (low vs high) and prior docetaxel chemotherapy for prostate cancer (no cycles, one to five cycles, or six cycles).

Allocation concealment	Centralized with use of Interactive Response Technology
Blinding	Double-blind trial. The investigator, sponsor, clinical staff and patients were blinded to treatment assignment. Radiographic assessments were performed at a sponsor designated facility for ICR.
ITT Analysis	Yes
Final analysis	No. The trial is ongoing and the final analysis is expected on May 2021.[33]
Early termination	No.
Ethics Approval	Yes.

Abbreviations: ADT = Androgen Deprivation Therapy; HR = hazard ratio; ICR = Independent Central Review; OS = overall survival; rPFS = Radiographic Progression-Free Survival

Study	ENZAMET
Treatment vs. Comparator	Enzalutamide with ADT vs NSAA with ADT
Primary outcomes	OS
Required sample size	1,100 participants were required to be included in the study. Four hundred and seventy deaths were required to provide 80% power to detect a HR of 0.75, assuming a 3-year survival rate of 65% in the NSAA group, and using a log-rank test and two-sided significance level α of 0.05.[3]
Sample size	1,125
Randomization method	Performed using implemented minimization with a random component. Randomization was stratified by volume of disease (high versus low), site, co-morbidities ([ACE-27] 0-1 versus 2-3), use of anti-resorptive therapy (denosumab, zoledronic acid or neither) at time of starting ADT, and planned use of docetaxel.
Allocation concealment	A central randomization system
Blinding	Open-label trial. Statisticians were blinded to treatment assignment and imaging reports were reviewed centrally.
ITT Analysis	Yes
Final analysis	No. The trial is ongoing and the final analysis is expected on Dec 2020.[35]

Early termination	No
Ethics Approval	Yes

Abbreviations: ADT = Androgen Deprivation Therapy; HR = hazard ratio; ICR = Independent Central Review; NSAA = non-steroidal anti-androgen; OS = overall survival

a) Trials

ARCHES Trial

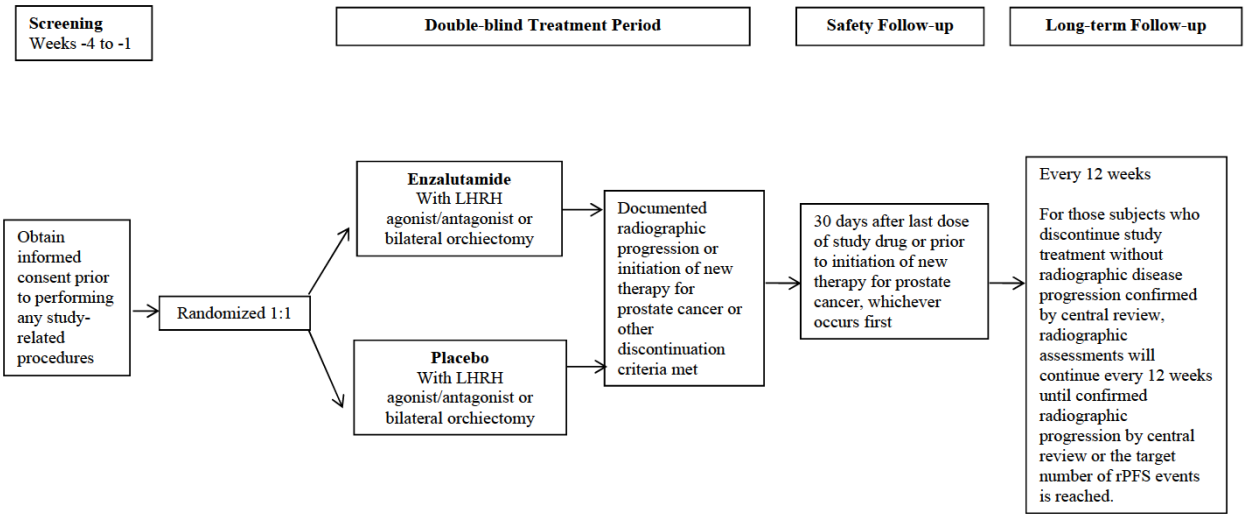
Trial Design

The ARCHES trial is an ongoing, multinational, randomized, double-blind, placebo-controlled, phase III trial that assesses the safety and efficacy of enzalutamide as compared to placebo in 1,150 men with metastatic hormone sensitive prostate cancer (mHSPC) regardless of prior docetaxel use or disease volume.[1] The trial was conducted in 202 centres within North and Latin America, Europe and Asia.[1] The majority of patients were recruited from Europe (59.4%).[1] It was sponsored by Astellas Pharma and Pfizer.[1]

Patients were included in the trial if they met the following criteria:[1] adult men with pathologically confirmed prostate adenocarcinoma without neuroendocrine differentiation, signet-cell or small-cell features (according to local regulation); metastatic prostate cancer documented by positive bone scan or metastatic lesions on CT or MRI scan; able to maintain ADT with an LHRH agonist or antagonist during study treatment or have a history of bilateral orchiectomy after day 1 of randomization; and an ECOG performance status of 0 or 1. Patients who had prior disease progression while receiving ADT and/or docetaxel were excluded from the trial. Further details on the inclusion criteria and exclusion criteria are provided in Table 4.

The study design is illustrated in Figure 2. The trial consists of five phases: randomization, double-blind treatment, safety follow-up, long-term follow-up and an open-label extension phase.

Figure 2: ARCHES Trial



LHRH: luteinizing hormone-releasing hormone

Source: Armstrong et al., 2019. Copyright 2019 American Society of Clinical Oncology. Reprinted in accordance with CC BY-NC 4.0.[1]

In the randomization phase, patients were randomized on a 1:1 ratio to receive either enzalutamide (160 mg/day) with ADT or placebo with ADT. Randomization was stratified by disease volume (low vs high) and prior docetaxel chemotherapy for prostate cancer (no cycles, one to five cycles, or six cycles).

During the double-blind treatment phase, at baseline, radiographic imaging assessments were performed using CT or MRI and bone scans, and subsequent imaging was performed at week 13 and every 12 weeks thereafter.[1] All radiographic assessments were confirmed by an ICR. Patients received their assigned therapy until unacceptable toxicity, radiographic progression, starting a new therapy for the treatment of prostate cancer or they met other discontinuation criteria.[1]

Patients entered the safety follow-up phase after 30 days of the last dose of their assigned therapy or prior to the initiation of a new therapy for prostate cancer, whichever occurred first. In the long-term follow-up phase, patients who discontinued their study treatment without radiographic disease progression as confirmed by ICR were assessed every 12 weeks until confirmed radiographic disease progression or the target number of rPFS events was reached.[1] All patients were followed for OS.

The addition of the open-label extension phase was added as a protocol amendment.[1] The open-label extension phase was planned to occur when the double-blind treatment phase was unblinded and if enzalutamide showed a statistically significant difference on the primary outcome as compared to placebo.[1] All eligible patients, who entered the open-label extension phase, could receive enzalutamide at the discretion of the patient and the study investigator. Although the open-label extension phase is ongoing, the results of this CADTH Report will focus on the results at the 14-Oct-2018 data cut-off.

Statistical Analysis

Database Cut-off: The database cut-off for the ARCHES trial was 14-Oct-2018 and this represents a follow-up of 14.4 months.[1]

Power Calculation and Sample Size: The ARCHES trial was designed to provide sufficient power for rPFS and OS. The required sample size for the trial was 1,100 patients. Two hundred and sixty-two rPFS events (i.e., radiographic progression at any time or death from any cause within 24 weeks after study drug discontinuation, whichever occurred first) were required to provide 90% power to detect a hazard ratio (HR) of 0.67 (30 months with enzalutamide vs. 20 months with placebo), using a log-rank test and two-sided significance α of 0.05.[1] For OS, 342 deaths were required to provide 80% power to detect a HR of 0.73 (55 months with enzalutamide vs. 40 months with placebo) for OS, using a log-rank test and two sided significance level α of 0.04.[1]

Interim Analyses:. No interim analyses were planned for rPFS; however, an interim analysis was planned for OS at the time of the final analysis of rPFS using the O'Brien-Fleming alpha spending function.[1] It was stated in the protocol that if OS was significant at the time of the interim analysis, then no further analysis of OS would be completed.[1]

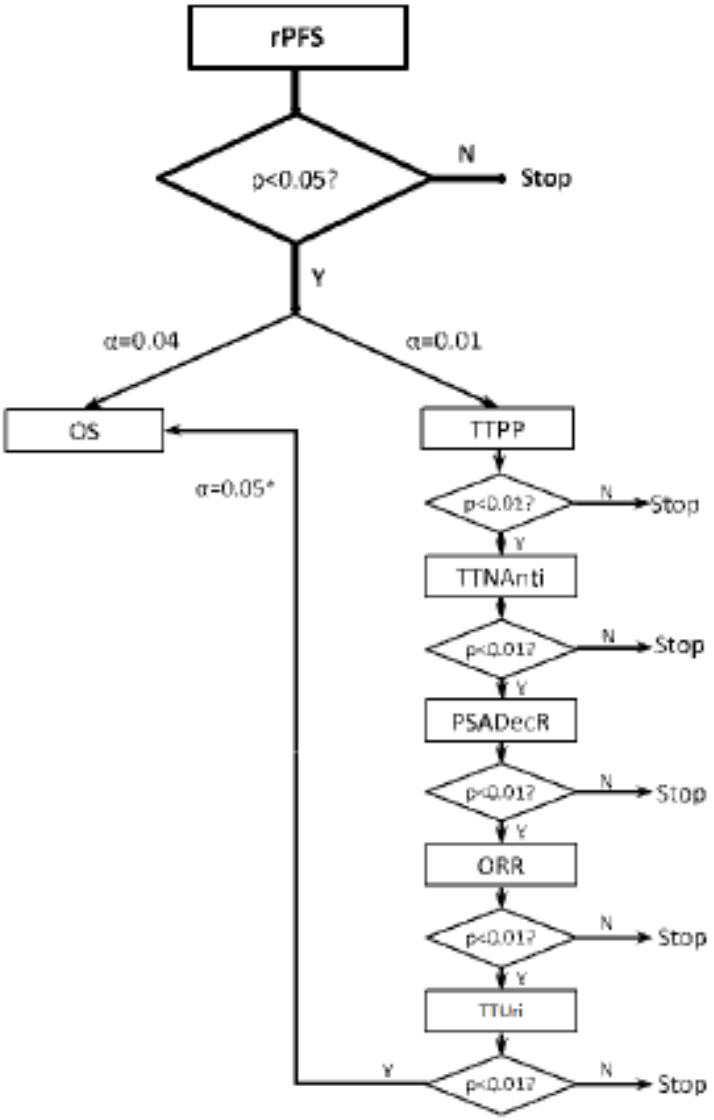
Analysis Set: Efficacy outcomes were evaluated in the ITT population, which was composed of all patients who were randomized in the trial. The ITT population was analyzed according to the assigned treatment group regardless of whether or not the study treatment was administered.[1] Safety analyses were conducted in the safety set, which was composed of all patients who received at least one dose of the study drug.[1]

Endpoints: The primary endpoint was rPFS as assessed by ICR. Secondary outcomes included: OS, time to first SSE, time to castration resistance, time to deterioration of QoL, time to deterioration in urinary symptoms, time to start of new antineoplastic therapy, time to PSA progression, PSA undetectable rate (< 0.2 ng/mL), ORR and time to pain progression. Exploratory outcomes were combined response (soft tissue lesions and bone lesions), PSA reduction, HRQoL and safety.[1]

Multiplicity: The trial adjusted for multiplicity by using a parallel testing strategy at the time of the primary analysis (i.e., when 262 events had occurred) (Figure 3).[1] Here, rPFS was evaluated using a two-sided significance α of 0.05 while a parallel testing strategy was applied for OS (allocated type 1 error rate of 0.04) and the other secondary outcomes (allocated type 1 error rate of 0.01).[1]

Protocol Amendments: Three major protocol amendments occurred on 02-Jun-2016, 14-Dec-2017 and 10-Dec-2018.[1] The CADTH Methods Lead has reviewed these amendments and determined that none of them were of concern because they did not impact the integrity of the study.

Figure 3: Parallel testing approach used for the ARCHES trial



rPFS: radiographic progression-free survival; OS: overall survival; TTPP: time to PSA progression; TTNAnti: time to initiation of new antineoplastic therapy; PSADecR: rate of PSA decline to <0.2 ng/mL; ORR: objective response rate; TTUri: the time to deterioration in urinary symptoms from the QLQ-PR25
*OS will be tested at 0.05 only, if all other 5 secondary endpoints analyses are statistically significant at 0.01.

Source: Armstrong et al., 2019. Copyright 2019 American Society of Clinical Oncology. Reprinted in accordance with CC BY-NC 4.0.[1]

ENZAMET Trial

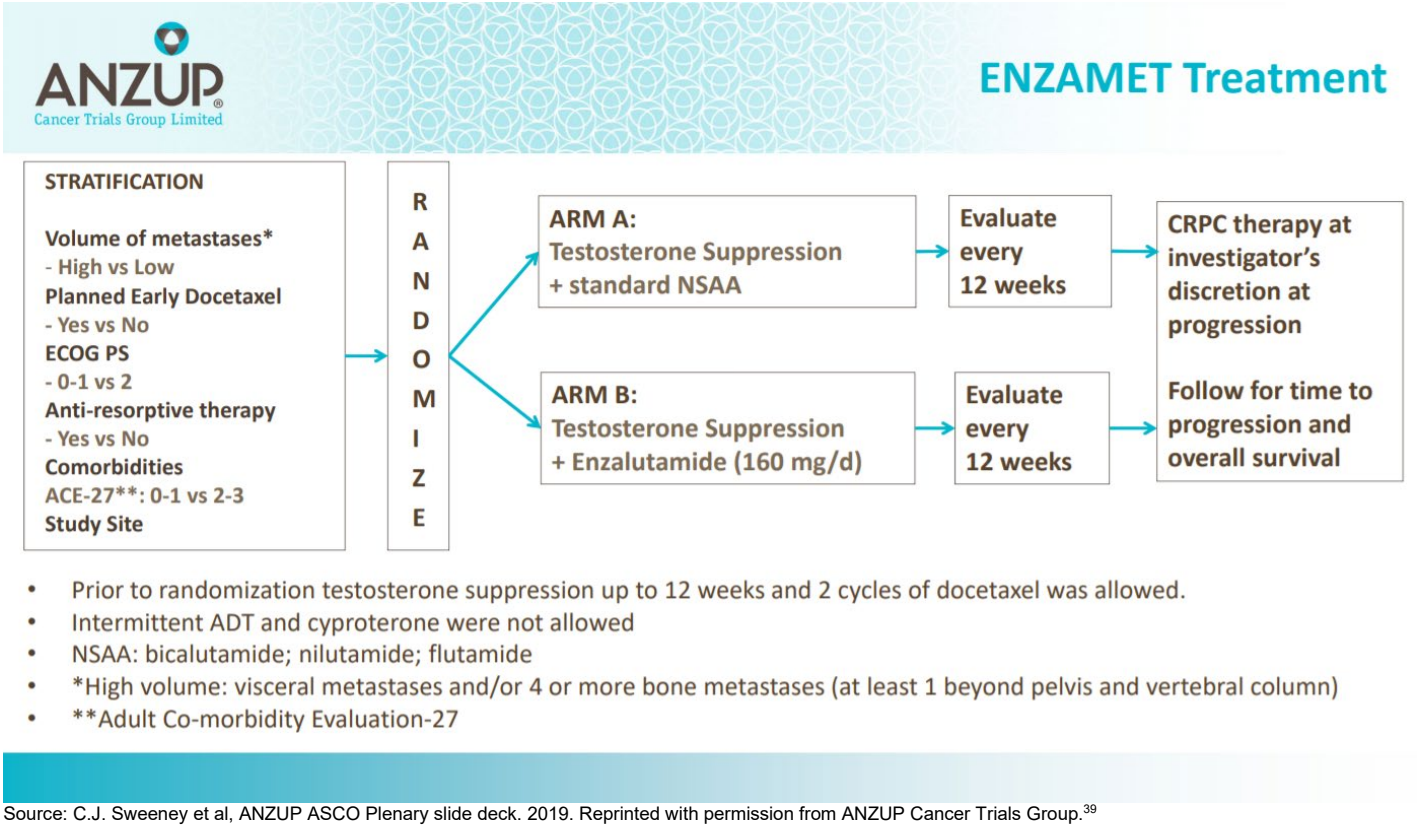
Trial Design

The ENZAMET trial is an ongoing, multinational, open-label, randomized phase III trial that assesses the safety and efficacy of enzalutamide as compared to standard care in 1,125 men with mHSPC.[3] The trial was conducted in 83 sites within Australia, Canada, Ireland, New Zealand, the United Kingdom and the United States. [3] The majority of patients were recruited from Australia.[3] The trial was led by the Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP) and the National Health and Medical Research Council (NHMRC) Clinical Trials Centre, University of Sydney. Regional sponsorship was provided by Cancer Trials Ireland, the Canadian Cancer Trials Group and the Dana–Farber Cancer Institute, as well as Astellas Pharma.

Patients were included in the trial if they met the following criteria:[3] adult men with prostatic adenocarcinoma with metastases on CT, bone scanning with technetium-99, or both; and an ECOG performance status of 0 to 2. Patients were eligible for the trial if they had testosterone suppression that was initiated up to 12 weeks before randomization, or if they had previous adjuvant testosterone suppression for up to 24 months that was completed at least 12 months earlier.[3] In addition, patients who started docetaxel prior to study entry were still eligible if they were tolerating full doses of docetaxel (75mg/m^2) with ADT, met all the eligibility criteria for the trial while receiving docetaxel and had no more than two cycles prior to randomization. The first dose of docetaxel should be given at least four weeks after starting enzalutamide, and no more than six weeks after randomization.

The study design is illustrated in Figure 4. The trial consists of four phases: randomization, open-label treatment, safety follow-up and long-term follow-up.

Figure 4: ENZAMET trial



Source: C.J. Sweeney et al, ANZUP ASCO Plenary slide deck. 2019. Reprinted with permission from ANZUP Cancer Trials Group.[39]

Prior to randomization, treating clinicians and patients decided if early treatment with docetaxel would be undertaken.[3] Similar decisions were made about the use of concomitant "anti-resorptive" therapy, which was used to delay SREs when initiating ADT (i.e., denosumab, zoledronic acid or any other therapy at doses proven to prevent SREs).

In the randomization phase, patients were centrally randomized on a 1:1 ratio to receive either enzalutamide (160 mg/day) with ADT or NSAA with ADT and all patients were on a background of LHRHA (or surgical castration). The type of NSAA that was chosen was at the discretion of the treating clinician, and it could include: bicalutamide (50 mg/d), nilutamide (150mg/d) or flutamide (250mg/tid).[3] Randomization was stratified by disease volume (low vs high), study site, anti-resorptive therapy (yes vs no), comorbidities according to the ACE-27 (0 to 1 vs 2 to 3) and early planned use of docetaxel (yes vs no).[3]

During the open-label treatment phase, assessments occurred at baseline, day 29, week 12 and then every 12 weeks until clinical progression.[3] Patients received imaging with a CT scan or MRI and whole body bone scan a baseline and at evidence of PSA clinical progression, whichever occurred first.[3] Patients received their assigned therapy until unacceptable toxicity or clinical progression.[3] Clinical progression was defined as progression on imaging (PCWG2 criteria for bone lesions and RECIST 1.1 for soft tissue lesions), development of symptoms attributable to cancer progression or initiation of other anticancer treatment for prostate cancer.[3] Patients who discontinued their assigned therapies could receive a subsequent therapy at the discretion of the treating clinician.[3]

Patients entered the safety follow-up phase 30 days after the last dose of their assigned therapy. Clinical assessments were also conducted on the 30-day safety visit.[3]

Finally, in the long-term follow-up phase, patients who discontinued their study treatment without clinical progression (i.e., toxicity, patient or clinician preference, or PSA progression without clinical progression), were assessed every 12 weeks until clinical progression.[3]

Statistical Analysis

Database Cut-off: The database cut-off for the ENZAMET trial was 28-Feb-2019 and this represents a follow-up of median 34.4 months.[3]

Power Calculation and Sample Size: Four hundred and seventy deaths were required to provide 80% power to detect a HR of 0.75, assuming a 3-year survival rate of 65% in the NSAA group, and using a log-rank test and two-sided significance level α of 0.05.[3]

Interim Analyses: An interim analysis was planned for OS when 50%, 67% and 80% of the required events (i.e., 470 deaths) had occurred using the Lan–DeMets alpha spending function.[3] Initially, when the trial was first designed, the interim analysis for OS would be conducted when 67% of the required number of deaths had occurred. However, following the results from the LATITUDE and STAMPEDE trials, two extra interim analyses were planned when 50% and 80% of the required events had occurred using the Lan–DeMets alpha spending function. The data cut-off of 28-Feb-2019 represents an interim analysis for OS.[3]

Analysis Set: Efficacy analyses were evaluated using the ITT principle.[3] Safety analyses were conducted in the safety set, which was composed of all patients who received at least one dose of the study drug.[3]

Endpoints: The primary endpoint was OS. Secondary outcomes were PSA PFS and clinical PFS. Exploratory outcomes were HRQoL and safety.

Multiplicity: All analyses in the trial were performed using a two-sided α of 0.05. To account for type 1 error, hypothesis tests were grouped into discrete families and the subsequent p-value was then evaluated within each family.[3] The Benjamini–Hochberg method was used to calculate the adjusted p-values within each discrete family.[3] The following families were considered: (1) adjusted analyses for OS; (2) subgroup analyses for OS; (3) subgroup analyses for PSA PFS; and (4) subgroup analyses for clinical PFS.[3] It should be noted that the analysis of PSA PFS and clinical PFS were not adjusted for multiple testing.

Protocol Amendments: Two major protocol amendments occurred on 07-Nov-2014 and 01-Mar-2018.[3] These amendments were reviewed by the CADTH review team and it was determined that none of them were of concern as they were not likely to impact the integrity of the study.

b) Populations

ARCHES Trial

Overall, the baseline characteristics were well balanced (Table 6). The median age in the trial was 70 years (enzalutamide: 70.0 [range: 46 to 92] vs placebo: 70.0 [range: 42 to 92]) and the majority of patients in both groups had a White (enzalutamide: 81.2% vs placebo: 79.9%) or Asian (enzalutamide: 13.1% vs placebo: 13.9%) ethnicity and had an ECOG performance status of 0 (enzalutamide: 78% vs placebo 76.9%). A large proportion of patients had a Gleason score of ≥8 (enzalutamide: 67.2% vs placebo: 64.8%) and more than half of the patients in the trial had a high volume of disease (enzalutamide: 61.7% vs placebo: 64.8%). The majority of patients did not receive prior docetaxel (enzalutamide: 82.1% vs placebo: 82.3%) but they had previous use of ADT for ≤ 3 months (enzalutamide: 72.1% vs placebo: 68.4%). The majority of patients in the trial had bone only (44.6% for all) or bone and soft tissue (39.8%) metastasis based on ICR.[2] The amount of bone lesions based on ICR varied for all patients in the trial (1 bone lesion: 13.3%, 2 to 4 bones lesions: 25.5%, 5 to 9: 17.5%, 10 to 19: 19.6% and ≥ 20 [including too numerous to count]: 8.6%).[2]

Table 6: Baseline characteristics of the patients enrolled in the ARCHES Trial

Characteristic	Enzalutamide Plus ADT (n = 574)	Placebo Plus ADT (n = 576)
Age (years)		
Median	70.0	70.0
Range	46-92	42-92
Age category, years		
< 65	148 (25.8)	152 (26.4)
65-74	256 (44.6)	255 (44.3)
≥ 75	170 (29.6)	169 (29.3)
Race[a]		
White	466 (81.2)	460 (79.9)
Asian	75 (13.1)	80 (13.9)
Black or African American	8 (1.4)	8 (1.4)
American Indian or Alaska Native	0	0
Native Hawaiian or other Pacific Islander	0	0
Other	2 (0.3)	3 (0.5)
Missing	23 (4.0)	25 (4.3)
Geographic region		
Europe	341 (59.4)	344 (59.7)
Asia-Pacific	104 (18.1)	113 (19.6)
North America	86 (15.0)	77 (13.4)
South America	32 (5.6)	30 (5.2)
Other	11 (1.9)	12 (2.1)
ECOG performance status score on day 1		
0	448 (78.0)	443 (76.9)
1	125 (21.8)	133 (23.1)
Total Gleason score at initial diagnosis		
< 8	171 (29.8)	187 (32.5)
≥ 8	386 (67.2)	373 (64.8)
Confirmed metastases at screening[b]		
Yes	536 (93.4)	531 (92.2)
No	34 (5.9)	45 (7.8)
Unknown	4 (0.7)	0
Localization of confirmed metastases at screening[b]		
Bone only	268 (46.7)	245 (42.5)
Soft tissue only	51 (8.9)	45 (7.8)
Bone and soft tissue	217 (37.8)	241 (41.8)
Distant metastasis at initial diagnosis		
M1	402 (70.0)	365 (63.4)
M0	83 (14.5)	86 (14.9)
MX/unknown	88 (15.3)	125 (21.7)
Disease volume		
High[c]	354 (61.7)	373 (64.8)
Low	220 (38.3)	203 (35.2)

(continued on following page)

Characteristic	Enzalutamide Plus ADT (n = 574)	Placebo Plus ADT (n = 576)
Prior local therapy		
Radical prostatectomy	72 (12.5)	89 (15.5)
Radiation therapy	73 (12.7)	72 (12.5)
No. of cycles of prior docetaxel chemotherapy		
0	471 (82.1)	474 (82.3)
1-5	14 (2.4)	11 (1.9)
6	89 (15.5)	91 (15.8)
Previous use of ADT[d]		
None	39 (6.8)	61 (10.6)
≤ 3 months	414 (72.1)	394 (68.4)
> 3 months	121 (21.1)	120 (20.8)
Unknown[e]	0	1 (0.2)
Median duration of prior ADT, months (range)[f]	1.6 (0.03-55.3)	1.6 (0.03-198.8)
Previous use of antiandrogen[g]	205 (35.8)	229 (39.9)
Median PSA, ng/mL (range)[g]	5.4 (0-4,823.5)	5.1 (0-19,000.0)
Modified QLQ-PR25 urinary symptoms score, mean (SD)[h]	35.2 (25.3)	35.8 (25.4)
FACT-P total score, mean (SD)[i]	113.9 (19.8)	112.7 (19.0)
BPI-SF item 3 (worst pain), mean (SD)[j]	1.8 (2.4)	1.8 (2.3)
BPI-SF pain severity score, mean (SD)[j]	1.4 (1.8)	1.4 (1.7)

NOTE. Data are No. (%) unless otherwise indicated.
Abbreviations: ADT, androgen deprivation therapy; BPI-SF, Brief Pain Inventory–Short Form; ECOG, Eastern Cooperative Oncology Group; FACT-P, Functional Assessment of Cancer Therapy–Prostate; MX, distant metastasis cannot be assessed (not evaluated by any modality); M0, no distant metastasis; M1, distant metastasis; PSA, prostate-specific antigen; QLQ-PR25, Quality of Life Prostate-Specific questionnaire; SD,standard deviation.
[a]By country regulations, race is not collected in France.
[b]Assessed by independent central review after investigator assessment at study entry.
[c]Defined by CHAARTED criteria6 as presence of metastases involving the viscera, or, in the absence of visceral lesions, four or more bone lesions, one or more of which must be in a bony structure beyond the vertebral column and pelvic bone; some study sites incorrectly reported disease volume information for some patients at the time of randomization, which was corrected during medical review on study entry, resulting in a difference of approximately 20 patients with either high or low disease volume between the treatment arms.
[d]Includes the time since bilateral orchiectomy for patients who had prior bilateral orchiectomy.
[e]The patient had prior ADT; however, the duration of ADT use was unknown.
[f]ITT patients who had received prior ADT (enzalutamide plus ADT, n = 535; placebo plus ADT, n = 514).
[g]Safety-analysis-set patients (enzalutamide plus ADT, n = 572; placebo plus ADT, n = 574).
[h]ITT patients who had a baseline modified QLQ-PR25 urinary symptoms score (enzalutamide plus ADT, n = 539; placebo plus ADT, n = 546). Only items Q31-Q33 from the urinary symptoms subscale were assessed. All items and scale scores of the QLQ-PR25 are linearly transformed to a 0 to 100 scale. A higher score in the urinary symptoms subscale indicates more symptoms.27
[i]ITT patients who had a baseline Functional Assessment of Cancer Therapy–Prostate total score (enzalutamide plus ADT, n = 550; placebo plus ADT, n = 553). The Functional Assessment of Cancer Therapy–Prostate total score ranges from 0 to 156, with the higher scores indicating more favorable quality of life.26
[j]ITT patients who had baseline average Brief Pain Inventory–Short Form worst pain and pain severity scores (enzalutamide plus ADT, n = 542; placebo plus ADT, n = 552). The Brief Pain Inventory–Short Form average score ranges from 0 to 10, with higher scores indicating worse pain.

