CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Apalutamide (Erleada) for metastatic Castration Sensitive Prostate Cancer

April 22, 2020

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INQUIRIES

Inquiries and correspondence about the pan-Canadian Oncology Drug Review (pCODR) should be directed to:

pan-Canadian Oncology Drug Review
154 University Avenue, Suite 300
Toronto, ON
M5H 3Y9

Telephone: 613-226-2553
Toll Free: 1-866-988-1444
Fax: 1-866-662-1778
Email: info@pcodr.ca
Website: www.cadth.ca/pcodr

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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 apalutamide (Erleada) for metastatic castration sensitive prostate cancer (mCSPC). 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 regarding apalutamide (Erleada) for mCSPC conducted by the Clinical Guidance Panel (CGP) and the pCODR 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 on apalutamide (Erleada) for mCSPC, a summary of submitted Provincial Advisory Group Input on apalutamide (Erleada) for mCSPC , and a summary of submitted Registered Clinician Input on apalutamide (Erleada) for mCSPC, 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 apalutamide in combination with androgen deprivation therapy (ADT) for patients with metastatic, castration-sensitive prostate cancer (mCSPC).

Apalutamide is an orally administered androgen receptor inhibitor binding directly to the ligand-binding domain of the androgen receptor. Apalutamide has a Health Canada indication reflecting the requested patient population for reimbursement.

The Health Canada approved indication is for the treatment of mCSPC. Apalutamide is administered orally at a recommended dose of 240mg (four 60mg tablets) once daily. Patients should concurrently be receiving a gonadotropin-releasing hormone (GnRH) analogue or should have a bilateral orchiectomy.[1]

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included one randomized-controlled trial (RCT). The results of the TITAN trial (N=1052) are presented below.

TITAN

The TITAN trial was a phase III, randomized, double-blind, placebo-controlled, multinational trial comparing apalutamide with placebo, when administered with concurrent androgen deprivation therapy (ADT), in patients with mCSPC. To be eligible for inclusion in the trial, patients had to have mCSPC documented by positive bone scan, an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) grade of 0 or 1. Subjects could have received up to six cycles of docetaxel for mCSPC with the last dose administered ≤2 months prior to randomization. All subjects could have received ≤6

months of ADT prior to randomization and could have received a maximum of one course of radiation or surgical intervention for mCSPC.[2]

Eligible patients were randomized in a 1:1 ratio to receive apalutamide (240 mg per day) (n=525) or matched placebo (n=527), added to ADT. Patients were stratified according to Gleason score at diagnosis (≤7 vs. >7, on a scale of 2 to 10, with higher scores indicating higher-grade cancer that may be more aggressive) geographic region (North America and European Union vs. all other countries) and previous treatment with docetaxel (yes vs. no).[2]

The dual-primary efficacy endpoints of this study were radiographic progression-free survival (rPFS) and overall survival (OS). Key secondary outcomes included: time to pain progression, time to cytotoxic chemotherapy, time to chronic opioid use, and time to skeletal-related events (SRE). Quality of life was an exploratory outcome.

Demographic and clinical characteristics appeared well balanced at baseline between the apalutamide + ADT and placebo + ADT treatment groups. Subjects were predominantly white (68%) males with a median age of 68 years (range: 43 to 94 years).[2] Twenty-three percent of subjects were over the age of 75.[2] Most subjects had metastatic disease (M1) at initial diagnosis.[2] Gleason score of 7 or less was recorded for 33% of subjects in the apalutamide + ADT group and 32% in the placebo + ADT group. Overall, 37% of subjects (38% apalutamide + ADT group and 36% in the placebo + ADT group), had low volume disease defined as no visceral metastases and less than four bone lesions. The majority of subjects had an ECOG PS of 0 with 63% in the apalutamide + ADT group and 66% in the placebo + ADT group. Median PSA level was 5.97 (range 0-2,682) for those in the apalutamide + ADT group and 4.02 (range 0-2,229) in the placebo + ADT group.[2]

Efficacy

The key efficacy outcomes of the TITAN trial are presented in Table 1. As of the 23-November-2018 data cut-off date (final analysis for rPFS and first of two interim analyses for OS), after a median follow-up time of 22.7 months:

- The percentage of patients with rPFS at 24 months was 68.2% in the apalutamide + ADT group and 47.5% in the placebo + ADT group (hazard ratio for radiographic progression or death, 0.48; 95% confidence interval [CI], 0.39 to 0.60; P<0.001), for a 52% lower risk of radiographic progression or death in the apalutamide + ADT group.[2]

- The rate of OS at the interim overall survival analysis was 82.4% in the apalutamide + ADT group and 73.5% in the placebo + ADT group (hazard ratio for death, 0.67; 95% CI, 0.51 to 0.89; P = 0.005), resulting in a 33% reduction in the risk of death in the apalutamide + ADT group.[2] Median OS in either treatment groups had not been reached.

- Treatment with apalutamide + ADT significantly delayed the initiation of cytotoxic chemotherapy resulting in a 61% reduction of risk for subjects in the apalutamide + ADT group compared with the placebo + ADT group (HR=0.391; 95% CI: 0.27 - 0.56; p < 0.001).[2]

- Twenty-four percent of subjects in the apalutamide + ADT group and 28% of subjects in the placebo + ADT group had pain progression.{Agarwal, 2019 #4} A

trend in time to pain progression favored treatment with apalutamide + ADT over placebo + ADT (HR=0.83, 95% CI: 0.65-1.05); however, statistical significance was not reached (p=0.12).[2]

- Median time to chronic opioid use favored treatment with apalutamide + ADT (HR=0.77, 95% CI: 0.54-1.11; p=0.16.[2,3] As the between-group difference in the time to pain progression was determined not to be statistically significant, further secondary endpoints were not formally tested.[2]

- Fifty-three skeletal-related events (10%) were recorded in the apalutamide + ADT group and 64 events (12%) were recorded in the placebo + ADT group.[2] Median time to skeletal-related events, favored treatment with apalutamide + ADT (HR=0.80, 95% CI: 0.56, 1.15;).[2,3] Nominal p-value was 0.23.

Quality of Life

Patient-reported outcomes in the TITAN trial were prespecified exploratory endpoints and assessed via the Brief Pain Inventory-Short Form (BPI-SF), Brief Fatigue Inventory (BFI), Functional Assessment of Cancer Therapy-Prostate (FACT-P), and EuroQoL 5D questionnaire 5 level (EQ-5D-5L). Overall, no statistically significant differences in PROs were observed between the two treatment groups.[4]

Patient experience of pain and fatigue (intensity and interference) did not differ between the groups for the duration of treatment. Median time to worst pain intensity progression was 19·09 months (95% CI 11·04–not reached) in the apalutamide + ADT group versus 11·99 months (8·28–18·46) in the placebo + ADT group (HR 0·89 [95% CI 0·75–1·06]; p=0·20).[4]

Analysis of change from baseline in the FACT-P scores and the EQ-5D-5L data with the use of a mixed-effect repeated-measures model showed no changes from baseline in the apalutamide + ADT treatment group and no differences compared to ADT alone, suggesting maintenance of HRQoL in both groups.[2,4]

Harms

As of the 23-November-2018 data cut-off date, adverse events (AEs) of any cause and grade were reported in almost all subjects in the apalutamide + ADT and placebo + ADT groups (96.8% and 96.6%, respectively). The most frequently reported AEs reported in ≥10% of patients were hot flashes (23% with apalutamide + ADT versus 16% with placebo + ADT), fatigue (20% vs 17%), hypertension (18% vs 16%), back pain (17% vs 19%), arthralgia (17% vs 15%), pain in an arm or leg (12% vs 13%), pruritus (11% vs 5%), and anemia (9% vs 14%).[2] Adverse events of special interest were consistently more frequent in patients receiving apalutamide + ADT than those receiving placebo. These included rash (27.1% vs 8.5%), falls (7.4% vs 7.0%), fractures (6.3% vs 4.6%), hypothyroidism (6.5% vs 1.1%) and seizures (0.6% vs 0.4%)[2]

Frequencies of grade 3 or 4 events (42.2% in the apalutamide + ADT group and 40.8% in the placebo + ADT group) and of serious adverse events (19.8% in the apalutamide + ADT group and 20.3% in the placebo + ADT group) did not differ substantially between the two groups.[2] The most common adverse event of grade 3 or higher that was considered by the investigator to be related to apalutamide was rash of any type (6.3%). Treatment

emergent AEs leading to death were reported for 10/524 (1.9%) patient in the apalutamide + ADT group, and 16/527 patient (3.0%) in the placebo + ADT group.[2]

Table 1: Highlights of Key Outcomes in TITAN trial[2,3]

	Apalutamide + ADT (n=525)	Placebo + ADT (n=527)
Co-primary Outcomes		
rPFS		
Number of events, n (%)	358 (68.2)	250 (47.5)
Median PFS (months)	NE	22.1
HR (95% CI)	0.48 (0.39-0.60)	
P-value	p<0.001	
OS		
Number of events, n (%)	83 (15.8)	117 (22.2)
Median OS (months)	NE	NE
HR (95% CI)	0.67 (0.51-0.89)	
P-value	p=0.005	
Key Secondary Outcomes		
Time to Cytotoxic Chemotherapy		
Number of events, n (%)	478 (91%)	411 (78%)
Median time (months)	NE	NE
HR (95% CI)	0.39 (0.27-0.56)	
P-value	P<0.001	
Time to pain progression		
Number of events, n (%)	128 (24)	148 (28)
Median time (months)	NE	NE
HR (95% CI)	0.83 (0.65-1.05)	
P-value	P=0.12	
Time to chronic opioid use		
Number of events, n (%)	NR	NR
Median time (months)	NE	NE
HR (95% CI)	0.77 (0.54-1.11)	
P-value	P=0.164	
Time to skeletal-related events		
Number of events, n (%)	[redacted]	
Median time (months)		
HR (95% CI)	0.80 (0.56-1.15)	
P-value	Nominal P=0.255	
HRQoL		
FACT-P total score		
Median time to deterioration (months)	8.87	9.23
HR (95% CI)	1.02 (0.85-1.22)	
P-value	P=0.85	
***Harms* Outcome, n (%)**		
Grade ≥3	221 (42.2)	215 (40.8)
AE (any grade)	507 (96.8)	509 (96.6)
Any serious AE	104 (19.8)	107 (20.3)
Any AE leading to discontinuation of trial intervention	42 (8.0)	28 (5.3)
Any AE leading to death	10 (1.9)	16 (3.0)

AE = adverse event, **CI =** confidence interval, **HR =** hazard ratio, **NE** = could not be estimated, **NR** = not reported, *HR < 1 favours apalutamide

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

Limitations

Overall, TITAN is a well-designed RCT and there were no major concerns with the conduct of the trial. However, the following limitations and potential sources of bias of the TITAN trial were noted by the pCODR Methods Team:

- With no active treatment in the control arm, there is a lack of direct comparison to other relevant agents, such as docetaxel, abiraterone acetate + prednisone and enzalutamide.
- Control patients did not receive first-line therapy for mCRPC until they demonstrated radiographic progression, and only 190 of 271 patients (70%) on the placebo arm reported to have radiographic progression received additional cancer therapy. The extent to which this exaggerate the trial results in favour of apalutamide + ADT is unknown.
- 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 410 events have occurred.
- All subgroup analyses were univariate and sensitivity analyses were not conducted. Subgroup analyses on subjects with low or high volume mCSPC disease were conducted without alpha spending assigned and without adjustment for multiplicity. In addition, all the subgroup analyses should be considered exploratory or hypothesis generating due to small sample sizes.

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

Summarize additional evidence that was included in the pCODR review, e.g. patient advocacy group input, Provincial Advisory Group (PAG) input, Registered Clinician Input, and other (supplemental topics and/or comparison with other literature).

One patient group, the Canadian Cancer Survivor Network (CCSN) provided input on apalutamide + ADT (Erleada) for mCSPC.

The three most commonly reported symptoms that affect patients' quality of life and/or day-to-day living were fatigue, hot flashes, and anxiety. Radiotherapy and hormone therapy were most commonly mentioned as available therapies to treat prostate cancer in addition to chemotherapy (docetaxel). Hormone therapies including anti-androgen treatment such as bicalutamide (Casodex), LHRH agonists such as goserelin acetate (Zoladex) and leuprolide acetate (Lupron, Eligard), LHRH antagonists such as degarelix acetate (Firmagon), and GnRH agonists such as triptorelin pamoate (Trelstar) were reported. Of note, anti-androgen therapies and LHRH agonists were the most commonly reported hormone therapeutic agents. Patients reported issues with treatment accessibility to include limited availability in their community, hardship due to cost, travel costs related to accessing therapy/treatment, and supplies or issues with administration.

Seventeen respondents had access to apalutamide throughout various centres in Ontario, BC, and Manitoba; six patients had taken apalutamide for up to one month and eleven patients had taken apalutamide for two to three months. Only one patient temporarily stopped taking apalutamide for severe diarrhea but resumed taking apalutamide after a

dose reduction from four to two pills. The most commonly reported side effects of apalutamide were fatigue and hot flashes; however, these were also the most commonly rated side effects to be acceptable. Conversely, bowel incontinence, loss of bone mass, and feelings of depression (worsened after taking medication) were most commonly rated as not acceptable. Ultimately, the majority of patients reported an improved ability to control symptoms, a reduction in side effects from current medications or treatments, increased ease of use, and improved management of disease progression with apalutamide and there was a uniformly positive recommendation of making apalutamide available to all patients with mCSPC.

Provincial Advisory Group (PAG) Input

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

Clinical factors:

- Clarity of eligible patient population.
- Appropriate treatments for metastatic, castration sensitive disease after apalutamide.

Economic factors:

- Additional healthcare resources (e.g., pharmacy, nursing, clinic visits) required.

Registered Clinician Input

A total of four registered clinician inputs from three individual oncologists and one joint input from three oncologists on behalf of Cancer Care Ontario (CCO) Genitourinary (GU) Drug Advisory Committee (DAC) provided input on the review of apalutamide (Erleada) for the treatment of metastatic castration-sensitive prostate cancer (mCSPC). Namely, individual inputs were submitted on behalf of oncologists practicing in Ontario, Alberta, and British Columbia (BC). The CCO clinicians highlighted that apalutamide is the only drug in this setting that is volume agnostic, which serves a key advantage. Funding of apalutamide would provide accessibility to a therapeutic option for mCSPC; namely, an oral agent that targets the androgen receptor. Docetaxel and abiraterone are presently used to treat the indication under review. However, at this time, docetaxel is reported to only be funded in Ontario and Alberta but not BC. Additionally, abiraterone is not funded across Canada.

There were different clinical opinions on whether patients with an Eastern Cooperative Oncology Group (ECOG) status of 2 or greater should receive apalutamide plus ADT in clinical practice; the BC clinician noted that there is no robust evidence to show clinical benefit in patients with an ECOG status of 2 or greater. Alternatively, the Alberta clinician noted there is no reason that these patients would not benefit from this treatment combination. Clinicians from CCO stated that patients with an ECOG status of 2 may receive this treatment combination based on clinical discretion but patients with an ECOG status of 3 or 4 are not likely to benefit. CCO clinicians and the BC clinician supported the treatment of patients who had more than six months of ADT with apalutamide plus ADT in clinical practice; however, the Alberta oncologist stated there is no evidence to support this. Moreover, the majority of clinicians felt that there is no specific high-risk subgroup that is more likely to benefit from apalutamide and ADT for mCSPC; however, the BC oncologist stated that patients with high PSA and a Gleason score of 8-10 would likely benefit more from apalutamide and ADT. Nonetheless, the BC oncologist supported the use of apalutamide in all patients with mCSPC. Clinicians highlighted the absence of head to

head studies comparing apalutamide and docetaxel but indicated that apalutamide is better tolerated. There was general support to administer docetaxel in patients with a significant amount of tumour burden or a very aggressive phenotype. Accordingly, the Alberta clinician specified that apalutamide would be preferred for low-volume, low-risk mCSPC while docetaxel would be reserved for high-volume mCSPC especially for those with visceral metastases.

Apalutamide and abiraterone were described as having similar efficacy but differences in safety. Namely, apalutamide requires less monitoring compared to abiraterone plus prednisone, which requires regular monitoring of electrolytes and liver function due to the mineralocorticoid effect of abiraterone potentially causing fluid retention. Furthermore, the abiraterone plus prednisone combination may be problematic for those with diabetes due to the glucocorticoid effect of prednisone. Thus, apalutamide arguably exhibits better safety and tolerability compared to docetaxel and abiraterone. Following progression with apalutamide plus ADT in this setting, the majority of clinicians stated that they would likely administer chemotherapy and radiation (radium-223). Main toxicities of apalutamide were summarized to include rash, fatigue, and hypertension. Contraindications were highlighted according to the pivotal trial: severe angina, myocardial infarction, congestive heart failure, arterial or venous thromboembolic events, a history of or predisposition to seizure, and recent ventricular arrhythmias. The BC oncologist noted they would not want to administer apalutamide to patients with considerable amount of visceral disease or previous use of docetaxel as these two subgroups did not show considerable benefit in the pivotal trial.

Summary of Supplemental Questions

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

- **Summary and critical appraisal of sponsor-submitted network meta-analysis comparing apalutamide with other relevant treatments for men with metastatic hormone-sensitive prostate cancer.**

In the absence of head-to-head trial data for apalutamide compared to other relevant treatments for men with mCSPC, the sponsor submitted a network meta-analysis (NMA) comparing apalutamide with other relevant treatments in this patient population. [redacted]. *Non-disclosable information was used in this pCODR Guidance Report and the Sponsor requested this efficacy information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the Sponsor that it can be publicly disclosed.*

Please refer to section 7.1 for the complete critical appraisal of the Sponsor provided network-meta analysis.

- **Summary and critical appraisal of a published network meta-analysis comparing apalutamide with other relevant treatments for men with metastatic hormone-sensitive prostate cancer by Marchioni et al.**[5]

A published NMA was identified comparing apalutamide to other relevant treatments for men with mCSPC. 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, apalutamide 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, apalutamide showed statistically significantly lower risk of disease progression compared to ADT alone, and compared to docetaxel, but not compared to abiraterone or enzalutamide. 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. Apalutamide showed statistically significantly lower odds of AEs compared to docetaxel, or docetaxel plus bisphosphonates, and abiraterone showed statistically significantly higher odds of AEs compared to apalutamide. The results of the sensitivity analysis also showed no statistically significantly higher odds of AEs for apalutamide compared to ADT alone.

Several limitations to the NMA were identified. There was a lack of clarity surrounding the inclusion and exclusion criteria for the NMA, with some criteria not clearly defined, and the use of a web-based platform for the initial screening causing uncertainty as to whether some potentially relevant studies may have been missed. Furthermore, there was a large amount of clinical heterogeneity between the included studies, with various patient inclusion/exclusion criteria that can make the comparability of the trials challenging (i.e. different ADT treatments in the trials, disease stage and previous treatments allowed). Due in part to these limitations, results of this NMA must be interpreted with caution.

Please refer to section 7.2 for the critical appraisal of the published network-meta analysis by Marchioni et al.[5]

- **Summary and critical appraisal of a published network meta-analysis (NMA) comparing first-line treatments for mCSPC, specifically combinations of androgen deprivation therapy (ADT) and one (or more) of taxane-based chemotherapy, and androgen receptor-targeted therapies by Sathianathen et al.**[6]

A published NMA was identified comparing apalutamide to other relevant treatments for men with mCSPC. 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 pCODR Review Team, as CGP had stated preferring treatment with chemotherapy for patients with better performance status, visceral metastases and more disease burden. Six trials were identified from a SLR.

For the outcome of OS in the full group, apalutamide showed statistically significantly improved OS compared to ADT alone, but not compared to any of the other combination treatments (abiraterone, enzalutamide, docetaxel). Enzalutamide had the largest effect on OS compared to ADT alone, and showed statistically significantly improved OS compared to docetaxel. For the subgroup analysis of OS in the low-volume disease group, apalutamide did not show statistically significant differences for OS compared to ADT alone or to any of the combination treatments (abiraterone, docetaxel, or enzalutamide). For the subgroup analysis of OS in the high-volume disease group, apalutamide showed

statistically significantly improved OS compared to ADT alone, but not compared to any of the other combination treatments (abiraterone, enzalutamide, docetaxel).