Source: Armstrong et al., 2019. Copyright 2019 American Society of Clinical Oncology. Reprinted in accordance with CC BY-NC 4.0.[1]

Stenzl et al (2019) performed a post hoc analyses, where patients in the ARCHES Trial were stratified based on disease volume (CHAARTED criteria) and risk (LATITUDE criteria).[27] High disease volume was defined as the presence of visceral metastases OR ≥ 4 bone lesions with ≥1 beyond the vertebral bodies and pelvis and high risk was defined as patients with ≥ 2 high risk features: Gleason score of ≥ 8, ≥ 3 bone lesions or presence of measurable visceral metastases. The baseline characteristics of the post hoc subgroup analysis is presented in Table 7.

Table 7: Baseline characteristics of the patients stratified by CHAARTED criteria and LATITUDE criteria using data from the ARCHES trial

Table 2. Baseline demographics and disease characteristics

Characteristics	ITT population (n=1150)	
	Enzalutamide + ADT (n=574)	Placebo + ADT (n=576)
Median age, years (range)	70.0 (46–92)	70.0 (42–92)
ECOG PS, n (%)		
0	448 (78.0)	443 (76.9)
1	125 (21.8)	133 (23.1)
CHAARTED criteria disease volume,[a] n (%)		
Low	220 (38.3)	203 (35.2)
High	354 (61.7)	373 (64.8)
LATITUDE criteria risk groups, n (%)		
Low risk	275 (47.9)	281 (48.8)
High risk	261 (45.5)	250 (43.4)
M0[b]	34 (5.9)	45 (7.8)
Unknown	4 (0.7)	0
Total Gleason score at initial diagnosis, n (%)		
<8	171 (29.8)	187 (32.5)
⩾8	386 (67.2)	373 (64.8)
Number of cycles of prior docetaxel, n (%)		
0	471 (82.1)	474 (82.3)
1–5	14 (2.4)	11 (1.9)
6	89 (15.5)	91 (15.8)
Previous use of ADT,[c] n (%)		
None	39 (6.8)	61 (10.6)
⩽3 months	414 (72.1)	394 (68.4)
>3 months	121 (21.1)	120 (20.8)
Unknown[d]	0	1 (0.2)
Median duration of prior ADT,[e] months (range)	1.6 (0.03–55.3)	1.6 (0.03–198.8)
Previous use of antiandrogen,[f] n (%)	205 (35.8)	229 (39.9)
Median PSA at study entry,[f,g] ng/mL (range)		
Overall	5.4 (0–4823.5)	5.1 (0–19,000.0)
Low-volume disease	2.38 (0–1006.0)	2.90 (0–649.0)
High-volume disease	9.51 (0–4823.5)	6.42 (0–19,000.0)
Low risk	3.61 (0–4823.5)	4.45 (0–2746.5)
High risk	11.76 (0–4177.0)	6.76 (0–19,000.0)
FACT-P total score,[h] mean (SD)	113.9 (19.8)	112.7 (19.0)

[a]Some study sites incorrectly reported disease-volume information for some patients at the time of randomization, which was corrected during medical review on study entry, resulting in a difference of approximately 20 patients with either high or low disease volume between the treatment arms; [b]Assessed by independent central review after investigator assessment at study entry; [c]Includes the time since bilateral orchiectomy for patients who had prior bilateral orchiectomy; [d]The patient had prior ADT; however, the duration of ADT use was unknown; [e]ITT patients who had received prior ADT (enzalutamide plus ADT, n=535; placebo plus ADT, n=514); [f]Safety analysis set patients (enzalutamide plus ADT, n=572; placebo plus ADT, n=574); [g]PSA level at initial diagnosis of prostate cancer prior to study entry was not collected; [h]ITT patients who had a baseline FACT-P total score (enzalutamide plus ADT, n=550; placebo plus ADT, n=553). The FACT-P total score ranges from 0–156, with the higher scores indicating more favorable quality of life.[10]
ECOG PS=Eastern Cooperative Oncology Group performance status; FACT-P=Functional Assessment of Cancer Therapy–Prostate; ITT=intent to treat; M0, nonmetastatic; PSA=prostate-specific antigen; SD=standard deviation.

Table 3. Patient subgroup distribution at baseline by CHAARTED and LATITUDE criteria

Risk by LATITUDE criteria	Disease volume by CHAARTED criteria	
	Low (n=423)	High (n=727)
Low (n=556), n (%)*		
Overall	292 (27.4)	264 (24.7)
Enzalutamide + ADT	146 (27.2)	129 (24.1)
Placebo + ADT	146 (27.5)	135 (25.4)
High (n=511), n (%)*		
Overall	77 (7.2)	434 (40.7)
Enzalutamide + ADT	48 (9.0)	213 (39.7)
Placebo + ADT	29 (5.5)	221 (41.6)

*The percentages were calculated using the risk group population (overall, N=1067; enzalutamide + ADT, N=536; placebo + ADT, N=531).
ADT=androgen deprivation therapy.

Source: Stenzl et al. poster, ESMO 2019[40]

ENZAMET Trial

Overall, the baseline characteristics were well balanced (Table 8).[3] The median age in the trial was 69 years (enzalutamide: 69.2 [interquartile range (IQR): 63.2 to 74.5] vs NSAA: 69.0 [IQR: 63.6 to 74.5]) and a large proportion of patients had a Gleason score of 8 to 10 (enzalutamide: 60% and NSAA: 57%). ECOG performance status was balanced between the groups with 72.1% and 71.9% of patients having ECOG score of 0 and 26.9% and 26.6% of patients having ECOG score of 1 in the enzalutamide and NSAA groups, respectively. Eleven percent of patients in the enzalutamide group and 12% in the NSAA group had visceral metastases. More than half of the patients in the trial had a high volume of disease (enzalutamide: 52% and NSAA: 53%). Almost 10% of patients in the enzalutamide group (10.3%) and 9.8% in the NSAA group received bone anti-resorptive therapy and most of the patients had 0 to 1 ACE-27 stratum (enzalutamide: 74.6% and NSAA:75.0%). A large proportion of patients had previous LHRHA therapy (enzalutamide: 73% vs NSAA: 74%) and antiandrogen therapy (enzalutamide: 51% vs NSAA: 56%). The majority of patients in the trial had ≥1 bone lesions (enzalutamide: 79.8% vs NSAA: 81.7%) and approximately a third had N1 stage (node positive) disease (enzalutamide: 36.4% vs NSAA: 34.5%). Most of the patients in the trial were recruited from Australia.

[redacted].[4]

[redacted].[4]

[redacted][4](*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Table 8: Baseline characteristics of the patients enrolled in the ENZAMET Trial

Characteristic		Anti-androgen (N=562)	Enzalutamide (N=563)
Age (years)	Mean (SD)	68.8 (8.3)	68.9 (8.1)
	Median (IQR)	69.0 (63.6 to 74.5)	69.2 (63.2 to 74.5)
ECOG Performance Status	0	405 (72.1%)	405 (71.9%)
	1	151 (26.9%)	150 (26.6%)
	2	6 (1.1%)	8 (1.4%)
Country	Australia	321 (57.1%)	324 (57.5%)
	Canada	107 (19.0%)	97 (17.2%)
	Ireland	43 (7.7%)	39 (6.9%)
	New Zealand	19 (3.4%)	20 (3.6%)
	UK	50 (8.9%)	63 (11.2%)
	United States	22 (3.9%)	20 (3.6%)
Planned use of early docetaxel	No	313 (55.7%)	309 (54.9%)
	Yes	249 (44.3%)	254 (45.1%)
Volume of disease	High	297 (52.8%)	291 (51.7%)
	Low	265 (47.2%)	272 (48.3%)
Prior local therapy		235 (41.8%)	238 (42.3%)
Bone anti-resorptive therapy		58 (10.3%)	55 (9.8%)
ACE-27 stratum	0-1	419 (74.6%)	422 (75.0%)
	2-3	143 (25.4%)	141 (25.0%)
Number of bone metastases	1 - 3	165 (29.4%)	161 (28.6%)
	4 or more	294 (52.3%)	288 (51.2%)
	None	103 (18.3%)	114 (20.2%)
Visceral metastases	No	495 (88.1%)	501 (89.0%)
	Yes	67 (11.9%)	62 (11.0%)
	Adrenal	6 (1.1%)	1 (0.2%)
	Liver	11 (2.0%)	13 (2.3%)
	Lung	48 (8.5%)	55 (9.8%)
	Pleura	5 (0.9%)	3 (0.5%)
	Other	4 (0.7%)	0 (0.0%)
T stage*	T0	3 (0.5%)	1 (0.2%)
	T1	30 (5.3%)	23 (4.1%)
	T2	131 (23.3%)	124 (22.0%)
	T3	198 (35.2%)	229 (40.7%)
	T4	60 (10.7%)	56 (9.9%)
	TX	72 (12.8%)	54 (9.6%)
	Unknown	68 (12.1%)	76 (13.5%)

Characteristic		Anti-androgen (N=562)	Enzalutamide (N=563)
N stage*	N0	237 (42.2%)	226 (40.1%)
	N1	194 (34.5%)	205 (36.4%)
	NX	65 (11.6%)	63 (11.2%)
	Unknown	66 (11.7%)	69 (12.3%)
M stage*	M0	157 (27.9%)	155 (27.5%)
	M1	347 (61.7%)	335 (59.5%)
	MX	27 (4.8%)	27 (4.8%)
	Unknown	31 (5.5%)	46 (8.2%)
Months since primary diagnosed	Mean (SD)	23.9 (40.2)	26.9 (45.3)
	Median (IQR)	3.1 (1.7 to 32.7)	2.0 (2.0 to 39.1)
Months since metastases diagnosed	Mean (SD)	3.1 (7.2)	2.9 (6.9)
	Median (IQR)	1.9 (1.0 to 2.8)	1.9 (0.9 to 2.8)
Gleason Score	≤7	163 (29.0%)	152 (27.0%)
	8-10	321 (57.1%)	335 (59.5%)
	Missing	78 (13.9%)	76 (13.5%)
BMI	Mean (SD)	28.1 (4.8)	28.5 (5.0)
	Median (IQR)	27.7 (25.0 to 30.7)	27.8 (25.2 to 31.1)
Prior adjuvant ADT		40 (7.1%)	58 (10.3%)
Prior anti-androgen**		316 (56.2%)	285 (50.6%)
Prior LHRHA**		418 (74.4%)	411 (73.0%)
Bilateral orchiectomy		8 (1.4%)	5 (0.9%)
Prior docetaxel**		83 (14.8%)	95 (16.9%)

* Stage at first diagnosis. ** Commenced within 12 weeks of randomization. Abbreviations: ADT, androgen deprivation therapy; BMI, body mass index; IQR, interquartile range; LHRHA, luteinizing hormone releasing hormone agonist / antagonist; SD, standard deviation.

Source: From NEJM, Davis et al., Enzalutamide with standard first-line therapy in metastatic prostate cancer, 381(2):121-131. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[3]

c) Interventions

ARCHES Trial

Treatment Dosing Schedule

Patients received either 160 mg (given as four 40 mg tablets) oral dose of enzalutamide or a matching placebo.[1] All patients in the trial were also on a background of ADT (either bilateral orchiectomy or LHRH agonist/antagonist).[33] The study treatment was continued until radiographic disease progression (confirmed by ICR), unacceptable toxicity, initiation of an investigational agent or new prostate cancer therapy.[1]

The use of concomitant "anti-resorptive" therapies (i.e., bisphosphonates and denosumab) were prohibited unless they were stabilized for 2 weeks prior to randomization and held constant, as tolerated, throughout study treatment or administered for diagnosis of osteoporosis.[1]

At the 14-Oct-2018 data cut-off, the median duration of exposure was 12.8 months (range: 0.2 to 26.6) in patients who received enzalutamide and 11.6 months (range: 0.2 to 24.6) in patients who received placebo.

Dose modifications, interruptions or reductions

Patients who experienced a treatment-related AE of grade 3 could have their assigned therapy interrupted for one week or until the AE improved to grade 2 or less. These patients could then be restarted at the original dose or a reduced dose (120 mg or 80 mg).[1] Enzalutamide was interrupted during the evaluation of symptoms suspicious of PRES (headache, lethargy, confusion, blindness and other visual and neurological distributions, with or without hypertension).[1]

Concomitant Therapies

The following medications were prohibited within 4 weeks of day 1 and during the study treatment: 5-α reductase inhibitors; estrogens; cyproterone acetate; biologic or other agents with antitumor activity against prostate cancer; systemic glucocorticoids greater than the equivalent of 10 mg per day of prednisone intended for the treatment of prostate cancer; herbal medications that have known hormonal antiprostate cancer activity and/or are known to decrease PSA levels; androgens; investigational agents. Bisphosphonates and denosumab were prohibited unless stabilized for two weeks prior to randomization and were tolerable or they were for osteoporosis.[1]

Concomitant medications were taken by 94.0% of patients during the trial (N=1,077/1,146).[6] The most common concomitant medications were: endocrine therapy (enzalutamide: 92.0% vs placebo: 95.5%) and drugs for treatment of bone diseases (enzalutamide: 0.9% vs placebo: 1.6%).[6] Use of concomitant medications was similar between the active and placebo treatment groups. [6]

ENZAMET Trial

Treatment Dosing Schedule

Patients received either 160 mg (given as four 40 mg tablets) oral dose of enzalutamide or a conventional NSAA (i.e. bicalutamide 50mg daily, nilutamide 150mg daily, or flutamide 250mg three times a day) until disease progression or unacceptable toxicity.[3] The NSAA was selected at the discretion of the treating clinician and cyproterone was not permitted.[3] All patients were on a background of LHRHA or received surgical castration with bilateral orchidectomy at the discretion of the treating clinician. Patients who were treated with a LHRHA could have received either goserelin, leuprorelin, triptorelin, or degarelix or another LHRHA agent. The LHRHA must have been started no earlier than 12 weeks before randomization or within 2 weeks of starting the assigned treatment. Surgical castration should have been performed less than 12 weeks before randomization but orchidectomy was permitted at any time after randomization as long as ADT has been instituted already in accordance with protocol requirements.[3]

At the 28-Feb-2019 data cut-off, the median duration of exposure was 29.5 months (range: 0.1 to 58.4) in the enzalutamide group and 22.1 months (range: 0.0 to 58.6) in the NSAA group. Overall, 25.8% of patients were receiving enzalutamide for at least 36 months (N=145) as compared to 14.3% still receiving NSAA (N=80).[4]

Dose modifications, interruptions or reductions
Patients who experienced a treatment-related AE of grade 3 could have their assigned therapy interrupted. These patients could then be restarted at the original dose or a reduced dose (120 mg/d or 80 mg/d).[3] Enzalutamide could be reduced to 120 mg/d for chronic long-term grade 2 AEs. Dose modifications were also permitted at the approval of the study sponsor.[3]

Concomitant Therapies
The following medications were prohibited during the study treatment: investigational agents; St John's Wort; and grapefruit juice. Patients were permitted to use treatment (or prevention) for: osteoporosis, bone as per clinical guidelines, palliative radiotherapy and use of early docetaxel.[3]

Prior and concomitant therapies were not reported for this interim analysis.

d) Patient Disposition

ARCHES Trial

The patient disposition for the ARCHES trial is presented in Figure 5. A total of 1,150 patients were randomized to receive either enzalutamide (N = 574) or placebo (N = 576).[1] Two patients in the enzalutamide group and two in the placebo group did not receive their assigned therapies.[1]

At the 14-Oct-2018 data cut-off, 76.1% of patients (N = 437) were still receiving enzalutamide and 57.6% of patients were still receiving placebo (N= 332).[1] In the enzalutamide group, 23.5% of patients discontinued their assigned treatment (N = 135) while 42.0% of patients discontinued treatment with placebo (N=242). The most common reasons for discontinuation in the enzalutamide and placebo groups were progressive disease (11.3% vs. 29.7%).

Overall, 12.2% of patients in the enzalutamide group and 14.2% in placebo group had one or more major protocol deviations. The most common major protocol deviation was that patients were entered into the study even though they did not satisfy the entry criteria (enzalutamide: 8.9% and placebo: 8.8%). The most common exclusion criteria violation was that patients may have received any prior pharmacotherapy, radiation therapy or surgery for metastatic prostate cancer (enzalutamide: 2.1% vs. placebo:4.5%). [6] Given, the low number of protocol deviations this should not bias the trial results.

Figure 5: Patient disposition in the ARCHES trial at the 14-Oct-2018 database cut-off

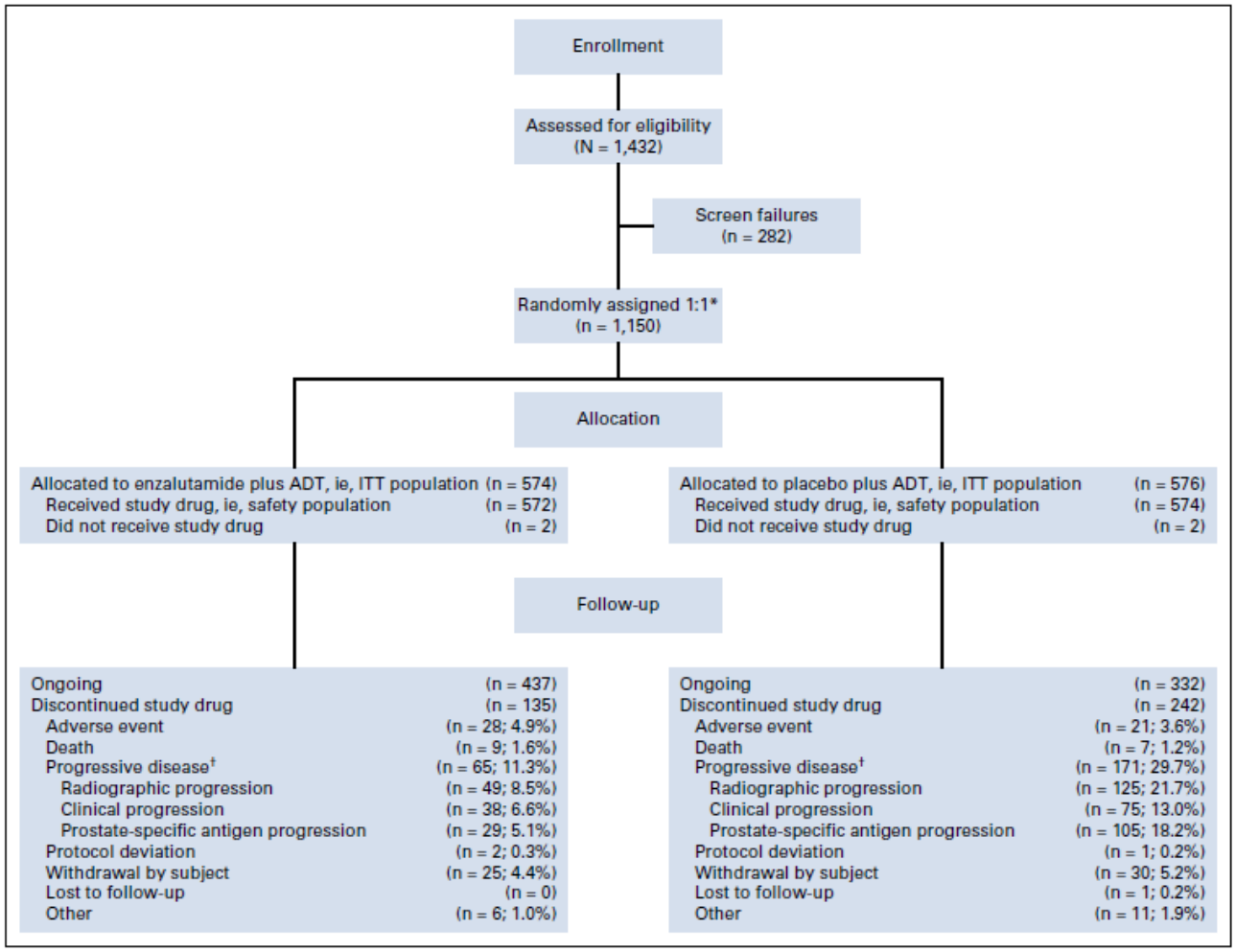


FIG 1. CONSORT diagram. (*) Randomization 1:1 was stratified by volume of disease (low *v* high) and prior docetaxel therapy for prostate cancer (no cycles, one to five cycles, or six cycles); high volume of disease was defined as presence of metastases involving the viscera, or in the absence of visceral lesions, four or more bone lesions, one or more of which must have been in a bony structure beyond the vertebral column and pelvic bone, per CHAARTED (ClinicalTrials.gov identifier: NCT00309985) criteria.[6] (†) Progressive disease types are not mutually exclusive; the same patient may be reported in multiple categories. ADT, androgen deprivation therapy; ITT, intent-to-treat.

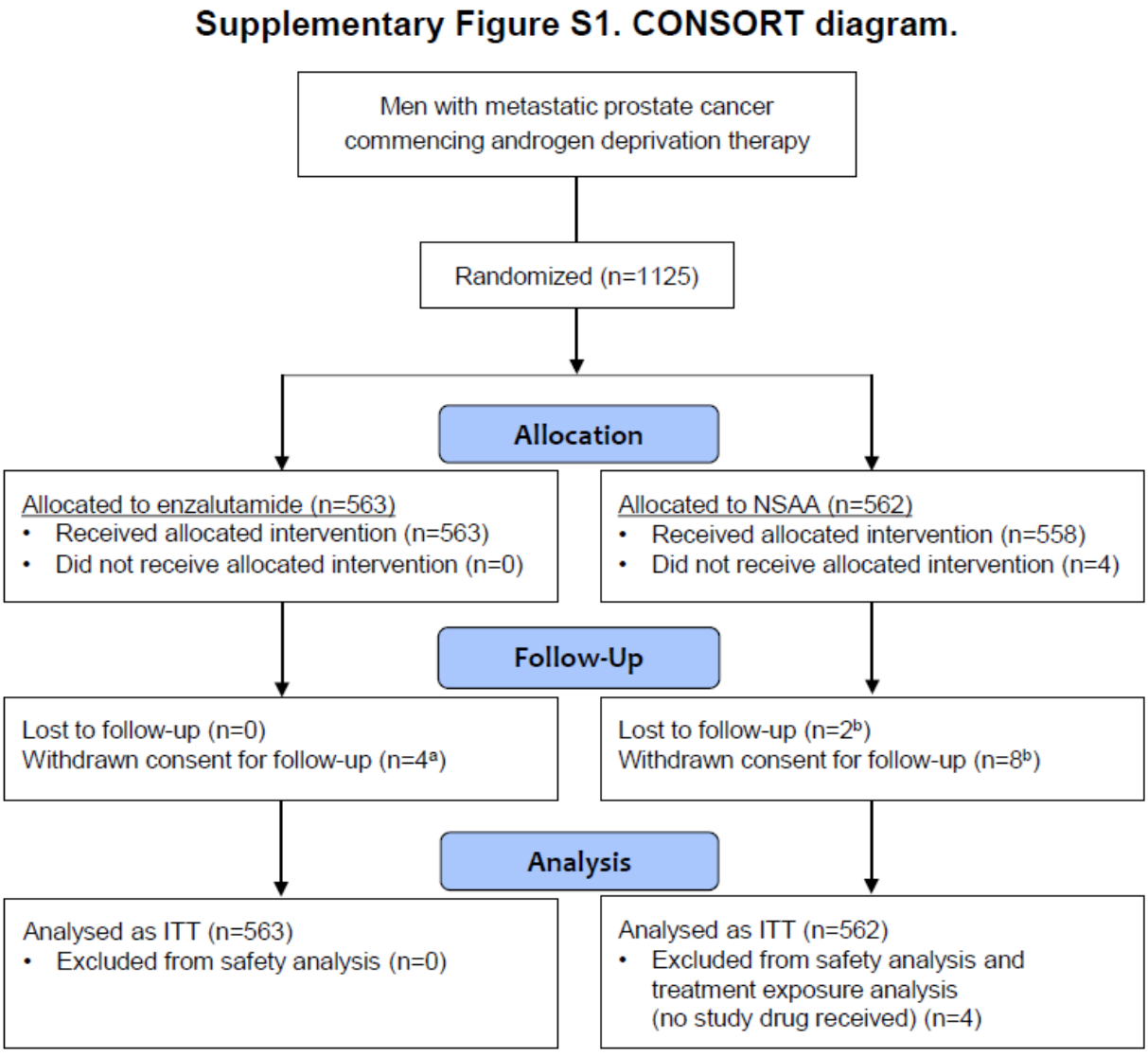
Source: Armstrong et al., 2019. Copyright 2019 American Society of Clinical Oncology. Reprinted in accordance with CC BY-NC 4.0.[1]

ENZAMET Trial

The patient disposition for the ENZAMET trial is presented in Figure 6. A total of 1,125 patients were randomized to receive either enzalutamide (N = 563) or placebo (N = 562).[3] Four patients in the NSAA group did not receive their assigned therapies.

At the database cut-off, 64.3% of patients (N = 362) were still receiving enzalutamide and 35.9% of patients were still receiving NSAA (N= 202).[3] In the enzalutamide group, 35.7% of patients discontinued their assigned treatment (N = 201) while 63.3% of patients discontinued treatment with NSAA (N=356). The most common reason for discontinuation in the enzalutamide and NSAA groups was clinical progressive disease determined by radiographic imaging.

Figure 6: Patient disposition in the ENZAMET trial at the 28-Feb-2019 database cut-off



[a] Median survival follow-up for the 4 enzalutamide patients who withdrew consent was 7.2 months (IQR: 2.0 to 24.4).
[b] Median survival follow-up for the 10 NSAA patients who withdrew consent or were lost to follow-up was 7.7 months (IQR: 0.4 to 12.0). Two of these patients withdrew consent immediately post-randomization.

Source: From NEJM, Davis et al., Enzalutamide with standard first-line therapy in metastatic prostate cancer, 381(2):121-131. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[3]

e) Limitations/Sources of Bias

Overall, the ARCHES Trial was a well-designed RCT and there were no major concerns with the conduct of the trial. The randomization method and sample size were adequate, and a stratified randomization procedure was used based on known prognostic factors to minimize potential imbalances between the study groups that might lead to biased results. The study was double-blinded to minimize bias in the assessment of study outcomes and the efficacy analysis was conducted according to the ITT principal. The study protocol was approved by institutional review boards or independent ethics committees at each study center and

the trial was conducted in accordance with Good Clinical Practice guidelines. However, there are some limitations and potential sources of bias, which include:

- With no active treatment in the control arm, there is a lack of direct comparison to other relevant agents, such as docetaxel, abiraterone acetate in combination with prednisone and apalutamide.

- At the time of the data analysis, OS data was immature (median OS was not reached in either group) making the actual degree of long- term benefit unknown. Follow-up for long-term survival is ongoing and planned when 342 events have occurred. In addition, future analyses of OS may be confounded because patients are allowed enter the open-label of the trial and receive enzalutamide.

- All subgroup analyses used a univariable analysis. Subgroup analyses on subjects with low or high volume of disease or prior docetaxel chemotherapy for prostate cancer were conducted without alpha spending assigned and without adjustment for multiplicity. All the subgroup analyses should be considered exploratory or hypothesis generating due to small sample sizes.

- Patient-reported and HRQoL outcomes were exploratory endpoints in the ARCHES trial and were not included in the statistical hierarchy or adjusted for multiplicity. Furthermore, selection bias over time should be considered when interpreting results of the HRQoL assessment, as the long-term responders tend to be the healthier patients. Overall, interpretation of HRQoL end points is limited. It should be noted that time to deterioration of urinary symptoms was included in the statistical hierarchy.

Overall, the ENZAMET trial was a well-designed RCT and there were no major concerns with the conduct of the trial. The randomization method and sample size were adequate, and a stratified randomization procedure was used based on known prognostic factors to minimize potential imbalances between the study groups that might lead to biased results. The efficacy analysis was conducted according to the ITT principal. The study protocol was approved by institutional review boards or independent ethics committees at each study center and the trial was conducted in accordance with Good Clinical Practice guidelines. However, there are some limitations and potential sources of bias, which include:

- The ENZAMET Trial used an open-label study design. This study design has the potential to bias the outcome results, including: clinical or rPFS, patient reported outcomes and safety. However, bias was minimized by reviewing the imaging reports centrally. It was noted the images themselves were not reviewed centrally, which could increase the risk of detection bias.