For the outcome of PFS, apalutamide showed statistically significantly decreased PFS compared to abiraterone, and enzalutamide showed statistically significantly improved PFS compared to abiraterone. Abiraterone did not show statistically significant differences for PFS compared to ADT alone or to docetaxel.

Several limitations to the NMA were identified. There was a lack of clarity surrounding the inclusion and exclusion criteria for the NMA, with some criteria not clearly defined. Furthermore, there was a large amount of clinical heterogeneity between the included studies, with various patient inclusion/exclusion criteria that can make the comparability of the trials challenging (i.e. different ADT treatments in the trials, disease stage and previous treatments allowed). Additionally, this NMA analyses only the outcomes of OS and PFS, without including other potentially relevant outcomes such as AEs or HRQoL data. Due in part to these limitations, results of this NMA must be interpreted with caution.

Please refer to section 7.3 for the critical appraisal of the network-meta analysis by Sathianathen et al.[6]

Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR 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 Apalutamide + ADT for metastatic castration sensitive prostate cancer

Domain	Factor	Evidence (TITAN trial)	Generalizability Question	CGP Assessment of Generalizability
Population	ECOG Performance Status	The TITAN trial limited eligibility to patients with an ECOG PS of 0 or 1.	Are the trial results generalizable to patients with PS >1?	Benefit for patients with PS>1 is unclear due to lack of available evidence. However, the CGP agreed with the registered clinicians that patients with ECOG 2 considered clinically appropriate may benefit from apalutamide and should be eligible.
	PSMA-PET detected metastases	The TITAN trial required patients to have evidence of metastases including at least 1 bone metastasis based on conventional 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 not feel results could be generalized to this group. It should be noted that PSMA PET is currently not approved or funded in Canada.

Domain	Factor	Evidence (TITAN trial)	Generalizability Question	CGP Assessment of Generalizability
Intervention	Prior treatments	The TITAN trial allowed patients to have received up to 6 months of GnRHa in the adjuvant or neoadjuvant setting as long as it was completed >1 year prior to randomization.	Are the trial results generalizable to patients who have received >6 months of GnRHa or GnRHa <1 year before treatment with apalutamide?	Regarding patients who have received adjuvant ADT for >6 months with prior local therapy, CGP considered it acceptable to provide these patients with apalutamide so long as treatment with ADT had been completed more than one year from the timing of initiating apalutamide. Regarding patients who have received definitive ADT for mCSPC started at <6 months, CGP did not consider it acceptable to provide these patients with apalutamide.
		TITAN allowed patients to have a maximum of 1 course of radiation or surgical intervention as prior therapy for prostate cancer.	Are the results of the trial generalizable to patients who have had >1 course of RT or surgical intervention for their prostate cancer?	CGP supported generalizing trial results to patients who have had >1 course of RT or surgical intervention for prostate cancer.
		TITAN excluded patients who initiated treatment with a bisphosphonate or denosumab within 28 days prior to randomization.	Are the results of the trial generalizable to patients on bone-modifying agents?	CGP were supportive of generalizing trial results to patients on bone-modifying agents. While most patients will not be on bone-modifying agents, CGP stated that patients probably should be assessed for them once they start apalutamide. CGP highlighted the need to remain attentive to the risk of fracture as men treated with ADT are at high risk for fracture, and patients in the TITAN trial experienced a 50% increase in risk of fracture after only two years of follow-up.
Comparator	Standard of care	In the TITAN trial, placebo (ADT alone) was used as the comparator. PAG is seeking data compared to ADT plus docetaxel. PAG is seeking guidance on preference for apalutamide or docetaxel in this mCSPC setting. PAG is	If the comparator is non-standard, are the results of the trial applicable in the Canadian setting?	Regarding preferred treatment choice, the Sponsor provided NMA supported similar OS benefit and less toxicity with ARATs compared to docetaxel.

Domain	Factor	Evidence (TITAN trial)	Generalizability Question	CGP Assessment of Generalizability
		seeking guidance for high-risk patients, whether apalutamide or abiraterone is the preferred treatment. Registered clinician input also indicated that docetaxel and abiraterone are presently used to treat the indication under review.	What is the preferred treatment choice between apalutamide or chemotherapy (e.g., docetaxel) plus ADT?	The CGP also highlighted the published NMA by Marchioni et al.[5] which indicated no difference in overall mortality with apalutamide compared to docetaxel or abiraterone. However, risk of disease progression and high-grade toxicity events were less with apalutamide compared to docetaxel, but not abiraterone. It is still unclear which ARAT is the preferred treatment. CGP stated that treatment choice would be based on patient preferences, side effect profile and treatment schedule. Regarding patients with low volume/low risk or high volume mCSPC, CGP were of the opinion that treatment choice would depend on consideration of all clinical variables and discussion with the patient.
Outcomes		None identified		
Setting	Trial centres	The trial was conducted in 260 sites in 23 countries including: Argentina (14), Australia (4), Brazil (19), Canada (6), China (20), Czech Republic (13), France (7), Germany (8), Hungary (6), Israel (5), Italy (10), Japan (14), Mexico (8), Poland (6), Republic of Korea (12), Romania (3), Russia (24), Spain (6), Sweden (7), Turkey (10), Ukraine (16), United Kingdom (10), United States of America (32)	Do the trial results apply to patients from Canadian centres? Are there any known differences in practice patterns between the countries listed and Canada?	CGP agreed that trial results were applicable to Canadian patients. CGP noted that drugs for CRPC may be less available in some countries, which would diminish expected benefit that may be observed among Canadian patients where apalutamide is readily available.
Abbreviations ECOG = Eastern Cooperative Oncology Group; PS = performance status; RT = radiation therapy				

1.2.4 Interpretation

Effectiveness

The TITAN trial tested the addition of apalutamide to standard androgen deprivation therapy in men with newly diagnosed mCSPC with at least one bone metastasis and demonstrated an improvement in cancer control that positively influenced clinically relevant endpoints important to patients, including OS. The risk of radiographic progression or death was reduced by half at two years and risk of death reduced by one-third at the same interval.

Overall survival results were considered preliminary with median survival not reached in either arm of the trial. Results were less compelling for patient-reported outcomes. Although time to worst pain progression appeared to be delayed by apalutamide + ADT this was not proven, and HRQoL and patient experience of pain and fatigue were not improved or worsened.

The study population was restricted to men with good performance status who had at least one bone metastasis. Most were asymptomatic and had minimal medical comorbidity. Similar to other trials in men with mCSPC, nearly two-thirds of men met criteria for "high volume" disease, and 80% had metastatic disease at the time of initial prostate cancer diagnosis. Among trial patients, 82.4% of patients in the apalutamide + ADT group and 73.5% of patients in the control arm were alive at two years. The trial was well conducted and took measures to eliminate sources of bias. However, there was no active treatment in the control group, and median follow up was relatively short at 22.7 months. Control patients did not receive first-line therapy for metastatic castration-resistant prostate cancer (mCRPC) until they demonstrated radiographic progression, and 190 of 527 patients (70%) in the placebo + ADT arm reported to have radiographic progression received additional cancer therapy. In real world practice most clinicians would not wait for radiographic progression before initiating treatment for mCRPC in patient with known mCSPC and rising PSA despite ADT. As well, it would be expected that nearly 100% of patient would receive treatment with either an androgen-receptor axis targeting drug therapies (ARAT) or docetaxel. These factors are likely to exaggerate the trial results in favour of apalutamide.

Notwithstanding the overall results of the trial, it is conceivable that a subgroup of men with excellent response to ADT might have minimal benefit from additional treatment. Approximately 80% of men with an undetectable PSA level six to seven months after starting ADT were alive at 30 months in the SWOG 9346 trial, virtually identical to men treated with ADT plus apalutamide in the TITAN trial. As clinical trials investigating docetaxel, radiation, and the ARATs in mCSPC did wait or stratify for PSA response to ADT, it is impossible to identify these patients, or discern their level of benefit from the addition of these additional therapies.

Safety

Apalutamide + ADT appeared to be safe and reasonably well-tolerated by most patients. Adverse events led to death or discontinuation of therapy in 1.9% and 8.0% of patients treated with apalutamide + ADT, compared to 3.0% and 5.3% with placebo + ADT, respectively. Although grade 3 or 4 adverse events occurred at similar rates in both study arms (42.2% versus 40.8%, respectively), apalutamide + ADT was compared the placebo + ADT, so specific drug toxicity comparisons must be made with some caution.

By definition "adverse events" observed in the placebo + ADT group would be due to standard therapy (ADT), the effects of disease progression or other factors. Only in the apalutamide + ADT group could adverse events be potentially related to experimental drug therapy. For example, a higher rate of hot flushes with apalutamide + ADT is likely due to more intensive suppression of androgen effects. However, similar rates of fatigue and pain in both arms suggest that these are either due to common factors such as ADT or to different causes such as adverse effects of apalutamide in the experimental group and symptomatic cancer progression in the placebo + ADT control group. Overall, despite greater disease suppressive effects proven with apalutamide + ADT, the symptomatic experience of patients (described by adverse events) was similar to placebo. Interestingly, patient input reflected a similar

adverse event experience to that described the TITAN trial. Patients were pleased with PSA reduction but perhaps unaware that in mCSPC this would be expected with ADT alone.

Adverse events of special interest due to apalutamide + ADT included rash, fracture and hypothyroidism. Nearly 30% of men treated with apalutamide + ADT experienced drug-related rash and this was severe (Grade 3 or 4) in 6.3%. Patients experiencing rash related to treatment with apalutamide were managed with antihistamines and topical glucocorticoids, dose interruption and dose reduction. Men treated with ADT are known to have accelerated bone loss, so the 50% increase in risk of fracture after only two years of follow up (6.3% versus 4.6% with placebo) places men treated with apalutamide + ADT in a high 10-year fracture risk category. This suggests not only a need for attentiveness to skeletal protective measures by clinicians in patients receiving apalutamide + ADT but also consideration of additional anti-osteoporotic therapy such as bisphosphonates or denosumab. The percentage of patients with hypothyroidism was higher by 5% in men receiving apalutamide + ADT which implies a need for monitoring that is not routine in this population.

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 apalutamide 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 are clearly a significant medical advance. For example, in men with “high burden” mCSPC in the E3805 trial, chemotherapy with six cycles of docetaxel improved median overall survival nearly 1.5 years compared to ADT alone[7]. CGP regarded this improvement in median OS as noteworthy and clinically meaningful.

Several treatments added to ADT have now been shown to improve the OS of men with mCSPC. The need for apalutamide + ADT for this indication requires consideration of the data supporting other therapies. Docetaxel and abiraterone were the first to show OS benefit in men with higher burden mCSPC when added to ADT. More recent data suggest benefit across the spectrum of mCSPC, including low- and high-volume disease patients, with these drugs as well as apalutamide and enzalutamide in the TITAN and ENZAMET trials, respectively. Both docetaxel and abiraterone plus prednisone are established standards of care in men with higher burden disease, and recent data suggest these benefits are independent of disease burden. Prostate radiation in men with low burden *de novo* metastatic disease appears to improve OS. More recently enzalutamide added to ADT has also been reported to improve OS in mCSPC.

A recent network meta-analysis reported similar OS benefits with docetaxel, abiraterone/prednisone, apalutamide, and enzalutamide in men with mCSPC[5]. However, the ARATs did show non-statistically significant lower overall mortality rates, statistically significant lower disease progression rates and lower rates of high-grade adverse events compared to docetaxel. Compared to docetaxel, the Sponsor-provided NMA supported similar OS benefit and less toxicity with ARATs. However, it is still unclear which ARAT is the preferred treatment. Registered clinician input reflects this uncertainty in preferred ARAT

agent but recognizes the need for alternatives to docetaxel. The totality of these data support ARAT therapy such as apalutamide for mCSPC patients considered at higher risk for high grade toxicity from docetaxel.

1.3 Conclusions

The Clinical Guidance Panel concluded that there is a net overall clinical benefit to apalutamide + ADT in the treatment of mCSPC based on one high-quality RCT that demonstrated a clinically meaningful and statistically significant benefit in rPFS, preliminary evidence of OS benefit, similar adverse event profiles compared with placebo in men treated with ADT, and lack of decline in HRQoL.

The TITAN trial randomized 1052 men diagnosed with mCSPC to either apalutamide 240 mg daily or placebo within six months of starting ADT. Radiological progression-free and OS were the co-primary endpoints. At median follow up just under two years, rPFS was unequivocally positive and preliminary OS analysis showed a one-third reduction in the risk of death. Short follow up, use of placebo control, and delayed and incomplete treatment of progressing patients in the control arm could modestly exaggerate treatment benefit. Overall toxicity was similar and HRQoL was maintained but not improved.

In most jurisdictions in Canada, docetaxel is the only option publicly funded for mCSPC. The toxicity of docetaxel is increased in men with mCSPC compared to CRPC, probably for pharmacological reasons [8,9]. So additional non-cytotoxic options providing similar benefits with less toxicity risk are recognized as a 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 it does do not identify the preferred ARAT drug. 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 comorbidity, and may have mCSPC very sensitive to treatment with ADT alone, generalizability of clinical trial data to real world patients should be done thoughtfully. Although apalutamide + ADT improves disease control and OS in mCSPC, and has similar overall toxicity to placebo + ADT; it does not appear to improve HRQoL which ideally would be the case. Apalutamide + ADT appears to increase risk of rash, fracture and hypothyroidism compared to ADT alone, and clinicians must both consider these when considering treatment, and be vigilant for them when providing it. With no predictive test for net benefit from adding apalutamide to ADT, some men could have minimal benefit; physicians should be cautious and consider that apalutamide may benefit some patients, but consideration to possible harms must be applied when prescribing it.

Finally, despite inclusion of mCSPC patients receiving docetaxel in the TITAN and ENZAMET trials, there is also no high-level evidence supporting combination or sequencing of the options potentially available for mCSPC. Beyond ADT, apalutamide should not be routinely combined with other drug therapies.

Provincial Advisory Group's (PAG) Related Implementation Questions:

- As the TITAN trial compared apalutamide plus ADT to placebo plus ADT, PAG identified that ADT or chemotherapy plus ADT are also treatments standard for patients with

mCSPC. With respect to the use of docetaxel plus ADT as a relevant comparator, CGP considered apalutamide + ADT of similar efficacy and associated with less risk high-grade toxicity than docetaxel.

- Regarding generalizability to patients with an ECOG PS >1 or patients who had received more than six months of ADT, CGP agreed that appropriate patients with an ECOG PS of 2 may benefit from the addition of apalutamide. Patients who received more than six months of ADT as a component of prior curative treatment for localized disease may benefit. Patients receiving ADT for more than six months for mCSPC should not be eligible for apalutamide.
- In response to specific high-risk subgroups of patients who may be more likely to benefit from the addition of apalutamide to ADT, CGP noted inter-clinician variability in the identification of the optimal patient for factors such as more prolonged prior ADT therapy, lower disease burden and whether or not patients had *de novo* metastatic disease.
- Regarding patients who are currently being treated for mCSPC with other treatments (e.g. ADT alone) or who were recently treated but who have not progressed, CGP suggested that they not be considered eligible for apalutamide + ADT.
- As apalutamide + ADT is recommended for patients until disease progression or unacceptable toxicity, concern was raised that there may be additional nursing resources and increased frequent clinic visits for monitoring of blood work and side effects compared to docetaxel or ADT alone. CGP agreed that compared to docetaxel, apalutamide requires continuing uninterrupted therapy, which requires monitoring for disease progression and long-term adverse effects such as hypothyroidism and fractures.
- Concerning the tablet burden of apalutamide, CGP agreed that the 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). CGP stated that patients have not particularly complained about the administration of the pills for apalutamide in their practice and are generally accepting of this dosing. However, the issue of convenience for the patient is not entirely clear, as apalutamide requires adherence to daily tablets for at least 20 months (as reported) and likely at least 24 months on average compared to six intravenous chemotherapy treatments for docetaxel. It is likely that post-treatment monitoring is similar for both groups of patients but may be increased for patients on active therapy with apalutamide which could impact out-patient clinic utilization.
- There is a lack of direct evidence indicating the preferred treatment between apalutamide + ADT and other ARAT therapies or chemotherapy. Network meta-analyses support similar survival benefit of apalutamide compared to docetaxel and abiraterone, and indicate less high grade toxicity than docetaxel. However, CGP remain unclear regarding the preferred ARAT treatment.

2 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR 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.[10]

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.[11] Nearly all patients with mCSPC initially respond to ADT but all eventually progress to castration-resistant prostate cancer (CRPC).

The SWOG 9346 trial compared continuous to intermittent ADT in men with mCSPC.[12] All men initially received seven months of treatment with ADT plus bicalutamide and predictors of OS were analyzed. Baseline features such as reduced performance status, the presence of pain, high tumor Gleason grade, and higher PSA levels were modest independent predictors of higher mortality. However, the strongest predictor of OS was PSA response to ADT after six to seven months. Men with undetectable PSA had an 84% reduction in mortality risk compared to men not achieving this, a median overall survival of 75 months, and comprised 43% of patients.

Over the past decade, clinical trials have demonstrated improved survival with the addition of chemotherapy or new ARATs to ADT in men with mCSPC. OS benefits with docetaxel and abiraterone acetate appeared limited to men with higher burden disease in the CHAARTED and LATITUDE trials.[13,14] However, more recent data support benefit regardless of disease burden, and both docetaxel and abiraterone are now currently offered as standard management options for patients with mCSPC.[15,16] In men with low burden de novo mCSPC, subgroup analysis of the STAMPEDE clinical trial suggested an OS benefit with the addition of prostate radiation therapy.[17] Over the past year, two large international RCTs (TITAN and ENZAMET) have reported OS benefit with the ARAT drugs apalutamide and enzalutamide, respectively.[2,18] Apalutamide and the TITAN trial are the focus of this report.

Treatment for Castration-Resistant Prostate Cancer:

The majority of patients treated with ADT progress to a diagnosis of CRPC defined as disease progression despite castrate testosterone levels. In men without metastases treated with ADT, biochemical progression manifested by a rising PSA alone is often the initial sign of disease progression to CRPC. Recent trials studying apalutamide, enzalutamide, and darolutamide have reported benefits in this non-metastatic (M0) CRPC population.[19-21] For men with metastatic CRPC (mCRPC), initial treatment with abiraterone plus prednisone or enzalutamide is typically used. Both drugs have demonstrated OS benefits compared to placebo in randomized phase III studies and are the most frequently used first-line treatments for this population.[22,23] When patients suffer disease progression despite these ARATs they are usually treated with docetaxel

chemotherapy. Docetaxel was approved by Health Canada for the treatment of mCRPC based on a pivotal trial published in 2004.[24] Other potential treatment options include radium-223 and cabazitaxel.[25,26]

Expected place of ARATs in treatment of mCSPC:

Apalutamide is an oral androgen receptor inhibitor, which binds directly to the ligand-binding domain of the androgen receptor and prevents androgen-receptor translocation, DNA binding, and androgen-receptor–mediated transcription.[27] Apalutamide was studied in men with M0 CRPC in the SPARTAN study, which reported improvement in metastasis-free survival, time to symptomatic progression, and a trend to improved OS.[11] Both apalutamide and enzalutamide have been studied in large clinical trials enrolling broader populations of men with newly diagnosed mCSPC.[2,18] Both of these trials have reported clinical benefits with the addition of ARAT to ADT including OS. These trial results suggest that the first-line treatment for men with newly diagnosed mCSPC should also consider the inclusion of apalutamide within a new standard of care.

2.3 Evidence-Based Considerations for a Funding Population

In addition to apalutamide, several other therapies added to standard ADT have been reported to benefit men with mCSPC including docetaxel, abiraterone/prednisone, enzalutamide, and prostate radiation.[2,15-18] Aside from patient-specific factors, it is unclear which provide optimal clinical value. ADT should be continued will 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. Evidence for use of these therapies in combination in mCSPC is very limited.