- The database cut-off of 28-Feb-2019 represents an interim analysis of the ENZAMET trial. Although the effect of enzalutamide appears to be protective on OS as compared to NSAA, follow-up for long-term survival is ongoing and planned when 470 events have occurred.

- The subgroup analysis comparing the effect of disease burden and early use of docetaxel was conducted due to clinical interest. It should be noted that the trial was neither designed nor powered to reliably analyze the results in these subgroups, and therefore, they should be interpreted with caution.

- To account for the type 1 error associated with all the planned adjusted and subgroup analyses, hypothesis tests were grouped into discrete families, and the p-value was evaluated within each family. [3] However, the effect of enzalutamide as compared to NSAA on PSA PFS and clinical PFS was not adjusted for multiple testing, and therefore, these results should be interpreted with caution.

- Patient-reported and HRQoL outcomes were exploratory endpoints in the ENZAMET trial and were not included in the adjustment for multiplicity. Furthermore, the effect of selection bias should be considered over time because the long-term responders tend to be the healthier patients. Overall, interpretation of HRQoL end points is limited.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

ARCHES TRIAL

Radiographic Progression-Free Survival

rPFS as assessed by ICR was the primary outcome in the ARCHES trial. rPFS was calculated as the time from randomization to the first objective evidence of radiographic disease progression (rPD) as assessed by ICR or death up to 24 weeks after study drug discontinuation, whichever occurred first.1 rPD was defined by RECIST 1.1 for soft tissue disease or the appearance of two or more new bone lesions on a bone scan. The protocol-specified documentation for radiographic evidence of disease progression is shown in Table 9. Deaths were due to any cause within 24 weeks (2 scan cycles) from study drug discontinuation.1 The 24 week cut-off from study drug discontinuation was selected for deaths because it ensures a similar follow-up period as for monitoring of radiographic progression (i.e., two 12-week radiologic assessment cycles post-treatment discontinuation).[1]

Table 9: Protocol-specified Documentation for Radiographic Evidence of Disease Progression

Date Progression Detected (Visit)†	ARCHES-specified Primary Endpoint Definition			PCWG2 Criteria for Primary Endpoint
	Criteria for Progression	Criteria for Confirmation of Progression (Requirement and Timing)	Criteria for Documentation of Disease Progression on Confirmatory Scan	
Week 13	Bone lesions: ≥ 2 new lesions compared to baseline bone scan	Timing: ≥ 6 weeks after progression identified or at week 25 visit	≥ 2 new bone lesions on bone scan compared to week 13 scan (≥ 4 new lesions compared to baseline bone scan)†	No change
	Soft tissue lesions: progressive disease on CT or MRI by RECIST 1.1	No confirmatory scan required for soft tissue disease progression	Not applicable	Not applicable
Week 25 or Later	Bone lesions: ≥ 2 new lesions on bone scan **compared to best response on treatment** (i.e., smallest number bone lesions on bone scan during treatment period)	No confirmatory scan required	Not applicable	Bone lesions: ≥ 2 new lesions on bone scan **compared to baseline** (or compared to week 13 in case of ≥ 2 new bone lesions appearing at week 13)
	Soft tissue lesions: progressive disease on CT or MRI by RECIST 1.1	No confirmatory scan required for soft tissue disease progression	Not applicable	Not applicable

CT: computed tomography; MRI: magnetic resonance imaging; PCWG2: Prostate Cancer Clinical Trials Working Group 2; RECIST 1.1: Response Evaluation Criteria in Solid Tumours version 1.1.

† Progression detected by bone scan at an unscheduled visit prior to week 25 required the same criteria for documentation of disease progression as week 13 with a confirmatory scan at least 6 weeks later or at the next scheduled scan.

Source: Armstrong et al., 2019. Copyright 2019 American Society of Clinical Oncology. Reprinted in accordance with CC BY-NC 4.0.[1]

Kaplan-Meier analyses were used to obtain the estimates of rPFS for each treatment group with corresponding 95% confidence intervals (CIs). Differences in treatment effect were tested using a stratified log-rank p-value. Stratified Cox proportional hazards models were used to estimate the HRs with their corresponding 95% CIs.[1]

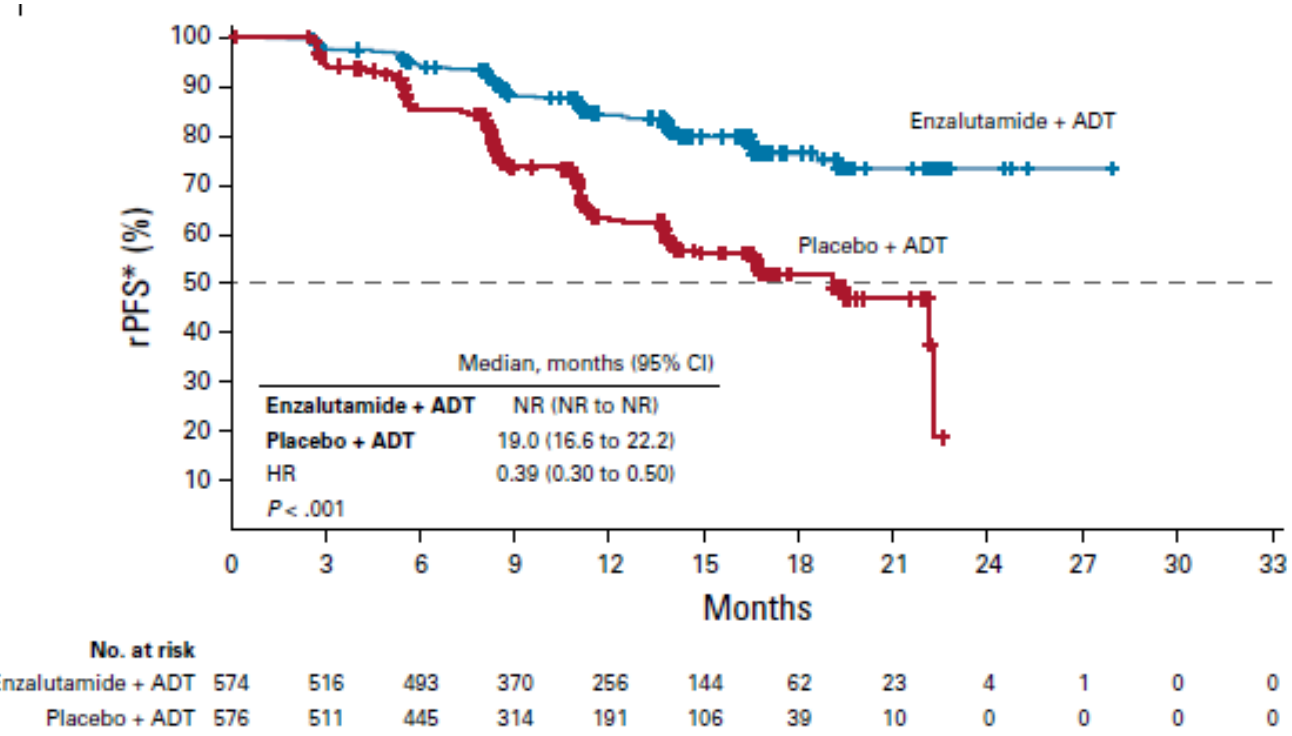
To assess the robustness of the rPFS effect estimates, several prespecified sensitivity analyses were performed, which include:[1]

- Impact of study drug discontinuation as an additional event
- Impact of new antineoplastic therapy and occurrence of a SSE as additional events
- Impact of all deaths (with no time limit) as events
- Impact of rPD documented between per protocol visits
- 'Missing' data impact - Last scan not documented as NE
- Missing' data impact - Absence of 2 consecutive scans
- Censoring rPD on competing risks: new antineoplastic therapy and occurrence of a SSE

- ‘Missing’ data impact and censoring rPD on competing risks: new antineoplastic therapy, occurrence of a SSE, and study drug discontinuation in M1 patients (patients identified from the baseline assessments made by ICR) based on ICR assessments
- rPFS in M1 patients (patients identified from the baseline assessments made by ICR)
- Impact of rPD documented by investigators
- Impact of rPD according to PCWG2 criteria and documented by investigators
- Impact of rPD according to PCWG2 criteria and documented by ICR

At the 14-Oct-2018 data cut-off, 13.8% of patients in the enzalutamide group had radiographic progression and 2.1% died within 24 weeks of treatment discontinuation in the absence of radiographic progression (N=79 and N=12) relative to 32.6% and 2.3% of patients in the placebo group (N =188 and N=13).[1] The median rPFS was not reached with enzalutamide plus ADT (95% CI, not reached to not reached) versus 19.0 months (95% CI: 16.6 to 22.2 months) with placebo plus ADT.[1] The Kaplan-Meier curves are presented in Figure 7. Enzalutamide was associated with a significant improvement in rPFS as compared to placebo (HR: 0.39, 95% CI: 0.30 to 0.50; p-value ≤0.001).[1] More patients in the enzalutamide group were censored as compared to the placebo group (84.49% vs. 65.63%, respectively).[2] most common reason for censoring in both groups was due to no rPFS event before the data cut-off (enzalutamide: 92.37% and placebo: 92.06%).[2] Similar estimates were ob[served for all the prespecified sensitivity analyses.

Figure 7: rPFS Kaplan-Meier curves using data from the ARCHES trial at the 14-Oct-2018 cut-off date



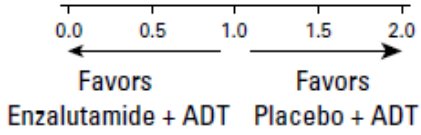
ADT = androgen-deprivation therapy; CI = confidence interval; ENZA = enzalutamide; HR = hazard ratio; mHSPC = metastatic hormone-sensitive prostate cancer; mo = month; NR = not reached; PBO = placebo; rPFS = radiographic progression-free survival.
Source: Armstrong et al., 2019. Copyright 2019 American Society of Clinical Oncology. Reprinted in accordance with CC BY-NC 4.0.[1]

Armstrong et al (2019) performed prespecified subgroup analyses testing the effect of enzalutamide versus placebo on rPFS (Figure 8). The estimates from the subgroups were consistent with the overall estimates of rPFS, including disease volume and prior

docetaxel chemotherapy.[1] However, the subgroup analysis did not adjust for stratification factors or multiplicity and should be interpreted with caution.

Figure 8: Subgroup analysis of rPFS using data from the ARCHES trial at the 14-Oct-2018 cut-off date

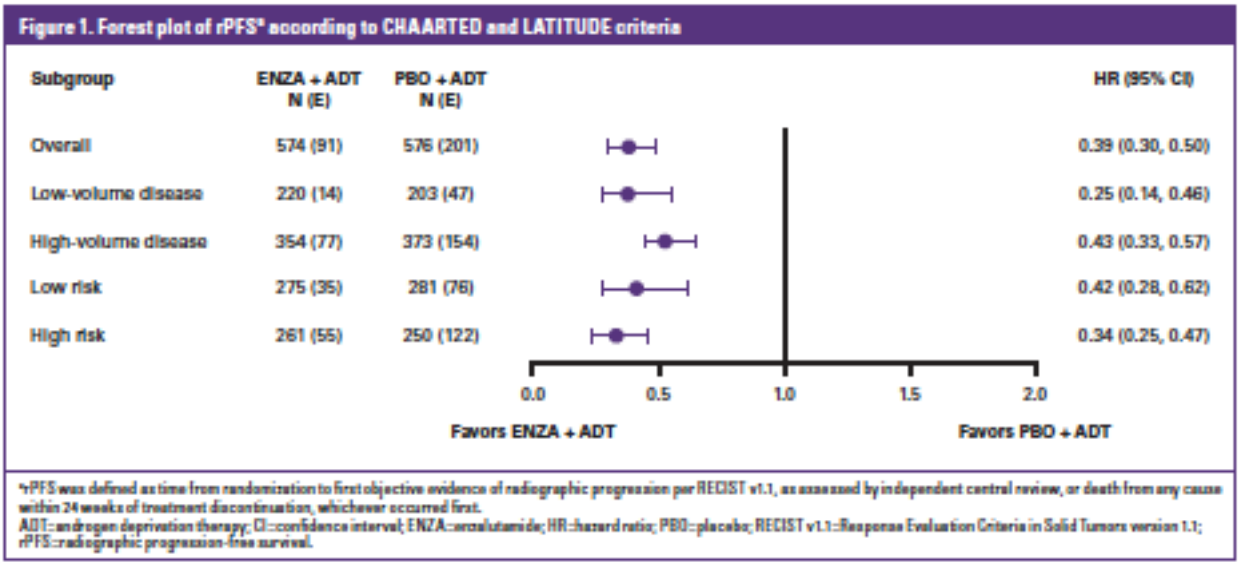
Subgroup	Enzalutamide + ADT No. of patients (E)	Placebo + ADT No. of patients (E)	HR (95% CI)[†]
All patients	574 (91)	576 (201)	0.39 (0.30 to 0.50)
Age < 65 years	148 (21)	152 (58)	0.29 (0.17 to 0.47)
Age ≥ 65 years	426 (70)	424 (143)	0.44 (0.33 to 0.58)
Geographic region – Europe	341 (55)	344 (122)	0.42 (0.31 to 0.58)
Geographic region – North America	86 (14)	77 (29)	0.30 (0.16 to 0.57)
Geographic region – rest of the world	147 (22)	155 (50)	0.40 (0.24 to 0.66)
ECOG status 0 at baseline	448 (67)	443 (146)	0.38 (0.29 to 0.51)
ECOG status 1 at baseline	125 (24)	133 (55)	0.43 (0.27 to 0.70)
Gleason score at initial diagnosis < 8	171 (21)	187 (47)	0.42 (0.25 to 0.70)
Gleason score at initial diagnosis ≥ 8	386 (65)	373 (151)	0.36 (0.27 to 0.48)
Disease localization at baseline – bone only	268 (35)	245 (82)	0.33 (0.22 to 0.49)
Disease localization at baseline – soft tissue only	51 (5)	45 (12)	0.42 (0.15 to 1.20)
Disease localization at baseline – bone and soft tissue	217 (50)	241 (104)	0.42 (0.30 to 0.60)
Baseline PSA value at or below overall median	293 (41)	305 (96)	0.38 (0.26 to 0.54)
Baseline PSA value above overall median	279 (50)	269 (104)	0.41 (0.30 to 0.58)
Low volume of disease	220 (14)	203 (47)	0.25 (0.14 to 0.46)
High volume of disease	354 (77)	373 (154)	0.43 (0.33 to 0.57)
No prior docetaxel therapy	471 (70)	474 (166)	0.37 (0.28 to 0.49)
Prior docetaxel therapy	103 (21)	102 (35)	0.52 (0.30 to 0.89)
Previous use of ADT or orchiectomy	535 (88)	515 (179)	0.41 (0.32 to 0.53)
No previous use of ADT or orchiectomy	39 (3)	61 (22)	0.19 (0.06 to 0.62)



ADT = androgen-deprivation therapy; CI = confidence interval; E = number of events; ECOG = Eastern Cooperative Oncology Group; No. = number; PSA = prostate-specific antigen.
Source: Armstrong et al., 2019. Copyright 2019 American Society of Clinical Oncology. Reprinted in accordance with CC BY-NC 4.0.[1]

Stenzl et al (2019) performed a post hoc analyses, where patients in the ARCHES Trial were stratified based on disease volume (CHAARTED criteria) and risk (LATITUDE criteria).[27] The estimates from the subgroups were consistent with the overall estimates of rPFS (Figure 9).

Figure 9: Forest plots of the subgroup analysis for rPFS stratified by CHAARTED criteria and LATITUDE criteria using data from the ARCHES trial at the 14-Oct-2018 cut-off date



Source: Stenzl et al. poster, ESMO 2019[40]

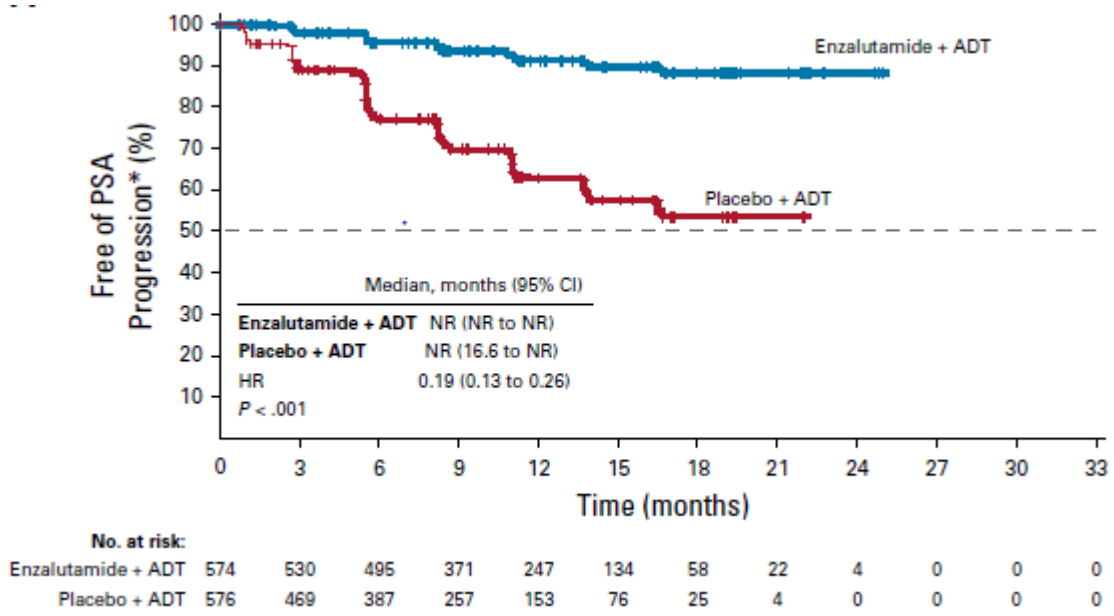
Time to PSA Progression

Time to PSA progression was a key secondary outcome in the ARCHES trial. It was defined as the time from randomization to a ≥ 25% increase and an absolute increase of ≥ 2 ng/mL above the nadir (i.e. lowest PSA value observed postbaseline or at baseline), which was confirmed by a second consecutive value at least 3 weeks later.[1] Only PSA assessments taken prior to the start of a new antineoplastic therapy were used.[1] The statistical analysis was similar to the primary analysis for rPFS; however, a prespecified 2-sided significance level of 0.01 was used for the analysis.[1]

In the enzalutamide group, 7.8% of patients had PSA progression (N=45) relative to 32.8% of patients in the placebo group (N=189).[2] The Kaplan-Meier curves are presented in Figure 10. The median time to PSA progression was not reached for both treatment groups. Enzalutamide was associated with a significant improvement in the time to PSA progression as compared to placebo (HR: 0.19, 95% CI: 0.13 to 0.26; p-value < 0.001).[1]

Stenzl et al (2019) performed a post hoc analyses, where patients in the ARCHES Trial were stratified based on disease volume (CHAARTED criteria) and risk (LATITUDE criteria).[27] The estimates from the subgroups were consistent with the overall estimates of time to PSA progression.

Figure 10: Time to PSA progression Kaplan-Meier curves using data from the ARCHES trial at the 14-Oct-2018 cut-off date



ADT = androgen-deprivation therapy; CI = confidence interval; ENZA = enzalutamide; HR = hazard ratio; mHSPC = metastatic hormone-sensitive prostate cancer; mo = months; NR = not reached; PBO = placebo; PSA = prostate-specific antigen.
Source: Armstrong et al., 2019. Copyright 2019 American Society of Clinical Oncology. Reprinted in accordance with CC BY-NC 4.0.[1]

Time to initiation of new antineoplastic therapy

Time to initiation of new antineoplastic therapy was a key secondary outcome and it was defined as the time from randomization to the initiation of antineoplastic therapy (including cytotoxic and hormonal therapies) subsequent to the study treatments.[1] The statistical analysis was similar to the primary analysis for rPFS; however, a prespecified 2-sided significance level of 0.01 was used for the analysis.

Eight percent of patients in the enzalutamide group initiated a new antineoplastic therapy (N=46) compared to 23.1% of patients in the placebo group (N=133).[2] The median time to initiating a new antineoplastic therapy was 30.2 months (95% CI: NR) for enzalutamide and was not reached for placebo.[1] Enzalutamide was associated with a significant improvement in the time to initiation of new antineoplastic therapy as compared to placebo (HR: 0.28, 95% CI: 0.20 to 0.40; p-value < 0.0001).[1]

Table 10 shows a summary of the first new antineoplastic prostate cancer therapies patients received in the ARCHES trial. Overall, 23.1% of those in the placebo group started a new therapy as compared to 8.0% in the enzalutamide group.[1] The majority of patients in the enzalutamide group received another type of therapy (30.4%) followed by abiraterone (28.3%) and docetaxel (23.9%).[1] In contrast, more patients in placebo group received docetaxel (39.1%) followed by abiraterone (21.1%) or enzalutamide (21.1%).[1]

Stenzl et al (2019) performed a post hoc analyses, where patients in the ARCHES Trial were stratified based on disease volume (CHAARTED criteria) and risk (LATITUDE criteria).[27] The estimates from the subgroups were consistent with the overall estimates of time to initiating a new antineoplastic therapy.

Table 10: Summary of the first new antineoplastic prostate cancer therapy in the ARCHES Trial

First New Anti-Neoplastic Prostate Cancer Therapy	Enzalutamide + ADT	Placebo + ADT
Overall, n	46	133
Docetaxel, n (%)	11 (24)	52 (39)
Abiraterone, n (%)	13 (28)	28 (21)
Enzalutamide, n (%)	4 (9)	28 (21)
Bicalutamide, n (%)	4 (9)	12 (9)
Other, n (%	14 (30)	15 (11)

ADT = androgen-deprivation therapy; n = number of patients. Note: Percentages based on overall number of patients who required subsequent anti-neoplastic therapy.
Source: Armstrong et al., 2019. Copyright 2019 American Society of Clinical Oncology. Reprinted in accordance with CC BY-NC 4.0.[1]

Rate of PSA Decline to < 0.2 ng/mL

Rate of PSA Decline to < 0.2 ng/mL was a key secondary outcome and it was defined as the proportion of patients with detectable (≥ 0.2 ng/mL) PSA at baseline, which become undetectable (< 0.2 ng/mL) during study treatment.[1] Only PSA assessments taken were taken prior to the initiation of new antineoplastic therapy were analyzed.[1] Differences in response rates were compared using a stratified Cochran-Mantel-Haenszel score test with a significance level of 0.01.[1]

Patients in the enzalutamide group had a higher PSA undetectable rate was compared to those in the placebo group (68.1% [N=348] vs 17.6% [N=89]; p <0.001).[1] The absolute difference between the two groups was 50.5% (95% CI: 45.3, 55.7; P < 0.0001).[2]

Stenzl et al (2019) performed a post hoc analyses, where patients in the ARCHES Trial were stratified based on disease volume (CHAARTED criteria) and risk (LATITUDE criteria).[27] The estimates from the subgroups were consistent with the overall estimates of PSA progression.

Objective Response Rate
ORR was a key secondary outcome and it was defined as the proportion of patients who had measurable disease at baseline and had a complete or partial response in their soft tissue as assessed by ICR using RECIST 1.1.[1] Differences in response rates were compared using a stratified Cochran-Mantel-Haenszel score test with a significance level of 0.01.

ORR was significantly higher for enzalutamide (ORR: 83.1% [N=147]) as compared to placebo (ORR: 63.7% [N=116]) (p-value for difference ≤ 0.001).[1]

Stenzl et al (2019) performed a post hoc analyses, where patients in the ARCHES Trial were stratified based on disease volume (CHAARTED criteria) and risk (LATITUDE criteria).[27] The estimates from the subgroups were consistent with the overall estimates of ORR.

Time to Deterioration of Urinary Symptoms

Time to deterioration of urinary symptoms was defined as the time from randomization to the first deterioration in urinary symptoms. This was classified as an increase in urinary symptoms scores, using the modified urinary symptoms scale derived from a selected subset of symptoms from the QLQ-PR25 questionnaire module by ≥ 50% of the standard deviation observed in the modified urinary symptoms scale at baseline.[1] The statistical analysis was similar to the primary analysis for rPFS; however, a prespecified 2-sided significance level of 0.01 was used for the analysis.[1]

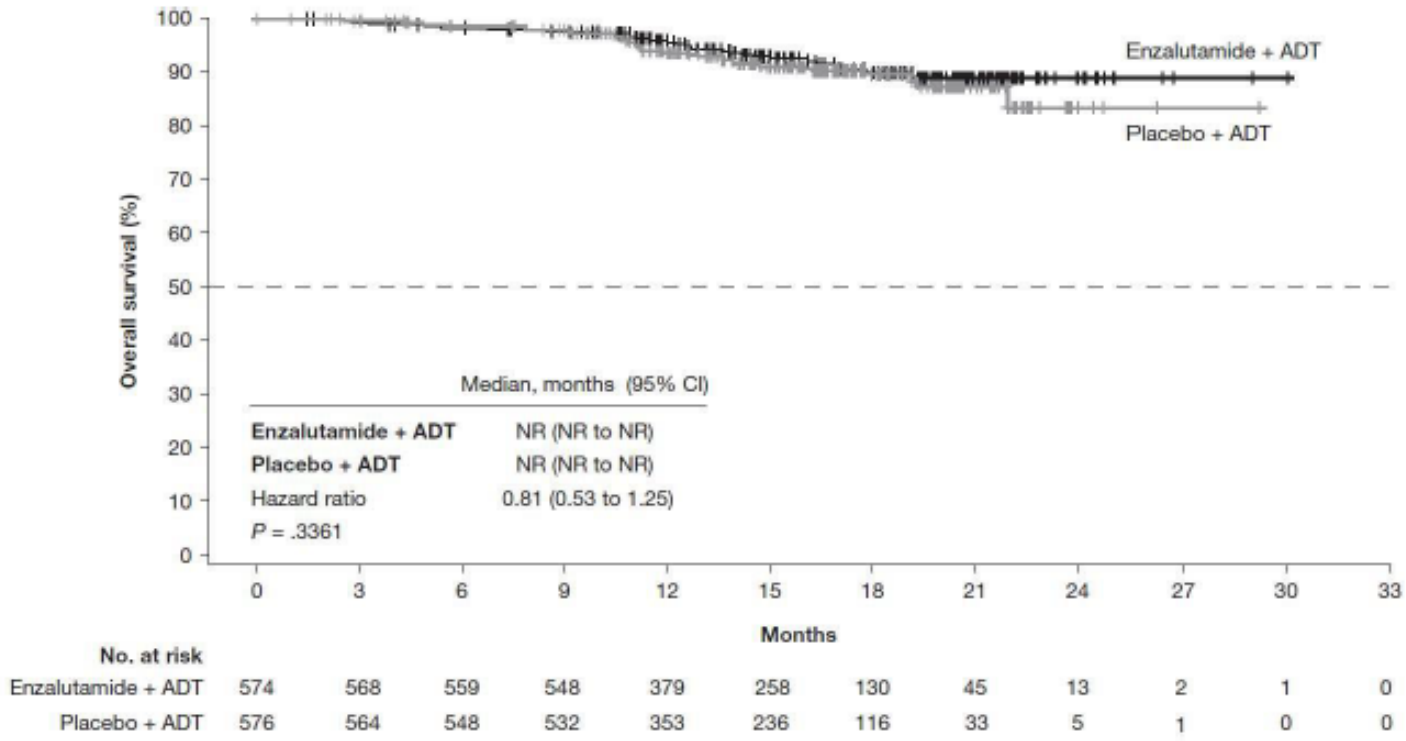
Almost a third of all patients in the enzalutamide and placebo groups experienced a deterioration of urinary symptoms (32.06% [N=184] vs 34.9% [N=201], respectively).[2] The median time to deterioration of urinary symptoms was not reached in the enzalutamide group and it was 16.8 months (95% CI: 14.06 to NR) in the placebo group.[2] There was no difference between the treatment groups for time to deterioration of urinary symptoms (HR: 0.88, 95% CI: 0.72 to 1.08; p-value = 0.2162).[1]

Overall Survival

OS was a secondary outcome in the ARCHES trial. It was defined as the time from randomization to death due to any cause.[1] The 14-Oct-2018 data cut-off represents an interim analysis for OS. The statistical analysis was similar to the primary analysis for rPFS. An O'Brien Fleming alpha spending function was used to determine the stopping boundaries for the interim analysis and control the two-sided α of 0.04.[1] At the data cut-off, only 24.6% (N=84) of the total 342 events that were required for the final OS analysis, and thus, the stopping boundary for OS at the interim analysis was 0.0000054, which would imply that the OS results may be immature.[2]

In the enzalutamide group, 6.8% of patients died (N=39) while 7.8% of patients in the placebo group died (N=45).[2] The median OS was not reached for both treatment groups. The Kaplan-Meier curves are presented in Figure 11. There was no difference between the two treatment groups on the effect of OS (HR: 0.81, 95% CI: 0.53 to 1.25; p-value = 0.3361).[1] The results of OS are immature and should be interpreted with caution. The post hoc analysis by Stenzl et al (2019) showed that the estimates of OS were immature.[27]

Figure 11: OS Kaplan-Meier curves using data from the ARCHES trial at the 14-Oct-2018 cut-off date



ADT = androgen-deprivation therapy; CI = confidence interval; ENZA = enzalutamide; HR = hazard ratio; NR = not reached; OS = overall survival; PBO = placebo.
Source: Armstrong et al., 2019. Copyright 2019 American Society of Clinical Oncology. Reprinted in accordance with CC BY-NC 4.0.[1]

Time to First Symptomatic Skeletal Related Events
Time to first SSE was an exploratory outcome and it was defined as the time from randomization to the occurrence of a first SSE. SEE was measured as a radiation or surgery to bone, clinically apparent pathologic bone fracture, or spinal cord compression.[1] The statistical analysis was similar to the primary analysis for rPFS.

In the enzalutamide group, 5.4% of patients had an SSE (N=31) while 9.7% of patients in the placebo group died (N=56).[2] The median time to first SSE was not reached for both treatment groups. Enzalutamide was associated with a significant improvement in the time to first SSE as compared to placebo (HR: 0.52, 95% CI: 0.33 to 0.80; p-value = 0.0026).[1]

Stenzl et al (2019) performed a post hoc analyses, where patients in the ARCHES Trial were stratified based on disease volume (CHAARTED criteria) and risk (LATITUDE criteria).[27] The estimates from the subgroups were consistent with the overall estimates of time to SSE.

Time to Castration Resistance
Time to castration-resistance was an exploratory outcome and it was defined as the time from randomization to the first castration-resistant event, which was classified as radiographic disease progression, PSA progression, or SSE with castrate levels of testosterone [< 50 ng/dL], whichever occurs first.[1] The statistical analysis was similar to the primary analysis for rPFS.

More patients in the placebo group had castration-resistance 44.6% (N=257) than in the enzalutamide group (15.7% [N=90]).[2] The median time to castration-resistance was 13.8 months in the placebo group and it was not reached for the enzalutamide group.[2] Enzalutamide was associated with a significant improvement in the time to castration-resistance as compared to placebo (HR: 0.28, 95% CI: 0.22 to 0.36; p-value < 0.001).[1]

Stenzl et al (2019) performed a post hoc analyses, where patients in the ARCHES Trial were stratified based on disease volume (CHAARTED criteria) and risk (LATITUDE criteria).[27] The estimates from the subgroups were consistent with the overall estimates of time to castration resistance.

Time to deterioration of QoL
Time to deterioration of QoL was an exploratory outcome and it was defined as the time from randomization to a 10-point reduction on the FACT-P total score.[1] The statistical analysis was similar to the primary analysis for rPFS.

Almost half of all patients in the enzalutamide and placebo groups had a 10-point reduction on the FACT-P total score (48.8% [N=280] vs 47.6% [N=274]).[2] The median time to deterioration of QoL was 11.3 months (95% CI: 11.0 to 13.8) in the enzalutamide group and it was 11.1 (95% CI: 8.5 to 13.8) in the placebo group.[1] There was no difference between the two treatment groups on the effect of time to deterioration of QoL (HR: 0.96, 95% CI: 0.81 to 1.14; p-value = 0.6548).[1]

Time to pain progression
Time to pain progression was an exploratory outcome and it was defined as the time from randomization to an increase of ≥ 30% on the pain severity score from baseline using the BPI-SF.[1] The statistical analysis was similar to the primary analysis for rPFS.

More than half of all patients in the enzalutamide and placebo groups had an increase of ≥ 30% on the pain severity score (56.5% [N=324] vs 57.1% [N=329]).[2] The median time to pain progression was 8.3 months (95% CI: 8.3 to 10.9) in the enzalutamide group and 8.3 (95% CI: 5.7 to 8.4) in the placebo group.[2] There was no difference between the two treatment groups on the effect of time to pain progression (HR: 0.92, 95% CI: 0.78 to 1.07; p-value = 0.2715).[1]

ENZAMET Trial

Overall Survival
OS was the primary outcome in the trial and it was defined as time from randomization to death due to any cause.[3] Kaplan-Meier analyses were used to obtain the estimates of OS for each treatment group with corresponding 95% CIs. Differences in treatment effect were tested using an unstratified log-rank p-value. Unadjusted Cox proportional hazards models were used to estimate the HRs with their corresponding 95% CIs.

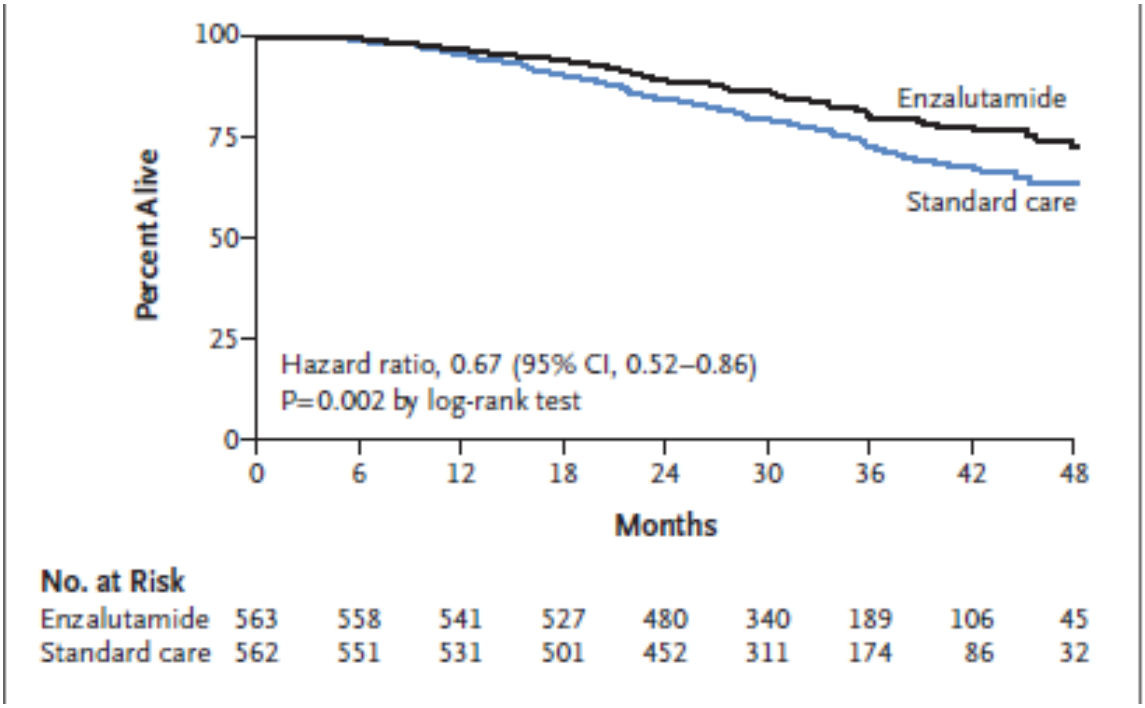
Subgroup analyses were prespecified for the following factors: Gleason score (≤7 vs. 8 to 10); age (<70 years or ≥70 years); ECOG performance status (0 vs. 1 or 2); the presence of visceral metastases in the lung, liver, or other organs; volume of disease (high or low); planned use of early docetaxel; planned use of anti-resorptive therapy; ACE-27 comorbidity score (0 or 1 vs. 2 or 3); prior treatment (radiation, surgery, or neither); and geographic region (Australia or New Zealand vs. North America vs. Ireland or United

Kingdom).[3] In addition, the effect of enzalutamide on disease burden and use of early docetaxel was considered as a subgroup of clinical interest.[3]

It was noted by the Sponsor that the subgroup of patients without planned use of docetaxel use most closely aligns with the ARCHES population; however, this subgroup analysis was not individually prespecified for testing with alpha-control.[4]

At the 28-Feb-2018 data cut-off, 18.1% of patients died (N=102) in the enzalutamide group compared to 25.4% of patients in the placebo group (N=143).[3] The median OS was not reached for both treatment groups. The Kaplan-Meier curves are presented in Figure 12. Treatment with enzalutamide was associated with a significantly improved OS as compared to the NSAA group (HR: 0.67, 95% CI: 0.52 to 0.86; p-value = 0.002).[3] The survival rate at three-years was 80% (N=94) in the enzalutamide group and 72% (N=130) in the NSAA group.[3]

Figure 12: OS Kaplan-Meier curves using data from the ENZAMET Trial at the 28-Feb-2019 cut-off date



CI = confidence interval; HR = hazard ratio; NSAA = non-steroidal anti-androgen. Source: Davis et al. (2019).
Source: From NEJM, Davis et al., Enzalutamide with standard first-line therapy in metastatic prostate cancer, 381(2):121-131. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[3]

The subgroup analyses for OS are presented in Figure 13. The protective effect of enzalutamide on OS was observed in the pre-specified subgroups, which included: age, ECOG performance status, Gleason score at initial diagnosis, volume of disease, planned early use of docetaxel and ACE-27 scores. Overall, the subgroup analysis results were consistent with the ITT results. However, after adjusting for multiply testing, there were no significant differences among the subgroups.

Figure 13: Subgroup analysis for OS using data from the ENZAMET Trial at the 28-Feb-2019 cut-off date

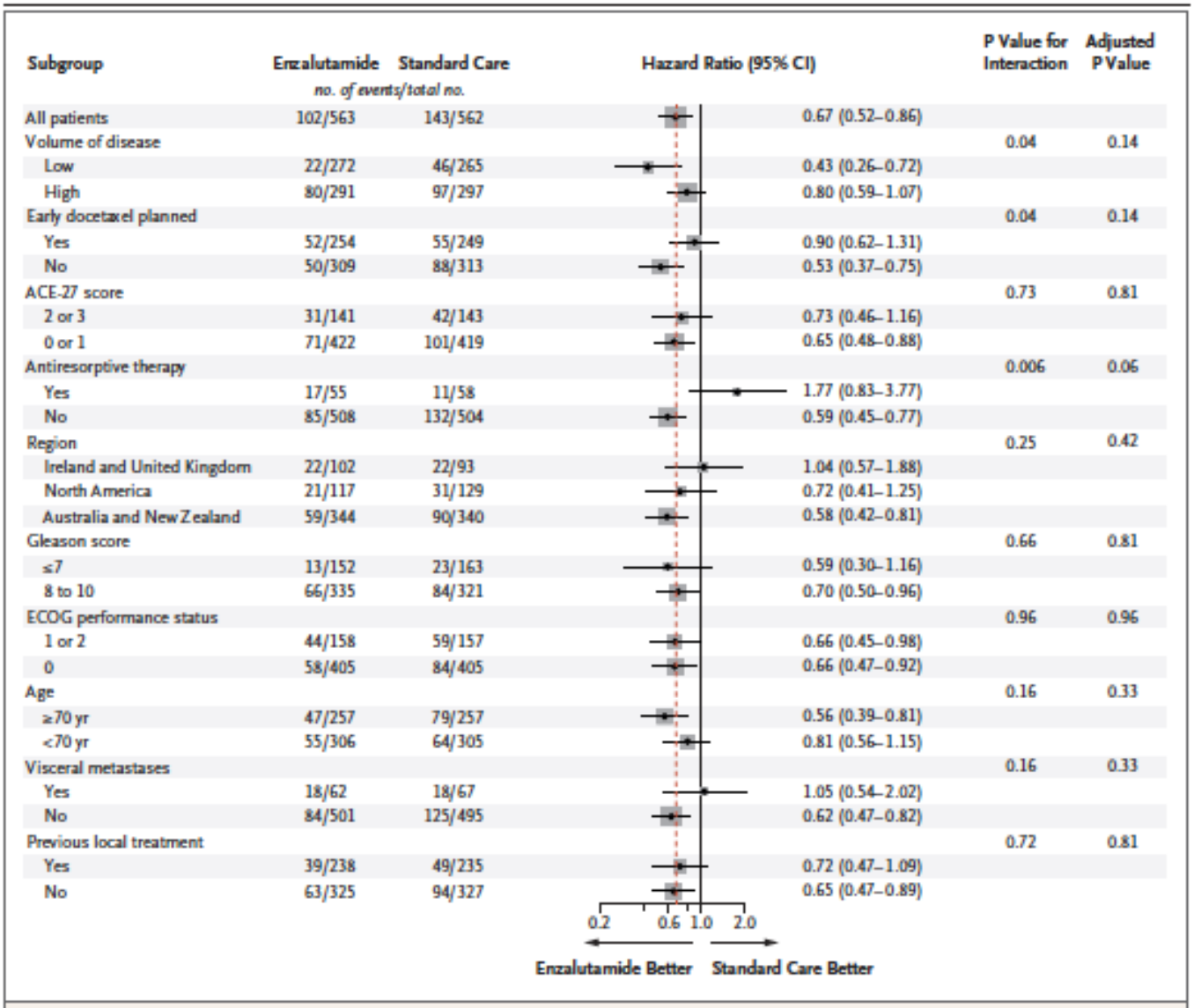


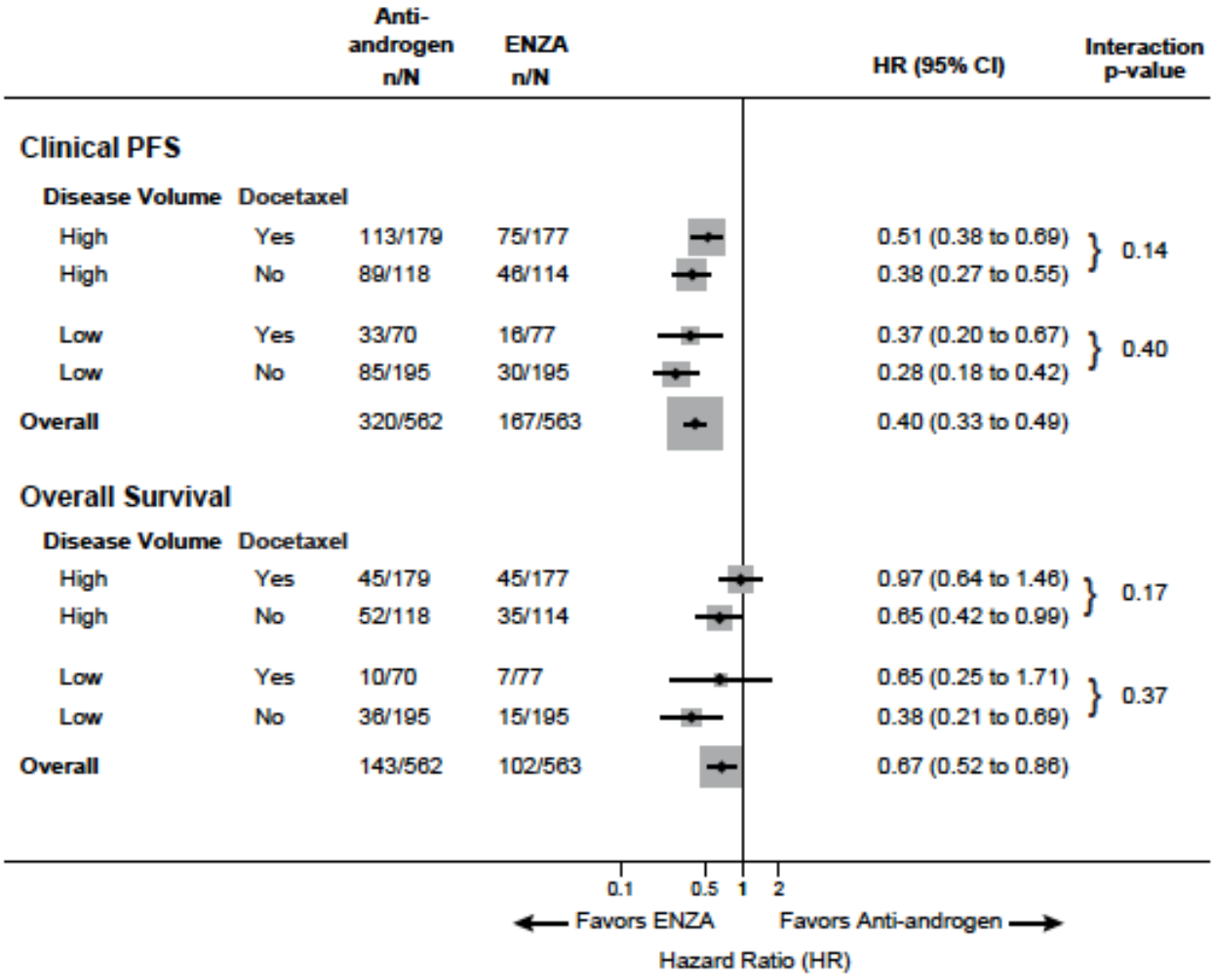
Figure 2. Subgroup Analysis of Overall Survival.

Shown are the results of subgroup analysis of overall survival in 10 key subgroups of patients in the enzalutamide group and the standard-care group. Hazard ratios and 95% confidence intervals are provided. The size of the gray shaded boxes is proportional to the number of events in the subgroup. The dashed vertical line indicates the overall hazard ratio in all the patients. Scores on the Eastern Cooperative Oncology Group (ECOG) performance-status scale range from 0 (no disability) to 5 (death). Scores on the Adult Comorbidity Evaluation 27 (ACE-27) are 0 (none) or 1 (mild) vs. 2 (moderate) or 3 (severe).

Source: From NEJM, Davis et al., Enzalutamide with standard first-line therapy in metastatic prostate cancer, 381(2):121-131. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[3]

The subgroup assessing the effect of disease burden and use of early docetaxel on enzalutamide and OS was identified as a subgroup of clinical interest (Figure 14). There did not appear to be a significant difference between these subgroups; however, there were a small number of OS events.

Figure 14: Subgroup analysis for OS comparing disease burden and use of docetaxel using data from the ENZAMET Trial at the 28-Feb-2019 cut-off date



Source: From NEJM, Davis et al., Enzalutamide with standard first-line therapy in metastatic prostate cancer, 381(2):121-131. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[3]

Based on the protocol, patients who discontinued their assigned therapies could receive a subsequent therapy at the discretion of the treating clinician.[3] The type of subsequent therapies for those who died of prostate cancer are presented in Table 11.[3] The most common types of subsequent therapies for the enzalutamide group were: docetaxel (33.0%), no treatment (31.8%) and abiraterone acetate that was combined with prednisone or prednisolone (30.7%).[3] In contrast, the most common types of subsequent therapies for the placebo group were: enzalutamide (45.2%), abiraterone acetate that was combined with prednisone or prednisolone (35.7%), docetaxel (34.8%) and cabazitaxel (30.4%).[3]

Table 11: Subsequent anticancer therapies for patients who died in the ENZAMET Trial

Participants who Died of Prostate Cancer

Therapy	Anti-androgen (N=115)	Enzalutamide (N=88)
Enzalutamide	52 (45.2%)	0 (0%)
Abiraterone acetate*	41 (35.7%)	27 (30.7%)
Other novel antiandrogen	1 (0.9%)	1 (1.1%)
Docetaxel	40 (34.8%)	29 (33.0%)
Cabazitaxel	35 (30.4%)	19 (21.6%)
Other chemotherapy	13 (11.3%)	14 (15.9%)
Immune checkpoint inhibitor	1 (0.9%)	5 (5.7%)
Lutetium-177 PSMA	1 (0.9%)	3 (3.4%)
PARP inhibitor	4 (3.5%)	1 (1.1%)
Radium-223 dichloride	7 (6.1%)	9 (10.2%)
Sipuleucel-T	0 (0%)	0 (0%)
No treatment	13 (11.3%)	28 (31.8%)

Note: These treatments were given after a progression event in all four cases where patient or physician preference was listed as the reason.
* Abiraterone acetate was combined with prednisone or prednisolone.
Abbreviations: PARP, poly-ADP ribose polymerase; PSMA, prostate-specific membrane antigen ligand.
Source: From NEJM, Davis et al., Enzalutamide with standard first-line therapy in metastatic prostate cancer, 381(2):121-131. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[3]

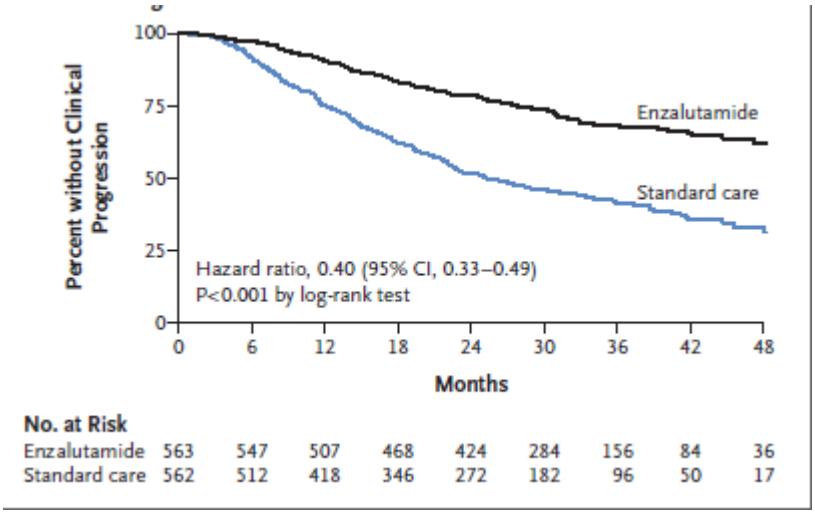
Clinical PFS

Clinical PFS was a secondary outcome in the trial and it was defined as time from randomization to first evidence of disease progression or death from any cause, whichever occurs first, or the date of last known follow-up without clinical progression.[3] Clinical progression was defined as progression on imaging (PCWG2 criteria for bone lesions and RECIST 1.1 for soft tissue lesions), development of symptoms attributable to cancer progression or initiation of other anticancer treatment for prostate cancer.[3] The statistical analysis was similar to the primary analysis for OS.

At the cut-off, 29.1% of patients had progression or died (N=167) compared to 56.9% of patients in the placebo group (N=320).[3] [redacted].[7] (*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

The Kaplan-Meier curves are presented in Figure 15. The rate at three-years was 68% in the enzalutamide group and 41% in the NSAA group.[3] Treatment with enzalutamide was associated with a significantly improved clinical PFS as compared to the NSAA group (HR: 0.40, 95% CI: 0.33 to 0.49; p-value < 0.001).[3] The effect of enzalutamide on clinical PFS remained significant after adjusting for multiple testing.[3]

Figure 15: Clinical PFS Kaplan-Meier curves using data from the ENZAMET Trial at the 28-Feb-2019 cut-off date



CI = confidence interval; HR = hazard ratio; NSAA = non-steroidal anti-androgen.
Source: From NEJM, Davis et al., Enzalutamide with standard first-line therapy in metastatic prostate cancer, 381(2):121-131. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[3]

Based on the protocol, patients who discontinued their assigned therapies could receive a subsequent therapy at the discretion of the treating clinician.[3] The type of subsequent therapies for those who had clinical PFS is presented in Table 12. The most common types of subsequent therapies for the enzalutamide group were: no treatment (32.9%), abiraterone acetate that was combined with prednisone or prednisolone (27.5%) and docetaxel (26.9%).[3] In contrast, the most common types of subsequent therapies for the placebo group were: enzalutamide (44.1%), abiraterone acetate that was combined with prednisone or prednisolone (35.3%) and docetaxel (21.6%).[3]

Table 12: Subsequent anticancer therapies for patients who discontinued treatment in the ENZAMET Trial

Participants with Clinical Progression-Free Survival Endpoint		
Therapy	**Anti-androgen (N=320)**	**Enzalutamide (N=167)**
Enzalutamide	141 (44.1%)	0 (0%)
Abiraterone acetate*	113 (35.3%)	46 (27.5%)
Other novel antiandrogen	2 (0.6%)	1 (0.6%)
Docetaxel	69 (21.6%)	45 (26.9%)
Cabazitaxel	64 (20.0%)	34 (20.4%)
Other chemotherapy	20 (6.3%)	22 (13.2%)
Immune checkpoint inhibitor	6 (1.9%)	10 (6.0%)
Lutetium-177 PSMA	4 (1.3%)	6 (3.6%)
PARP inhibitor	11 (3.4%)	4 (2.4%)
Radium-223 dichloride	22 (6.9%)	14 (8.4%)
Sipuleucel-T	2 (0.6%)	0 (0%)
No treatment yet	49 (15.3%)	55 (32.9%)

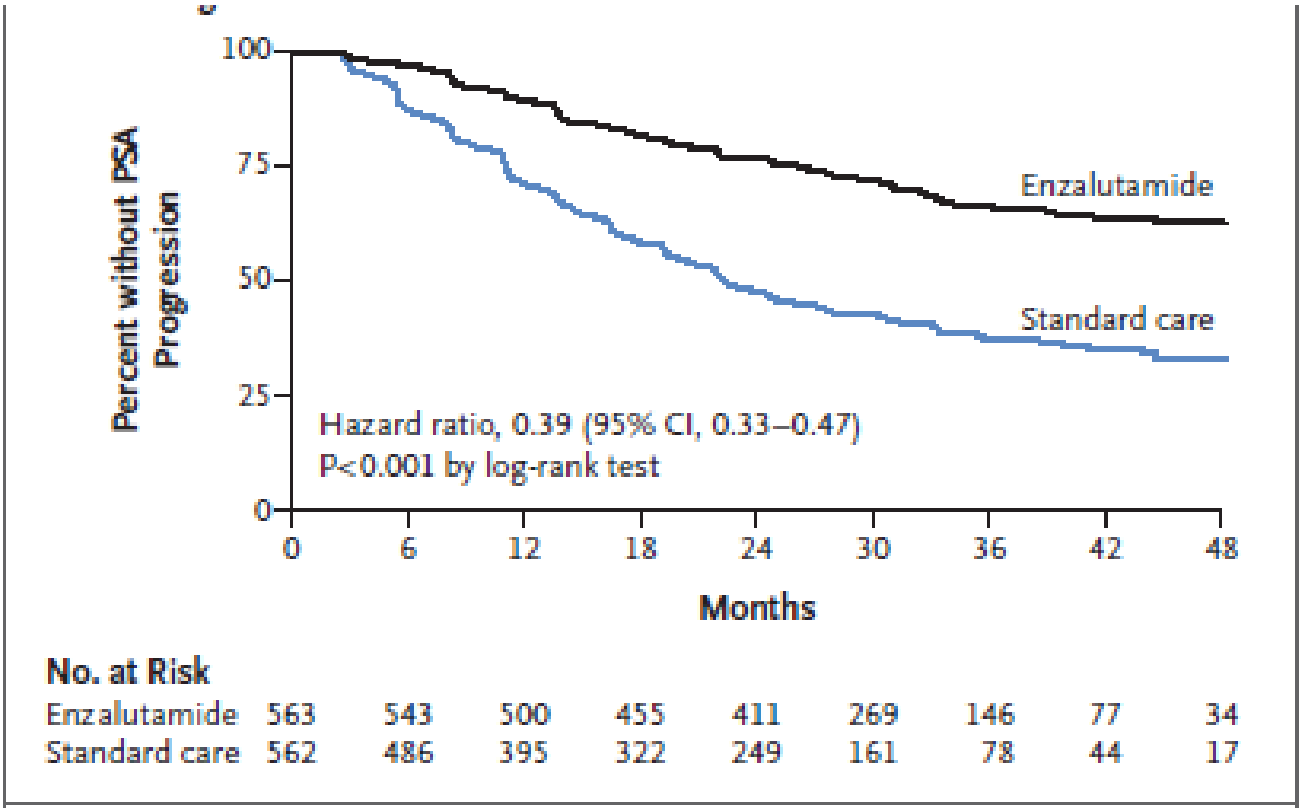
Note: These treatments were given after a progression event in all four cases where patient or physician preference was listed as the reason.
* Abiraterone acetate was combined with prednisone or prednisolone.
Abbreviations: PARP, poly-ADP ribose polymerase; PSMA, prostate-specific membrane antigen ligand.
Source: From NEJM, Davis et al., Enzalutamide with standard first-line therapy in metastatic prostate cancer, 381(2):121-131. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[3]

PSA PFS

PSA PFS was a secondary outcome in the trial and it was defined as time from randomization to first evidence of PSA progression, clinical progression, or death from any cause, whichever occurs first, or the date of last PSA test without PSA progression.[3] PSA progression is classified as a rise in PSA by more than 25% AND more than 2ng/mL above the nadir (lowest PSA point), which was reconfirmed by performing a repeat PSA test at least 3 weeks later.[3] Clinical progression was defined as progression on imaging (PCWG2 criteria for bone lesions and RECIST 1.1 for soft tissue lesions), development of symptoms attributable to cancer progression or initiation of other anticancer treatment for prostate cancer.[3] The statistical analysis was similar to the primary analysis for OS.