2.4 Other Patient Populations in Whom the Drug May Be Used

Apalutamide has not been approved for any other indication than prostate cancer, and no direct evidence is available supporting the use of apalutamide in men with metastatic castration-resistant prostate cancer (before or after docetaxel chemotherapy).

mCSPC may be identified by PSMA-PET imaging in some men who otherwise only have a rising PSA as a sign of CSPC, and it is unclear whether these therapies added to ADT are worthwhile in this population.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

The Canadian Cancer Survivor Network (CCSN) provided input on apalutamide (Erleada) for metastatic castration-sensitive prostate cancer (mCSPC) based on a survey that was released on October 1, 2019. There were a total of 60 respondents; of these, 57 identified as male and three as female, 21 had taken apalutamide, and six were caregiver respondents. Additionally, of the total respondents, 29 were from British Columbia (BC), three were from New Brunswick, two were from Alberta, and one was from Quebec; however, the total provincial breakdown was not provided. The three most commonly reported symptoms that affect patients' quality of life and/or day-to-day living were fatigue, hot flashes, and anxiety. Radiotherapy and hormone therapy were most commonly mentioned as available therapies to treat prostate cancer in addition to chemotherapy (docetaxel). Hormone therapies including anti-androgen treatment such as bicalutamide (Casodex), LHRH agonists such as goserelin acetate (Zoladex) and leuprolide acetate (Lupron, Eligard), LHRH antagonists such as degarelix acetate (Firmagon), and GnRH agonists such as triptorelin pamoate (Trelstar) were reported. Of note, anti-androgen therapies and LHRH agonists were the most commonly reported hormone therapeutic agents. Patients reported issues with treatment accessibility to include limited availability in their community, hardship due to cost, travel costs related to accessing therapy/treatment, and supplies or issues with administration. Seventeen respondents had access to apalutamide throughout various centres in Ontario, BC, and Manitoba; six patients had taken apalutamide for up to one month and eleven patients had taken apalutamide for two to three months. Only one patient temporarily stopped taking apalutamide for severe diarrhea but resumed taking apalutamide after a dose reduction from four to two pills. The most commonly reported side effects of apalutamide were fatigue and hot flashes; however, these were also the most commonly rated side effects to be acceptable. Conversely, bowel incontinence, loss of bone mass, and feelings of depression (worsened after taking medication) were most commonly rated as not acceptable. Ultimately, the majority of patients reported an improved ability to control symptoms, a reduction in side effects from current medications or treatments, increased ease of use, and improved management of disease progression with apalutamide and there was a uniformly positive recommendation of making apalutamide available to all patients with mCSPC.

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 advocacy groups.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with mCSPC

Respondents reported being diagnosed with PSA testing (73%), biopsy (63%), rectal exam (58%), blood work (32%), incidental finding or physical exam by family doctor (27%), reporting of symptoms and/or discomforts (17%), a combination of any of the above (20%), and other, which included ultrasound and MRI (6.7%). Most of the respondents reported being diagnosed at Late Stage (4) (n=7), followed by Middle Stage (2 or 3) (n=3) then Early Stage (n=1). Of note, one patient was diagnosed during high PSA test monitoring.

Moreover, patients reported symptoms or problems they experienced with prostate cancer that has affected their quality of life and/or day-to-day living. Among 17 respondents, fatigue was the most commonly reported as noted by 13 patients. Followed by hot flashes (n=11), anxiety (n=9), erectile dysfunction (n=6), loss of muscle mass (n=6), depression (n=4), shortness of breath (n=4), weight gain (n=3), weight loss (n=3), urinary incontinence (n=2), diarrhea (n=2), constipation (n=2), loss of bone mass (n=1), dizziness (n=1), pencil

thin stools (n=1), and other (n=4). Namely, some other symptoms or problems included "*difficulty urinating*" and "*abdominal cramping after a day with unusually lose bowel.*"

3.1.2 Patients' Experiences with Current Therapy for mCSPC

Seven out of seventeen respondents reported experiencing issues with accessing current therapies; namely, the limited availability in their community (n=2), travel costs related to accessing therapy/ treatment (n=2), supplies or issues with administration (n=2), and hardship due to cost (n=1) were reported. One respondent highlighted the issue of *"delays due to processing for coverage."* However, ten out of seventeen patients did not report any issues; insurance and compassionate access programs were noted to facilitate the accessibility to apalutamide. This is accounted in the following patient quotations.

- "*I am thankful that I am receiving Erleada and hormone injections compassionately. If this were not the case it would cause a huge financial hardship*."
- "*I have insurance*."

Two respondents received no treatments before apalutamide, eight respondents received one treatment before apalutamide, two respondents received two treatments before apalutamide and one respondent received three or more treatments prior to apalutamide. Androgen deprivation therapy (ADT) and radiation therapy were most commonly used prior to apalutamide in addition to surgery, chemotherapy, and hormone therapy. Furthermore, chemotherapy agents such as docetaxel (Taxotere), anti-androgen therapies including apalutamide (Erleada) and bicalutamide (Casodex), LHRH agonists including goserelin acetate (Zoladex) and leuprolide acetate (Lupron, Eligard), LHRH antagonists such as degarelix acetate (Firmagon), and GnRH agonists such as triptorelin pamoate (Trelstar) were reported as agents currently used to treat prostate cancer or as therapeutic agents used in the past. Among these, anti-androgens and LHRH agonists were the most commonly reported therapeutic agents. one patient's experience with current treatment is accounted in the following quotation: "*treated with radiation and pronounced cured. PSA readings rose slightly after a few years. Taking hormone treatments which are not controlling PSA adequately.*"

3.1.3 Impact of mCSPC and Current Therapy on Caregivers

Caregivers were asked about the issues they encounter or have encountered as caregivers for someone with prostate cancer. Among five respondents, anxiety or worrying and hours spent in medical appointments were most commonly reported (n=4). Followed by, emotional drain (n=3), management of medication (n=2), management of side effects (n=2), lifestyle changes (n=2), fatigue (n=1), and monetary concerns (absence at work, driving expenses) (n=1). Additionally, caregivers were asked how caring for someone with prostate cancer affected their daily routine or lifestyle; an effect on the caregiver's work was commonly mentioned as depicted in the following quotations.

- "*I decided to retire when my husband had a recurrence*."
- "*Absence at work, lifestyle is changed, lots of time spend on medication appointment*."
- "*Spend time taking him to see doctor and for treatment*."

Furthermore, caregivers were asked to identify the most challenging adverse side effect related to their loved one's cancer or treatment; fatigue, urinary and rectal incontinence, severe rashes, and nose bleeds were stated as demonstrated in the following caregiver accounts.

- "*His fatigue and the urinary and at times rectal incontinence*."

• "*The new medicine interrupted his health balance and caused severe rashes and nose bleeding so we had to spend more time in the hospital to fix those side effects. Now he is still very tired.*"

Lastly, caregivers were asked whether there was anything else they would like to share about their experiences, caregivers highlighted the following.

• "*I work on looking after myself so I can help him in large and small ways.*"

• "*Spend a lot of time and energy to take care so that always need to change lifestyle and life plan to follow up the treatment. Too tired.*"

• "*Anxiety- not knowing what to expect next.*"

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for Apalutamide

Sixteen respondents indicated their expectations for long-term health and well-being as a result of taking apalutamide; prolonging life span was the most commonly stated expectation, which is detailed in the following patient responses.

- "*Hopefully to control my psa.*"
- "*Delay in the progress and spread of cancer.*"
- "*I am hoping that it will keep me alive for a number of years. It would be wonderful if the night problems went down.*"
- "*Prolong your lifespan and other options for treatment once this is no longer effective.*"
- "*I'm hoping it will prolong my life, as well as can be expected, having to live with cancer.*"
- "*I'm hoping that apalutamide will help keep my prostate cancer in check and prolong my life.*"

"*Longer survival and major adverse effect reduction ie spread of metastatic disease.*"

3.2.2 Patient Experiences To Date with Apalutamide

Seventeen respondents had experience with apalutamide and accessed this treatment through various centres in Ontario, BC, and Manitoba. Six patients had taken apalutamide for up to one month and 11 patients had taken apalutamide for two to three months. Of note, one of the respondents stopped taking apalutamide due to diarrhea and subsequently initiated treatment with a reduced dosage from four pills to two pills, as accounted in the following quotation— "*I initially took it for 3 weeks and had severe diarrhea. My medical oncologist said to stop taking it for 2 weeks. The diarrhea stopped right away; and after 2 weeks my medical oncologist said to resume taking apalutamide - but 2 pills daily rather than the original 4 pills.*"

Respondents were asked whether they were able to manage issues better on apalutamide compared to previous therapies. Twelve out of thirteen indicated they were better able to control symptoms, five out of eight reported a reduction in side effects from current medications or treatment, 12 out of 13 noted an ease of use compared to other therapies, and eight out of ten reported better management of disease progression. Furthermore, 16 patients noted the experienced side effects as a result of apalutamide, fatigue and hot flashes were most commonly experienced as reported by ten and eight respondents respectively. Followed by, weight gain (n=3), loss of muscle mass (n=3), erectile dysfunction (n=3), hormonal changes (n=2), dizziness (n=2), feelings of anxiety (worsened after taking medication) (n=2), nausea and/or vomiting (n=1), decreased appetite (n=1),

diarrhea (n=1), and weight loss (n=1). Of note, one respondent experienced no side effects and one respondent indicated that they experienced some energy loss, mild aches, and pains but were not sure whether these were attributed to aging at 77. Moreover, four respondents stated that it was too early to tell since they just started taking the medication, as stated by one patient "*at the time of doing this survey, I have only been on it for 5 days. I have yet to experience any side effects from it or any other treatments*."

Sixteen respondents additionally rated side effects as acceptable or not acceptable. Fatigue was the most commonly rated side effect to be acceptable (n=14) followed by hot flashes (n=8). Conversely, bowel incontinence was the most commonly rated side effect to be not acceptable (n=5) followed by loss of bone mass (n=4) and feelings of depression (worsened after taking medication) (n=4). Table 3.1 details all the reports.

Table 3.1 Summary of the Tolerability of Apalutamide Side Effects (number of respondents)

Side effect	Acceptable	Not acceptable
Fatigue	14	0
Nausea and/or vomiting	2	3
Dizziness	4	3
Diarrhea	5	3
Weight gain	7	0
Weight loss	6	2
Develop breasts or have tenderness	4	2
Feelings of depression (worsened after taking medication)	2	4
Feelings of anxiety (worsened after taking medication)	4	3
Loss of muscle mass	6	2
Loss of bone mass	2	4
Hot flashes	8	3
Urinary incontinence	5	3
Bowel incontinence	2	5
Infertility	6	0
Hormonal changes	6	0
Erectile dysfunction	7	0

Respondents were asked to describe any positive and negative effects of apalutamide; positives included a substantial reduction in PSA levels but negatives included diarrhea, hot flashes, and difficulty sleeping—patient responses follow.

- "*Positive effect is that my psa has dropped substantially*."

- "*The diarrhea was not manageable when I was taking 4 pills daily; but with only 2 pills it is manageable*."
- "*Experience some side effects but all are tolerable*."
- "*Feeling better and weight gain. Hot flashes and difficulties sleeping are negative*."

Additionally, respondents were asked whether the benefits of apalutamide outweigh the side effects; the majority indicated that the benefits outweigh the side effects but one respondent noted that it is too early to determine—responses were stated as follows.

- "*Yes the side effects have been very limited (so far) and I am feeling better*."
- "*Yes...with the combination of hormone therapy and apalutamide my PSA has gone down with each monthly blood work; and is now down to 0.36*."
- "*Instead of cytotoxic chemo far less side effects, similar benefits*."
- "*Since it is very early in my journey (3 months) I have had short period of blurred vision and slight fatigue but the pills have greatly affected the lowering of my psa readings*."

Furthermore, respondents were asked what challenges, if any, they faced in dealing with the side effects of apalutamide. Most reported that they did not have any challenges in dealing with the side effects but the noted challenges are accounted in the following quotations.

- "*Trouble going out*."
- "*I wake up at night to urinate, but this has been going on for a long time. I have hot flashes at night*."
- "*Fatigue and diarrhea – but with the reduced dosage the diarrhea is manageable with Imodium*."

Ultimately, respondents taking apalutamide were asked whether they would recommend that apalutamide be made available to all eligible patients with mCSPC. Responses were uniformly positive; of note, there were a few qualified yeses due to the short length of time being treated with apalutamide. Responses in the patients' own words follow.

- "*Yes because it has made a change in my controlling of it*."
- "*Yes, need to have more options for prostate cancer delay in order to hopefully find a cure*."
- "*If it manages psa yes. The side effects I have experienced so far seem to just deepen the hormone therapy but that may be the quid pro quo*."
- "*I think it is important to make this drug available to all prostate cancer patients. It feels to me like it is the only hope I have of dealing with my cancer*."
- "*Yes as it is an easy treatment only 4 pills a day*."
- "*I would definitely recommend it. In combination with hormone therapy my PSA has dropped significantly*."

3.3 Companion Diagnostic Testing

Not applicable.

3.4 Additional Information

None to report.

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) participating in pCODR. PAG identified the following as factors that could impact the implementation of apalutamide (Erleada) for mCSPC:

Clinical factors:

- Clarity of eligible patient population.
- Appropriate treatments for metastatic, castration sensitive disease after apalutamide.

Economic factors:

- Additional healthcare resources (e.g., pharmacy, nursing, clinic visits) required.

Please see below for more details.

4.1 Currently Funded Treatments

PAG noted that there is no standard of care for metastatic Castration-Sensitive Prostate Cancer (mCSPC), patients are treated with ADT alone, chemotherapy (e.g., docetaxel), or ADT plus chemotherapy. The TITAN trial compared apalutamide plus ADT versus ADT alone, which is a relevant comparator; PAG is also seeking data compared to ADT plus docetaxel.

4.2 Eligible Patient Population

PAG is seeking clarity on whether or not the following patients would be eligible for treatment with apalutamide:

- Patients with an ECOG performance status of 2 or greater,
- Patients who had more than 6 months of ADT.

PAG is also seeking guidance on whether there is a specific high-risk subgroup (e.g., Gleason score 8-10, high PSA at diagnosis, etc.) that is more likely to benefit from the addition of apalutamide to ADT for the treatment of mCSPC.

If recommended for reimbursement, PAG noted that patients who are currently treated with other treatments (e.g., ADT alone) or recently treated (e.g., docetaxel for six cycles) and who have not progressed, would need to be addressed on a time-limited basis.

Although apalutamide has already been reviewed for non-metastatic castrate resistant prostate cancer, there is a potential for indication creep to use apalutamide for metastatic castration-resistant prostate cancer.

4.3 Implementation Factors

Apalutamide is available in one tablet strength and the dose is four tablets daily. Dose adjustments are made by adjusting the number of tablets and there would be minimal drug wastage. However, the four tablets daily are a high tablet burden and may be difficult for some patients.

PAG noted that apalutamide is an oral treatment that can be administered at the patient's home and chemotherapy chair time is not required. However, increased pharmacy resources would be required for dispensing apalutamide. PAG also identified that there may be additional nursing resources and increased frequent clinic visits for monitoring of blood work and side effects compared to docetaxel or ADT alone. For example, docetaxel for six cycles requires six clinic visits, while apalutamide is recommended until disease progression or unacceptable toxicity.

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 preference for apalutamide or docetaxel in this mCSPC setting.

Abiraterone for newly diagnosed high-risk mCSPC without small-cell histologic features is under review at pCODR. PAG is seeking guidance for high-risk patients, whether apalutamide or abiraterone is the preferred treatment.

PAG is seeking information on the appropriate treatment for castration resistant metastatic disease after treatment with apalutamide in the castration sensitive metastatic disease setting. Treatments available for castration resistant metastatic disease include abiraterone, enzalutamide and chemotherapy. PAG noted that apalutamide and enzalutamide are the same class of drug and seeking information on the use of enzalutamide in the metastatic, castration resistant setting after apalutamide or whether patients previously treated with apalutamide should be treated with other targeted androgen receptor agents (e.g., abiraterone) or chemotherapy in the subsequent line of therapy.

4.5 Companion Diagnostic Testing

None required.

4.6 Additional Information

None provided.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

A total of four registered clinician inputs from three individual oncologists and one joint input from three oncologists on behalf of Cancer Care Ontario (CCO) Genitourinary (GU) Drug Advisory Committee (DAC) provided input on the review of apalutamide (Erleada) for the treatment of metastatic castration-sensitive prostate cancer (mCSPC). Namely, individual inputs were submitted on behalf of oncologists practicing in Ontario, Alberta, and British Columbia (BC). The CCO clinicians highlighted that apalutamide is the only drug in this setting that is volume agnostic, which serves a key advantage. Funding of apalutamide would provide accessibility to a therapeutic option for mCSPC; namely, an oral agent that targets the androgen receptor. Docetaxel and abiraterone are presently used to treat the indication under review. However, at this time, docetaxel is reported to only be funded in Ontario and Alberta but not BC. Additionally, abiraterone is not funded across Canada.

There were different clinical opinions on whether patients with an Eastern Cooperative Oncology Group (ECOG) status of 2 or greater should receive apalutamide plus ADT in clinical practice; the BC clinician noted that there is no robust evidence to show clinical benefit in patients with an ECOG status of 2 or greater. Alternatively, the Alberta clinician noted there is no reason that these patients would not benefit from this treatment combination. Clinicians from CCO stated that patients with an ECOG status of 2 may receive this treatment combination based on clinical discretion but patients with an ECOG status of 3 or 4 are not likely to benefit. CCO clinicians and the BC clinician supported the treatment of patients who had more than six months of ADT with apalutamide plus ADT in clinical practice; however, the Alberta oncologist stated there is no evidence to support this. Moreover, the majority of clinicians felt that there is no specific high-risk subgroup that is more likely to benefit from apalutamide and ADT for mCSPC; however, the BC oncologist stated that patients with high PSA and a Gleason score of 8-10 would likely benefit more from apalutamide and ADT. Nonetheless, the BC oncologist supported the use of apalutamide in all patients with mCSPC. Clinicians highlighted the absence of head to head studies comparing apalutamide and docetaxel but indicated that apalutamide is better tolerated. There was general support to administer docetaxel in patients with a significant amount of tumour burden or a very aggressive phenotype. Accordingly, the Alberta clinician specified that apalutamide would be preferred for low-volume, low-risk mCSPC while docetaxel would be reserved for high-volume mCSPC especially for those with visceral metastases.

Apalutamide and abiraterone were described as having similar efficacy but differences in safety. Namely, apalutamide requires less monitoring compared to abiraterone plus prednisone, which requires regular monitoring of electrolytes and liver function due to the mineralocorticoid effect of abiraterone potentially causing fluid retention. Furthermore, the abiraterone plus prednisone combination may be problematic for those with diabetes due to the glucocorticoid effect of prednisone. Thus, apalutamide arguably exhibits better safety and tolerability compared to docetaxel and abiraterone. Following progression with apalutamide plus ADT in this setting, the majority of clinicians stated that they would likely administer chemotherapy and radiation (radium-223). Main toxicities of apalutamide were summarized to include rash, fatigue, and hypertension. Contraindications were highlighted according to the pivotal trial: severe angina, myocardial infarction, congestive heart failure, arterial or venous thromboembolic events, a history of or predisposition to seizure, and recent ventricular arrhythmias. The BC oncologist noted they would not want to administer apalutamide to patients with considerable amount of visceral disease or previous use of docetaxel as these two subgroups did not show considerable benefit in the pivotal trial.

Please see below for a summary of specific input received from the registered clinicians.

5.1 Current Treatments for mCSPC

Docetaxel and abiraterone were stated as current therapies for mCSPC across Ontario, BC, and Alberta but reported to be variably funded across these provinces. Across these provinces, abiraterone was

obtained through special access and compassionate programs. Namely, CCO stated that docetaxel and abiraterone (compassionate) are therapeutic options for patients with high volume disease and there are no additional options for low volume disease. The BC oncologist noted that docetaxel and abiraterone exhibit similar efficacy but are not currently funded, while the Alberta oncologist stated that docetaxel is the only funded treatment for this indication.

5.2 Eligible Patient Population

5.2.1 Implementation Question: In clinical practice, is there evidence to extend the use of apalutamide plus ADT to (provided all other eligibility criteria are met):

a) Patients with an ECOG performance status of 2 or greater?