At the 28-Feb-2019 database cut-off, 30.9% of patients had progression or died (N=174) compared to 59.3% of patients in the placebo group (N=333).[3] The median PSA PFS was not reached for the enzalutamide group and it was [redacted] in the placebo group.[7](*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).* The Kaplan-Meier curves are presented in Figure 16. The rate at three-years was 67% in the enzalutamide group and 37% in the NSAA group.[3] Treatment with enzalutamide was associated with a longer PSA PFS as compared to the NSAA group (HR: 0.39, 95% CI: 0.33 to 0.47; p-value < 0.001).[3]

Figure 16: PSA PFS Kaplan-Meier curves using data from the ENZAMET Trial at the 28-Feb-2019 cut-off date



CI = confidence interval; HR = hazard ratio; PSA = prostate-specific antigen; NSAA = non-steroidal anti-androgen.

Source: From NEJM, Davis et al., Enzalutamide with standard first-line therapy in metastatic prostate cancer, 381(2):121-131. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[3]

Quality of Life

ARCHES Trial

In the ARCHES trial, HRQoL was measured using the BPI-SF, FACT-P, QLQ-PR25 and EQ-5D-5L.[8,9] The MID for the BPI-SF Item 3 (worst pain) and the BPI-SF pain severity score was ≥2-point change from baseline and it was ≥1-point change from baseline for the BPI-SF pain inference score.[9] The MID for the FACT-P total score was 10. In the absence of established thresholds, the threshold to define deterioration for the QLQ-PR25 instrument was based on distribution-based and anchor-based analyses.[9] The threshold for the following QLQ-PR25 items were: 12.68 for modified urinary symptoms, 9.04 for urinary symptoms, 33.33 for incontinence aids, 8.33 for bowel symptoms/function, 5.80 for hormonal treatment-related symptoms, 16.67 for sexual activity and 10.91 for sexual functioning.[9] The MID was 7 for the EQ-5D-5L visual analog scale.[9]

PRO instruments were measured at baseline, week 13, and every 12 weeks during the study until disease progression.[9] In the trial, the completion rates were calculated at each visit among patients who were expected to have PRO assessments based on a minimum requirement for scoring of at least one scale with non-missing values. Longitudinal changes from baseline to week 73 were assessed using mean scores and mixed-model repeated measures and were adjusted for baseline PRO score, volume of disease, and prior docetaxel therapy. This time point was chosen to minimize the impact of missing data given that the median rPFS for the

placebo group was 20 months.[7] It should be noted that the HRQoL analysis was not included in the testing hierarchy, and therefore, no adjustments were made for type 1 error.

Stenzl et al (2020) reported that the completion rates were high for all questions completed at week 73 (87% to 88%).[9] Here, completion rates were based on the number of patients remaining on study and so available to be assessed at each time point.

The change in least-squares mean for PRO scores at week 73 using a mixed-model for repeated measures are presented in Table 13. The BPI-SF item 3 (pain at its worst [in the last 24 hours]) and FACT-P total scores remained stable over time. In addition, the mean scores for pain severity and pain interference, as measured by the BPI-SF remained stable during the study. The authors also commented that there were no statistical differences from baseline to week 73 for the BPI-SF score, any of the FACT-P subscales, or the EQ-5D-5L.[9] However, there was a significant difference for the FACT-P PWB score, which favored placebo over enzalutamide (difference: –1.02 [95% CI: –1.90 to –0.13]) but there was no clinically meaningful difference.[9]

Table 13: Change in least-squares mean for PRO scores at week 73 (mixed-model for repeated measures).

Instrument[a]	Least-squares mean (SE)		TD at week 73
	ENZA + ADT	PBO + ADT	(95% CI)
EORTC QLQ-PR25 scores[b]			
Modified urinary symptoms	−2.22 (1.84)	−1.18 (2.01)	−1.04 (−6.20, 4.11)
Urinary symptoms	−0.56 (1.30)	−0.02 (1.42)	−0.54 (−4.19, 3.11)
Bowel symptoms/function	0.92 (0.73)	0.59 (0.79)	0.33 (−1.72, 2.38)
Treatment-related symptoms	7.08 (1.00)	4.61 (1.09)	2.46 (−0.35, 5.27)
Incontinence aids[c]	−4.08 (3.22)	3.99 (3.04)	−8.07 (−16.44, 0.30)
Sexual functioning	−3.07 (4.91)	−16.67 (9.30)	13.59 (−7.86, 35.1)
Sexual activity	−2.45 (1.61)	−4.87 (1.74)	2.42 (−2.12, 6.95)
FACT scores[c]			
FACT-P total	−3.17 (1.30)	−1.71 (1.42)	−1.47 (−5.12, 2.18)
Physical wellbeing	−1.42 (0.32)	−0.40 (0.34)	−1.02 (−1.90, −0.13)*
Functional wellbeing	−0.41 (0.40)	−0.15 (0.43)	−0.26 (−1.37, 0.85)
Emotional wellbeing	−0.30 (0.28)	0.06 (0.31)	−0.36 (−1.16, 0.44)
Social wellbeing	0.47 (0.35)	−0.37 (0.38)	0.84 (−0.12, 1.80)
Prostate cancer subscale	−1.01 (0.47)	−0.50 (0.52)	−0.51 (−1.84, 0.81)
Prostate cancer subscale-pain	−1.01 (0.29)	−0.56 (0.32)	−0.45 (−1.29, 0.38)
FACT Advanced Prostate Symptom Index	−0.77 (0.37)	−0.01 (0.40)	−0.76 (−1.79, 0.27)
Trial outcome index	−3.15 (0.98)	−1.28 (1.07)	−1.88 (−4.62, 0.87)
FACT-General	−1.94 (0.95)	−1.08 (1.04)	−0.86 (−3.54, 1.82)
BPI-SF scores[b]			
Worst pain (item 3)	0.54 (0.19)	0.33 (0.20)	0.21 (−0.32, 0.73)
Severity	0.49 (0.15)	0.38 (0.16)	0.11 (−0.30, 0.52)
Interference	0.71 (0.15)	0.58 (0.17)	0.14 (−0.29, 0.57)
EQ-5D-5L scores[c]			
Visual analogue scale	0.28 (1.16)	0.19 (1.27)	0.10 (−3.14, 3.33)

ADT = androgen deprivation therapy; BPI-SF = Brief Pain Inventory Short Form; CI = confidence interval; ENZA = enzalutamide; EORTC QLQ-PR25 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Prostate 25; EQ-5D-5 L = EuroQoL 5-Dimensions, 5-Levels; FACT = Functional Assessment of Cancer Therapy; FACT-P = FACT-Prostate; PBO = placebo; PRO = patient-reported outcome; SE = standard error; TD = treatment difference for ENZA versus PBO.

* $p = 0.024$ from the mixed-model repeated measures analyses.

[a] For BPI-SF scores and EORTC QLQ-PR25 bowel symptoms and function, hormonal treatment–related symptoms, and urinary symptoms scores, a positive change from baseline value indicates worsening of symptoms. For FACT-P scores and EQ-VAS, a positive change from baseline value indicates improvement. Therefore, a negative number for the least-squares mean difference at week 73 favours ENZA + ADT over PBO + ADT for BPI-SF scores and bowel symptoms and function, hormonal treatment–related symptoms, and urinary symptoms and problems, whereas a positive number favours ENZA + ADT over PBO + ADT for FACT-P scores and EQ-VAS.

[b] A positive change from baseline indicates worsening of symptoms.

[c] A positive change from baseline indicates improvement of symptoms.

Source: Stenzl et al. 2020. Copyright 2020 Elsevier. Reprinted in accordance with CC BY-NC 4.0.[9]

ENZAMET Trial

In the ENZAMET trial, HRQoL was assessed using the QLQ-C30, QLQ-PR25 and the EQ-5D-5L instruments. Only data from the QLQ-C30 instrument will be reported. The Sponsor noted that the results for the QLQ-PR25 and the EQ-5D-5L instruments have not yet been reported by ANZUP.[7]

Stockler et al (2019) reported the effect of HRQoL as a composite endpoint.[10] The a priori definition was the earliest of death, clinical progression, cessation of study treatment, or a 10 point worsening from baseline on scales from 0 to 100 for QLQ-C30 domains: Physical Function, Cognitive Function, Fatigue, and Global Health and Quality of Life. PRO instruments were measured at baseline, week 4 and 12, and every 12 weeks during the study until clinical progression.[10] In the trial, the completion rates were adjusted for

study attrition and were calculated at each visit among patients who were expected to have PRO assessments.[10] Longitudinal changes from baseline to Year 3 were assessed using differences in least squares means with mixed model for repeated measures.

Stockler et al (2019) reported that the completion rates for the QLQ-C30 ranged from 94% at week 12 to 78% at week 156 in the 1,016 men with a baseline assessment.[10] There was no significant difference between the two treatment groups for the QLQ-C30 Global Health (difference: -2.07 [95% -5.98 to 1.84]) and the MID was not met (Table 14).[7]

Table 14: QLQ-C30 Global Health and QoL change from baseline and last-square mean difference at Week 156 (Year 3)

(Non-Disclosable information was used in this CADTH Guidance Report and the Sponsor requested this clinical information not be disclosed pursuant to the CADTH Disclosure of Information Guidelines. This information will remain redacted until notification by the Sponsor that it can be publicly disclosed).

Source: Checkpoint Response[7]

Harms Outcomes

ARCHES Trial

The safety set in the ARCHES trial consisted of patients who had received at least one dose of the study treatment.[1] There was a total of 1,146 patients in the safety set, with 572 patients in the enzalutamide group and 574 patients in the placebo group.[1] At the 14-Oct-2018 data cut-off, the median duration of therapy was 12.8 months (range: 0.2 to 26.6) in the enzalutamide group and 11.6 months (range: 0.2 to 24.6) in the placebo group.[1]

Overall, 7.2% of patients in the enzalutamide group and 5.2% in the placebo group discontinued their assigned therapies due to an AE.[1] Only 4.4% of patients in the enzalutamide group had an AE that led to a to dose reduction as compared to 1.9% of patients in the placebo group (Table 15).[2]

Table 15: Overview of the treatment-emergent adverse events and deaths in the ARCHES Trial

	Enzalutamide+ADT (n = 572)		Placebo+ADT (n = 574)	
	n (%)	#E	n (%)	#E
Any TEAE	487 (85.1)	2475	493 (85.9)	2221
NCI-CTC Grade 3 and 4 TEAEs	135 (23.6)	231	142 (24.7)	225
Drug-related† TEAEs	303 (53.0)	856	268 (46.7)	624
Serious TEAEs‡	104 (18.2)	189	112 (19.5)	185
Drug-related† Serious TEAEs‡	22 (3.8)	34	16 (2.8)	23
TEAEs Leading to Death	14 (2.4)	18	10 (1.7)	11
Drug-related† TEAEs Leading to Death	0	0	1 (0.2)	1
TEAEs Leading to Permanent Discontinuation of Study Drug	41 (7.2)	50	30 (5.2)	37
Drug-related† TEAEs Leading to Permanent Discontinuation of Study Drug	16 (2.8)	19	12 (2.1)	15
TEAEs Leading to Dose Reduction	25 (4.4)	38	11 (1.9)	13
Deaths§	39 (6.8)	NA	45 (7.8)	NA

Data cutoff date: 14 Oct 2018

All randomized patients who received at least 1 dose of study drug (safety population).

A TEAE was defined as an AE that occurred or worsened at any time from the first study drug intake up to the date of end of treatment plus 30 days, study discontinuation or the start of new antineoplastic therapy, whichever occurred first. AE grading was based on NCI-CTCAE v4.03.

ADT: androgen deprivation therapy; AE: adverse event; #E: number of events; NA: not applicable; NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; SAE: serious adverse event; TEAE: treatment-emergent adverse event.

† Possible or probable, as assessed by the investigator, or records where relationship was missing.

‡ Included SAEs upgraded by the sponsor based on review of the sponsor's list of Always Serious terms, if any upgrade was done.

§ All reported deaths after the first study drug administration.

Source: End-of-Text Table 12.6.1.1

Source: ARCHES trial synopsis, 2019[2]

Treatment-emergent adverse events (TEAEs) of any grade were reported in most patients in the trial (enzalutamide: 85.1% and 85.9%) (Table 16).[2] The most frequently reported TEAEs reported in ≥5% of patients were hot flashes (enzalutamide: 27.1% vs placebo: 22.3%), fatigue (19.6% vs 15.3%), arthralgia (12.2% vs 10.6%) and back pain (7.5% vs 10.8%).[2] The most frequently reported AE of special interest were musculoskeletal events (enzalutamide: 26.4% vs placebo: 27.7%) and fatigue (24.1% vs 19.5%).[1] Fractures of all grades occurred in 6.5% and 4.2% of patients in the enzalutamide and placebo groups, respectively.[2] Convulsion (i.e., seizure) occurred in 0.3% of patients in each group.[2] Grade 3 and 4 TEAEs were similar for both treatment groups (enzalutamide: 23.6% and 24.7%).[2]

Table 16: Treatment-emergent adverse events reported in at least 5% of patients in the ARCHES Trial

MedDRA v21.0 Preferred Term	Overall Incidence, n (%)	
	Enzalutamide+ADT (n = 572)	Placebo+ADT (n = 574)
Overall	**487 (85.1)**	**493 (85.9)**
Hot flush	155 (27.1)	128 (22.3)
Fatigue	112 (19.6)	88 (15.3)
Arthralgia	70 (12.2)	61 (10.6)
Back pain	43 (7.5)	62 (10.8)
Weight increased	35 (6.1)	44 (7.7)
Hypertension	46 (8.0)	32 (5.6)
Diarrhoea	34 (5.9)	33 (5.7)
Oedema peripheral	29 (5.1)	38 (6.6)
Nausea	37 (6.5)	29 (5.1)
Asthenia	31 (5.4)	28 (4.9)
Constipation	28 (4.9)	31 (5.4)
Musculoskeletal pain	36 (6.3)	23 (4.0)
Dizziness	29 (5.1)	20 (3.5)

Data cutoff date: 14 Oct 2018

All randomized patients who received at least 1 dose of study drug (safety population).

ADT: androgen deprivation therapy.

Source: End-of-Text Table 12.6.1.16

Source: ARCHES trial synopsis, 2019[2]

Slightly more patients in the placebo group had a serious TEAE as compared to the enzalutamide group (19.5% vs 18.2%) (Table 17).[2] The most frequently reported serious TEAEs reported in ≥0.5% of patients treated with enzalutamide was malignant neoplasm progression (enzalutamide: 1.0% vs placebo: 0.5%) and it was spinal cord compression for those treated with placebo (enzalutamide: 0.5% vs placebo: 1.0%).[2] In the enzalutamide group, 3.8% of patients had a drug-related SAE relative to 2.8% in the placebo group.[1]

Overall, 2.4% of patients in the enzalutamide group and 1.7% in the placebo group died.[1] None of the deaths in the enzalutamide group were related to the therapy as assessed by the investigator. However, one death in the placebo group (i.e., general physical health deterioration) was reported to be related to the therapy.[1]

Table 17: Serious treatment-emergent adverse events reported in at least 0.5% of patients in the ARCHES Trial

MedDRA v21.0 Preferred Term	Overall Incidence, n (%)	
	Enzalutamide+ADT (n = 572)	Placebo+ADT (n = 574)
Overall	**104 (18.2)**	**112 (19.5)**
Anaemia	4 (0.7)	3 (0.5)
Atrial fibrillation	2 (0.3)	4 (0.7)
Sepsis	3 (0.5)	3 (0.5)
Fall	3 (0.5)	2 (0.3)
Malignant neoplasm progression	6 (1.0)	3 (0.5)
Basal cell carcinoma	4 (0.7)	4 (0.7)
Spinal cord compression	3 (0.5)	6 (1.0)
Syncope	3 (0.5)	0
Hydronephrosis	4 (0.7)	3 (0.5)
Urinary retention	3 (0.5)	4 (0.7)
Haematuria	4 (0.7)	2 (0.3)
Pulmonary embolism	3 (0.5)	3 (0.5)

Data cutoff date: 14 Oct 2018

All randomized patients who received at least 1 dose of study drug (safety population).

Sorting order: ascending order by system organ class code and descending by the number of patients of total group by preferred term. In case of ties ascending order by preferred term code is applied.

ADT: androgen deprivation therapy.

Source: End-of-Text Table 12.6.1.7

Source: ARCHES trial synopsis, 2019[2]

ENZAMET Trial

The safety set in the ENZAMET trial consisted of patients who had received at least one dose of the study treatment.[3] There was a total of 1,121 patients in the safety set, with 563 patients in the enzalutamide group and 558 patients in the NSAA.[3] At the 28-Feb-2019 data cut-off, the median duration of therapy was 29.5 months (range: 0.1 to 58.4) in the enzalutamide group and 22.1 months (range: 0.0 to 58.6) in the NSAA group.[3]

More patients in the enzalutamide group discontinued study treatment due to an adverse event than the NSAA group (N=33 vs N=14). It was noted that six patients in the enzalutamide group discontinued due to a seizure while one patient discontinued enzalutamide because of clinical progression before the seizure event.[3]

More patients in the NSAA group had grade 1 and grade 2 AEs (7% and 14% (grade 1) and 36% and 41% (grade 2) in the enzalutamide and NSAA groups, respectively).[3] However, more patients in the enzalutamide group had a grade ≥ 3 AE than the NSAA group (57.0% vs 43.0%) (Table 18).[3] The number of patients with febrile neutropenia events, reported in at least 2% of patients, was similar across the treatment groups (N enzalutamide: 37 and N NSAA: 32) and all but 2 of these events occurred during early docetaxel treatment (67 out of 69).[3] [redacted].[3]

[redacted].[4]

(*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).* In addition, fatigue of any grade

and grade 2 (clinically significant) was reported in more patients in the enzalutamide group than the NSAA group (all grade: N=465 and N=363; grade 2: N = 142 and N = 80).[3]

For adverse events occurring during the first 6 months, it was reported that patients treated with enzalutamide and early docetaxel were more likely to have grade 2 peripheral sensory neuropathy (9%) compared to the NSAA group (3%).[3] Among those who did not receive early docetaxel treatment, 2 of 312 (1%) in NSAA group had an event while there were no events in the enzalutamide group.[3] Three patients treated with enzalutamide and early docetaxel had a grade 3 peripheral sensory neuropathy event compared to one patient in the NSAA group.[3]

Overall, there were 385 serious AEs reported among 235 patients in the enzalutamide group and 297 serious AEs in 189 patients in the NSAA group (reported in at least 0.5% of patients in either treatment group).[3] It was reported that the rate of serious AEs during treatment exposure was similar across groups (0.34 per-year [95% CI, 0.29-0.40] in enzalutamide vs. 0.33 per-year [0.28-0.39] in NSAA).[3]

Table 18: Incidence of adverse events in the ENZAMET Trial

Table 2. Adverse Events.

Adverse Event	Enzalutamide (N=563)	Standard Care (N=558)
Any adverse event — no. of patients (%)*		
Grade 1	40 (7)	77 (14)
Grade 2	202 (36)	230 (41)
Grade 3	277 (49)	194 (35)
Grade 4	38 (7)	40 (7)
Grade 5	6 (1)	7 (1)
Serious adverse event		
No. of patients (%)	235 (42)	189 (34)
No. of events	385	297
Rate during treatment exposure (95% CI) — no./yr†	0.34 (0.29–0.40)	0.33 (0.28–0.39)
Adverse event leading to treatment discontinuation at any time — no. of patients	33	14
Grade 3 to 5 adverse event — no. of patients (%)‡		
Febrile neutropenia	37 (7)	32 (6)
Hypertension	43 (8)	25 (4)
Neutrophil count decreased	31 (6)	16 (3)
Fatigue	31 (6)	4 (1)
Syncope	20 (4)	6 (1)
Surgical or medical procedure	13 (2)	10 (2)
Anemia	4 (1)	5 (1)
Fall	6 (1)	2 (<1)
Thromboembolic event	4 (1)	4 (1)
Acute coronary syndrome	3 (1)	4 (1)
Myocardial infarction	5 (1)	2 (<1)
Chest pain from cardiac cause	3 (1)	2 (<1)
Stroke	1 (<1)	2 (<1)
Seizure§	2 (<1)	0
Delirium	0	1 (<1)

*When a patient had multiple events identified by a particular term, the worst grade is shown.
†The rate of serious adverse events per year of treatment exposure was estimated with the use of a negative binomial regression model.
‡These adverse events occurred in at least 2% of the patients in either group or were selected as being events of special interest. In the enzalutamide group, 6 grade 5 adverse events were reported: death from an unknown cause in 2 patients and 1 patient each with stroke, myocardial infarction, aspiration pneumonia, and acidosis. In the standard-care group, 7 grade 5 adverse events were reported: sepsis in 2 patients and 1 patient each with cardiac arrest, sudden death from an unknown cause, gastric hemorrhage, urinary tract infection, and symptomatic progression of prostate cancer.
§ Seizure of any grade occurred in 7 patients in the enzalutamide group and in no patients in the standard-care group.

Source: From NEJM, Davis et al., Enzalutamide with standard first-line therapy in metastatic prostate cancer, 381(2):121-131. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[3]

Overall, six grade 5 AEs occurred in the enzalutamide group (two patients died from an unknow cause, and one patient each had a stroke, myocardial infarction, aspiration pneumonia, or acidosis). In the NSAA group, seven grade 5 AEs occurred (sepsis in two patients and 1 patient each had cardiac arrest, sudden death from an unknown cause, gastric hemorrhage, urinary tract infection, or symptomatic progression of prostate cancer).[3]

6.4 Ongoing Trials

Table 19: Ongoing trials of enzalutamide in patients with mCSPC

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Study China ARCHES[34] (NCT04076059) Characteristics Randomized, double-blind, placebo-controlled phase III trial Sample Size N= 180 Number of centres and number of countries Patient Enrolment Dates 2-September-2019 Final Analysis Date September-2023 Funding Astellas Pharma China, Inc.	<u>Key Inclusion Criteria:</u> 1. Diagnosed with histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation, signet cell or small cell histology. 2. Metastatic prostate cancer documented by positive bone scan (for bone disease) or metastatic lesions on CT or MRI scan (for soft tissue). 3. Disease spread is limited to regional pelvic lymph nodes are not eligible. 4. Maintain ADT with LHRH agonist or antagonist during study treatment or have a history of bilateral orchiectomy (i.e., medical or surgical castration). 5. ECOG performance status of 0 or 1. <u>Key Exclusion Criteria:</u> 1. Received any prior pharmacotherapy, radiation therapy or surgery for metastatic prostate cancer (except): A. Up to 3 months of ADT with LHRH agonists or antagonists or orchiectomy with or without concurrent antiandrogens, with no radiographic evidence of disease progression or rising PSA levels; B. 1 course of palliative radiation or surgical therapy to treat symptoms resulting from metastatic disease if it was administered at least 4 weeks; C. Up to 6 cycles of docetaxel therapy with final treatment administration completed within 2 months and no evidence of disease progression during or after the completion of docetaxel therapy; D. Up to 6 months of ADT with LHRH agonists or antagonists or orchiectomy with or without concurrent antiandrogens if subject was treated with docetaxel, with no radiographic evidence of disease progression or rising PSA levels prior to day 1; E. Prior ADT given for < 39 months in duration and > 9 months before randomization as neoadjuvant/adjuvant therapy. 2. Major surgery within 4 weeks. 3. Treatment with 5-α reductase inhibitors; estrogens, cyprotoerone acetate or androgens; systemic glucocorticoids greater than the equivalent of 10 mg per day of prednisone; or prior aminoglutethimide, ketoconazole, abiraterone acetate or enzalutamide within 4 weeks.	Enzalutamide+ ADT Placebo + ADT	<u>Primary:</u> Time to PSA progression <u>Secondary:</u> Duration of rPFS Time to SSE Time to castration resistance Percentage of participants with PSA response (≥ 50%) Percentage of participants with PSA response (≥ 90%) Time to initiation of new antineoplastic therapy PSA undetectable rate (< 0.2 ng/mL) ORR

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
	4. Known or suspected brain metastasis or active leptomeningeal disease or history of CVD. 5. Received bisphosphonates or denosumab within 2 weeks unless administered at stable dose or to treat diagnosed osteoporosis.		

Abbreviations: ADT = androgen deprivation therapy; CT = computed tomography; CVD = cardiovascular disease; ECOG = Eastern Cooperative Oncology Group; LHRH= luteinizing hormone-releasing hormone; MRI = magnetic resonance imaging; ORR = objective response rate; PSA = prostate-specific antigen; rPFS = radiographic progression-free survival; SSE = Symptomatic Skeletal Event

7 Supplemental Questions

The following supplemental questions were identified during the development of the protocol for the CADTH review on enzalutamide for men with mCSPC:

- Summary and critical appraisal of the Sponsor-submitted NMA comparing enzalutamide with other relevant treatments for men with metastatic hormone-sensitive prostate cancer (mHSPC).
- Summary and critical appraisal of a published NMA comparing enzalutamide with other relevant treatments for men with mHSPC.
- Summary and critical appraisal of a published enzalutamide comparing first-line treatments for mCSPC, specifically combinations of ADT and one (or more) of taxane-based chemotherapy, and androgen receptor-targeted therapies.

The full summaries and critical appraisals of the three NMAs are provided in sections 7.1 to 7.3. The summaries in section 7.2 and 7.3 were written for the CADTH review of Apalutamide (Erleada) mCSPC and have been re-printed.

7.1 Summary of sponsor-submitted network meta-analysis comparing enzalutamide with other relevant treatments for patients with metastatic hormone-sensitive prostate cancer

Objective

To summarize and critically appraise the methods and findings of the sponsor-submitted NMA comparing enzalutamide plus ADT with other relevant treatments (i.e., abiraterone, docetaxel, apalutamide, NSAA, and ADT alone or placebo with ADT) for men with mCSPC (used interchangeably for the term mHSPC).[38] For the CADTH critical appraisal, only the results for the total population, high volume and low volume populations will be reviewed because these patient populations were analyzed in the submitted economic evaluation..

Methods

Systematic Review

The Sponsor provided an NMA based on a systematic literature review (SLR) to evaluate the relative efficacy of enzalutamide compared with other potentially relevant treatments for patients with mHSPC. The predefined SLR was conducted on July 2019. PubMed/MEDLINE, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials and Database of Abstracts of Reviews of Effects were searched for relevant systematic reviews and meta-analyses, RCTs, non-randomized studies, observational comparative studies, case-cohort studies and registries. In addition, the search was supplemented with a search performed on May 22, 2019 using other relevant databases: American Society of Clinical Oncology and American Society of Clinical Oncology Genitourinary Cancers symposium, American Urological Association, European Association of Urology, European Society for Medical Oncology, National Comprehensive Cancer Network, NICE and International Society for Pharmacoeconomics and Outcomes Research (ISPOR). There were no restrictions of language or date of publication.

The Sponsor stated in a Checkpoint Response that the studies were selected by two separate specialists and any discrepancies were discussed with a third specialist. Data abstraction was conducted by a single specialist and it was reviewed by a second specialist and any discrepancies were discussed with a third specialist. Finally, all of the abstracted data pertaining to the NMA was reviewed by a third specialist.[7] Quality assessment of all the full-text RCT publications were conducted using the quality assessment as suggested in the NICE Single Technology Appraisal guidance.

Network Meta-Analysis

The main inclusion criteria for the NMA are stated in Table 20. A feasibility assessment was conducted using the guidance from the Australian Pharmaceutical Benefits Advisory Committee to determine which trials from the SLR could be included in an NMA.

Table 20: PICOS Inclusion Criteria for Study Selection in NMA

PICOS	Inclusion Criteria	Rationale
Population	Adult patients (age ≥18 years) with mHSPC*	The goal is to assess the relative efficacy of enzalutamide compared with current treatment in the mHSPC setting
Interventions	ADT (i.e., GnRH analogues, such as goserelin, buserelin and leuprorelin) or Orchiectomy Abiraterone Docetaxel Antiandrogens (e.g. bicalutamide, flutamide, nilutamide) Apalutamide Darolutamide Radiotherapy	These are the currently licensed or under development therapies in the mHSPC setting of interest for the cost-effectiveness model
Comparators	All above comparators Placebo	
Outcomes	rPFS OS Time for first SSE Time to castration-resistance Time to first use of new antineoplastic therapy Time to PSA progression Time to treatment discontinuation	These outcomes are considered the most relevant ones in the context of the cost-effectiveness model
Study Design	RCTS with any blinding status	RCTs are the gold standard of clinical evidence, minimizing the risk of confounding and allowing the comparison of the relative efficacy of interventions

Abbreviations: RCTs =m Randomized clinical trials; PSA; SSE = symptomatic skeletal event; Radiographic progression-free survival (rPFS); Overall survival (OS)
In case of studies including mixed populations only those reporting outcomes separately for mHSPC patients were included.
Source: Sponsor's Submission[38]

Bayesian NMA models were conducted to simultaneously synthesize the results of the included trials for each outcome to obtain the relative treatment effects for enzalutamide to other relevant therapies using HRs with corresponding 95% credible intervals (CrIs). The report stated that fixed-effect and random-effect models were performed.

[redacted].[38]

(*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Inconsistency in the NMA was assessed using the Bucher method.

[redacted]. [38] (*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Statistical heterogeneity was calculated using the I^2 statistic while exploratory analyses were performed to determine the effects of clinical and methodological heterogeneity. Sensitivity analyses were also performed to account for the heterogeneity across trials, such as including and excluding certain studies and performing subgroup analyses on certain populations of interest.

Only the results for the total population, low and high-volume subgroups will be considered for this review.

Results

Study and Patient Characteristics

[redacted]. [38] (*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

[redacted].[38]
(*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Table 21: Overview of the eligible studies for the NMA

(*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Source: Sponsor's Submission[38]

[redacted][38] *(Non-Disclosable information was used in this CADTH Guidance Report and the Sponsor requested this clinical information not be disclosed pursuant to the CADTH Disclosure of Information Guidelines. This information will remain redacted until notification by the Sponsor that it can be publicly disclosed).*

The patient characteristics for the eligible studies in the NMA are presented in Table 22. All of the included trials were conducted in men aged ≥18 years of age with mCSPC.

Table 22: Patient characteristics for the eligible studies for the total population NMA

(*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Source: Sponsor's Submission[38]

Feasibility Assessment for the NMA

Due to the wide range in publication dates of these studies (from mid-1980s to present day), the Sponsor stated that it is expected that a certain degree of heterogeneity would exist with respect to patient characteristics (e.g., ECOG scores, proportion of high and low volume disease and prior use of local therapy, etc.).

[redacted].[38] (*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

[redacted].[38]

(*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Table 23: rPFS definitions used in the non-CAB/MAB studies included in the NMA

(*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Source: Sponsor's Submission[38]

[redacted].[38] (*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Results of the Network Meta-Analysis for the total population

The NMA base case scenario assessed the total population of mCSPC patients (i.e., all comers) as this description aligned with the Sponsor's requested population for reimbursement. [redacted].[38] (*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

The base case scenario NMA network included 19 studies (from 21 publications) that compared six treatments. The characteristics of the studies included published (manuscript form) randomized controlled trials that encompassed the following six treatment regimens:

- placebo + ADT or orchiectomy,
- non-steroidal anti-androgen (NSAA) + ADT or orchiectomy,
- docetaxel + ADT,
- abiraterone + prednisone (AAP) + ADT,
- apalutamide + ADT,
- enzalutamide + ADT

Figure 17: Master evidence network - total population – used for base case analysis and sensitivity analysis 1

(*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Source: Sponsor's Submission[38]

Figure 18: Master evidence network - total population – used for sensitivity analyses 2 and 3

(*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Source: Sponsor's Submission[38]

Table 24: Analysis scenarios - total population

(*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Source: Sponsor's Submission[38]

Results for radiographic progression-free survival in the total population

[redacted][38] (*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Figure 19: Evidence network for rPFS - total population

(*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Source: Sponsor's Submission[38]

Table 25: Pair-wise estimates of treatment effects (HR) for rPFS primary and sensitivity FE models - total population

(*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Source: Sponsor's Submission[38]

Results for overall survival in the total population

[redacted].[38] (*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

[redacted].[38] (*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for*

the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).

Figure 20: Evidence network for OS - total population - base case and sensitivity analysis 1

(*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Source: Sponsor's Submission[38]

Figure 21: Evidence network for OS - total population - sensitivity analyses 2 and 3

(*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Source: Sponsor's Submission[38]

Table 26: Pair-wise estimates of treatment effects (HR) for OS primary and sensitivity FE models – total population

(*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Source: Sponsor's Submission[38]

Table 27: Pair-wise estimates of treatment effects (HR) for OS primary and sensitivity RE models - total population

(*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Source: Sponsor's Submission[38]

[redacted][38] (*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

[redacted]

[redacted][38] (*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Table 28: Inconsistency assessment for OS – total population

(*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Source: Sponsor's Submission[38]

Results for time to symptomatic skeletal event in the total population

[redacted][38] (*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Figure 22: Evidence network for TSSE - total population

(*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Source: Sponsor's Submission[38]

Table 29: Pair-wise estimates of treatment effects (HR) for TSSE FE model - total population

(*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Source: Sponsor's Submission[38]

Results for time to castration resistance in the total population

[redacted][38] (*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Figure 23: Evidence network for TCR - total population

(*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Source: Sponsor's Submission[38]

Table 30 Pair-wise estimates of treatment effects (HR) for TCR FE model - total population

(*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Source: Sponsor's Submission[38]

Results for time to initiation of new antineoplastic treatment in the total population

[redacted].[38] (*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Results for time to PSA progression in the total population

[redacted].[38] (*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Figure 24: Evidence network for time to PSA progression- total population

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Source: Sponsor's Submission[38]

Table 31: Pair-wise estimates of treatment effects (HR) for TPSA FE model - total population

(*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Source: Sponsor's Submission[38]

Results of the Network Meta-Analysis for the high volume patients

[redacted].[38] (*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Table 32: Analysis scenarios - high-volume population

(*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Source: Sponsor's Submission[38]

Results for radiographic progression-free survival in the high volume population

[redacted].[38] (*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Figure 25: Evidence network for rPFS - high-volume population

(*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Source: Sponsor's Submission[38]

Table 33: Pair-wise estimates of treatment effects (HR) for rPFS FE model - high-volume population

(*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Source: Sponsor's Submission[38]

Results for OS in the high-volume disease population

[redacted][38] (*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Figure 26:Evidence network for OS - high-volume population – base case

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Source: Sponsor's Submission[38]

Table 34: Pair-wise estimates of treatment effects (HR) for OS FE model - high-volume population

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Source: Sponsor's Submission[38]

Results for time to symptomatic skeletal event in the high volume population

[redacted][38] (*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Figure 27: Evidence network for TSSE – high-volume population

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Sponsor's Submission[38]

Table 35: Pair-wise estimates of treatment effects (HR) for TTSE FE model - high-volume population

(*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Source: Sponsor's Submission[38]

Results for time to castration resistance in the high volume population

[redacted][38] (*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Figure 28: Evidence network for TCR - high-volume population

(*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Source: Sponsor's Submission[38]

Table 36: Pair-wise estimates of treatment effects (HR) for TCR FE model - high-volume population

(*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Source: Sponsor's Submission[38]

Results for time to initiation of a new antineoplastic treatment in the high volume population

[redacted][38] (*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Results for time to PSA progression in the high volume population

[redacted].[38] (*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Results of the Network Meta-Analysis for the low volume patients

[redacted].[38] (*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Results for radiographic progression-free survival in the low volume population

[redacted][38] (*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Figure 29: Evidence network for rPFS - low-volume population

(*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Source: Sponsor's Submission[38]

Table 37: Pair-wise estimates of treatment effects (HR) for rPFS FE model - low-volume population

(*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Source: Sponsor's Submission[38]

Results for overall survival in the low volume population

[redacted][38] (*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Figure 30: Evidence network for OS (low-volume population

(*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Source: Sponsor's Submission[38]

Table 38: Pair-wise estimates of treatment effects (HR) for OS primary FE analyses - low-volume population

(*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Source: Sponsor's Submission[38]

Results for time to symptomatic skeletal events in the low volume population

[redacted][38] (*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Figure 31:Evidence network for TSSE - low-volume population

(*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Source: Sponsor's Submission[38]

Table 39: Pair-wise estimates of treatment effects (HR) for TSSE primary FE analyses - low-volume population

(*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Source: Sponsor's Submission[38]

Results for time to castration resistance in the low volume population

[redacted][38] (*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Figure 32: Evidence network for TCR - low-volume population

(*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Source: Sponsor's Submission[38]

Table 40: Pair-wise estimates of treatment effects (HR) for TCR FE model - low-volume population

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Source: Sponsor's Submission[38]

Results for time to initiation of a new antineoplastic treatment in the low volume population

[redacted].[38] (*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Results for time to PSA progression in the low volume population

[redacted].[38] (*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Critical Appraisal of Network Meta-Analysis

The quality of the sponsor-submitted NMA was assessed according to recommendations of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons and Network Meta-Analyses.[41] Details and commentary for each of the relevant items identified by the ISPOR group are provided in Table 41.

Table 41: Adapted ISPOR Questionnaire to Assess the Credibility of an Indirect Treatment Comparison or Network Meta-Analysis adapted from Jansen et al.[41]

ISPOR Questions	Details and Comments
1. Is the population relevant?	The population is relevant to the patient population under CADTH review.
2. Are any critical interventions missing?	The NMA appeared to include all relevant interventions for this patient population.
3. Are any relevant outcomes missing?	The NMA reported outcomes for OS, rPFS, time to SSE, time to castration resistance, time to initiation of new antineoplastic treatment and time to PSA progression. However, safety outcomes and HRQoL were not reported.
4. Is the context (e.g., settings and circumstances) applicable to your population?	The context may not be fully applicable to the population. Some of the comparators included are not relevant and approved for the Canadian context or they are not all currently approved for market in Canada.
5. Did the researchers attempt to identify and include all relevant randomized controlled trials?	The researchers performed a SLR to identify all trials with clear inclusion criteria. The publication described the information sources, their search strategy and their selection criteria. However, there is lack of information on the screening process.
6. Do the trials for the interventions of interest form one connected network of randomized controlled trials?	The trials in the analysis for each outcome form a connected network of RCTs.
7. Is it apparent that poor quality studies were included thereby leading to bias?	The quality of studies was evaluated and reported. The Sponsor stated that there was insufficient information to conclude whether blinding of participants of the outcome assessment or missing data was performed properly in some of the trials.
8. Is it likely that bias was induced by selective reporting of outcomes in the studies?	Selective outcome reporting was evaluated by the authors in the risk of bias. Risk of selective outcome reporting was reported as low.
9. Are there systematic differences in treatment effect modifiers (i.e. baseline patient or study characteristics that impact the treatment effects) across the different treatment comparisons in the network?	There are differences in the patient and study characteristics from the included studies that may have affected the results of the NMA. Clinical heterogeneity was present in the previous treatments, disease state and treatment arms between the studies. There was also some missing data for these clinical features. Furthermore, there was heterogeneity in the inclusion criteria of the trials.
10. If yes (i.e. there are such systematic differences in treatment effect modifiers), were these imbalances in effect modifiers across the different treatment comparisons identified prior to comparing individual study results?	The imbalances in the potential effect modifiers were identified prior to comparing the individual studies. They were discussed in the publication as a potential limitation to the NMA.
11. Were statistical methods used that preserve within-study randomization? (No naïve comparisons)	It is unclear based on the methods provided whether within-study randomization was preserved.
12. If both direct and indirect comparisons are available for pairwise contrasts (i.e. closed loops), was agreement in treatment effects (i.e. consistency) evaluated or discussed?	The consistency of both direct and indirect comparisons was evaluated where feasible.
13. In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?	Both direct and indirect comparisons were reported where applicable.
14. With inconsistency or an imbalance in the distribution of treatment effect modifiers across the different types of comparisons in the network of trials, did the researchers attempt to minimize this bias with the analysis?	The researchers did not attempt to minimize imbalances in the analysis. They did however complete a sensitivity analysis excluding studies for the different outcomes and patient populations.

ISPOR Questions	Details and Comments
15. Was a valid rationale provided for the use of random effects or fixed effect models?	Both fixed-effect and random-effect models were performed. However, random-effect models were only fitted for those networks that included more than one study that informed at least one comparison.
16. If a random effects model was used, were assumptions about heterogeneity explored or discussed?	The assumptions about heterogeneity were explored and discussed in this publication.
17. If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with pre-specified covariates performed?	Subgroup analyses were conducted to explore potential sources of clinical heterogeneity.
18. Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	Graphical representations of the evidence networks and number of RCTs are provided.
19. Are the individual study results reported?	Individual study results were not provided.
20. Are results of direct comparisons reported separately from results of the indirect comparisons or network meta-analysis?	The results of the direct comparisons of the treatments are reported.
21. Are all pairwise contrasts between interventions as obtained with the network meta-analysis reported along with measures of uncertainty?	All pairwise point estimates and CIs are provided.
22. Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	The p-value analysis stating the probabilities of being the preferred treatments and uncertainties were not provided.
23. Is the impact of important patient characteristics on treatment effects reported?	The impact of important patient characteristics on treatment effects reported or discussed.
24. Are the conclusions fair and balanced?	Some of the conclusions appear to be fair and balanced, however it is difficult to make conclusions. Some limitations of the NMA are recognized and reported, however, a number of important limitations were missed (as discussed in the limitations sections of this critical appraisal).
25. Were there any potential conflicts of interest?	No conflict of interest information was provided; however, the report was submitted by the sponsor of the enzalutamide submission.
26. If yes, were steps taken to address these?	Not applicable.

Summary

In the absence of head-to-head trial data for enzalutamide compared to other relevant treatments for men with mCSPC, the Sponsor submitted an NMA comparing enzalutamide with other relevant treatments for this patient population. In conclusion, enzalutamide + ADT showed statistically significant benefit versus placebo + ADT for the OS and rPFS outcomes in the total mCSPC population. Enzalutamide + ADT was also compared with NSAA + ADT for the OS outcome and this difference in benefit was statistically significant. When compared against docetaxel + ADT, enzalutamide + ADT was statistically significantly better for the rPFS outcome and demonstrated a trend (but was not statistically significant) towards a HR improvement for the OS outcome. When compared with the two remaining regimens (i.e., abiraterone + prednisone + ADT and apalutamide + ADT), enzalutamide + ADT demonstrated numerically improved HRs (which were not statistically significant) for both the rPFS and OS outcomes.

[redacted].[38] (*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Several limitations of the study must be considered. There was a lack of clarity on exclusion criteria of the trials and the screening process and no list of excluded studies was included. Furthermore, it was unclear if the authors initially reviewed subgroups from

studies that included patients with low volume and high volume. This would be problematic in the NMA if the initial randomization in the individual studies was not stratified by disease burden (e.g., randomization is not maintained in the subgroup analysis in the individual study, thereby creating a methodological issue in the NMA).

Although the Sponsor explored the effects of clinical and methodological heterogeneity, there was still a presence of heterogeneity among the studies with respect to ECOG scores, high and low volume proportions, previous local [redacted][38] (*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed)* but this does not indicate whether clinical heterogeneity is still present. [redacted][38] (*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).* Based on the review teams assessment of the NMA, the ADT groups were also varied between the studies (e.g. medical vs chemical castration), and some of the ADT protocols in the studies were not clearly reported (e.g. reporting solely "ADT" with no further details). There were also inconsistencies between included studies on outcome definitions. Although the Sponsor defined their outcome definitions, the definitions for these outcomes were not always consistent in the included studies. This is apparent in the inclusion/exclusion of certain studies based on PFS definitions. Additionally, there was heterogeneity in study design as a mix of open-label and double-blind trials were included.

Secondly, the standard Bayesian MNA methods assume the proportionality of hazards, which was used for the OS and rPFS outcomes. This assumption was tested and found to apply for the majority of cases. [redacted][38] (*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Currently approved treatment for Canadian men with mHPSC include ADT, chemotherapy (e.g., docetaxel) or chemotherapy plus ADT; the NMA included additional treatments (e.g., abiraterone and apalutamide), that are currently not publicly available in Canada but accessible via patient access programs. Additionally, some outcomes were not included that would have been relevant to the populations (e.g. HRQoL and safety data).

<u>Comparisons between the NMAs</u>

Overall, the conclusions surrounding the efficacy outcomes for enzalutamide in combination with ADT for patients with mCSPC were similar between the three NMAs, however some inconsistencies between the results were noted.

Due to differences in the inclusion and exclusion criteria for each NMA, various trials were included in each of the networks. The Sponsor-submitted NMA and published NMA by Marchioni et al (2020)[36] had the broadest inclusion criteria and identified the largest number of trials. The Sponsor-submitted NMA included only treatments that are currently approved or under review for use in the Canadian population. However, CGP noted that all of the drugs included in the two published NMAs are Health Canada approved for other indications and are potentially available for use by clinicians in an off-label manner, especially for patients with mCSPC.

AEs were evaluated in the published network NMA by Marchioni et al (2020)[36] only, and therefore the results cannot be compared to the other NMAs. The Sponsor-submitted included subgroup analysis for all outcomes based on disease volume while the NMA by

Sathianathen et al (2020)[37] only included subgroup analyses for OS based on disease volume. The CGP identified these subgroup analyses as relevant; however, limitations in both analyses must be noted. It was unclear whether methods were taken to ensure randomization from the individual studies was maintained in the subgroup analysis, thereby creating a methodological issue in the NMA. Results from this analysis must therefore be interpreted with caution.

Common limitations were noted in all three of the NMAs. None of the NMAs considered clinical heterogeneity between the included trials. Differences in the trials included in each NMA were apparent in factors such as the therapies and treatments allowed for inclusion into the trial, performance status and disease stage. The ADT groups were also varied between the studies (e.g. medical vs chemical castration), and some of the ADT protocols in the studies were not clearly reported (e.g. reporting solely “ADT + placebo”, with no further details). Only the Sponsor-submitted NMA discussed any potential inconsistencies that may exist between included studies on outcome definitions in the original studies.

Due to the above limitations, the comparative efficacy estimates obtained may be biased, and it is not possible to quantify or identify the direction of the bias. As a result, the estimates may over- or underestimate the true treatment effect associated with enzalutamide, and therefore, the results should be interpreted with caution.

7.2 Summary a published network meta-analysis comparing first-line treatments for mCSPC, specifically ARAT therapies (e.g. apalutamide, docetaxel, docetaxel plus bisphosphonate, abiraterone, enzalutamide, bisphosphonates, celecoxib and celecoxib plus bisphosphonate)

Objective

To summarize and critically appraise the methods and findings of the published network NMA comparing first-line treatments for mCSPC (used interchangeably for the term metastatic hormone-sensitive prostate cancer (mHSPC) in this publication), specifically androgen receptor axis targeted therapy (ARAT) therapies, (e.g., apalutamide, docetaxel, docetaxel plus bisphosphonate, abiraterone, enzalutamide, bisphosphonates, celecoxib and celecoxib plus bisphosphonate) for the first-line treatment of mCSPC.[36]

Methods

Systematic Review

The published NMA was based on a SLR of papers published up until June 2019 from the following databases: PubMed, Web of Science, Scopus and Science Direct. The search strategy was adapted to the different databases and used various combinations of the terms: “prostate cancer”, “metastatic”, “de novo”, “hormone sensitive”, “neoplasm”, “prostate”, and “cancer”. Additional records were also identified from the references in the selected manuscripts and from previously identified systematic literature reviews. Selection and identification of studies were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria[42] and the Population, Intervention, Comparator, Outcomes (PICO) methodology (www.prisma-statement.org) (Table 42).

After duplicate removal, exclusion criteria were applied on the identified records using the Rayyan web-based platform. The Rayyan platform screened titles and abstracts, followed by full-text article screening of potentially relevant references. Following screening by the web-based platform, two independent reviewers ascertained whether inclusion criteria were met, and a third reviewer resolved discrepancies. Full text articles with at least one outcome of interest were included. Only studies with original or primary data were included. When there were multiple papers referring to the same cohort, only the most recent paper was considered, and the others were excluded.

Data were extracted from relevant full-text studies into a Microsoft Excel workbook. The HRs and 95% CIs for death and disease progression for treatment versus control arms for the mHPSC population was extracted. Studies without subgroups specific to mHPSC were excluded. The absolute frequencies of AEs were extracted along with the overall population size for each treatment arm. AE data was not available according to metastatic status in most studies (e.g., specific to the population with mHPSC), so the main analysis of AEs included patients regardless of their metastatic status. A sensitivity analysis was performed that excluded studies allowing the inclusion of patients without metastatic disease.

The risk of bias for each study and outcome was evaluated and depicted graphically as summaries using Review Manager (RevMan, version 5.3, The Cochrane Collaboration). Funnel plots were used to detect publication bias and Egger's regression test was used to test for asymmetry in the plots.

Table 42: Study selection criteria to identify trials for the systematic literature search

Population	Patients with mHPSC
Intervention	Treated with novel systemic compounds (not further defined by publication authors)
Comparators	ADT only or in association with any systemic treatment
Outcomes	Primary: OS Secondary: PFS; High-grade AE (grade 3-5)
Study design	RCT (phase not specified by publication authors)
Language	English

Abbreviations: AE: Adverse event; ADT: Androgen deprivation therapy; mHPSC: metastatic hormone-sensitive prostate cancer; OS: Overall survival; PFS: Progression-free survival; RCT: Randomized controlled trial

Network Meta-Analysis

All ARATs included in the NMA were given in combination with an ADT backbone. OS was defined by the authors as time from treatment initiation to death from any cause or to the last follow-up available. PFS was defined by the authors as the time from treatment initiation to either radiological or clinical progression, death or to the last follow-up available.

The logHR and standard errors (SE) were calculated from the HRs and 95% CIs for the survival outcomes. For multi-arm trials, estimates and associated uncertainties were determined from available comparisons. The odds ratios (OR) of AEs were estimated from the frequencies reported in the included studies.

The analyses were conducted using a frequentist approach using version 1.0.1 of the netmeta package in the R environment. For binary outcomes, the inverse variance method was used. A network diagram was created for each outcome. The publication stated that random effects models were used due to the possible heterogeneity in the included studies. Pooled HRs and ORs were depicted in forest plots compared to ADT alone or docetaxel (plus ADT).

Design based decomposition of the Cochran Q was performed to assess the whole network and consistency between designs. Direct, indirect and NMA treatment estimates were compared to check for NMA consistency. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to rate the quality of NMA treatment effect estimates.

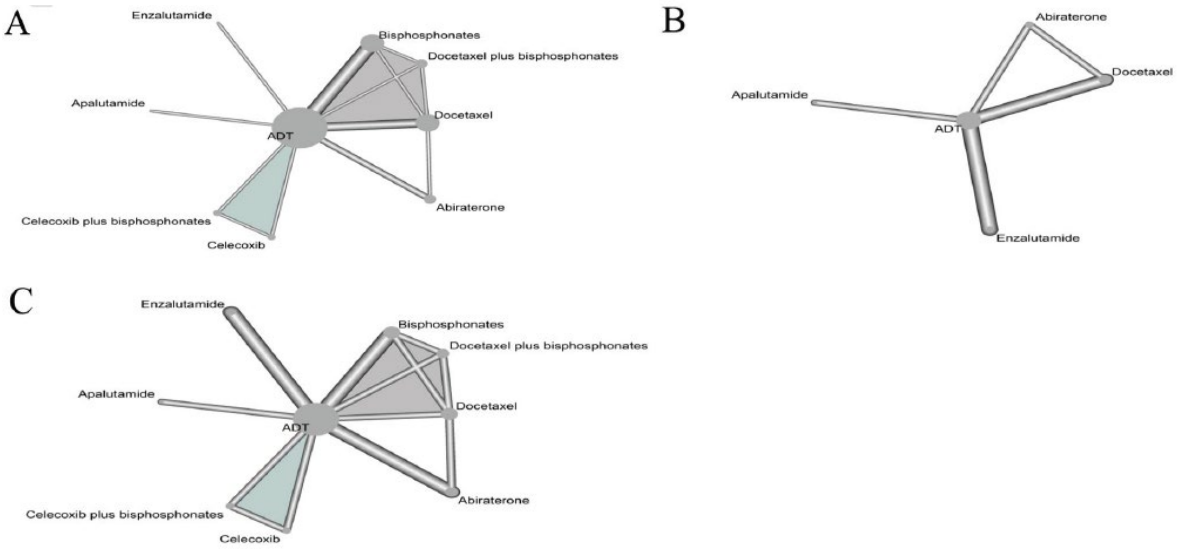
Results

Networks

The literature search identified 12,402 records (after duplicates were removed), which were screened by the Rayyan platform. Following screening by the web-based platform, 429 records were further screened by the two independent reviewers. The NMA included 13 studies, and the networks are depicted in Figure 33.

All thirteen identified studies were included in the analysis of OS, seven studies were included in the analysis of PFS, and ten studies were included in the analysis of AEs. Reasons for studies being excluded from the analysis for PFS were: 'definition of progression included the PSA failure' (ZAPCA, CALGB, STAMPEDE arms D versus F), 'definition of progression included only progression of symptomatic bone metastases, while no routinely scan was performed in asymptomatic bone metastatic patients' (MRC-PRO), and 'no stratification in M0 vs. M1 patients was reported in the text' (STAMPEDE arm G, STAMPEDE arms B versus C versus E). The reason for studies being excluded from the analysis for AEs was: 'data not clearly reported and/or stratified' (CHAARTED, GETUG AFU 15, MRC-PROS).

Figure 33: Evidence networks for A) overall mortality, B) disease progression (PFS), and C) high grade adverse events.



Thickness of each arm is proportional to number of studies participating in network. Diameter of each junction point is proportional to number of studies including respective treatment. Shadowed areas indicate multi-arm studies.

Source: Republished with permission of Wolters Kluwer Health, Inc., from New anti-androgen compounds compared to docetaxel in metastatic hormone sensitive prostate cancer: results from a network meta-analysis, Marchioni M et al, J Urol. 2020 Apr;203(4):751-759; permission conveyed through Copyright Clearance Center, Inc.[36]

Of the 13 included studies, five studies were double blind RCTs, and eight studies were open label RCTs. The primary endpoint was OS for eight studies (STAMPEDE arm G, STAMPEDE arms B versus C versus E, CHAARTED, GETUG AFU 15, LATITITUDE, ENZAMET, STAMPEDE arms D versus F, STAMPEDE arms C versus G), rPFS for two studies (ARCHES, TITAN), and one study each for bone PFS (MRC-PRO5), skeletal related events-free survival (CALGB), and failure free survival (ZAPCA). The analysis included 10,800 patients with mHPSC, of which 4,653 (43.1%) were treated with ADT alone or in combination with non-steroidal anti-androgen (NSA), 1,066 (9.9%) with docetaxel, 1,324 (12.3%) with abiraterone acetate, 1,137 (10.5%) with enzalutamide, and 525 (4.9%) with apalutamide. Years of enrollment ranged from 1994 to 2018. Median follow up ranged from 14.4 to 83.2 months. One study (ENZAMET) explicitly included the combination of ADT and NSAA as a control arm. One trial (STAMPEDE) included comparisons between different active treatments. The authors stated that there was some variability and population differences that were evident between the studies. In trials reporting on these patient characteristics, median age ranged from 63 to 72 years, and median PSA ranged from 6.9 to 70 ng/mL.

The authors reported that the overall quality of the included trials was rated as high with low risk of selection and reporting bias for the main outcomes, however there was a high risk of performance and detection bias. For the outcome of AEs, the authors reported that the risk of attrition and reporting bias was rated as high due to incomplete information about this outcome and no analyses conducted depending on the metastatic status of the patient. Egger's test showed a low risk of publication bias for all outcomes.

Results for OS

In total, there were 4,006 deaths recorded. The results of the pooled effect analysis suggested each of the combination treatments showed statistically significantly lower risk of overall mortality compared to ADT alone, except for celecoxib (Table 43). Enzalutamide did not show statistically significant differences for overall mortality compared to any of the other combination treatments (docetaxel, docetaxel plus bisphosphonate, abiraterone, enzalutamide, bisphosphonates, celecoxib and celecoxib plus bisphosphonate).

The publication stated the model failed to show statistical heterogeneity within design (I^2=0%, tau^2= 0, p=0.664) and inconsistency between design (p=0.380). The authors rated GRADE quality for direct comparisons as high; however, rated the NMA evidence as intermediate and low in most cases.