There were differing opinions on whether patients with an ECOG status of 2 or greater should receive apalutamide plus ADT in clinical practice. The Alberta oncologist stated that there is no reason to believe that patients with an ECOG performance status of 2 or greater may not benefit from apalutamide and ADT in clinical practice even though they were excluded from the pivotal trial. They noted that apalutamide would be a safer option than docetaxel. Similarly, clinicians from CCO noted that patients with an ECOG status of 2 should be eligible for treatment with apalutamide and ADT based on clinician discretion; however, they stated that patients with an ECOG status of 3 or 4 are not likely to benefit from this therapy combination. Alternatively, the BC oncologist stated that there is no robust evidence to show clinical benefit in patients with an ECOG status of 2 or greater as the pivotal trial did not include patients with an ECOG status greater than 1. Of note, the individual clinician input of the oncologist practicing in Ontario did not include a response to this question.

b) Patients who had more than 6 months of ADT?

Clinicians expressed differences of opinion on whether patients who had received more than six months of ADT should receive apalutamide plus ADT in clinical practice. The Alberta oncologist stated that there is no evidence to use apalutamide and ADT in patients who have received ADT for more than six months. Alternatively, clinicians from CCO stated that clinicians would appreciate leeway with this cut-off. Similarly, the BC oncologist stated that the pivotal trial only investigated ADT up to six months; however, they expressed their opinion that the efficacy of apalutamide in non-metastatic castration resistant prostate cancer to prevent radiographic progression-free survival displays the effectiveness of the use of apalutamide in men treated with prolonged ADT. Of note, the individual clinician input of the oncologist practicing in Ontario did not include a response to this question.

5.2.2 Implementation Question: In clinical practice, is there a specific high-risk subgroup (e.g., Gleason score 8-10, high PSA at diagnosis, etc.) that is more likely to benefit from the addition of apalutamide to ADT for the treatment of mCSPC?

The majority of clinicians felt that there is no specific high-risk subgroup that is more likely to benefit from apalutamide and ADT as mCSPC treatment. The CCO oncologists and Alberta oncologist stated that there is no specific high-risk subgroup that is more likely to benefit from the addition of apalutamide to ADT for mCSPC treatment. CCO specified that such groups would be determined from post-hoc and un-specified analyses. Moreover, the Alberta oncologist noted that the inclusion/exclusion criteria of the pivotal (TITAN) trial were less restrictive than the criteria used in the *CHAARTED (Androgen Ablation Therapy With or Without Chemotherapy in Treating Patients with Metastatic Prostate Cancer)* and *LATITUDE (Abiraterone Acetate Plus Low-Dose Prednisone Androgen Deprivation Therapy (ADT) versus ADT Alone in Newly Diagnosed Participants with High-Risk, Metastatic Hormone-Naïve Prostate Cancer)* trials. The TITAN trial included an "all-comer" population in which all subgroups seemed to benefit; the TITAN trial demonstrated benefit even in patients who have received docetaxel for mCSPC. Currently, docetaxel is used in high-volume patients; however, apalutamide is better tolerated than docetaxel and serves as an option for patients who are ineligible for chemotherapy. Alternatively, the BC oncologist stated that patients with high PSA and Gleason Score

(8-10) are likely to benefit more, but they noted that the subgroup analysis in the TITAN trial of apalutamide plus ADT versus ADT alone in mCSPC showed benefit regardless of tumour grade and PSA value. Thus, they support the indication of administering apalutamide and ADT in all patients with mCSPC. Of note, the individual clinician input of the oncologist practicing in Ontario did not include a response to this question.

5.3 Relevance to Clinical Practice

All oncologists providing input had experience with administering apalutamide for mCSPC. Notably, the CCO clinicians stated that this space is no longer a complete unmet need. The Ontario oncologist of the individual input highlighted that there are no major issues with apalutamide in regard to clinical practice. The oncologist practicing in Alberta stated that apalutamide can be more broadly used in an "all-comer" mCSPC population without consideration for high-volume, high-risk criteria. Moreover, the oncologist practicing in BC stated that they would use apalutamide in patients with de novo mCSPC. Alternatively, they may not want to administer apalutamide to patients with considerable amount of visceral disease or previous use of docetaxel as these two subgroups did not show considerable benefit in the pivotal trial.

When clinicians were asked how apalutamide is different than currently available treatments with respect to efficacy, safety, and tolerability, there was agreement that apalutamide demonstrates similar efficacy to abiraterone. Specifically, the CCO clinicians noted that there is no comparison to abiraterone; nonetheless, apalutamide is an important therapy as it is the only drug that is volume agnostic. The Alberta oncologist stated that apalutamide is better tolerated than chemotherapy and requires less intense monitoring than abiraterone plus prednisone while demonstrating similar efficacy and arguably better safety and tolerability. The BC oncologist stated that currently apalutamide exhibits similar efficacy to docetaxel and abiraterone; however, docetaxel and apalutamide improve overall survival but abiraterone does not. Abiraterone is similar to apalutamide in that they are both oral agents that target the androgen receptor and are not currently funded for mCSPC.

The CCO clinicians highlighted the main toxicities of apalutamide to include rash, fatigue, and hypertension. Oncologist from Alberta highlighted relative contraindications of apalutamide to include history of seizures, hypothyroidism, or uncontrolled hypertension; the BC oncologist expanded on this list by stating the contraindications that were used to exclude patients from the pivotal trial: severe angina, myocardial infarction, congestive heart failure, arterial or venous thromboembolic events, a history of or predisposition to seizure, and recent ventricular arrhythmias.

5.4 Sequencing and Priority of Treatments with Apalutamide

5.4.1 Implementation Questions: Please consider if there is evidence to support the optimal treatment sequencing with apalutamide plus ADT with available treatments:

a) What treatment options (e.g., abiraterone, enzalutamide and chemotherapy) would be available following progression with apalutamide plus ADT in this setting? Apalutamide and enzalutamide are the same class of drug, in clinical practice, would patients receive enzalutamide in the metastatic, castration resistant setting after apalutamide? Or would patients previously treated with apalutamide be treated with other targeted androgen receptor agents (e.g., abiraterone) or chemotherapy in the subsequent line of therapy?

Following progression with apalutamide plus ADT in this setting, all clinicians stated that the next treatment option would be chemotherapy or radiation therapy (radium-223), except for the Alberta oncologist who indicated chemotherapy and alternatively abiraterone plus prednisone as subsequent treatment options. This clinician justified the consideration of abiraterone plus prednisone since many patients in the pivotal trial appeared to benefit from this combination as a second-line therapy. Namely, the BC clinician noted that after apalutamide, patients would likely need a taxane-based therapy (docetaxel or cabazitaxel) or radium-223 if there is only bone metastases. Due to cross-resistance, there would be very little benefit of another androgen-receptor targeted therapy. The CCO clinicians stated that most patients should receive docetaxel following progression with apalutamide in this setting but only if it is tolerable. Additionally, they presumed that there would not be any patients that receive enzalutamide after apalutamide. Furthermore, abiraterone was considered as an option for patients who are ineligible for chemotherapy or have metastases that are not limited to their bones; they highlighted that chemotherapy is inexpensive, complete after 18 weeks, and there is reasonable quality of life data. However, clinicians from COO stated that there is risk of adverse events such as neuropathy and febrile neutropenia with chemotherapy.

b) In what clinical scenarios would apalutamide or docetaxel be the preferred treatment in the mCSPC setting? Please comment on the preference considering patient preference, efficacy, safety, and administration.

Clinicians from CCO and the BC oncologist noted that there are no head-to-head studies comparing apalutamide and docetaxel to identify specific clinical scenarios in which one would be the better therapy in the mCSPC setting. Nonetheless, CCO clinicians specified that they would probably treat patients with a very aggressive phenotype with chemotherapy first. Similarly, the BC oncologist stated that patients with a significant amount of tumour burden may be better treated with docetaxel and the Alberta oncologist would reserve docetaxel for high-volume patients and especially for those with visceral metastases. Accordingly, the Alberta oncologist would administer apalutamide for low-volume low-risk mCSPC. The BC oncologist would also administer docetaxel in patients with a history of or predisposition to seizure and hypothyroidism, in addition to, patients that do not want long-term therapy and may prefer the six month course of docetaxel. Moreover, the Ontario oncologist stated they would use docetaxel for a minority of patients (e.g. “neuroendocrine/ non PSA producers”).

c) At the time of registered clinician input, abiraterone for newly diagnosed high-risk mCSPC without small-cell histologic features is under review at pCODR. For high-risk patients, in what clinical scenarios would apalutamide or abiraterone be the preferred treatment? Please comment on the preference considering patient preference, efficacy, safety, and administration.

Apalutamide and abiraterone were described to exhibit similar efficacy but differences in safety. Overall, apalutamide was summarized to require less monitoring compared to abiraterone plus prednisone, which requires regular monitoring of electrolytes and liver function due to the mineralocorticoid effect of abiraterone potentially causing fluid retention. Additionally, the abiraterone and prednisone combination was highlighted to be problematic for those with diabetes due to the glucocorticoid effect of prednisone.

The Alberta oncologist would prefer to use abiraterone in patients with high-risk disease with two out of three defined criteria and less commonly in low-risk patients as low-risk patients received apalutamide in the pivotal trial. They specified their preference to use apalutamide in patients with a history of heart failure or diabetes and in those whom monitoring electrolytes and liver function every two weeks would be problematic. They made clear that while patients with heart failure were excluded from the pivotal trial, apalutamide would be the safer option over

abiraterone as it does not have the same issues with fluid retention that requires close monitoring even in patients without a history of heart failure

The BC oncologist who has administered apalutamide and abiraterone stated that efficacy, administration, tolerability (both are very well tolerated), and safety of both therapies are similar. Apalutamide does not require prednisone and does not have the mineralocorticoid effects of abiraterone. Alternatively, abiraterone does not reduce the seizure threshold (i.e. increase the likelihood of a seizure) unlike apalutamide, which was noted to be rare. They also noted that apalutamide requires much less lab testing, no LFT changes, and no concerns of diabetes or high blood glucose. Alternatively, abiraterone is not associated with hypothyroidism or skin rash. In their opinion, they feel that patient preference would be similar.

Clinicians from CCO stated that apalutamide might be preferred for patients who cannot receive prednisone (e.g. due to diabetes). Alternatively, patients with fatigue or poor appetite may benefit from abiraterone plus prednisone and that seizure risk is a contraindication for apalutamide. Of note, the individual clinician input of the oncologist practicing in Ontario did not include a response to this question.

5.5 Companion Diagnostic Testing

No companion diagnostic testing required.

5.6 Additional Information

None to report.

6 SYSTEMATIC REVIEW

6.1 Objectives

The primary objective of this review is to evaluate the efficacy and safety of apalutamide (Erleada) in combination with androgen deprivation therapy (ADT) compared to placebo plus ADT in patients with metastatic castration-sensitive prostate cancer (mCSPC).

Supplemental Questions and Comparison with Other Literature most relevant to the pCODR review and to the Provincial Advisory Group were identified while developing the review protocol and are outlined in section 7 and section 8.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold.

Table 3. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators	Outcomes
Published and unpublished RCTs. In the absence of RCTs, fully published non-comparative clinical trials investigating efficacy and safety of apalutamide	Patients with a diagnosis of metastatic castration-sensitive prostate cancer	Apalutamide (240 mg PO once daily) in addition to ADT	Placebo + ADT Docetaxel (DOC) ± ADT Abiraterone acetate + prednisone (AAP) ± ADT Enzalutamide ± ADT	Efficacy • **Progression-free survival (radiographic)** • **Overall survival** • Time to cytotoxic chemotherapy • Time to pain progression • Time to chronic opioid use • Time to skeletal-related events • **Time to PSA progression** • Second progression-free survival • Time to symptomatic local progression Safety • AEs • SAEs Patient-reported outcomes/**HRQoL**

ADT = androgen deprivation therapy; AE = adverse events; HRQoL = health-related quality of life; mg = milligram; RCT = randomized controlled trial; PO = oral; SAE = serious adverse events;

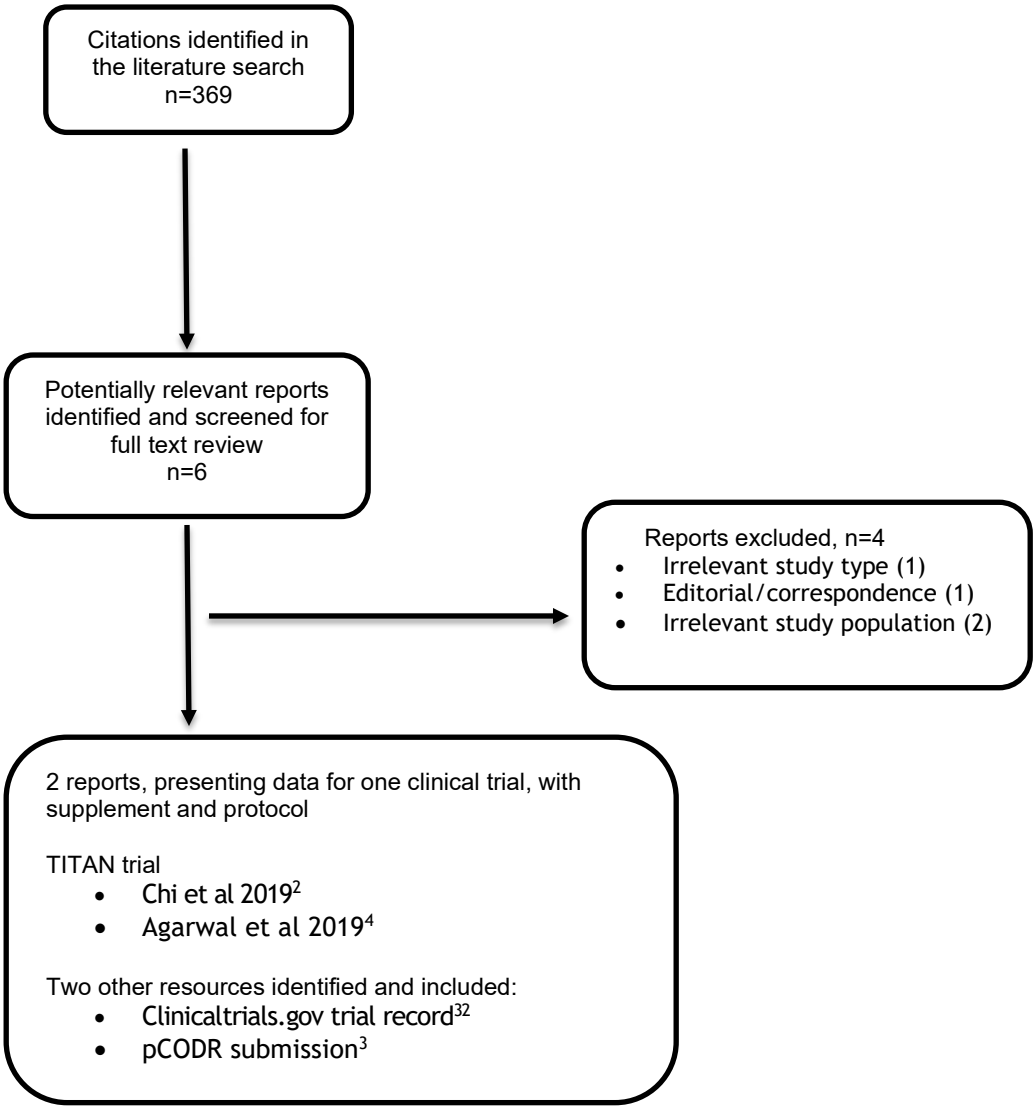
** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

6.3 Results

6.3.1 Literature Search Results

Of the 6 potentially relevant reports identified, one study published as two reports was included in the pCODR systematic review[2,3] and 4 studies were excluded. Studies were excluded because they had irrelevant study designs[28], were published as correspondence[29] or had irrelevant populations.[30 31] Other resources included the clinicaltrials.gov record[32] and the pCODR submission.[3]

Figure 1. QUOROM Flow Diagram for Inclusion and Exclusion of studies



Note: Additional data related to the TITAN trial were also obtained through requests to the Submitter by pCODR

6.3.2 Summary of Included Studies

One randomized clinical trial[2] was identified that met the selection criteria and is included in this systematic review (Please see Table 4). TITAN was a multinational, multicentre, phase III randomized, double-blind trial that evaluated the efficacy and safety of apalutamide plus ADT versus placebo plus ADT in patients with metastatic castration-sensitive prostate cancer (mCSPC).

6.3.2.1 Detailed Trial Characteristics

Relevant summary information on trial characteristics are summarized in Table 4 and quality characteristics of this trial are reported in Table 5.

Table 4. Summary of Trial Characteristics of the Included Studies[2,32]

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
TITAN NCT02489318 CR107614 Randomized, controlled, double-blind, Phase III study 1,052 randomized (apalutamide+ ADT n=525; placebo+ADT n=527). 260 sites in 23 countries from Europe, North America, the Middle East and the Asia-Pacific region. Dates of Randomization: December 2015 to July 2017 Data cut-off dates: Clinical data cutoff for the final analysis for radiographic PFS (and first of two prespecified interim analysis for OS, based on 50% death events) was November 23, 2018 Estimated study completion date: July 12, 2021 Funding: Janssen Research and Development	<u>Key Inclusion Criteria:</u> • Documented adenocarcinoma of the prostate • Metastatic disease documented on the basis of at least one lesion on bone scanning, with or without visceral or lymph-node involvement • ECOG PS score of 0 or 1 • Patients were castration sensitive (i.e., patients were not receiving ADT at the time of disease progression) Allowed previous treatment for prostate cancer was limited to a max of 6 cycles of docetaxel for low-volume mCSPC, ADT for no more than 6 months for mCSPC or no more than 3 years for localized prostate cancer, one course of radiation or surgical therapy for symptoms associated with metastatic disease, and other localized treatments for prostate cancer completed at least 1 year before randomization • Antiandrogen therapy must have been discontinued before randomization <u>Key Exclusion Criteria:</u> • Pathological finding consistent with small cell, ductal or neuroendocrine carcinoma of the prostate • Known brain metastases • Lymph nodes or viscera (i.e., liver or lung) as only site of metastasis • Other prior malignancy within 5 years prior to randomization	<u>Intervention:</u> Apalutamide: 240-mg (4 x 60-mg tablets); taken orally once daily <u>Comparator:</u> Placebo (4 tablets); taken orally once daily <u>ADT Administration:</u> Subjects in both groups receive and remain on a stable regimen of ADT (GnRHa or surgical castration). The choice of the GnRHa (agonist or antagonist) at discretion of the Investigator. Dose and frequency of administration consistent with prescribing information	<u>Primary:</u> • PFS (radiographic) • OS <u>Secondary:</u> • Time to cytotoxic chemotherapy • Time to pain progression • Time to chronic opioid use • Time to skeletal-related events <u>Exploratory:</u> • Time to PSA progression • Second PFS • Time to symptomatic local progression <u>Safety</u> • AEs • SAEs Patient-reported outcomes/HRQoL as measured by: • BPI-SF • BFI • FACT-P • EQ-5D-5L

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
	• Patients with severe angina, myocardial infarction, congestive heart failure, arterial or venous thromboembolic events, a history of or predisposition to seizure, or recent ventricular arrhythmias • Prior treatment with other next-generation anti-androgens (e.g., enzalutamide), CYP17 inhibitors (e.g., abiraterone acetate), immunotherapy (e.g., sipuleucel-T), radiopharmaceutical agents or other treatments for prostate cancer • Initiation of treatment with a bisphosphonate or denosumab for the management of bone metastasis within 28 days prior to randomization		

Abbreviations: ADT = androgen deprivation therapy; AE = adverse event; BPI-SF = Brief Pain Inventory – Short Form; BFI = Brief Fatigue Inventory; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = EuroQOL 5D questionnaire 5 level; FACT-P = Functional Assessment of Cancer Therapy - Prostate; HRQoL = health-related quality of life; IV = intravenously; mCSPC = metastatic castration sensitive prostate cancer; OS = overall survival; PFS = progression free survival; PFS2 = second progression-free survival;

Table 5: Select quality characteristics of included studies of apalutamide + ADT in patients with metastatic castration-sensitive prostate cancer (mCSPC)

Study	Treatment vs. Comparator	Primary outcome	Required sample size	Sample size	Randomization method	Allocation concealment	Blinding	ITT Analysis	Final analysis	Early termination	Ethics Approval
TITAN	Apalutamide vs placebo	rPFS OS	1000	1052	IWRS	Yes	Yes	Yes	No	No	Yes

rPFS = radiographic progression-free survival; OS = overall survival; IWRS = interactive web response system

a) Trials

The TITAN trial is a phase III, randomized, double-blind, placebo-controlled, multinational trial comparing apalutamide with placebo, when administered with concurrent androgen deprivation therapy (ADT), in patients with mCSPC. The trial was conducted in 260 sites across 23 countries in North America (including six centers in Canada), Europe and Asia-Pacific region. TITAN evaluates whether the addition of apalutamide to ADT prolongs radiographic progression-free survival and overall survival compared with placebo plus ADT in patients with mCSPC. The trial design was developed by the Sponsor with input from the first author (Chi[2]) and the protocol steering committee.