Table 43: Comparison of each treatment[a] for risk of overall mortality

	Hazard ratios [95%CI] derived from meta-analysis of direct evidences							
Abiraterone			1.13 [0.77;1.66]					**0.64 [0.56;0.73]**
0.98 [0.72;1.33]	**Apalutamide**							**0.67 [0.51;0.89]**
0.98 [0.74;1.30]	1.00 [0.69;1.46]	**Enzalutamide**						**0.67 [0.52;0.86]**
0.89 [0.76;1.05]	0.90 [0.67;1.22]	0.90 [0.69;1.19]	**Docetaxel**					**0.77 [0.68;0.87]**
0.76 [0.64;0.90]	0.77 [0.57;1.04]	0.77 [0.59;1.02]	**0.85 [0.74;0.99]**	**Bisphosphonates**				**0.87 [0.77;0.98]**
0.86 [0.70;1.06]	0.87 [0.63;1.21]	0.87 [0.65;1.18]	0.97 [0.81;1.16]	1.13 [0.95;1.35]	**Docetaxel plus bisphosphonates**			**0.79 [0.66;0.95]**
0.70 [0.54;0.91]	0.71 [0.50;1.02]	0.71 [0.51;1.00]	0.79 [0.61;1.02]	0.92 [0.72;1.19]	0.82 [0.62;1.08]	**Celecoxib**		0.94 [0.75;1.18]
0.84 [0.65;1.10]	0.86 [0.60;1.23]	0.86 [0.61;1.21]	0.95 [0.73;1.23]	1.11 [0.86;1.44]	0.98 [0.74;1.31]	1.21 [0.93;1.57]	**Celecoxib plus bisphosphonates**	**0.78 [0.62;0.98]**
0.66 [0.58;0.75]	**0.67 [0.51;0.89]**	**0.67 [0.52;0.86]**	**0.74 [0.66;0.83]**	**0.87 [0.77;0.97]**	**0.77 [0.65;0.91]**	0.94 [0.75;1.18]	**0.78 [0.62;0.98]**	**ADT**
Hazard ratios [95%CI] derived from network meta-analysis (direct and indirect evidences)								

[a] Each treatment is in combination with ADT

The lower-left of the table show the results from the network meta-analysis (direct and indirect evidences), the upper-right of the table (gray background) show the results deriving from direct comparisons only. Statistically significant comparisons are reported in bold. Comparisons should be read from the left to the right in both the lower-left and upper-right of the table.

Source: Republished with permission of Wolters Kluwer Health, Inc., from New anti-androgen compounds compared to docetaxel in metastatic hormone sensitive prostate cancer: results from a network meta-analysis, Marchioni M et al, J Urol. 2020 Apr;203(4):751-759; permission conveyed through Copyright Clearance Center, Inc.[36]

Results for PFS

In total, there were 1,265 disease progressions recorded. The results of the pooled effect analysis suggested each of the combination treatments showed statistically significantly lower risk of disease progression compared to ADT alone (Table 44). Enzalutamide had the largest effect on PFS compared to ADT (HR=0.40; 95%CI: 0.34-0.46) and also showed statistically significantly lower risk of disease progression compared to docetaxel (HR=0.61; 95% CI: 0.49-0.75). Additionally, abiraterone showed statistically significantly lower risk of disease progression compared to docetaxel (HR=0.71; 95% CI: 0.59-0.86).

The publication stated the model failed to show statistical heterogeneity within design (I^2=0%, tau^2= 0, p=0.774) and inconsistency between design (p=0.804). The authors rated the GRADE quality for direct comparisons as high; however, rated the NMA evidence as intermediate and low in most cases.

Table 44. Comparison of each treatment[a] for risk of disease progression

	Hazard ratios [95%CI] derived from meta-analysis of direct evidences			
Abiraterone			**0.69 [0.50;0.95]**	**0.47 [0.40;0.56]**
0.97 [0.74;1.26]	**Apalutamide**			**0.48 [0.39;0.60]**
1.17 [0.94;1.46]	1.21 [0.93;1.58]	**Enzalutamide**		**0.40 [0.34;0.46]**
0.71 [0.59;0.86]	**0.74 [0.57;0.95]**	**0.61 [0.49;0.75]**	**Docetaxel**	**0.65 [0.56;0.75]**
0.47 [0.40;0.54]	**0.48 [0.39;0.60]**	**0.40 [0.34;0.46]**	**0.65 [0.57;0.75]**	**ADT**
Hazard ratios [95%CI] derived from network meta-analysis (direct and indirect evidences)				

[a] Each treatment is in combination with ADT
The lower-left of the table show the results from the network meta-analysis (direct and indirect evidences), the upper-right of the table (gray background) show the results deriving from direct comparisons only. Statistically significant comparisons are reported in bold. Comparisons should be read from the left to the right in both the lower-left and upper-right of the table.

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Results for AEs

The results of the pooled effect analysis showed statistically significantly higher odds of AEs for abiraterone (OR= 1.90; 95%CI: 1.42-2.54), docetaxel (OR= 2.30; 95%CI: 1.61-3.28), and docetaxel plus bisphosphonates (OR= 2.38; 95%CI: 1.57-3.63) compared to ADT alone (Table 45). The other combination treatments did not show statistically significantly higher odds of AEs compared to ADT alone. Enzalutamide showed statistically significantly lower odds of AEs compared to docetaxel (OR= 0.56; 95%CI: 0.35-0.92) and docetaxel plus bisphosphonates (OR= 0.54; 95%CI: 0.32-0.93).

The authors stated the model showed high within design statistical heterogeneity (I^2=66.9%, tau^2= 0.042, p=0.009), but a low risk of inconsistency between design (p=0.161). The authors rated the GRADE quality for direct comparisons as intermediate, however rated the NMA evidence as low in most cases.

A sensitivity analysis was performed that excluded the STAMPEDE trial due to the limited information on AEs reported only in patients with metastasis. The results of the sensitivity analysis did not show statistically significantly higher odds of AEs for abiraterone, apalutamide, enzalutamide, or bisphosphonates compared to ADT alone.

Table 45: Comparison of each treatment[a] for risk of high-grade adverse events (main analysis including all studies regardless of metastatic status)

	Odds ratios [95%CI] derived from meta-analysis of direct evidences							
Abiraterone			0.93 [0.54;1.60]					**1.82 [1.32;2.50]**
1.88 [1.08;3.27]	**Apalutamide**							1.01 [0.63;1.62]

1.46 [0.94;2.28]	0.78 [0.44;1.39]	**Enzalutamide**						1.30 [0.93;1.81]
0.83 [0.56;1.21]	**0.44 [0.24;0.79]**	**0.56 [0.35;0.92]**	**Docetaxel**	**2.29 [1.44;3.66]**	1.01 [0.63;1.61]			**2.28 [1.45;3.59]**
1.63 [1.08;2.46]	0.87 [0.49;1.53]	1.11 [0.70;1.77]	**1.97 [1.32;2.94]**	**Bisphosphonates**	**0.44 [0.28;0.70]**			1.19 [0.86;1.66]
0.80 [0.49;1.29]	**0.42 [0.23;0.80]**	**0.54 [0.32;0.93]**	0.96 [0.62;1.51]	**0.49 [0.32;0.76]**	**Docetaxel plus bisphosphonates**			**2.26 [1.44;3.56]**
2.11 [1.19;3.76]	1.12 [0.57;2.23]	1.44 [0.79;2.63]	**2.56 [1.39;4.71]**	1.30 [0.72;2.35]	**2.65 [1.38;5.09]**	**Celecoxib**	1.03 [0.61;1.75]	0.90 [0.55;1.48]
2.18 [1.22;3.88]	1.16 [0.58;2.30]	1.49 [0.82;2.71]	**2.64 [1.43;4.87]**	1.34 [0.74;2.43]	**2.74 [1.43;5.25]**	1.03 [0.61;1.75]	**Celecoxib plus bisphosphonates**	0.87 [0.53;1.43]
1.90 [1.42;2.54]	1.01 [0.63;1.62]	1.30 [0.93;1.81]	**2.30 [1.61;3.28]**	1.17 [0.85;1.61]	**2.38 [1.57;3.63]**	0.90 [0.55;1.48]	0.87 [0.53;1.43]	**ADT**

Odds ratios [95%CI] derived from network meta-analysis (direct and indirect evidences)

[a] Each treatment is in combination with ADT

The lower-left of the table show the results from the network meta-analysis (direct and indirect evidences), the upper-right of the table (gray background) show the results deriving from direct comparisons only. Statistically significant comparisons are reported in bold. Comparisons should be read from the left to the right in both the lower-left and upper-right of the table.

Source: Republished with permission of Wolters Kluwer Health, Inc., from New anti-androgen compounds compared to docetaxel in metastatic hormone sensitive prostate cancer: results from a network meta-analysis, Marchioni M et al, J Urol. 2020 Apr;203(4):751-759; permission conveyed through Copyright Clearance Center, Inc.[36]

Critical Appraisal of Network Meta-Analysis

The published NMA was critically appraised according to recommendations of ISPOR Task Force on Indirect Treatment Comparisons and Network Meta-Analyses.[41] Details and commentary for each of the relevant items identified by the ISPOR group are provided in Table 46.

Table 46: Adapted ISPOR Questionnaire to Assess the Credibility of an Indirect Treatment Comparison or Network Meta-Analysis adapted from Jansen et al.[41]

ISPOR Questions	Details and Comments
1. Is the population relevant?	The population is relevant to the patient population under CADTH review.
2. Are any critical interventions missing?	The NMA appeared to include all relevant interventions for this patient population.
3. Are any relevant outcomes missing?	The NMA reported outcomes for OS, rPFS, time to SSE, time to castration resistance, time to initiation of new antineoplastic treatment and time to PSA progression. However, safety outcomes and HRQoL was not reported.
4. Is the context (e.g., settings and circumstances) applicable to your population?	The context may not be fully applicable to the population. Some of the comparators included are not relevant and approved for the Canadian context. CGP indicated use of all treatments included in this NMA may not approved for use among mHPSC patients but may be done so off-label at the discretion of the physician and considering patient conditions and preferences.

ISPOR Questions	Details and Comments
5. Did the researchers attempt to identify and include all relevant randomized controlled trials?	The researchers performed a SLR to identify all trials with clear inclusion criteria. The publication described the information sources, their search strategy and their selection criteria. While the PICO criteria were written in the text, the criteria were not defined further (e.g. the terminology “novel treatments”, with no further details provided).
6. Do the trials for the interventions of interest form one connected network of randomized controlled trials?	The trials in the analysis for each outcome form a connected network of RCTs.
7. Is it apparent that poor quality studies were included thereby leading to bias?	The quality of studies was evaluated and reported. The authors reported that the overall quality of the included trials was high with low risk of selection and reporting bias for the main outcomes, however there was a high risk of performance and detection bias. For the outcome of AEs, the authors reported that the risk of attrition and reporting bias was high due to incomplete information about this outcome and no analyses conducted by metastatic status.
8. Is it likely that bias was induced by selective reporting of outcomes in the studies?	Selective outcome reporting was evaluated by the authors in the risk of bias. Risk of selective outcome reporting was reported as low for OS, one trial was unclear about risk of selective outcome reporting for PFS, and four trials were high risk and one trial was unclear risk for selective outcome reporting for high grade AEs.
9. Are there systematic differences in treatment effect modifiers (i.e. baseline patient or study characteristics that impact the treatment effects) across the different treatment comparisons in the network?	There are differences in the patient and study characteristics from the included studies that may have affected the results of the NMA. Clinical heterogeneity was present in the previous treatments, disease state and treatment arms between the studies. There was also some missing data for these clinical features. Furthermore, there was heterogeneity in the inclusion criteria of the trials, trial design (open-label vs double-blind), outcome definitions and study duration.
10. If yes (i.e. there are such systematic differences in treatment effect modifiers), were these imbalances in effect modifiers across the different treatment comparisons identified prior to comparing individual study results?	The imbalances in the potential effect modifiers were not identified prior to comparing the individual studies. They were discussed in the publication as a potential limitation to the NMA.
11. Were statistical methods used that preserve within-study randomization? (No naïve comparisons)	It is unclear based on the methods provided whether within-study randomization was preserved.
12. If both direct and indirect comparisons are available for pairwise contrasts (i.e. closed loops), was agreement in treatment effects (i.e. consistency) evaluated or discussed?	The consistency of both direct and indirect comparisons was evaluated where feasible.
13. In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?	Both direct and indirect comparisons were reported where applicable.
14. With inconsistency or an imbalance in the distribution of treatment effect modifiers across the different types of comparisons in the network of trials, did the researchers attempt to minimize this bias with the analysis?	The researchers did not attempt to minimize imbalances in the analysis. They did however complete a sensitivity analysis excluding studies which included patients without metastatic disease for the outcome of AEs.
15. Was a valid rationale provided for the use of random effects or fixed effect models?	The rationale for using a random effects model was stated as being due to the possibility of heterogeneity in the included trials.
16. If a random effects model was used, were assumptions about heterogeneity explored or discussed?	The assumptions about heterogeneity were not explored or discussed in this publication.
17. If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with pre-specified covariates performed?	No subgroup analyses were conducted to explore potential sources of clinical heterogeneity.

ISPOR Questions	Details and Comments
18. Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	Graphical representations of the evidence networks and number of RCTs are provided.
19. Are the individual study results reported?	Individual study results were not provided.
20. Are results of direct comparisons reported separately from results of the indirect comparisons or network meta-analysis?	The results of the direct comparisons of the treatments are reported.
21. Are all pairwise contrasts between interventions as obtained with the network meta-analysis reported along with measures of uncertainty?	All pairwise point estimates and CIs are provided.
22. Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	The publication includes the p value analysis stating the probabilities of being the preferred treatments. No uncertainties are provided.
23. Is the impact of important patient characteristics on treatment effects reported?	The impact of important patient characteristics on treatment effects is not reported or discussed.
24. Are the conclusions fair and balanced?	Some of the conclusions appear to be fair and balanced, however it is difficult to make conclusions about the safety profile due to the method of analysis performed for the outcome of AEs. Some limitations of the NMA are recognized and reported, however, a number of important limitations were missed (as discussed in the limitations sections of this critical appraisal).
25. Were there any potential conflicts of interest?	The publication stated that no indirect commercial, personal, academic, political, religious or ethical incentive is associated with publishing the article
26. If yes, were steps taken to address these?	Not applicable.

Summary

A published NMA was identified comparing enzalutamide to other relevant treatments for men with mHPSC. This NMA compared relevant treatments combined with ADT for the outcomes of OS, PFS and AEs. Thirteen trials were identified from a SLR. For the outcome of OS, enzalutamide showed statistically significantly lower risk of overall mortality compared to ADT alone but was not compared to any of the other combination treatments (abiraterone, enzalutamide, docetaxel, bisphosphonates, docetaxel plus bisphosphonates, celecoxib, or celecoxib plus bisphosphonates). For the outcome of PFS, enzalutamide showed statistically significantly lower risk of disease progression compared to ADT alone and compared to docetaxel plus bisphosphonates. In the overall analysis for the outcome of AEs (including all studies, regardless of the metastatic status of the patients), apalutamide did not show statistically significantly higher odds of AEs compared to ADT alone. Enzalutamide showed statistically significantly lower odds of AEs compared to docetaxel and docetaxel plus bisphosphonates.

Several limitations of the study must be considered. The authors did not clearly describe the methodology and reporting of results. There was a lack of clarity on exclusion criteria, with no details provided for both the web-based screening and the further screening by the reviewers. No list of excluded studies was provided. The PICO criteria were not explicitly clear (e.g. the terminology “novel treatments” with no further details provided). The initial screening of the references was performed by a web-based platform, and not by manual screening by the reviewers. The authors stated that this screening was performed by “applying exclusion criteria using the Rayyan web-based platform”, without providing further details. This screening brought the numbers of potential references from 12,402 to 429, which is a large decrease. It is not described how accurate this screening program is and whether potentially relevant literature may have been missed by the program. The authors of the NMA were also unclear as to how they screened for studies that included populations with or without metastatic disease, and some terminology in the publication was not clear (e.g. “stratification”). Further, it was unclear if the authors initially reviewed subgroups from studies that included patients with and without mHPSC and subsequently only included the subgroup with mHPSC. This would be problematic in the NMA if the initial randomization in the individual studies was not stratified by mHPSC (e.g., randomization is not maintained in the subgroup analysis in the individual study, thereby creating a methodological issue in the NMA).

In terms of risk of bias for the included studies, while the authors reported that they found the overall quality of the included trials to be high with low risk of selection and reporting bias for the main outcomes, they rated the risk of performance and detection bias as high. For the outcome of AEs, the authors reported the risk of attrition and reporting bias to be high due to incomplete information and the lack of subgroup analyses by the patients' metastatic status. It was also noted by the authors that while the GRADE quality for direct comparisons of the AE outcome was intermediate, it was low in most cases for the NMA evidence.

While the authors performed a sensitivity analysis which excluded the trial with patients without metastatic disease (STAMPEDE), the results were not consistent with the overall analysis, and the authors did not comment further on the inconsistencies between the overall analysis and the sensitivity analysis. No further sensitivity analyses were included.

Several sources of clinical heterogeneity must be noted. Study and patient populations varied between the included articles and no formal assessment of the clinical heterogeneity was included. Some of the trials did not have baseline data on several parameters, making it difficult to ascertain whether the study populations were similar. Differences were apparent in factors such as the prior number of therapies and treatments allowed for inclusion into the trial, performance status and disease stage. The ADT groups were also varied between the studies (e.g. medical vs chemical castration), and some of the ADT protocols in the studies were not clearly reported (e.g. reporting solely "ADT" with no further details). There were also inconsistencies between included studies on outcome definitions. While the authors of this publication defined their outcome definitions, the definitions for these outcomes were not always consistent in the included studies. This is apparent in the inclusion/exclusion of certain studies based on PFS definitions. There was also a large range in follow-up times reported between the studies (range: 14.4 to 83.2 months), and it was unclear whether the authors used similar follow-up times points between studies to reduce heterogeneity. Additionally, there was heterogeneity in study design as a mix of open-label and double-blind trials were included.

Currently approved treatment for Canadian men with mHPSC include ADT, chemotherapy (e.g., docetaxel) or chemotherapy plus ADT; the NMA included many treatments, some of which are not relevant for the Canadian context (e.g., docetaxel plus bisphosphonate, abiraterone, enzalutamide, bisphosphonates, celecoxib and celecoxib plus bisphosphonate); however, CGP stated that all of the drugs included in this NMA are Health Canada approved for other indications, and available for use by clinicians in an off-label manner, especially for patients with mHPSC). Additionally, some outcomes were not included that would have been relevant to the populations (e.g. health related quality of life data).

7.3 Summary of a published NMA comparing first-line treatments for mCSPC, specifically combinations of ADT and one (or more) of taxane-based chemotherapy, and androgen receptor-targeted therapies.

Objective

To summarize and critically appraise the methods and findings of the published NMA comparing first-line treatments for mCSPC (used interchangeably for the term metastatic hormone-sensitive prostate cancer (mHSPC) in this publication), specifically combinations of ADT and one (or more) of taxane-based chemotherapy, and androgen receptor-targeted therapies.[37]

CGP had identified differences in treatment preference depending on disease burden of patients. For example, chemotherapy was stated as the preferred treatment choice for patients with high disease burden. This NMA addresses this as it includes a subgroup analysis of patients with low- and high-disease burden. Topics considered in this section are provided as supporting information. The information has not been systematically reviewed.

Methods

Systematic Review

The published NMA was based on an SLR of papers published from January 2014 up to June 2019 from the following databases: MEDLINE, Embase, Science-Direct, Cochrane Libraries, HTA database, and Web of Science. The search strategy used a range of keywords related to RCTs and mHSPC. Additional searches were performed of grey literature and the abstracts of oncology and urology meetings published in the five years preceding the review. RCTs and quasi-RCTs of patients with mHSPC who were receiving first-line therapy for metastatic disease, combining one (or more) of the interventions of interest, specifically taxane-based

chemotherapy (i.e. docetaxel), and androgen-axis-targeted therapies (i.e., abiraterone acetate, apalutamide, and enzalutamide), were eligible for inclusion in the NMA (Table 47).

Titles and abstracts were screened by two independent authors and a third author was consulted to resolve any discrepancies. Full texts of potentially relevant articles were then screened for inclusion to determine whether they met the eligibility criteria. When there were multiple reports referring to the same trial, only the most recent paper was included. Data were extracted from relevant full-text studies by two independent authors into a form developed *a priori*.

Table 47: Study selection criteria to identify trials for the SLR

Population	Patients with mHSPC receiving first-line therapy for metastatic disease
Interventions and comparators	Taxane-based chemotherapy or androgen-axis-targeted therapies
Outcomes	Primary: OS Secondary: PFS
Study design	RCT or quasi-RCT
Abbreviations: mHSPC: metastatic hormone sensitive prostate cancer; OS: Overall survival; PFS: Progression-free survival; RCT: Randomized controlled trial	

Network Meta-Analysis

The primary outcome for this NMA was OS, defined as time from randomization to death from any cause. Subgroup analysis of the primary outcome of OS was performed based on volume of disease (high vs. low, according to the CHAARTED criteria). PFS was also a secondary outcome of interest and was defined as time from randomization to PSA progression, and radiographic and or/clinical progression. The outcome definitions for the NMA were provided by the NMA authors, the definitions in the individual studies may have varied.

HRs and/or events of interest were extracted from the included studies. Pairwise meta-analysis of the studies was performed, although the results of this analysis was not reported. Indirect comparisons of treatment arms were performed using a Bayesian approach according to the NICE framework. Fixed-effects models were used, and random-effects models were performed as a sensitivity analysis (however no clear rationale was provided for this model choice). Analyses were conducted using Markov chain Monte Carlo methods and involved a 50,000 run-in iteration phase and a 50,000-iteration phase for parameter estimation. A non-informative prior distribution was used. Convergence was confirmed by inspection of the trace-and through the calculation of the Gelman-Rubin-Brooks statistic. A consistency model was fitted, and heterogeneity was assessed using a common variance. Treatment effects were estimated using posterior means and 95% CrIs and included both direct and indirect evidence. Heterogeneity was visually assessed using forest plots and the I2 statistic, whereby an I2> 50% was considered to present statistically significant heterogeneity. Model fit for both the fixed and random effects models was assessed using the Bayesian DIC. All analyses were conducted using RJAGS and R. Risk of bias (RoB) was assessed using the Cochrane RoB criteria (no details provided as to the number of authors conducting the assessments).

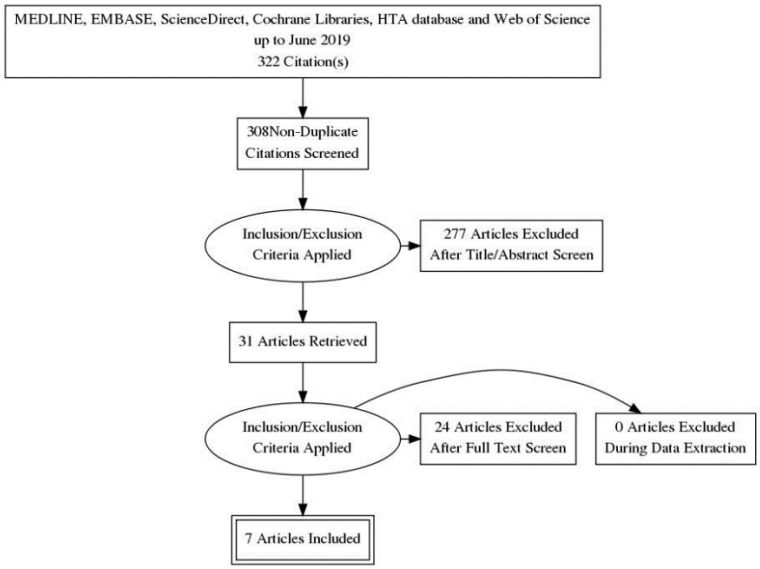
Results

Networks

The literature search identified 308 records (after duplicates were removed) (Figure 34), of which seven trials met the eligibility criteria. The ARCHES trial was further excluded as the survival data were considered immature. In addition, only the subgroup of patients who did not receive early docetaxel were included in the analysis. The network used an ADT group as the comparator and is depicted in Figure 35. Five trials (GETUG-AFU15, CHAARTED, LATITUDE, ENZAMET, and TITAN) reported data based on volume

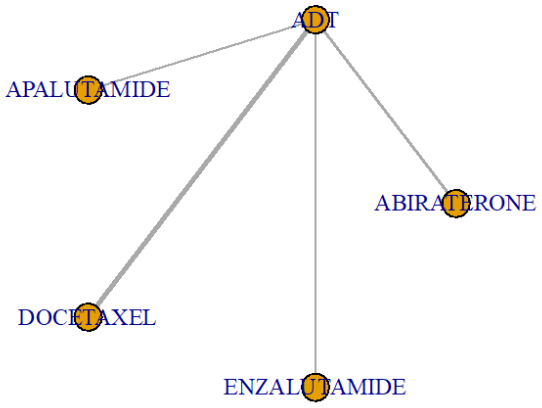
of disease and were therefore included in the subgroup analysis for volume of disease for the outcome of OS. Five trials (GETUG-AFU15, CHAARTED, STAMPEDE, ENZAMET, and TITAN) were included in the analysis of PFS for the full population. Details of whether the disease volume definitions for the subgroup analyses were applied retrospectively or as a pre-specified analysis in the studies was not reported in the NMA.

Figure 34: Study selection flow diagram



Source: Reprinted from European Urology, 77(3), Sathianathen, et al., Indirect comparisons of efficacy between combination approaches in metastatic hormone-sensitive prostate cancer: a systematic review and network meta-analysis, pp.365-72, Copyright 2020, with permission from Elsevier.[37]

Figure 35: Evidence networks for network meta-analysis of OS for overall analysis (both high and low volume disease patients).



Thickness of each arm is proportional to number of studies participating in network. Lines demonstrate studies with direct comparisons and line thickness corresponds to number of studies

Source: Reprinted from European Urology, 77(3), Sathianathen, et al., Indirect comparisons of efficacy between combination approaches in metastatic hormone-sensitive prostate cancer: a systematic review and network meta-analysis, pp.365-72, Copyright 2020, with permission from Elsevier.[37]

Of the five included studies, three trials used docetaxel + ADT (CHAARTED, STAMPEDE, GETUG-AFU 15), two used abiraterone + prednisone + ADT (STAMPEDE, LATITUDE), one used enzalutamide + ADT (ENZAMET), and one used apalutamide + ADT (TITAN). All experimental treatments were given in addition to the control treatments.

OS was the primary outcome of four trials (GETUG-AFU15, CHAARTED, STAMPEDE and ENZAMET), and two primary outcomes of OS and radiographic PFS were the outcomes for two trials (LATITUDE and TITAN). Median follow-up ranged from 22.7 months to 82.9 months. Two studies allowed patients with pre-treatment with docetaxel (ENZAMET: 15% in the control group,17% in the experimental group within three months prior to randomization; TITAN: 10% in the control group 11% in the experimental group). In studies reporting on these characteristics, Gleason grade groups 4 and 5 percentage of patients ranged from 57-97% in the control groups and from 55-98% in the treatment groups, age medians ranged from 63 years to 69 years in the control groups and from 63 years to 69.2 years in the treatment groups, and PSA median levels ranged from 25.8 ng/nL to 56 ng/nL in the control group and from 26.7 ng/nL to 52.1 ng/nL.

There was variation between the included studies for patient characteristics such as performance status (e.g., inclusion of patients with ECOG ≤ 1, ECOG ≤ 2, WHO ≤ 2, or Karnofsky ≥ 70), and disease stage (e.g. variation in inclusion criteria for metastatic disease). The definitions of disease volume were either not reported, or varied between studies, and allowance for different previous treatments was different between the trials. The control group treatments also varied between studies (e.g., medical or surgical castration, medical or surgical castration ± nonsteroidal antiandrogen, or 'ADT' with no further details provided), as did the treatment regimen for the analyses of docetaxel (e.g. 'Docetaxel up to nine cycles without prednisone', 'Docetaxel up to six cycles without prednisone', 'Docetaxel up to six cycles with prednisone 10 mg ± zoledronic acid').

The risk of bias of each individual study was assessed and reported in the supplemental data. It was reported in the publication that the trials were overall considered of moderate quality in terms of risk of bias. They assessed all studies to be at low risk of bias from sequence generation, allocation concealment, detection bias for the outcome of OS, attrition, and other bias. Bias from other sources (performance, detection for the outcome of PFS) had mixed assessments (low/high/unclear) and the report stated that downgrading of quality from risk of bias was primarily due to lack of blinding.

Results for OS

The results of the analysis for the full group (both low and high volume disease) suggested that each of the combination treatments was favoured over ADT alone for OS (Table 48 and Source: Reprinted from European Urology, 77(3), Sathianathen, et al., Indirect comparisons of efficacy between combination approaches in metastatic hormone-sensitive prostate cancer: a systematic review and network meta-analysis, pp.365-72, Copyright 2020, with permission from Elsevier.[37]

Figure 36). Enzalutamide was favoured over docetaxel (HR=0.66; 95% CrI: 0.45-0.94) and ADT (HR=0.53; 95% CrI: 0.37-0.75). The publication reported no statistical heterogeneity (I2=0%).

The results of the subgroup analysis of patients with low-volume disease suggested only enzalutamide was favoured over ADT alone for OS (HR=0.38; 95% CrI: 0.20-0.68), and enzalutamide was also favoured over docetaxel (HR=0.38; 95%CrI: 0.19-0.72) (Table 48 and Source: Reprinted from European Urology, 77(3), Sathianathen, et al., Indirect comparisons of efficacy between combination approaches in metastatic hormone-sensitive prostate cancer: a systematic review and network meta-analysis, pp.365-72, Copyright 2020, with permission from Elsevier.[37]

Figure 36). The publication reported no statistical heterogeneity (I2=8%).

The results of the subgroup analysis of patients with high-volume disease suggested that each of the combination treatments was favoured over ADT alone for OS (Table 48 and Source: Reprinted from European Urology, 77(3), Sathianathen, et al., Indirect comparisons of efficacy between combination approaches in metastatic hormone-sensitive prostate cancer: a systematic review and network meta-analysis, pp.365-72, Copyright 2020, with permission from Elsevier.[37]

Figure 36). Enzalutamide was favoured over ADT (HR=0.62; 95%CrI: 0.40-0.95). The publication reported no statistical heterogeneity (I2=1%).

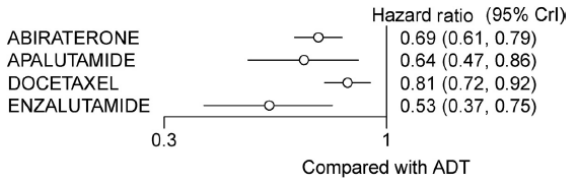
Table 48: Comparison of each treatment[a] for overall survival

	ADT	Abiraterone	Apalutamide	Docetaxel
Full group analysis (both low and high volume disease)				
ADT				
Abiraterone	**0.69 (0.61-0.79)**			
Apalutamide	**0.64 (0.47-0.86)**	0.92 (0.67-1.3)		
Docetaxel	**0.81 (0.72-0.92)**	1.2 (0.98-1.4)	1.3 (0.92-1.7)	
Enzalutamide	**0.53 (0.37-0.75)**	0.77 (0.53-1.1)	0.83 (0.52-1.3)	**0.66 (0.45-0.94)**
Low-volume disease				
ADT				
Abiraterone	0.72 (0.47-1.1)			
Apalutamide	0.63 (0.31-1.2)	0.87 (0.38-1.9)		
Docetaxel	1.0 (0.75-1.3)	1.4 (0.83-2.4)	1.6 (0.77-3.4)	
Enzalutamide	**0.38 (0.20-0.68)**	0.52 (0.24-1.1)	0.60 (0.24-1.5)	**0.38 (0.19-0.72)**
High-volume disease				
ADT				
Abiraterone	**0.71 (0.60-0.85)**			
Apalutamide	**0.69 (0.51-0.94)**	0.97 (0.68-1.4)		
Docetaxel	**0.72 (0.59-0.88)**	1.0 (0.78-1.3)	1.0 (0.72-1.5)	
Enzalutamide	**0.62 (0.40-0.95)**	0.88 (0.55-1.4)	0.90 (0.53-1.5)	0.86 (0.53-1.4)

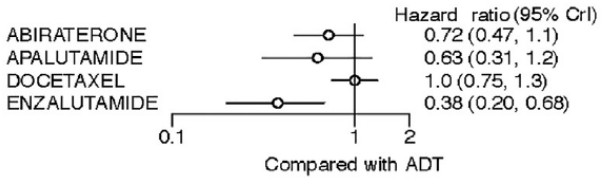
[a] Each treatment is in combination with ADT
Estimated HR reflect outcomes for treatment in rows compared to treatment in columns. Statistically significant comparisons are reported in bold.
Source: Reprinted from European Urology, 77(3), Sathianathen, et al., Indirect comparisons of efficacy between combination approaches in metastatic hormone-sensitive prostate cancer: a systematic review and network meta-analysis, pp.365-72, Copyright 2020, with permission from Elsevier.[37]

Figure 36: Overall survival for each treatment compared with ADT for A) full group analysis (regardless of disease volume), B) subgroup analysis of low-volume disease, and C) subgroup analysis of high-volume disease. Each treatment is in combination with ADT.

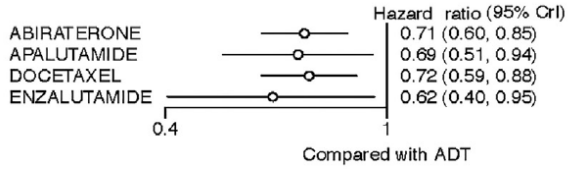
A – Full group analysis



B – Low-volume disease



C – High-volume disease



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Results for PFS

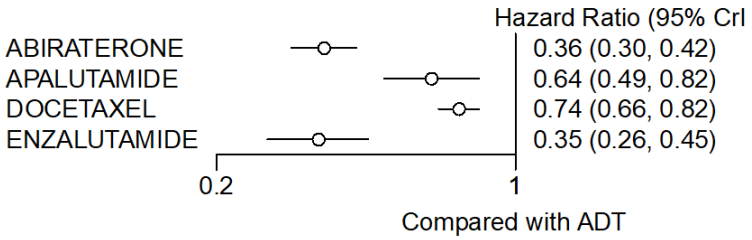
The results of the NMA for the overall analysis (both low and high volume disease) suggested that each of the combination treatments were favoured over ADT alone for PFS (Table 49 and Figure 37). Enzalutamide was also favoured over apalutamide (HR=0.54; 95% CrI: 0.37-0.79) and docetaxel (HR=0.47; 95% CrI: 0.35-0.63) but not over abiraterone. The publication reported no statistical heterogeneity (I2=4%), and a lower DIC for the fixed effect model than the random effects model (DIC 21.4 vs. 22.8).

Table 49: Comparison of each treatment[a] for progression-free survival

	ADT	Abiraterone	Apalutamide	Docetaxel
ADT				
Abiraterone	**0.36 (0.30-0.42)**			
Apalutamide	**0.64 (0.49-0.82)**	**1.8 (1.3-2.4)**		
Docetaxel	**0.74 (0.66-0.82)**	**2.1 (1.7-2.5)**	1.2 (0.88-1.5)	
Enzalutamide	**0.35 (0.26-0.45)**	0.97 (0.70-1.3)	**0.54 (0.37-0.79)**	**0.47 (0.35-0.63)**

[a] Each treatment is in combination with ADT
Estimated HR reflect outcomes for treatment in rows compared to treatment in columns. Statistically significant comparisons are reported in bold.
Source: Reprinted from European Urology, 77(3), Sathianathen, et al., Indirect comparisons of efficacy between combination approaches in metastatic hormone-sensitive prostate cancer: a systematic review and network meta-analysis, pp.365-72, Copyright 2020, with permission from Elsevier.[37]

Figure 37: Progression-free survival for each treatment compared with ADT



Source: Reprinted from European Urology, 77(3), Sathianathen, et al., Indirect comparisons of efficacy between combination approaches in metastatic hormone-sensitive prostate cancer: a systematic review and network meta-analysis, pp.365-72, Copyright 2020, with permission from Elsevier.[37]

Critical Appraisal of Network Meta-Analysis

The published NMA was critically appraised according to recommendations of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons and Network Meta-Analyses.[41] Details and commentary for each of the relevant items identified by the ISPOR group are provided in Table 50.

Table 50: Adapted ISPOR Questionnaire to Assess the Credibility of an Indirect Treatment Comparison or NMA adapted from Jansen et al.[41]

ISPOR Questions	Details and Comments
1. Is the population relevant?	The population was relevant to the patient population under CADTH review for the outcomes of OS and PFS.
2. Are any critical interventions missing?	The NMA appeared to include all relevant interventions for this patient population.
3. Are any relevant outcomes missing?	The NMA reported outcomes for OS and PFS only. AEs or HRQoL were not specified as outcomes for the NMA.
4. Is the context (e.g., settings and circumstances) applicable to your population?	The context may not have been fully applicable to the population. Some of the comparators included were not relevant and approved for clinical use in Canada for mHSPC. Additionally, patients who received early docetaxel with enzaulatmide and ADT were excluded from the NMA as well as patients who were treated with enzalutamide with ADT and compared to ADT alone.
5. Did the researchers attempt to identify and include all relevant randomized controlled trials?	The researchers performed a SLR to identify all trials with limited inclusion criteria described. The publication described the information sources, search strategy and selection criteria. Limited details of the

ISPOR Questions	Details and Comments
	inclusion criteria were provided; however, the criteria were not clearly defined.
6. Do the trials for the interventions of interest form one connected network of randomized controlled trials?	The trials in the analysis for each outcome formed a connected network of RCTs.
7. Is it apparent that poor quality studies were included thereby leading to bias?	The risk of bias of each individual study was assessed and reported in the supplemental data. The publication reported that the trials were overall considered moderate quality in terms of risk of bias. They assessed all studies to be at low risk of bias from sequence generation, allocation concealment, detection bias for the outcome of OS, attrition, and other bias. Bias from other sources (performance, detection for the outcome of PFS) had mixed assessments (low/high/unclear) and the report stated that downgrading of quality from risk of bias was primarily due to lack of blinding.
8. Is it likely that bias was induced by selective reporting of outcomes in the studies?	Selective outcome reporting was not explicitly reported by the authors in the risk of bias assessments. The authors ranked “other sources of bias” as low risk, and selective outcome reporting bias would likely be included under this category.
9. Are there systematic differences in treatment effect modifiers (i.e. baseline patient or study characteristics that impact the treatment effects) across the different treatment comparisons in the network?	There are differences in the patient and study characteristics from the included studies that may have affected the results of the NMA. Clinical heterogeneity was present in the previous treatments, disease state and treatment groups between the studies. There was also some missing data for these clinical features. Furthermore, there was heterogeneity in the inclusion criteria of the trials, trial design (open-label vs. double-blind), outcome definitions and study duration.
10. If yes (i.e. there are such systematic differences in treatment effect modifiers), were these imbalances in effect modifiers across the different treatment comparisons identified prior to comparing individual study results?	The imbalances in the potential effect modifiers were not identified prior to comparing the individual studies.
11. Were statistical methods used that preserve within-study randomization? (No naïve comparisons)	It is unclear based on the methods provided whether within-study randomization was preserved. It was unclear if the authors initially reviewed subgroups from studies that included patients with and without mHSPC, and subsequently only included the subgroup with mHSPC.
12. If both direct and indirect comparisons are available for pairwise contrasts (i.e. closed loops), was agreement in treatment effects (i.e. consistency) evaluated or discussed?	This was a star shaped network with no closed loops. There were only direct comparisons to ADT and no direct evidence for the combination treatments. All evidence for the comparisons for combination treatments (drug added on to ADT versus other drug added on to ADT) were only based on indirect evidence.
13. In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?	This was a star shaped network with no closed loops. There were only direct comparisons to ADT and no direct evidence for the combination treatments. All evidence for the comparisons for combination treatments (drug added on to ADT versus other drug added on to ADT) were only based on indirect evidence.
14. With inconsistency or an imbalance in the distribution of treatment effect modifiers across the different types of comparisons in the network of trials, did the researchers attempt to minimize this bias with the analysis?	The researchers did not attempt to minimize imbalances in the analysis.
15. Was a valid rationale provided for the use of random effects or fixed effect models?	The publication included a sensitivity analysis using a random-effects model; however, no rationale was provided as to why the fixed-effects

ISPOR Questions	Details and Comments
	model was provided as the primary analysis (although it was assumed that fixed-effects model was provided due to the lower DIC implying a better model fit). No further sensitivity analyses were performed.
16. If a random effects model was used, were assumptions about heterogeneity explored or discussed?	The publication included a sensitivity analysis using a random-effects model; however, the assumptions about heterogeneity were not explored or discussed.
17. If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with pre-specified covariates performed?	No subgroup analyses were conducted to explore potential sources of clinical heterogeneity.
18. Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	Graphical representations of the evidence networks and number of RCTs were provided.
19. Are the individual study results reported?	Individual study results were not provided.
20. Are results of direct comparisons reported separately from results of the indirect comparisons or network meta-analysis?	The results are were not reported separately.
21. Are all pairwise contrasts between interventions as obtained with the network meta-analysis reported along with measures of uncertainty?	All pairwise point estimates and CrIs were provided.
22. Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	The publication included the SUCRA rankings stating the probabilities of the preferred treatments. No uncertainties were provided.
23. Is the impact of important patient characteristics on treatment effects reported?	The impact of important patient characteristics on treatment effects was not reported or discussed.
24. Are the conclusions fair and balanced?	Some of the conclusions appeared to be fair and balanced; however, it was not possible to make conclusions about any “superiority” of the treatments. The authors described how the safety profiles and individual cases should be considered in treatment selection. Some limitations of the NMA were recognized and reported; however, a number of important limitations were missed (as discussed in the limitations sections of this critical appraisal).
25. Were there any potential conflicts of interest?	The corresponding author declared having served as an advisor and/or paid speaker for Astellas, Janssen, Bayer, Ferring, Ipsen and Astra Zeneca.
26. If yes, were steps taken to address these?	No steps were described to address any potential conflict of interest.

Summary

A published NMA was identified comparing ezalutamide to other relevant treatments for men with mHSPC. This NMA compared relevant treatments combined with ADT for the outcomes of OS and PFS. Subgroup analyses were performed for OS by low and high disease volume. The subgroup analysis of patients with low and high disease volume was of interest to the CADTH Review Team. Five relevant trials were identified from a SLR.

For the outcome of OS in the full group and the low volume disease subgroup, enzalutamide was favoured over ADT alone and docetaxel but not over any of the other combination treatments (apalutamide or abiraterone). For the subgroup analysis of OS in the high volume disease group, enzalutamide was not favoured over ADT alone or any of the combination treatments (abiraterone, docetaxel, or enzalutamide). For the subgroup analysis of OS in the high-volume disease group, enzalutamide was favoured over ADT alone but not over any of the other combination treatments (abiraterone, apalutamide, docetaxel). For the outcome of PFS, enzalutamide was favoured over ADT alone, apalutamide and docetaxel.

Several limitations of the study must be considered. The authors did not clearly describe the methodology for both the SLR and the NMA analyses. Only a broad description of inclusion criteria was provided. None of the specific comparator was described. There was also a lack of clarity on exclusion criteria, with no details provided, and no list of excluded studies was provided. This is apparent

in that one trial was originally included (ARCHES) but later excluded due to not having mature survival data. It is not clear why this study was deemed eligible for inclusion originally and then excluded at a later stage. Eligible studies were limited to publications published during January 2014 to June 2019, leading to the potential of excluding older trials that may still be relevant to the research question. A list of the conference abstracts that were searched was also not provided, and it is not clear whether full text screening was done by two independent authors.

The authors reported that they found the overall quality of the included trials to be high with low risk of selection and reporting bias for the main outcomes. However, they rated the risk of performance bias high for all trials except TITAN, and a mix of high and low for detection bias of PFS, with the TITAN trial assessed as 'unclear'. The authors stated that downgrading of quality from risk of bias was primarily due to lack of blinding. While OS is an objective endpoint, PFS is more subjective and prone to bias if unblinded. Additionally, it was not clear if the PFS in the individual studies was based on investigator or central assessment, or whether assessment was consistent across studies, which introduces a potential source of heterogeneity.

Furthermore, the network identified for the full analysis of OS (both low and high-volume disease), was a star shaped network with no closed loops. There were only direct comparisons to ADT and no direct evidence for the combination treatments. All evidence for the comparisons for combination treatments (drug added on to ADT versus other drug added on to ADT) were based only on indirect evidence and could therefore not be directly compared. No network map was provided for the OS analysis by disease burden or for the outcome of PFS; therefore, it was not possible to assess the connectivity of the networks.

Several sources of clinical heterogeneity must be noted. Study and patient populations varied between the included articles and no formal assessment of the clinical heterogeneity was included. Some of the trials did not have baseline data on several parameters, making it difficult to ascertain whether the study populations were similar. Differences were apparent in factors such as the therapies and treatments allowed for inclusion into the trial (e.g., variations in pre-treatment allowance, performance status, Gleason Grade, PSA, age range, and disease stage). The ADT groups were also varied between the studies (e.g. medical vs. chemical castration), and some of the ADT protocols in the studies were not clearly reported (e.g. reporting solely "ADT + placebo" with no further details). There was also no discussion in the publication about any inconsistencies between outcome definitions in the original studies. While the authors of this publication defined their outcome definitions, it was not clear whether these definitions were the same as those in the included studies. Furthermore, definition of disease volume was inconsistent between studies. While the publication stated that volume of disease was defined according to CHAARTED criteria, it was not clear how these criteria were chosen or applied, and the extent and validity to its application to trials using different criteria. It was not clear whether the definitions provided by the NMA authors were applied retrospectively, and/or whether the included studies also pre-specified definitions or applied their definitions as a post-hoc analysis. The follow-up times reported between the studies ranged from 22.7 to 82.9 months. It was unclear whether the NMA was based on outcome data taken from similar time points in each study to reduce clinical heterogeneity. Additionally, there was heterogeneity in study design as a mix of open-label and double-blind trials were included (study design for each of the trials was not reported in this publication; however, other NMAs that included the same trials reported this information).

Further, it was unclear if the authors initially reviewed subgroups from studies that included patients with and without mHSPC, and subsequently only included the subgroup with mHSPC (e.g. for docetaxel, in the STAMPEDE trial, several patient characteristics were listed as "not reported" separately for the metastatic subgroup). This is a potential source of bias in the NMA if the initial randomization in the individual studies was not stratified by mHSPC (e.g. randomization may not be maintained in the subgroup analysis for the individual studies, which could potentially bias the treatment effect estimate at the individual study level). The subgroup analyses for low and high-volume disease patients could also be potentially biased if randomization of the individual studies was not stratified on this variable. Stratification of randomization in the individual studies was not reported; thus, the potential for bias remains unknown.

While the efficacy outcomes were evaluated in this NMA, some outcomes were not included that would have been relevant to the populations (e.g. adverse events (AEs) and health related quality of life data (HRQoL)). Currently approved treatment for Canadian men with mHSPC include ADT, chemotherapy (e.g. docetaxel) or chemotherapy plus ADT; the NMA included some treatments, which are not currently approved in Canada for mHSPC. Additionally, as the treatment dosages were not reported in the NMA, it was not possible to evaluate the relevance of the treatment dosages to what it used in Canada.

8 Comparison with Other Literature

The CADTH CGP and the CADTH Methods Team did not identify other relevant literature providing supporting information for this review.

9 About this Document

This Clinical Guidance Report was prepared by the CADTH Genitourinary Clinical Guidance Panel and supported by the CADTH Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on enzalutamide (Xtandi) for metastatic castration sensitive prostate cancer. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant CADTH Economic Guidance Report. Details of the pCODR review process can be found on the CADTH website (www.cadth.ca/pcodr).

CADTH considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the Procedures for the CADTH pan-Canadian Oncology Drug Review. The sponsor, as the primary data owner, did not agree to the disclosure of some clinical information which was provided to pERC for their deliberations, and this information has been redacted in this publicly posted Guidance Report.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report.

Appendix 1: Literature Search Strategy and Detailed Methodology

1. Literature search via Ovid platform

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** February 2020**, Embase** 1974 to 2020 March 16**, Ovid MEDLINE(R) ALL** 1946 to March 17, 2020
Search Strategy:

#	Searches	Results
1	(enzalutamide* or xtandi* or kstandi* or MDV3100 or MDV-3100 or ASP-9785 or ASP9785 or 93T0T9GKNU).ti,ab,ot,kf,kw,hw,nm,rn.	8619
2	Prostatic neoplasms/	138371
3	(prostat* adj3 (neoplasm* or cancer* or carcinoma* or adenocarcinoma*)).ti,ab,kf,kw.	361748
4	(mHSPC or mCSPC).ti,ab,kf,kw.	395
5	or/2-4	387897
6	1 and 5	7707
7	6 use medall	1820
8	limit 7 to english language	1716
9	6 use cctr	597
10	*Enzalutamide/	1620
11	(enzalutamide* or xtandi* or kstandi* or MDV3100 or MDV-3100 or ASP-9785 or ASP9785).ti,ab,kw,dq.	6692
12	10 or 11	6761
13	exp Prostate carcinoma/ or prostate cancer/	326092
14	(prostat* adj3 (neoplasm* or cancer* or carcinoma* or adenocarcinoma*)).ti,ab,dq,kw.	360661
15	(mHSPC or mCSPC).ti,ab,dq,kw.	395
16	or/13-15	428381
17	12 and 16	6327
18	17 use oemezd	4035
19	18 not conference abstract.pt.	1892
20	limit 19 to english language	1769
21	18 and conference abstract.pt.	2143
22	limit 21 to english language	2143
23	limit 22 to yr="2015 -Current"	1793
24	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.	1171341
25	Randomized Controlled Trial/	1096617
26	exp Randomized Controlled Trials as Topic/	317668
27	"Randomized Controlled Trial (topic)"/	175547
28	Controlled Clinical Trial/	557229
29	exp Controlled Clinical Trials as Topic/	330098
30	"Controlled Clinical Trial (topic)"/	10619
31	Randomization/	188608
32	Random Allocation/	205455
33	Double-Blind Method/	438114
34	Double Blind Procedure/	170433
35	Double-Blind Studies/	284657
36	Single-Blind Method/	84780
37	Single Blind Procedure/	38247
38	Single-Blind Studies/	86774

39	Placebos/	349718
40	Placebo/	347420
41	Control Groups/	112222
42	Control Group/	112126
43	(random* or sham or placebo*).ti,ab,hw,kf,kw.	4579539
44	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	874666
45	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	3980
46	(control* adj3 (study or studies or trial* or group*)).ti,ab,kf,kw.	3086034
47	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw.	107340
48	allocated.ti,ab,hw.	205164
49	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw.	137617
50	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	32500
51	(pragmatic study or pragmatic studies).ti,ab,hw,kf,kw.	1222
52	((pragmatic or practical) adj3 trial*).ti,ab,hw,kf,kw.	14692
53	((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	21917
54	(phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kf,kw.	156748
55	or/24-54	6457057
56	(8 or 20) and 55	931
57	56 or 9	1528
58	remove duplicates from 57	1150
59	23 and 55	552
60	58 or 59	1702

2. Literature search via PubMed

A limited PubMed search was performed to retrieve citations not found in the MEDLINE search.

Search	Query	Items found
#22	Search **#21 AND publisher[sb]** Filters: **English**	24
#21	Search **#7 AND #20** Filters: **English**	435
#20	Search **#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19** Filters: **English**	2770477
#19	Search **(phase III[tiab] OR phase 3[tiab]) AND (study[tiab] OR studies[tiab] OR trial*[tiab])** Filters: **English**	41637
#18	Search **quasiexperimental study[tiab] OR quasi-experimental study[tiab] OR quasiexperimental studies[tiab] OR quasi-experimental studies[tiab] OR quasiexperimental trial*[tiab] OR quasi-experimental trial*[tiab]** Filters: **English**	4940
#17	Search **pragmatic study[tiab] OR pragmatic studies[tiab] OR pragmatic trial*[tiab] OR practical trial*[tiab]** Filters: **English**	1556
#16	Search **(equivalence[tiab] OR superiority[tiab] OR non-inferiority[tiab] OR noninferiority[tiab]) AND (study[tiab] OR studies[tiab] OR trial*[tiab)** Filters: **English**	34819
#15	Search **open-label[tiab] AND (study[tiab] OR studies[tiab] or trial*[tiab])** Filters: **English**	40378
#14	Search **random allocation[tiab] OR randomly allocated[tiab]** Filters: **English**	28526

Search	Query	Items found
#13	Search **nonrandom*[tiab] OR non-random*[tiab] OR quasi-random*[tiab] OR quasirandom*[tiab]** Filters: **English**	41054
#12	Search **control group*[tiab]** Filters: **English**	386901
#11	Search **(control[tiab] OR controlled[tiab]) AND (study[tiab] OR studies[tiab] OR trial*[tiab])** Filters: **English**	1698794
#10	Search **(singl*[tiab] OR doubl*[tiab] OR tripl*[tiab] OR trebl*[tiab]) AND (blind*[tiab] OR dumm*[tiab] OR mask*[tiab])** Filters: **English**	182746
#9	Search **random*[tiab] OR sham[tiab] OR placebo*[tiab]** Filters: **English**	1185323
#8	Search **Randomized Controlled Trial[pt] OR Randomized Controlled Trials as Topic[mh] OR Controlled Clinical Trial[pt] OR Controlled Clinical Trials as Topic[mh] OR Random Allocation[mh] OR Double-Blind Method[mh] OR Single-Blind Method[mh] OR Placebos[mh] OR Control Groups[mh]** Filters: **English**	769464
#7	Search **#2 AND #6** Filters: **English**	1693
#6	Search **#3 OR #4 OR #5** Filters: **English**	156146
#5	Search **mHSPC[tiab] OR mCSPC[tiab]** Filters: **English**	80
#4	Search **prostat*[tiab] AND (neoplasm*[tiab] OR cancer*[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab])** Filters: **English**	139347
#3	Search **Prostatic neoplasms[mh:noexp]** Filters: **English**	108733
#2	Search **MDV 3100[supplementary concept] OR enzalutamide*[tiab] OR xtandi*[tiab] OR kstandi*[tiab] OR MDV3100[tiab] OR MDV-3100[tiab] OR ASP-9785[tiab] OR ASP9785[tiab] OR 93T0T9GKNU[rn]** Filters: **English**	1798
#1	Search **MDV 3100[supplementary concept] OR enzalutamide*[tiab] OR xtandi*[tiab] OR kstandi*[tiab] OR MDV3100[tiab] OR MDV-3100[tiab] OR ASP-9785[tiab] OR ASP9785[tiab] OR 93T0T9GKNU[rn]**	1908

3. **Cochrane Central Register of Controlled Trials (CENTRAL)**
   (searched via Ovid)

4. Grey literature search via**:**

   Clinical trial registries:

   US National Library of Medicine. ClinicalTrials.gov
   https://clinicaltrials.gov/

   WHO
   http://apps.who.int/trialsearch/

   Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
   http://www.canadiancancertrials.ca/

   Health Canada Clinical Trials database
   https://health-products.canada.ca/ctdb-bdec/index-eng.jsp

   Search: Xtandi/enzalutamide, prostate cancer

   Select international agencies including:

US Food and Drug Administration (FDA)
https://www.fda.gov/

European Medicines Agency (EMA)
https://www.ema.europa.eu/

Search: Xtandi/enzalutamide, prostate cancer

Conference abstracts:

American Society of Clinical Oncology (ASCO)
https://www.asco.org/

European Society for Medical Oncology (ESMO)
https://www.esmo.org/

Search: Xtandi/enzalutamide, prostate cancer — last five years

Detailed Methodology

The literature search for clinical studies was performed by an information specialist from the CADTH Methods Team using the abovementioned search strategy, which was peer-reviewed according to the *PRESS Peer Review of Electronic Search Strategies* checklist (https://www.cadth.ca/resources/finding-evidence/press).[43]
Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, the Cochrane Central Register of Controlled Trials (CENTRAL) via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Xtandi/enzalutamide and prostate cancer.

Search filters were applied to limit retrieval to randomized controlled trials or controlled clinical trials. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents but not limited by publication year. The search is considered up to date as of July 23, 2020.

Grey literature (literature that is not commercially published) was identified by searching websites from relevant sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters).[44] Included in this search were the websites of regulatory agencies (US Food and Drug Administration and European Medicines Agency), clinical trial registries (US National Institutes of Health's clinicaltrials.gov and Canadian Partnership Against Cancer Corporation's Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) were searched manually for conference years not available in Embase. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the CADTH Clinical Guidance Panel. As well, the manufacturer of the drug was contacted for additional information, as required by the CADTH Review Team.

Study Selection

One member of the CADTH Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. One member of the CADTH Methods Team made the final selection of studies to be included in the review.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

Quality Assessment

Assessment of study bias was performed by one member of the CADTH Methods Team with input provided by the Clinical Guidance Panel and other members of the CADTH Review Team. SIGN–50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the CADTH Review Team.

Data Analysis

No additional data analyses were conducted as part of the CADTH review.

Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and CADTH:

- The Methods Team wrote a summary of background clinical information, a systematic review of the evidence, interpretation of the systematic review, and summaries of evidence for supplemental questions.
- The CADTH Clinical Guidance Panel provided guidance and developed conclusions on the net clinical benefit of the drug.
- CADTH wrote summaries of the input provided by patient advocacy groups, by the Provincial Advisory Group (PAG), and by Registered Clinicians.

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