The study consisted of four phases: 1) Screening Phase (up to 28 days before randomization), 2) Treatment Phase (cycle 1 day 1 until study drug is discontinued), 3) Follow-up Phase (once subject discontinues study drug, until death, withdrawal, lost to follow up or termination of study), and 4) Open-label Extension Phase (allows all subjects in the treatment phase to receive apalutamide plus ADT for up to three years).[2]

Subjects selected for participation in this study were patients with mCSPC documented by positive bone scan (≥1 bone lesion(s) on Technetium-99m [^{99m}Tc]). Subjects with a single bone lesion must have confirmation of the bone metastasis by CT or MRI. Androgen deprivation therapy (e.g., medical or surgical castration) must have been started ≥14 days prior to randomization. Subjects who started a GnRH agonist ≤28 days prior to randomization were required to take a first-generation anti-androgen for ≥14 days prior to randomization. The anti-androgen must have been discontinued prior to randomization. Subjects had an ECOG Performance Status (PS) grade of 0 or 1. Subjects could have received up to six cycles of docetaxel for mCSPC with the last dose administered ≤2 months prior to randomization. All subjects could have received ≤6 months of ADT prior to randomization and could have received a maximum of one course of radiation or surgical intervention for mCSPC. For localized prostate cancer, subjects may have received ≤3 years total of ADT and all other forms of prior therapies including rradiation therapy, prostatectomy, lymph node dissection, and systemic therapies as long as all such therapies were completed ≥1 year prior to randomization.

At its initial approval in June 2015, the TITAN protocol enrolled only patients with low volume disease while allowing prior docetaxel use (as long as stable disease was maintained before randomization). The protocol was amended in April 2016 (Amendment 1 – April 2016) to allow enrollment of patients with high volume disease.[2] The protocol was amended three additional times to provide guidance for the management of drug-related skin rashes (Amendment 2 - February 2017), to update the visit/lab schedules during the Open-label Extension Phase of the study (Amendment 3 – February 2018), and to change the timing of the interim analyses of overall survival due to a lower number of OS events than initially expected (Amendment 4 – September 2018).[2] Amendments 1 through 3 were considered to be substantial, while amendment 4 was more minor.

Eligible patients were randomized in a 1:1 ratio to receive apalutamide (240 mg per day) (n=525) or matched placebo (n=527), added to ADT. Patients were stratified according to Gleason score at diagnosis (≤7 vs. >7, on a scale of 2 to 10, with higher scores indicating higher-grade cancer that may be more aggressive), geographic region (North America and European Union vs. all other countries), and previous treatment with docetaxel (yes vs. no).

Response to study treatment and progressive disease was assessed according to modified RECIST, version 1.1, with the use of CT or MRI of the chest, abdomen, and pelvis during screening (≤6 weeks before randomization). Response was also assessed according to Prostate Cancer Working Group 2 Criteria (i.e. PSA: first ≥25% increase from baseline and ≥2 ng/mL above the nadir; soft-tissue lesions: follow Response Evaluation Criteria in Solid Tumors) with the use of bone scanning during cycles 3 and 5 and every fourth cycle thereafter.[1] Events of progression were assessed by the investigator. Scans from approximately 60% of the patients were randomly selected for independent central review.

Outcomes

The dual-primary efficacy endpoints of this study were radiographic progression-free survival (rPFS) and overall survival (OS). rPFS was defined as the time from randomization to first imagining-based documentation of progressive disease or death, whichever occurred first.[2] A patient was considered to have radiographic progressive disease if he had either progression of soft-tissue lesions measured by means of CT or MRI or new bone lesions on bone scanning. Overall survival was defined as the time from randomization to the date of death from any cause. The analysis of PFS and OS was based on the ITT population.[2]

A key secondary efficacy endpoint was time to pain progression, defined as the time from randomization to the date of the first observation of pain progression.[2] This outcome was assessed by the Brief Pain Inventory – Short Form (BPI-SF). Other secondary outcomes included time to cytotoxic chemotherapy, time to chronic opioid use i.e. first date of opioid use or first date of an increase in the total daily dose, and time to skeletal-related events (SRE). The SRE is defined as the occurrence of symptomatic pathological fracture, spinal cord compression, radiation to bone, or surgery to bone.[2]

A prespecified analysis in patients with low-volume or high-volume mCSPC was planned, and evaluation of efficacy in these subgroups was a secondary objective. High-volume disease was defined as visceral metastases and at least one bone lesion, or at least four bone lesions with at least one outside the axial skeleton. This definition was adapted from the Chemohormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (CHAARTED). Low-volume disease was defined as the presence of bone lesions not meeting the definition of high-volume disease.

Exploratory endpoints of the trial included the time to prostate-specific antigen (PSA) progression, second progression-free survival, and the time to symptomatic local progression. Second progression-free survival was defined as the time from randomization to the first occurrence of investigator-determined disease progression (PSA progression, progression on imaging, or clinical progression) while the patient was receiving first subsequent therapy for prostate cancer or death due to any cause, whichever occurred first.[2]

Patient-reported outcomes (PRO) for health-related quality of life were assessed by means of the Functional Assessment of Cancer Therapy–Prostate (FACT-P) questionnaire. Raw FACT-P scores range from 0 to 156, with higher scores indicating more favorable health-related quality of life. A change of 6 to 10 points in the FACT-P total score is the minimally important difference. FACT-P assessments were collected on day 1 of cycles 2 through 7, then every other cycle, at the end of the intervention period, and every four months for up to one year after discontinuation. BPI-SF assessments were collected six days before cycle 1, then at each cycle, the end of the intervention period, and every four months for up to one year after discontinuation. Safety was assessed monthly and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0.3.

Statistical Data Analyses

The TITAN trial was designed to enroll approximately 1000 patients. The rPFS endpoint was tested first at the two-sided 0.005 level of significance.[2] If rPFS was statistically significant, the alpha was recycled to overall survival. An overall type I error of 5% was planned.[2] A total of approximately 368 rPFS events would be required to provide at least 85% power in detecting a HR of 0.67 (median rPFS of 20 months for the control group [ADT] versus 30 months for the apalutamide + ADT group plus ADT) at a two-tailed significance level of 0.005.[2]

The OS endpoint also included two interim analyses that incorporated a group sequential design with overall type I error control. The alpha level for the first interim analysis of OS was 0.009 when rPFS was statistically significant and at which point 50% of required OS events (approximately 205) were assumed to have occurred.[2] For the final OS analysis, 410 events were required to provide sufficient power (approximately 80%) to detect a HR of 0.75 at a 2-tailed significance level of 0.045 with enrollment duration of approximately 30 months (approximately 1,000 subjects) and an assumed median OS of 69 months (based on published data in a similar patient population) for the control group (ADT).[2] The overall level of alpha (2-sided) was adequately controlled at 0.05 in the study.[2] Fixed sequence testing was used to test the secondary endpoints in the following pre-specified order, each with an overall two-sided significance level of 0.05: time to initiation of cytotoxic chemotherapy, time to pain progression, time to chronic opioid use, and time to skeletal-related event.[2]

Kaplan-Meier product limit method and Cox proportional hazards model were used to estimate the time-to-event variables and to obtain the hazard ratio (HR) along with the associated confidence intervals (CIs). Stratified log-rank test was used to test the treatment effect for time-to-event variables.[2]

Descriptive statistics of each PRO scale score from the FACT-P, BPI-SF, and BFI at baseline and follow-up assessments were summarized by treatment groups; time to degradation in each scale was analyzed using Kaplan-Meier method and stratified Cox proportional hazard model. The EQ-5D-5L data was summarized descriptively by treatment group and study visit.[2]

b) Populations

In the TITAN trial, a total of 1,052 subjects were randomly assigned to treatment (525 subjects to the apalutamide + ADT arm and 527 subjects to the placebo + ADT arm) and comprised the intention-to-treat (ITT) population. One subject was assigned to the apalutamide plus ADT arm but withdrew consent prior to treatment, resulting in 1,051 subjects in the safety population.[3] Study participants were recruited from 23 countries in Europe, the Asia-Pacific region and North America, including 30 patients from Canada.[3] Twenty-three percent of the patients, for both study arms, were enrolled in North America, and approximately 43% of the study participants were from Europe. The majority of patients were enrolled from the Rest of the World (67.0% in the apalutamide + ADT group and 67.2% in the placebo + ADT group).[3]

Demographic and clinical characteristics appeared well balanced at baseline between the apalutamide + ADT and placebo + ADT treatment groups (Table 6). Subjects were predominantly white (68%) males with a median age of 68 years

(range: 43 to 94 years).[2] Twenty-three percent of subjects were over the age of 75.[2] Most subjects had metastatic disease (M1) at initial diagnosis. Gleason score of 7 or less was recorded for 33% of subjects in the apalutamide + ADT group and 32% in the placebo + ADT group.[1] Overall, 37% of subjects (38% apalutamide + ADT group and 36% in the placebo + ADT group), had low volume disease defined as no visceral metastases and less than four bone lesions. The majority of subjects had an ECOG PS of 0: 63% in the apalutamide + ADT group and 66% in the placebo + ADT group. Median PSA level was 5.97 (range 0-2,682) for those in the apalutamide + ADT group and 4.02 (range 0-2,229) in the placebo + ADT group. The mean pain scores at baseline were low for the vast majority of patients in both groups.

Prior docetaxel was received by 11% of subjects in the apalutamide + ADT group and 10% in the placebo + ADT group (Table 6). These subjects were required to have maintained a response to docetaxel of stable disease or better prior to randomization in the study. Previous therapy for localized disease was received by 18% of patients in the apalutamide + ADT group and 15% in the placebo + ADT group. Among subjects with prior docetaxel treatment, there were a higher proportion of subjects in the apalutamide + ADT group with negative prognostic features (e.g., higher ECOG score [1 vs 0] and presence of visceral disease): 35% of subjects in the apalutamide + ADT group compared to 27% of subjects in the placebo + ADT group had an ECOG score of 1; 16% of subjects in the apalutamide + ADT group compared to 11% of subjects in the placebo + ADT group had presence of visceral disease. Additionally, subjects with prior docetaxel treatment in the apalutamide + ADT group had a higher median PSA at baseline (0.93 ug/L, apalutamide + ADT group and 0.57 ug/L, placebo + ADT group) as well as higher mean alkaline phosphatase values at baseline (120 U/L, apalutamide + ADT group arm and 95 U/L, placebo + ADT group).[3] The extent to which the imbalance in these patient characteristics may have influenced study outcomes is unknown. However, with a higher proportion of patients with poorer prognostic characteristics in the apalutamide + ADT group, it is unlikely that the benefits observed with apalutamide therapy are inflated because of these imbalances.

Table 6: Demographic and Clinical Characteristics of the Patients at Baseline*

Characteristic	Apalutamide (N=525)	Placebo (N=527)
Median age (range) — yr	69 (45–94)	68 (43–90)
ECOG performance-status score — no. (%)†		
0	328 (62.5)	348 (66.0)
1	197 (37.5)	178 (33.8)
2	0	1 (0.2)
Gleason score at initial diagnosis — no. (%)‡		
<7	41 (7.8)	39 (7.4)
7	133 (25.3)	130 (24.7)
>7	351 (66.9)	358 (67.9)
Metastatic stage at initial diagnosis — no. (%)		
M0	85 (16.2)	59 (11.2)
M1	411 (78.3)	441 (83.7)
MX	29 (5.5)	27 (5.1)
Disease volume — no. (%)		
Low	200 (38.1)	192 (36.4)
High	325 (61.9)	335 (63.6)
Previous treatment with docetaxel — no. (%)§	58 (11.0)	55 (10.4)
Previous therapy for localized prostate cancer — no. (%)¶	94 (17.9)	79 (15.0)
Median prostate-specific antigen level (range) — μg/liter	5.97 (0–2682)	4.02 (0–2229)
Mean baseline BPI-SF pain score — no. (%)		
0: no pain	198 (37.7)	200 (38.0)
1 to 3: mild pain	195 (37.1)	207 (39.3)
4 to 7: moderate pain	98 (18.7)	95 (18.0)
8 to 10: severe pain	12 (2.3)	11 (2.1)
Missing data	22 (4.2)	14 (2.7)

* Between-group differences were not evaluated statistically, but there were no substantial differences between the two groups. Percentages may not total 100 because of rounding. BPI-SF denotes Brief Pain Inventory–Short Form. Additional demographic and clinical characteristics are provided in Table S1 in the Supplementary Appendix.
† Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores reflecting greater disability.
‡ Scores on the Gleason scale range from 2 to 10, with higher scores indicating higher-grade cancer that may be more aggressive.
§ Of the patients with previous docetaxel use, 27 patients (47%) in the apalutamide group and 22 patients (40%) in the placebo group had a node stage of N1 at diagnosis.
¶ Previous therapies for localized prostate cancer included prostatectomy and radiotherapy.

Source: N Eng J Med, Chi et al., Apalutamide for metastatic, castration-sensitive prostate cancer, 381(1):13-24. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[2]

The types and frequencies of prior prostate cancer treatments are summarized in Table 7. As the table shows, the proportions of patients with a history of any given therapy were well balanced between the study groups. All 525 patients in the apalutamide + ADT group and all 527 patients in the placebo + ADT group had received hormonal therapy. Overall, 17.9% and 15.0% of patients in the apalutamide + ADT group and placebo + ADT group, respectively, had prior surgery or radiation therapy. One patient in the apalutamide + ADT group had received prior vandetanib, while no patients in the placebo + ADT group did.

Table 7. Prior Prostate Cancer Therapy

	Apalutamide (n=525)	Placebo (n=527)
Prostatectomy or radiotherapy – no. (%)	94 (17.9)	79 (15.0)
Prostatectomy only	26 (5.0)	27 (5.1)
Radiotherapy only	47 (9.0)	39 (7.4)
Both prostatectomy and radiotherapy	21 (4.0)	13 (2.5)
Hormonal therapy – no. (%)	525 (100)	527 (100)
First-generation antiandrogen	352 (67.0)	361 (68.5)
Gonadotropin-releasing hormone agonist	462 (88.2)	455 (86.3)
Gonadotropin-releasing hormone antagonist	56 (10.7)	53 (10.1)
Bilateral orchiectomy	33 (6.3)	40 (7.6)
Docetaxel – no. (%)	58 (11.0)	55 (10.4)
Vandetanib – no. (%)	1 (0.2)	0

Source: N Eng J Med, Chi et al., Apalutamide for metastatic, castration-sensitive prostate cancer, 381(1):13-24. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[2]

c) Interventions

Treatment Dosing Schedule

Patients receive either apalutamide at 240 mg, orally, once daily (4 x 60 mg tablets) or matched placebo administered orally once daily, in addition to continuous ADT (GnRHa or surgical castration). Patients in both groups were to continue receiving treatment until disease progression, unacceptable toxic effects or study end. Dose modifications for toxicity were permitted during the trial for certain patients who were unable to tolerate the protocol-specified dosing scheme.

The median number of cycles received was 23 for apalutamide and 19 for placebo (range 1-37 in each group).[2] The median duration of exposure was 20.5 months (range: 0 to 34 months) in patients who received apalutamide and 18.3 months (range: 0.1 to 34 months) in patients who received placebo. [3] A total of 66.2% of the patients in the apalutamide + ADT group and 46.1% of those in the placebo + ADT group were receiving the trial intervention at the clinical cutoff date (November 23, 2018).[2]

Dose delays, reductions or modifications

The majority of subjects were able to tolerate the full prescribed dose of study medication (92.7% apalutamide + ADT group and 97.9% of subjects in the placebo + ADT group.[3] More dose reductions (7.3%) and dose interruptions (23.5%) due to a TEAE were reported in the apalutamide +ADT group as compared with placebo + ADT group (2.1% and 12.1%, respectively).[3]

Concomitant Therapies

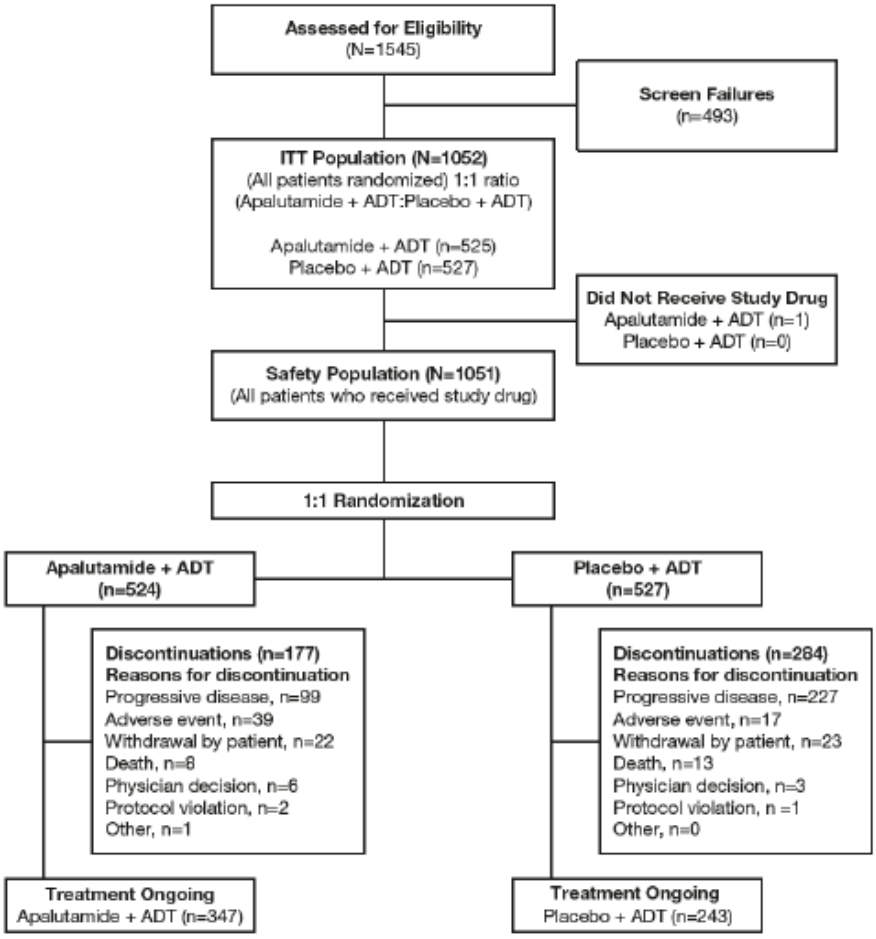
Supportive care medications were permitted, with their use following institutional guidelines.[2] The use of drugs known to decrease the seizure threshold and/or cause seizure were prohibited while receiving study treatment. Long-term use of systemic corticosteroids was not allowed; however, short-term (≤4 weeks) was permitted if clinically indicated.[2]

[redacted][3] *Non-disclosable information was used in this pCODR Guidance Report and the Sponsor requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the Sponsor that it can be publicly disclosed.* Bone-sparing agents were taken by 17% of apalutamide-treated subjects and 24% of placebo-treated subjects.[3] [redacted].[3] *Non-disclosable information was used in this pCODR Guidance Report and the Sponsor requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the Sponsor that it can be publicly disclosed.*

d) Patient Disposition

A total of 1,052 patients were randomly assigned to treatment (525 subjects to the apalutamide + ADT group and 527 subjects to the placebo + ADT group) and comprise the ITT population. One patient randomized to the apalutamide + ADT group did not receive study drug, resulting in 1051 patients in the Safety Analysis population. The median duration of treatment was 21 months for the apalutamide + ADT group and 18 months for the placebo + ADT group. A total of 45 patients across the two groups withdrew consent for the trial intervention. These patients were followed for survival and secondary end points, so their data were not missing. A total of 39 patients were either lost to follow-up or withdrew from all further data collection (Figure 2).

Figure 2. CONSORT Diagram



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After treatment discontinuation, subjects continued to be followed on study for survival, subsequent therapy, and secondary endpoints. If subjects discontinued treatment prior to determination of rPFS, every effort was made to obtain imaging assessments until rPFS was observed. As of the clinical cutoff (November 23, 2018), 66% (347/524) of subjects in the apalutamide + ADT group and 46% (243/527) of subjects in the placebo + ADT group still had treatment ongoing (Figure 2). A total of 177 patients in the apalutamide + ADT group (34%) and 284 patients in the placebo + ADT group (54%) discontinued study treatment.[2] The most common reasons for discontinuation of treatment included: progressive disease (19% in the apalutamide + ADT group versus 43% in the placebo + ADT group), AEs (8% in the apalutamide + ADT group versus 5% in the placebo + ADT group), and withdrawal by subject (4% in both the apalutamide + ADT and placebo + ADT groups).[2] Discontinuation because of death occurred in 1.5% of patients in the apalutamide + ADT group and 2.5% of patients in the placebo + ADT group[3]. Discontinuation because of protocol violations occurred in less than 1% of patients in both groups.[2,3]

Limitations/Sources of Bias

Overall, TITAN is 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 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, the following limitations and potential sources of bias of the TITAN trial were noted by the pCODR Methods Team:

- With no active treatment in the control arm, there is a lack of direct comparison to other relevant agents, such as docetaxel, abiraterone acetate + prednisone and enzalutamide.
- Patients in the control arm only received ADT in addition to placebo. However, in clinical practice, bicalutamide (hormonal therapy) is usually added to ADT especially for patients with high-volume disease. Other prostate cancer trials (i.e. Enzamet and SWOG 9346) have included bicalutamide with ADT.
- Control patients did not receive first-line therapy for mCRPC until they demonstrated radiographic progression, and only 190 of 271 patients (70%) on the placebo arm reported to have radiographic progression received additional cancer therapy. The extent to which this exaggerate the trial results in favour of apalutamide is unknown.
- 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 410 events have occurred.
- All subgroup analyses were univariate and sensitivity analyses were not conducted. Subgroup analyses on subjects with low or high volume mCSPC disease 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 TITAN 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.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

Efficacy analyses were performed using the 1,052 ITT population (525 patients in the apalutamide + ADT group and 527 in the placebo + ADT group)

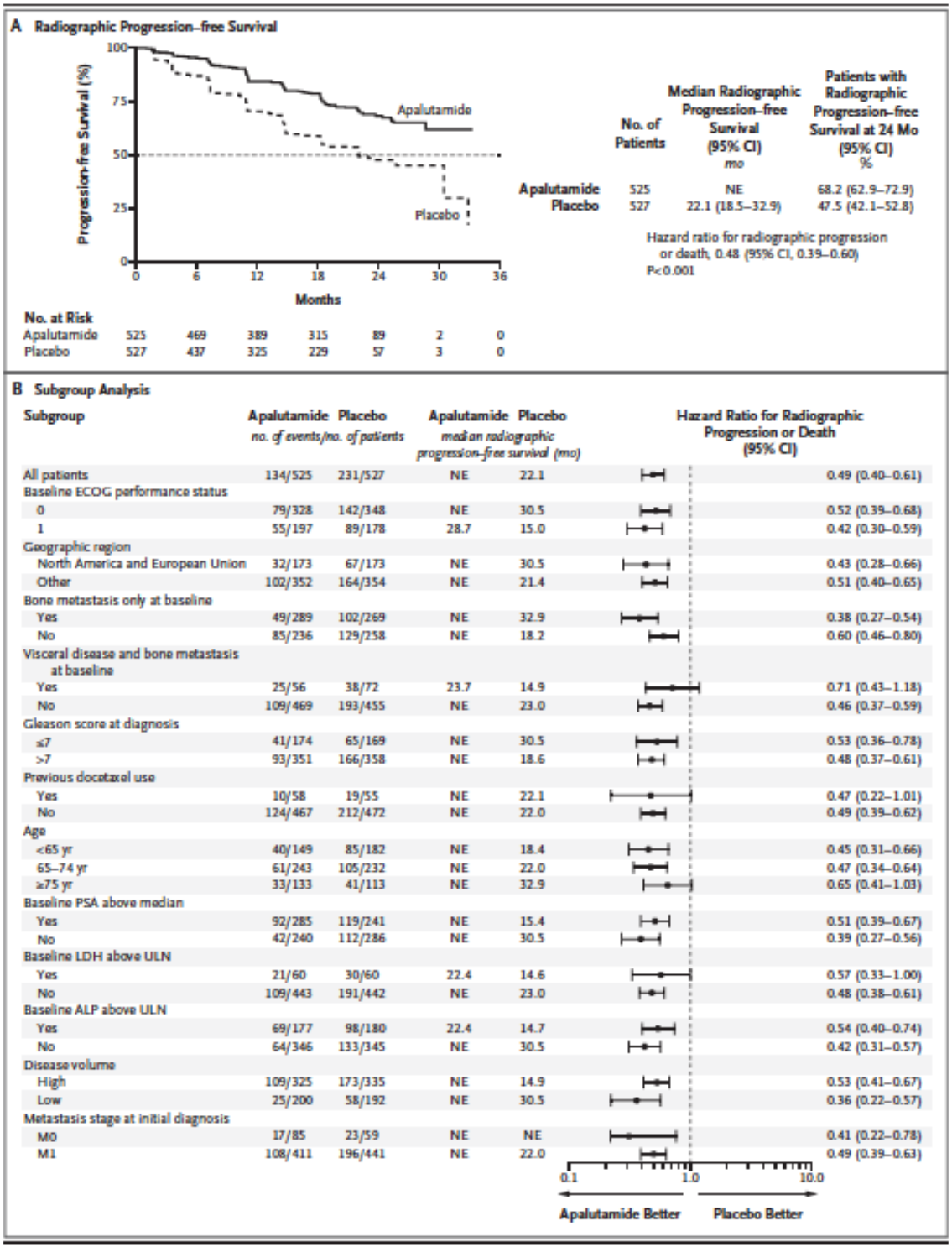
Co-primary Endpoint: Radiographic Progression-free Survival (rPFS)

rPFS was one of the primary outcomes in the TITAN trial. As of the 23-November-2018 clinical cutoff date, a total of 365 events of radiographic progression were observed (134 in the apalutamide + ADT group and 231 in the placebo + ADT group). The percentage of patients with radiographic progression–free survival at 24 months was 68.2% in the apalutamide + ADT group and 47.5% in the placebo + ADT group (hazard ratio for radiographic progression or death, 0.48; 95% confidence interval [CI], 0.39 to 0.60; P<0.001), for a 52% lower risk of radiographic progression or death in the apalutamide + ADT group (Figure. 3A).

Subgroup Analyses of rPFS

Pre-specified subgroup analyses of rPFS were conducted to assess the consistency of treatment effect across the following subgroups: ECOG performance status at baseline (0 vs 1), geographic region (North America and European Union vs Other), bone metastasis only at baseline (yes vs no), visceral disease and bone metastasis at baseline (yes vs no), Gleason score at diagnosis (≤7 vs >7), previous docetaxel use (yes vs no), age (<65 yr, 65-74 yr, ≥75 yr), baseline PSA above median (yes vs no), baseline LDH above ULN (yes vs no), disease volume (high vs low), and metastasis stage at initial diagnosis (M0 vs M1). The results of these subgroup analyses are presented in Figure 3B. As shown, rPFS benefit was consistent across all subgroups. No outliers were observed in the subgroup analysis; however, for the subgroup of visceral disease and bone metastasis at baseline (HR = 0.71; 95% CI: 0.43 – 1.18), previous docetaxel use (HR = 0.47; 95% CI: 0.22 – 1.01), age ≥75 (HR = 0.65; 95% CI: 0.41 – 1.03), and baseline LDH above ULN (HR = 0.57; 95% CI: 0.33-1.00) the 95% confidence interval of rPFS equaled or crossed 1.00, which indicates a statistically non-significant treatment effect in these subgroups.

Figure 3. Kaplan-Meier Estimate of Radiographic Progression-free Survival and Forest Plot of Radiographic Progression-free Survival According to Baseline Patient Characteristics



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Co-primary Endpoint: Overall Survival (OS)

OS was the other primary outcome in the TITAN trial. The first interim analysis for overall survival occurred after 200 deaths (83 in the apalutamide + ADT group and 117 in the placebo + ADT group) were observed. At 24 months, the rate of overall survival was 82.4% in the apalutamide + ADT group and 73.5% in the placebo + ADT group (hazard ratio for death, 0.67; 95% CI, 0.51 – 0.89; P = 0.005), resulting in a 33% reduction in the risk of death in the apalutamide + ADT group. Based on the statistical analysis plan, the interim OS results were significant, although the final analysis is not yet complete. The final OS analysis will be conducted after 410 events have occurred.[1]

Subgroup Analyses of OS

Pre-specified subgroup analyses of OS were conducted to assess the consistency of treatment effect across the previously mentioned subgroups. The treatment effect on overall survival consistently favored apalutamide + ADT over placebo + ADT, although many subgroups did not reach statistical significance. The subgroup of previous docetaxel use was an outlier and favoured placebo, although the results were not statistically significant (HR = 1.27; 95% CI: 0.52 – 3.09). However, the interpretation of results for the prior docetaxel and visceral disease at baseline subgroup are limited by the small sample size.[2] Moreover, baseline characteristics were not balanced within the prior docetaxel subgroup where, for example, PSA levels and ECOG performance status were higher in the apalutamide + ADT group in those subjects who had received prior docetaxel therapy.[3]

Secondary End Points
Secondary analyses are ordered according to the pre-specified hierarchical testing sequence.

Time to Cytotoxic Chemotherapy
Treatment with apalutamide + ADT significantly delays the initiation of cytotoxic chemotherapy resulting in a 61% reduction of risk for subjects in the apalutamide + ADT group compared with the placebo + ADT group (HR=0.39; 95% CI: 0.27 - 0.56; p < 0.001).[2]

[redacted].[3] *Non-disclosable information was used in this pCODR Guidance Report and the Sponsor requested this efficacy information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the Sponsor that it can be publicly disclosed.* The 24-month event-free rates favored the apalutamide + ADT group with point estimates that had non-overlapping 95% CIs. A Kaplan-Meier plot of time to initiation of cytotoxic chemotherapy shows favorability for apalutamide treatment (HR=0.39; 95%CI: 0.27-0.56; p<0.001).

[redacted].[3] *Non-disclosable information was used in this pCODR Guidance Report and the Sponsor requested this efficacy information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the Sponsor that it can be publicly disclosed.*

Time to pain progression

On the basis of the prespecified hierarchical testing sequence, the time to pain progression was tested next. Pain progression was defined as an average increase by 2 points from baseline to >4 on the BPI-SF worst pain intensity and a requirement for no change in use of opioids.[2] The median pain score at baseline was 1 in both treatment groups.[4] During the study, pain scores remained stable from baseline, with a low percentage of patients worsening by 1 point or ≥2 points and similar changes between groups.[3] Twenty-four percent of subjects in the apalutamide + ADT group and 28% of subjects in the placebo + ADT group had pain progression as defined above.[3] Median time to pain progression was not reached in either group (95% CI not reached in both groups); 25th percentiles were 20.53 months (95% CI 16.10–not reached) in the apalutamide + ADT group and 14.78 months (11.07–19.81) in the placebo + ADT group (HR 0.83 [0.65–1.05]; p=0.12).[4] Median time to worst pain intensity progression was 19.09 months (IQR 1.94–not reached; 95% CI 11.04–not reached) in the apalutamide + ADT group and 11.99 months (1.91–not reached; 8.28–18,46) in the placebo + ADT group and was similar between groups (HR 0.89 [95% CI 0.75–1.06]; p=0.20).[4]

Time to Chronic Opioid Use

Chronic opioid use was defined as administration of opioid analgesics lasting for ≥3 weeks for oral or ≥7 days for non-oral formulations for subjects who were not on opioids when they entered the study.[2] If subjects were already receiving opioids, chronic opioid use was defined as a ≥30% increase in total daily dose.[2] Few subjects received opioids (e.g., natural opium alkaloids, other opioids, and opioids in combination with non-opioid analgesics) prior to study entry (approximately 2-3%) and during study treatment (approximately 10-11%).[3]

Median time to chronic opioid use favored treatment with apalutamide + ADT (HR=0.77, 95% CI: 0.54-1.11; p=0.164) .[2,3] As the between-group difference in the time to pain progression was determined not to be statistically significant, further secondary endpoints were not formally tested.[2]

Time to Skeletal-Related Events

A skeletal-related event was defined as the occurrence of either a pathological fracture or spinal cord compression, or radiation to bone, or surgery to bone.[2] Fifty-three events (10%) were recorded in the apalutamide + ADT group and 64 events (12%) were recorded in the placebo + ADT group. Median time to skeletal-related events, favored treatment with apalutamide + ADT (HR=0.80, 95% CI: 0.56, 1.15; p=0.255).[2,3] Nominal p-value was 0.225.

Exploratory End Points

Time to PSA Progression

The median time to PSA progression was not reached for the apalutamide + ADT group and was 13 months for the placebo + ADT group. PSA reached undetectable levels (<0.2 ng per ml) in 68.4% of the patients in the apalutamide + ADT group and 28.7% of those in the placebo + ADT group.[2]

[redacted].[3] *Non-disclosable information was used in this pCODR Guidance Report and the Sponsor requested this efficacy information not be disclosed pursuant to the pCODR Disclosure of Information*

Guidelines. This information will remain redacted until notification by the Sponsor that it can be publicly disclosed.

PFS2

Time from randomization to progression on first subsequent therapy or death due to any cause whichever occurred earlier (PFS2), based on investigator-assessed progression, was significantly longer for subjects in the apalutamide + ADT group compared with the placebo + ADT group (HR=0.66; 95% CI: 0.50-0.87). Furthermore, fewer subjects received life-prolonging subsequent therapy for prostate cancer in the apalutamide + ADT group compared with the placebo + ADT group.[3]

Median PFS2 was not reached in either treatment group, [redacted]. *Non-disclosable information was used in this pCODR Guidance Report and the Sponsor requested this efficacy information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the Sponsor that it can be publicly disclosed.* The event-free rate at 24 months favored the apalutamide + ADT group (81% of subjects compared with 72% of subjects in the placebo + ADT group).[2] PFS2 shows favorability for apalutamide treatment (HR=0.66, 95% CI 0.50-0.87).[2]

Subsequent Therapies

A total of 87 patients in the apalutamide + ADT group and 190 in the placebo + ADT group received subsequent treatment for prostate cancer.[2] Hormonal therapies were the most common subsequent systemic prostate cancer therapies (25.9% in the apalutamide + ADT group, 36.2% in the placebo + ADT group) and these therapies included abiraterone acetate plus prednisone (12.4% in the apalutamide + ADT group, 16.6% in the placebo + ADT group), bicalutamide (9.4% in the apalutamide + ADT group, 11.4% in the placebo + ADT group) and enzalutamide (1.8% and 6.3%, in the apalutamide + ADT and placebo + ADT groups, respectively).[2] Thirty-five subjects (20.6%) in the apalutamide + ADT group and 73 (26.9%) in the placebo + ADT group received chemotherapy, including docetaxel (17.1% vs 24.7%, respectively) as a subsequent therapy.[2]

Quality of Life

Patient-reported outcomes in the TITAN trial were prespecified exploratory endpoints and assessment of the PRO data showed that subjects entering this study were relatively asymptomatic. At baseline, 198 (38%) of 525 patients in the apalutamide + ADT group and 200 (38%) of 527 in the placebo + ADT group reported no pain, and 195 (37%) in the apalutamide + ADT group and 207 (39%) in the placebo + ADT group reported mild pain.[4] There were few events of symptomatic local progression and no substantial difference between the two groups in the time to symptomatic local progression.[2] Median time to pain interference progression was not reached in either group (95% CI 28.58–not reached in the apalutamide + ADT group; not reached in the placebo + ADT group).[4] Twenty-fifth percentiles for time to pain interference progression were 9.17 months (5.55–11.96) in the apalutamide + ADT group and 6.24 months (4.63–7.43) in the placebo + ADT group.[4] Therefore, time to pain interference progression was similar between groups (HR 0.90 [95% CI 0.73–1.10]; p=0.29).[4] Median time to average pain progression was 22.1 months in the apalutamide + ADT group (IQR 2.79–not reached; 95% CI 13.83–not reached) and 14.7 months in the placebo + ADT group (IQR 2.66–not reached;

95% CI 10.25–22.05) and was similar between groups (HR 0.89 [95% CI 0.74–1.05]; p=0.15).[4]

HRQoL was assessed via the Brief Pain Inventory- Short Form (BPI-SF), Brief Fatigue Inventory (BFI), Functional Assessment of Cancer Therapy-Prostate (FACT-P), and EuroQoL 5D questionnaire 5 level (EQ-5D-5L). Overall, no statistically significant differences were observed between the two treatment groups.

The median time to deterioration as determined by FACT-P total score was 8.87 months (IQR 1.87–not reached; 95% CI 4.70–11.10) in the apalutamide + ADT group and 9.23 months (2.79–24.77; 7.39–12.91) in the placebo + ADT group (HR 1.02 [95% CI 0.85–1.22]; p=0.85).[4] There were no differences in the time to HRQoL deterioration between the treatment groups.

Analysis of change from baseline in the FACT-P, FACT-G, physical wellbeing, functional wellbeing, social and family wellbeing, and emotional wellbeing scores with the use of a mixed-effect repeated-measures model showed no changes from baseline in the apalutamide + ADT treatment group and no differences compared to ADT suggesting the maintenance of health-related quality of life (HRQoL).[2,4] There were no statistically significant differences observed between treatment groups for the EQ5D-5L health utility index, which declined over time, or the EQ-5D-5L visual analogue scale scores, which were maintained over time.[4] Specifically, the proportion of responses to the "side effect" bother item, were similar between the treatment groups, demonstrating that tolerability between apalutamide + ADT compared to ADT alone was similar.[3]

Harms Outcomes

Adverse events of any cause and grade were reported in almost all subjects in the apalutamide and placebo + ADT groups (Table 8). The most frequently reported AEs reported in ≥10% of patients were hot flashes (23% with apalutamide + ADT versus 16% with placebo + ADT), fatigue (20% vs 17%), hypertension (18% vs 16%), back pain (17% vs 19%), arthralgia (17% vs 15%), pain in an arm or leg (12% vs 13%), pruritus (11% vs 5%), and anemia (9% vs 14%). Adverse events of special interest were consistently more frequent in patients receiving apalutamide + ADT than those receiving placebo + ADT. These included rash (27.1% vs 8.5%), falls (7.4% vs 7.0%), fractures (6.3% vs 4.6%), hypothyroidism (6.5% vs 1.1%) and seizures (0.6% vs 0.4%). SAEs were reported for 19.8% of subjects in the apalutamide + ADT group and 20.3% of subjects in the placebo + ADT group.[2]

Rash that was related to treatment with apalutamide, commonly described as generalized or maculo-papular, was typically managed with antihistamines and topical glucocorticoids.[1] Skin rash led to treatment discontinuation, dose reduction, and dose interruption in 12 (2.3%), 28 (5.3%), and 44 (8.4%) of patients in the apalutamide + ADT group, respectively, versus 1(0.2%), 4 (0.8%) and 5 (0.9%) of patients in the placebo + ADT group, respectively.[2] Hypothyroidism did not lead to treatment discontinuation or dose modification and was monitored according to thyrotropin level and managed with levothyroxine.[2]

As shown in Table 9, frequencies of grade 3 or 4 events (42.2% in the apalutamide + ADT group and 40.8% in the placebo + ADT group) and of serious adverse events (19.8% in the apalutamide + ADT group and 20.3% in the placebo + ADT group) did not differ substantially between the two groups. The most common adverse event of grade 3 or higher that was considered by the investigator to be related to

apalutamide was rash of any type (6.3%). TEAEs leading to discontinuation was 8.0% vs 5.3% in apalutamide + ADT vs placebo + ADT groups, respectivley. TEAEs leading to death were reported for 10/524 (1.9%) patient in the apalutamide + ADT group, and 16/527 patient (3.0%) in the placebo + ADT group (Table 9).

Table 8: Summary of Adverse Events*

Event	Apalutamide (N=524)	Placebo (N=527)
	number of patients (percent)	
Any adverse event	507 (96.8)	509 (96.6)
Grade 3 or 4 adverse event	221 (42.2)	215 (40.8)
Any serious adverse event	104 (19.8)	107 (20.3)
Any adverse event leading to discontinuation of the trial intervention	42 (8.0)	28 (5.3)
Adverse event leading to death	10 (1.9)	16 (3.0)

* Shown are adverse events of any cause that occurred from the time of the first dose of the trial intervention through 30 days after the last dose. Adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.3. One patient who was assigned to the apalutamide group withdrew consent before treatment.

Source: N Eng J Med, Chi et al., Apalutamide for metastatic, castration-sensitive prostate cancer, 381(1):13-24. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[2]

Table 9: Individual Adverse Events*

Event	Apalutamide (N= 524)		Placebo (N= 527)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
	number of patients (percent)			
Events reported in ≥10% of patients in either group or events of grade ≥3 reported in ≥10 patients in either group				
Hot flush	119 (22.7)	0	86 (16.3)	0
Fatigue	103 (19.7)	8 (1.5)	88 (16.7)	6 (1.1)
Hypertension	93 (17.7)	44 (8.4)	82 (15.6)	48 (9.1)
Back pain	91 (17.4)	12 (2.3)	102 (19.4)	14 (2.7)
Arthralgia	91 (17.4)	2 (0.4)	78 (14.8)	5 (0.9)
Pain in an arm or leg	64 (12.2)	3 (0.6)	67 (12.7)	5 (0.9)
Pruritus	56 (10.7)	1 (0.2)	24 (4.6)	1 (0.2)
Weight increased	54 (10.3)	6 (1.1)	89 (16.9)	10 (1.9)
Anemia	48 (9.2)	9 (1.7)	71 (13.5)	17 (3.2)
Constipation	47 (9.0)	0	57 (10.8)	0
Asthenia	37 (7.1)	10 (1.9)	44 (8.3)	3 (0.6)
Bone pain	34 (6.5)	6 (1.1)	53 (10.1)	9 (1.7)
Rash, generalized	34 (6.5)	14 (2.7)	5 (0.9)	2 (0.4)
Blood alkaline phosphatase increased	16 (3.1)	2 (0.4)	28 (5.3)	13 (2.5)
Urinary retention	13 (2.5)	4 (0.8)	19 (3.6)	10 (1.9)
Adverse events of special interest				
Rash†	142 (27.1)	33 (6.3)	45 (8.5)	3 (0.6)
Fall	39 (7.4)	4 (0.8)	37 (7.0)	4 (0.8)
Fracture‡	33 (6.3)	7 (1.3)	24 (4.6)	4 (0.8)
Hypothyroidism§	34 (6.5)	0	6 (1.1)	0
Seizure¶	3 (0.6)	1 (0.2)	2 (0.4)	0

* Shown are adverse events of any cause that occurred from the time of the first dose of the trial intervention through 30 days after the last dose. Adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.3. One patient who was assigned to the apalutamide group withdrew consent before treatment.

† Rash was a grouped term including rash, butterfly rash, erythematous rash, exfoliative rash, follicular rash, generalized rash, macular rash, maculopapular rash, papules, papular rash, pruritic rash, pustular rash, genital rash, blister, skin exfoliation, exfoliative dermatitis, skin reaction, systemic lupus erythematosus rash, toxic skin eruption, mouth ulceration, drug eruption, conjunctivitis, erythema multiforme, stomatitis, and urticaria.

‡ Fracture was a grouped term including acetabulum fracture, ankle fracture, clavicle fracture, femoral neck fracture, femur fracture, fibula fracture, foot fracture, forearm fracture, fracture, fractured ischium, fracture pain, hand fracture, hip fracture, lower limb fracture, patella fracture, radius fracture, rib fracture, skull fracture, spinal compression fracture, spinal fracture, sternal fracture, thoracic vertebral fracture, tibia fracture, traumatic fracture, ulna fracture, upper limb fracture, and wrist fracture.

§ Hypothyroidism was a grouped term including autoimmune thyroiditis, blood thyrotropin increased, and hypothyroidism.

¶ Seizure was a grouped term including seizure and tongue biting.

Source: N Eng J Med, Chi et al., Apalutamide for metastatic, castration-sensitive prostate cancer, 381(1):13-24. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[2]

6.4 Ongoing Trials

No ongoing trials were identified as being relevant to this review.

7 SUPPLEMENTAL QUESTIONS

The following supplemental questions were identified during development of the review protocol as relevant to the pCODR review of apalutamide + ADT for men with metastatic hormone-sensitive prostate cancer:

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

Topics considered in this section are provided as supporting information. The information has not been systematically reviewed. The full summaries and critical appraisals of the three NMAs are provided in sections 7.1 to 7.3. A brief summary of all three NMAs is provided here:

Background

The CADTH-conducted literature search identified one randomized, double-blind, placebo-controlled, phase III trial that assessed apalutamide in combination with ADT versus placebo with ADT for patients with metastatic, castration sensitive prostate cancer (mCSPC). There is a lack of direct evidence comparing apalutamide + ADT to other active therapies. Given the absence of head-to-head trials, the Sponsor provided an unpublished network meta-analysis (NMA) that indirectly compared apalutamide + ADT to other relevant treatments. In addition, the pCODR Review Team identified two published NMAs comparing first-line treatments for mCSPC: Marchioni et al. (2019) and Sathianathen et al. (2020). A third published NMA (Di Nunno et al. 2019[33]) was later identified, however this NMA was not included in this report due to repetition and direct referencing to both Marchioni et al.[5] and Sathianathen et al.[6] Detailed summaries and critical appraisals of each NMA are further provided.

Brief Summary of NMA

Sponsor Provided NMA

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

[redacted]

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

Due to the lack of comparisons between the treatment groups, no conclusions could be made regarding the comparative efficacy of the treatments for this patient population. Further limitations of this NMA included the lack of consideration of the clinical heterogeneity of the trials, as well as the of lack clarity surrounding the additional inclusion/exclusion criteria and an *a prior* model for the analysis.

Published NMA by Marchioni et al. (2019)[5]

The objective of the published network NMA by Marchioni et al.[5] was to compare first-line treatments, specifically androgen receptor axis targeted therapy (ARAT) therapies for patients with mCSPC. A SLR was conducted to identify potentially relevant trials for the primary outcome of OS, and the secondary outcomes of progression-free survival (PFS) and high-grade adverse events (AEs). The analyses were conducted using a frequentist approach. The logHR and standard errors (SE) were calculated from the HRs and 95% confidence intervals (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. AE data was not available according to metastatic status in most studies (e.g.., specific to the population with mCSPC), 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.

Thirteen studies were identified (four being from different arms of the same trial), evaluating relevant first-line treatments for mCSPC. All treatments included in the NMA were given in combination with an ADT backbone. The treatment arms in the included trials were: apalutamide, abiraterone, enzalutamide, docetaxel, bisphosphonates, docetaxel plus bisphosphonates, celecoxib, and celecoxib plus bisphosphonates. For the outcome of OS, apalutamide 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, apalutamide showed statistically significantly lower risk of disease progression compared to ADT alone, and compared to docetaxel, but not compared to abiraterone or enzalutamide. 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. Apalutamide showed statistically significantly lower odds of AEs compared to docetaxel, or docetaxel plus bisphosphonates, and abiraterone showed statistically significantly higher odds of AEs compared to apalutamide. This result of the sensitivity analysis also showed no statistically significantly higher odds of AEs for apalutamide compared to ADT alone.

Several limitations to the NMA were identified. There was a lack of clarity surrounding the inclusion and exclusion criteria for the NMA, with some criteria not clearly defined, and the use of a web-based platform for the initial screening causing uncertainty as to whether some potentially relevant studies may have been missed. Furthermore, there was a large amount of clinical heterogeneity between the included studies, with various patient inclusion/exclusion criteria that can make the comparability of the trials challenging (i.e. different ADT treatments in the trials, disease stage and previous treatments allowed).

Published NMA by Sathianathen et al. (2020)[6]

The objective of the published NMA by Sathianathen et al.[6] was to compare first-line treatments for mCSPC, specifically combinations of androgen deprivation therapy (ADT) and one (or more) of taxane-based chemotherapy, and androgen receptor-targeted therapies. A SLR was conducted to identify potentially relevant trials for the primary outcome of OS and the secondary outcome of PFS. Subgroup analysis of the primary outcome of OS was performed based on volume of disease only. Pairwise metaa-analysis of the studies was performed, although the results of this analysis were not reported. Indirect comparisons of treatment arms were performed using a Bayesian approach. Fixed-effects models were used, and random-effects models were performed as a sensitivity analysis. Treatment effects were estimated using posterior means and 95% CrIs and included both direct and indirect evidence.

Six studies were identified (two being from different arms of the same trial), evaluating relevant first-line treatments for mCSPC. All treatments included in the NMA were given in combination with an ADT backbone. The treatment groups in the included trials were: apalutamide, abiraterone, enzalutamide, and docetaxel. For the outcome of OS in the full group, apalutamide was favoured over ADT alone, but not over any of the other combination treatments (abiraterone, enzalutamide, docetaxel). For the subgroup analysis of OS in the low-volume disease group, apalutamide showed no difference compared to ADT alone or to any of the combination treatments (abiraterone, docetaxel, or enzalutamide). For the subgroup analysis of OS in the high-volume disease group, apalutamide was favoured over ADT alone, but not over any of the other combination treatments (abiraterone, enzalutamide, docetaxel). For the outcome of PFS, apalutamide was favoured over ADT alone; however, abiraterone and enzalutamide were favoured over apalutamide.

Several limitations to the NMA were identified. There was a lack of clarity surrounding the inclusion and exclusion criteria for the NMA, with some criteria not clearly defined. Furthermore, there was a large amount of clinical heterogeneity between the included studies, with various patient inclusion/exclusion criteria that can make the comparability of the trials challenging (i.e. different ADT treatments in the trials, disease stage and previous treatments allowed). Additionally, this NMA analyses only assessed the outcomes of OS and PFS, without including other potentially relevant outcomes such as AEs or HRQoL data. Furthermore, eligible studies were limited to those published from January 2014 up to June 2019, leading to the potential of excluding older trials that may still be relevant to the research question. Due in part to these limitations, results of this NMA must be interpreted with caution.

Comparisons between the NMAs

Overall, the conclusions surrounding the efficacy outcomes for apalutamide 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 published NMA by Marchioni et al.[5] had the broadest inclusion criteria, and identified the largest number of trials, while the sponsor submitted NMA had the narrowest criteria, and identified the smallest number of trials. The Sponsor-submitted NMA included only treatments that are currently approved 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.[5] only, and therefore the results can not be compared to the other NMAs. Only the published NMA by Sathianathen et al.[6]

included subgroup analysis for OS based on disease volume. This subgroup analysis was identified as relevant by the CGP, however limitations to the analysis 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). There was also no discussion in the publication about any inconsistencies 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 apalutamide+ ADT. Results should be interpreted with caution.

7.1 Summary of manufacturer-submitted network meta-analysis comparing apalutamide + ADT with other relevant treatments for patients with metastatic hormone-sensitive prostate cancer

7.1.1 Objective

To summarize and critically appraise the methods and findings of the manufacturer-submitted network meta-analysis (NMA) comparing apalutamide plus ADT with other relevant treatments for men with metastatic castration-sensitive prostate cancer (mCSPC).

7.1.2 Findings

Methods

Systematic Review

[redacted]

Non-disclosable information was used in this pCODR Guidance Report and the Sponsor requested this efficacy information not be disclosed pursuant to the pCODR Disclosure of Information

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

Network Meta-Analysis

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

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Table 10: PICOS Inclusion Criteria for Study Selection in NMA

Source: Sponsor's Submission[3]

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Results

Study and Patient Characteristics

[redacted].

Source: Sponsor's Submission[3]

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Figure 4. Attrition diagram of studies considered for the NMA

[redacted]

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

Table 112: Summary of studies used in the NMA

Source: Sponsor's Submission[3]

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Results of the Network Meta-Analysis

The studies included in the NMA and their network are presented in Figure 5.

Figure 5: Network diagram of studies (ITT All-Comers)

Source: Sponsor's Submission[3]

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

a) Results for OS

The sponsor summarized that the results for OS from the NMA suggested that all active treatments offered a statistically significant advantage over placebo + ADT (Table 12). Median HR (95% CrI) was 0.671 (0.507; 0.890) for apalutamide + ADT; 0.660 (0.547; 0.797) for AAP + ADT; and 0.755 (0.669; 0.851) for docetaxel + ADT vs. placebo + ADT.

Table 12. OS All-comer Populations, Comparisons vs. Placebo + ADT

Source: Sponsor's Submission[3]

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

Figure 6. OS Forest Plot, Comparisons vs. Placebo + ADT

Source: Sponsor's Submission[3]

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b) Results for rPFS

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

Table 13. rPFS All-comer Populations, Comparisons vs. Placebo + ADT

Source: Sponsor's Submission[3]

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Figure 7. rPFS Forest Plot, Comparisons vs. Placebo + ADT

Source: Sponsor's Submission[3]

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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.[34] Details and commentary for each of the relevant items identified by the ISPOR group are provided in Table 14.

Strengths

The NMA was based on a SLR to identify all relevant studies. The risk of bias of each individual study was assessed using the Cochrane Risk of Bias Tool. The sponsor stated that little variability was seen in the definitions of the efficacy outcomes and that the statistical heterogeneity was non-significant for the three trials included in the direct evidence meta-analysis. Model convergence was tested by visual inspection of trace-plots. The methodology to conduct the analyses was reported (i.e., Bayesian analysis models). The outcome measures assessed (OS and rPFS) were appropriate to address the stated objectives of determining the relative efficacy of treatments. Appropriate tables and forest-plots were provided to clearly outline the results.

Limitations

The network of included studies was small, limiting the power of the network. While the stated objective of the ITC was to evaluate the relative efficacy of apalutamide + ADT compared to other relevant interventions, no statistical comparisons between the active treatments were provided, limiting the value of the ITC from a decision-making perspective.

Several sources of clinical heterogeneity must be noted. Variability in the definition of ADT was seen within and across studies. Although ADT involved either surgical or medical castration, the definition of medical castration also varied. In addition, the duration of docetaxel administration for studies involving that intervention differed with patients being treated trial for six cycles in two trials (CHAARTED and STAMPEDE), and up to nine cycles in another (GETUG-AFU 15). The inclusion criteria into the individual studies varied, with different prior exposures permitted between studies. Baseline characteristics were not reported for some of the trials (refer to table), which makes it difficult to assess heterogeneity according to some characteristics (e.g., ECOG PS, age). Follow up length differed between the studies in the network, ranging from 22.7 to 83.9 months. From the trial characteristics presented, OS cut-offs do not appear to be comparable and it is unclear whether appropriate cut-points for some trials were used to obtain comparable data in terms of length of follow-up. The sponsor also stated that while the overall risk of bias was generally low, CHAARTED had high risk of selection and performance biases. The clinical heterogeneity was not discussed or considered in the analysis.

Additionally, further eligibility criteria to allow for comparisons with the TITAN trial required the limitation to trials including one arm of ADT. The inclusion/exclusion criteria for the NMA was not explicitly clear on their criteria for being sufficiently comparable. The NMA report stated that studies were excluded if they did not report "data for an "all-comer" population

(defined as intent-to-treat (ITT) populations without subgroup characteristics such as volume burden, risk of disease, etc.)". The rationale for the impact of this exclusion on the results is unclear and ambiguous particularly given the "etc." A trial was excluded due to 'not being in the scope for Canada', however this explanation is not clear. The further exclusions were not included *a priori* in the PICOs criteria, and it is difficult to judge the validity of the inclusion/exclusion of some studies. A full list of excluded studies and the justifications were not included.

The *a priori* model was not specified; however, the report stated that both fixed- and random-effects models were used. No random-effects model was provided, and the report stated that this is due to the limited number of trials in the network. There was no assessment of model fit performed; therefore, it is unknown how a fixed effect model compared to a random effects model, or the use of different prior distributions may have affected the model and the appropriateness of the model used. As the model was not clearly provided, it is also unclear as to whether it included both direct and indirect comparisons when possible (e.g. for the three trials in the loop).

A further limitation of the NMA was the lack of sensitivity analyses performed; however, this is likely not feasible due to the limited number of included studies. No analyses were provided using a different model (fixed vs. random effects), using an informative prior, or for covariates. The potential effect of different lengths of dosing of docetaxel was not tested, nor was the varied definition of ADT between the studies. The limited number of trials identified may have precluded the possibility of performing these sensitivity analyses.

In terms of generalizability of the NMA, there is a lack of clarity as to the relevance to the intended population in Canada. The inclusion criteria for this analysis stipulated that comparators that "are approved, recommended or in development" could be included, putting into question whether all comparators would be relevant, as they are not all currently approved for market in Canada. Furthermore, while the analysis explored the outcomes related to efficacy, other outcomes such as safety and patient reported outcomes were not analyzed, and therefore no conclusions can be drawn about these.

Table 143. Appraisal of the network meta-analysis using ISPOR criteria[34]

ISPOR Questions	Details and Comments
1. Is the population relevant?	The population was relevant to the patient population of the submission.
2. Are any critical interventions missing?	While the NMA included all critical interventions for this patient population, comparisons between the interventions were not made.
3. Are any relevant outcomes missing?	The NMA reported on efficacy outcomes only. It would have been beneficial to include adverse events and possibly health quality of life related outcomes. Additionally, the interventions were not compared to each other, and only to ADT.
4. Is the context (e.g., settings and circumstances) applicable to your population?	In terms of generalizability of the NMA, there was a lack of clarity as to the relevance to the intended population in Canada. The inclusion criteria for this analysis stipulated that comparators that "are approved, recommended or in development" could be included, putting into question whether all comparators would be relevant, as they were not all currently approved for market in Canada.
5. Did the researchers attempt to identify and include all relevant randomized controlled trials?	Information sources and search strategy were clearly outlined in the SLR report. Study selection process was described in the SLR report. A list of included and excluded studies was provided. Additional clarity would have been beneficial for how the trials were judged as being sufficiently comparable in terms of study design, treatment and patient-level characteristics.
6. Do the trials for the interventions of interest form one connected network of randomized controlled trials?	The trials in the analysis formed 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. Validity of individual studies was assessed using the Cochrane Risk of Bias tool for RCTs, and this was reported in the SLR report. There is no apparent bias presented. The report stated that although overall, the risk of bias across trials was generally low, one study (CHAARTED) showed a high risk of selection and performance biases.
8. Is it likely that bias was induced by selective reporting of outcomes in the studies?	Selective outcome reporting was evaluated in the risk of bias. Risk of selective outcome reporting was generally low; however, the report stated that one study (CHAARTED) showed a high risk of selection bias.
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 were 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 not identified prior to comparing the individual studies. They were limitedly discussed in the report as a potential limitation to the NMA.
11. Were statistical methods used that preserve within-study randomization? (No naïve comparisons)	It is unclear whether methods were used to preserve within-study randomization.
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?	It was unclear whether the NMA evaluated the consistency between both direct and indirect comparisons when possible (e.g. for the three trials in the loop).
13. In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?	It was unclear as to whether the NMA included both direct and indirect comparisons when possible (e.g. for the three trials in the loop).
14. With inconsistency or an imbalance in the distribution of treatment effect modifiers across the different types of comparisons in the network	The researchers did not attempt to minimize imbalances in the analysis.

ISPOR Questions	Details and Comments
of trials, did the researchers attempt to minimize this bias with the analysis?	
15. Was a valid rationale provided for the use of random effects or fixed effect models?	Only fixed effects analyses were performed. The reasons for using this model were outlined. No assessment of model fit was performed.
16. If a random effects model was used, were assumptions about heterogeneity explored or discussed?	Not applicable. Fixed effects model only were performed.
17. If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with pre-specified covariates performed?	No subgroup analyses were conducted.
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?	Raw data for the individual studies were not reported.
20. Are results of direct comparisons reported separately from results of the indirect comparisons or network meta-analysis?	It was unclear as to whether it included both direct and indirect comparisons when possible (e.g. for the three trials in the loop).
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 for the active groups compared to ADT were provided. No estimated comparing the active treatment groups to each other were included.
22. Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	The report included the SUCRA rankings stating the probabilities of being 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 limitedly reported or discussed.
24. Are the conclusions fair and balanced?	The conclusions of the NMA must be interpreted with caution. No comparisons between the active treatments were made, and there was a lack of consideration of the clinical heterogeneity.
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 apalutamide submission.
26. If yes, were steps taken to address these?	Not applicable.

7.1.3 Summary

In the absence of head-to-head trial data for apalutamide compared to other relevant treatments for men with mCSPC, the sponsor submitted a NMA comparing apalutamide with other relevant treatments in this patient population. Four trials were identified (with one trial contributing three arms), evaluating apalutamide + ADT, AAP + ADT, docetaxel + ADT and placebo + ADT. Results of this NMA suggested that all active treatments offered a statistically significant advantage over placebo + ADT for both efficacy outcomes of OS and rPFS. However, no comparisons between active treatments were performed. As such, no conclusions can be made regarding the comparative efficacy of apalutamide + ADT, AAP + ADT, and docetaxel + ADT. Further limitations of this NMA included the lack of consideration of the clinical heterogeneity of the trials, as well as the of lack clarity surrounding the additional inclusion/exclusion criteria and an *a prior* model for the analysis.

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

7.1.1 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.

7.1.2 Findings

Methods

Systematic Review

The published NMA was based on a systematic literature search (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[35] and the Population, Intervention, Comparator, Outcomes (PICO) methodology (www.prisma-statement.org) (Table 15).

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 hazard ratios (HR) and 95% confidence intervals (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 adverse events (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 15: 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. Overall survival (OS) was defined by the authors as time from treatment initiation to death from any cause or to the last follow-up available. Progression free survival (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 (Figure 8). The NMA included 13 studies, and the networks are depicted in Figure 9.

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).

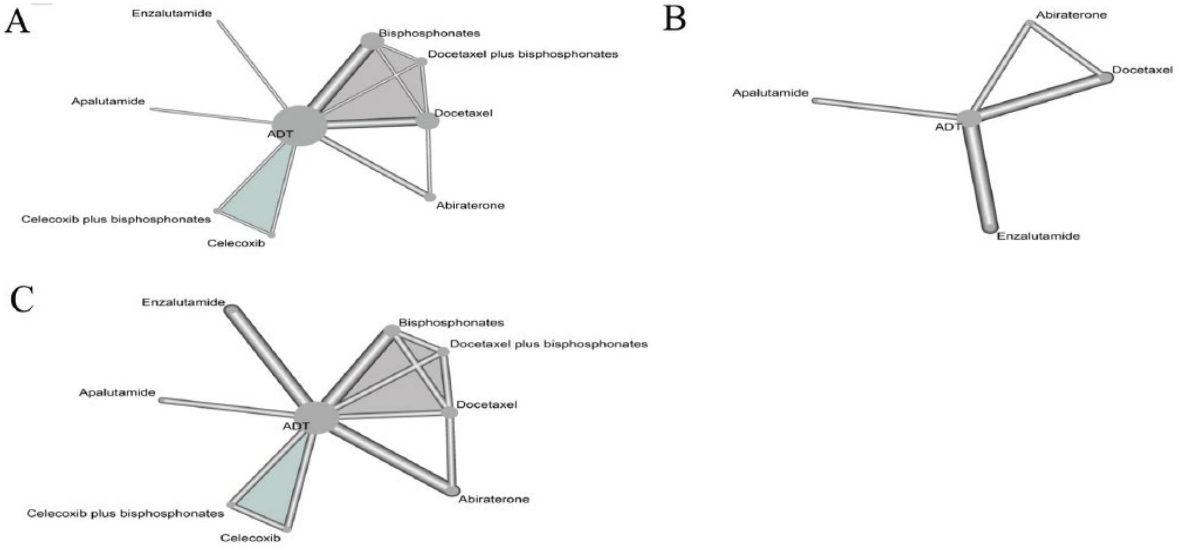

Figure 8. Evidence networks for A) overall mortality, B) disease progression (PFS), and C) high grade adverse events. Thickness of each arm is proportional to number of studies participating in network. Diameter of each junction point is proportional to number of studies including respective treatment. 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, [online ahead of print], 2019; permission conveyed through Copyright Clearance Center, Inc.[5]

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Of the 13 included studies, five studies were double blind randomized controlled trials (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 NSA 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 prostate specific antigen (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.

c) *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 16). Apalutamide 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 16: 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, [online ahead of print], 2019; permission conveyed through Copyright Clearance Center, Inc.[5]

d) *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 17). Apalutamide showed statistically significantly lower risk of disease progression compared to docetaxel (HR= 0.74; 95%CI: 0.57-0.95), but not to abiraterone (HR= 0.97; 95% CI: 0.74-1.26) or enzalutamide (HR= 1.21; 95%CI: 0.93-1.58). 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 17: 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.

New anti-androgen compounds compared to docetaxel in metastatic hormone sensitive prostate cancer: results from a network meta-analysis. In: pan-Canadian Oncology Drug Review sponsor submission: Erleada® (apalutamide) for metastatic castration-sensitive prostate cancer, 60mg tablets [unpublished manuscript]. Janssen Inc. Toronto (ON): Janssen Inc; 2019 Oct 15.[36]

e) *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 18). The other combination treatments did not show statistically significantly higher odds of AEs compared to ADT alone. Apalutamide showed statistically significantly lower odds of AEs compared to docetaxel (OR= 0.44; 95%CI: 0.24-0.79) and docetaxel plus bisphosphonates (OR= 0.42; 95%CI: 0.23-0.80). Abiraterone showed statistically significantly higher odds of AEs compared to apalutamide (OR= 1.88; 95%CI: 1.08-3.27).

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 18: 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, [online ahead of print], 2019; permission conveyed through Copyright Clearance Center, Inc.[5]

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[34]. Details and commentary for each of the relevant items identified by the ISPOR group are provided in Table 19.

Strengths

The NMA was based on a SLR to identify all relevant studies. Overall, the outcome measures assessed were mostly appropriate to address the objectives of the NMA. The authors rated the included studies as having a low risk of bias overall (however some limitations are noted below).

The authors stated that they used a random-effects model due to anticipated heterogeneity between studies. While this would not account for between study clinical heterogeneity, it does allow the incorporation of statistical heterogeneity into the effect estimates. Furthermore, direct, indirect and NMA treatment estimates were compared to check for NMA consistency. The studies included for each outcome formed connected networks. The authors rated the GRADE quality for direct comparisons for OS and PFS as high; however, rated the NMA evidence quality as intermediate and low in most cases. The risk of bias of each individual study was assessed and reported in the supplemental data (quality of data for AEs is further discussed below in limitations).

The NMA included treatments relevant to the Canadian context. While there is no current standard of care for these patients in Canada, patients are generally treated with ADT alone, chemotherapy (e.g. docetaxel), or chemotherapy (e.g. docetaxel) plus ADT. This NMA included ADT and combination treatments in comparison to apalutamide (however chemotherapy alone (e.g. docetaxel) was not compared to apalutamide alone, and this is discussed further in the limitations).

Limitations

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 (Table 1). 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).

Table 19: Adapted ISPOR Questionnaire to Assess the Credibility of an Indirect Treatment Comparison or Network Meta-Analysis adapted from Jansen et al.[34]

ISPOR Questions	Details and Comments
27. Is the population relevant?	The population is relevant to the patient population under CADTH review for the outcomes of OS and PFS, however the analysis for AEs did not distinguish based on metastatic status.
28. Are any critical interventions missing?	The NMA appeared to include all relevant interventions for this patient population.
29. Are any relevant outcomes missing?	The NMA reported outcomes for OS, PFS and AEs, but did not include HRQoL.
30. 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.
31. 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).
32. 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.
33. 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

ISPOR Questions	Details and Comments
	attrition and reporting bias was high due to incomplete information about this outcome and no analyses conducted by metastatic status.
34. 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.
35. 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.
36. 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.
37. 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.
38. 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.
39. 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.
40. 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.
41. 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.
42. 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.
43. 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.
44. 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.
45. Are the individual study results reported?	Individual study results were not provided.
46. 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.
47. 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.
48. 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.
49. 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.

ISPOR Questions	Details and Comments
50. 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).
51. 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
52. If yes, were steps taken to address these?	Not applicable.

7.1.3 Summary

A published NMA was identified comparing apalutamide 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, apalutamide 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, apalutamide showed statistically significantly lower risk of disease progression compared to ADT alone, and compared to docetaxel, but not compared to abiraterone or enzalutamide. 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. Apalutamide showed statistically significantly lower odds of AEs compared to docetaxel, or docetaxel plus bisphosphonates, and abiraterone showed statistically significantly higher odds of AEs compared to apalutamide. This result of the sensitivity analysis also showed no statistically significantly higher odds of AEs for apalutamide compared to ADT alone.

Several limitations to the NMA were identified. There was a lack of clarity surrounding the inclusion and exclusion criteria for the NMA, with some criteria not clearly defined, and the use of a web-based platform for the initial screening causing uncertainty as to whether some potentially relevant studies may have been missed. Furthermore, there was a large amount of clinical heterogeneity between the included studies, with various patient inclusion/exclusion criteria that can make the comparability of the trials challenging (i.e. different ADT treatments in the trials, disease stage and previous treatments allowed). Due in part to these limitations, results of this NMA must be interpreted with caution.

7.3 Summary and critical appraisal 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.

7.3.1 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.

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.

7.3.2 Findings

Methods

Systematic Review

The published NMA was based on a systematic literature search (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 randomized controlled trials (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 19).

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 19: 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 overall survival (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 Chemo-Hormonal Therapy versus Androgen Ablation Randomised Trial for Extensive Disease in Prostate Cancer (CHAARTED) criteria). Progression-free survival (PFS) was also a secondary outcome of interest and was defined as time from randomization to prostate-specific antigen (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.

Hazard ratios (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 National Institute for Health and Care Excellence (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% credible intervals (CrIs) and included both direct and indirect evidence. Heterogeneity was visually assessed using forest plots and the I^2 statistic, whereby an $I^2 > 50\%$ was considered to present statistically significant heterogeneity. Model fit for both the fixed and random effects models was assessed using the Bayesian deviance information criterion (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 9), of which seven trials met the eligibility criteria. One trial (ARCHES) was further excluded as the survival data were considered immature. The network used an ADT group as the comparator and is depicted in Figure 10. 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.

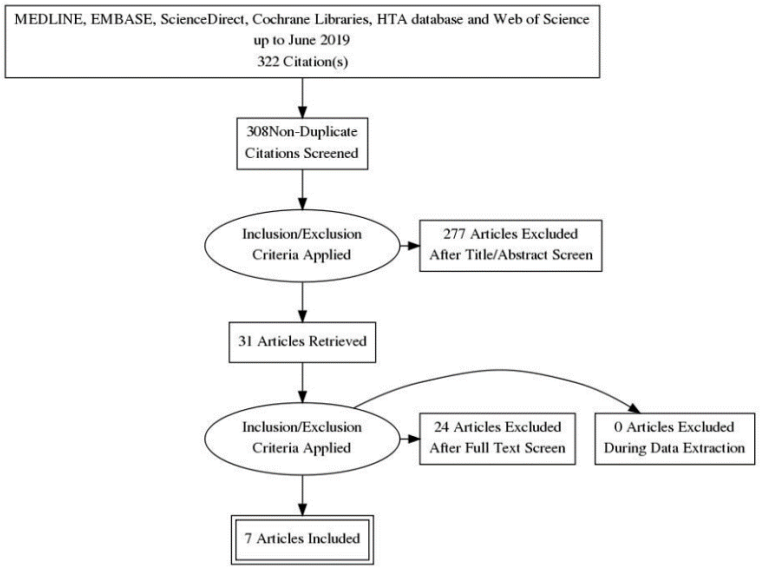


Figure 9. Study selection flow diagram
Source: reprinted from European Urology, 77(3), Sathianathen, et al., Indirect comparisons of efficacy between combination approaches in metastatic hormone-sensitive prostate cancer: a systematic review and network meta-analysis, pp.365-72, Copyright 2020, with permission from Elsevier.[6]

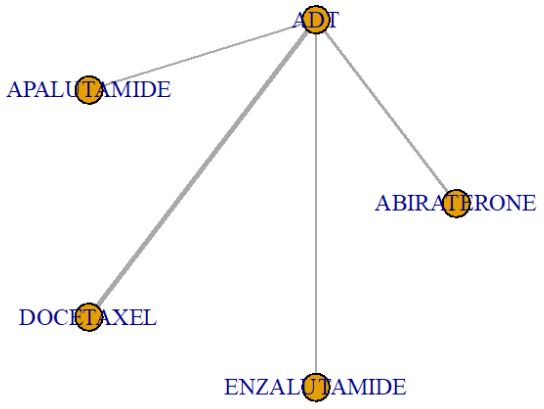


Figure 10. Evidence networks for network meta-analysis of OS for overall analysis (both high and low volume disease patients). Thickness of each arm is proportional to number of studies participating in network. Lines demonstrate studies with direct comparisons and line thickness corresponds to number 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.[6]

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.

f) *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 20 and Figure 11A). Apalutamide was not favoured over any of the other combination treatments (abiraterone, docetaxel, or enzalutamide), but enzalutamide was favoured over docetaxel (HR=0.66; 95% CrI: 0.45-0.94). The publication reported no statistical heterogeneity (I^2=0%), and a lower DIC for the fixed effect model than the random effects model (DIC 23.7 vs. 25.3).

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 20 and Figure 11B). Apalutamide was not favoured over ADT alone or any of the combination treatments (abiraterone, docetaxel, or enzalutamide). The publication reported no statistical heterogeneity (I^2=8%), and a lower DIC for the fixed effect model than the random effects model (DIC: 18.7 vs. 19.0).

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 20 and Figure 11C). Apalutamide was also not favoured over any of the combination treatments (abiraterone, docetaxel, or enzalutamide), nor were any other combination treatments when compared to each other. The publication reported no statistical heterogeneity (I^2=1%), and a lower DIC for the fixed effect model than the random effects model (DIC 18.1 vs. 19.4).

Table 20: Comparison of each treatment[a] for overall survival

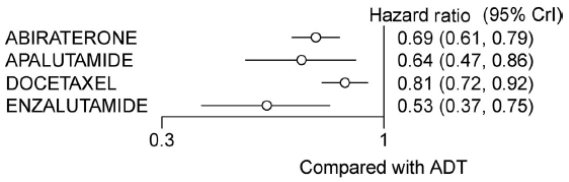
	ADT	Abiraterone	Apalutamide	Docetaxel
Full group analysis (both low and high volume disease)				
ADT				
Abiraterone	**0.69 (0.61-0.79)**			
Apalutamide	**0.64 (0.47-0.86)**	0.92 (0.67-1.3)		
Docetaxel	**0.81 (0.72-0.92)**	1.2 (0.98-1.4)	1.3 (0.92-1.7)	
Enzalutamide	**0.53 (0.37-0.75)**	0.77 (0.53-1.1)	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

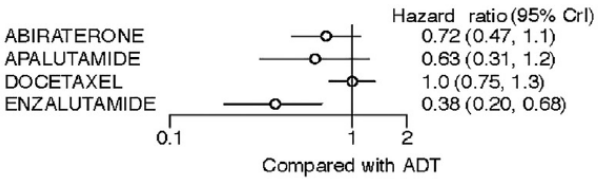
Estimated HR reflect outcomes for treatment in rows compared to treatment in columns. Statistically significant comparisons are reported in bold.

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.[6]

A – Full group analysis



B – Low-volume disease



C – High-volume disease

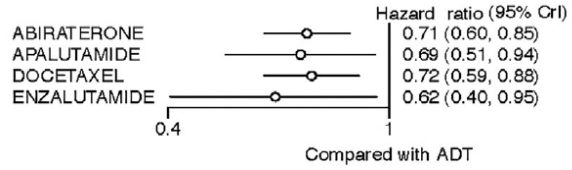


Figure 11. Overall survival for each treatment compared with ADT for A) full group analysis (regardless of disease volume), B) subgroup analysis of low-volume disease, and C) subgroup analysis of high-volume disease. Each treatment is in combination with ADT.

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g) *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 21 and Figure 12). 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. Apalutamide was not favoured over docetaxel. Abiraterone was favoured over apalutamide (apalutamide versus abiraterone: HR=1.8; 95%CrI: 1.3-2.4) and over docetaxel (docetaxel versus abiraterone: HR=2.1; 95%CrI: 1.7-2.5). The publication reported no statistical heterogeneity (I^2=4%), and a lower DIC for the fixed effect model than the random effects model (DIC 21.4 vs. 22.8).

Table 21: 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.[6]

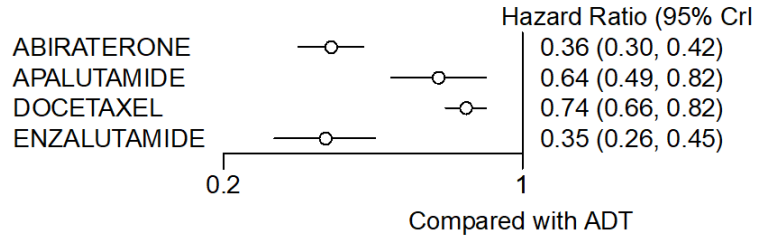

Figure 12. Progression-free survival for each treatment compared with ADT
Source: reprinted from European Urology, 77(3), Sathianathen, et al., Indirect comparisons of efficacy between combination approaches in metastatic hormone-sensitive prostate cancer: a systematic review and network meta-analysis, pp.365-72, Copyright 2020, with permission from Elsevier.[6]

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[34]. Details and commentary for each of the relevant items identified by the ISPOR group are provided in Table 22.

Strengths

The NMA was based on a SLR to identify all relevant studies. Overall, the outcome measures assessed were appropriate to address the objectives of the NMA of evaluating efficacy for the

different treatments of first-line treatments for mHSPC (however limitations are outlined below as other important outcomes in the mHSPC setting were not included).

The authors provided the results of both fixed-effects and random-effects models. The random-effects model allows the incorporation of statistical heterogeneity into the effect estimates. There did not appear to be any significant differences between the models, and the fixed-effects model was primarily reported, with the random-effects model results provided in a supplementary to the publication. The studies included formed a connected network, anchored on ADT. 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 moderate quality in terms of risk of bias (limitations are further discussed below).

Some of the treatments in the NMA were relevant to the Canadian context (although some treatments were also included that may not be relevant, and dosages were not reported, which precludes comparison to Canadian dosages). Current standard of care for these patients in Canada includes being treated with ADT alone, chemotherapy (e.g. docetaxel), or chemotherapy (e.g. docetaxel) plus ADT. This NMA also included ADT alone and combination treatments in comparison to apalutamide.

Limitations

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.
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. 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.

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.

Table 22: Adapted ISPOR Questionnaire to Assess the Credibility of an Indirect Treatment Comparison or NMA adapted from Jansen et al.[34]

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.

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 limited inclusion criteria described. The publication described the information sources, search strategy and selection criteria. Limited details of the 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

ISPOR Questions	Details and Comments
	fixed-effects 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.

7.1.3 Summary

A published NMA was identified comparing apalutamide 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 pCODR Review Team. Five relevant trials were identified from a SLR.

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

Several limitations to the NMA were identified that increase the uncertainty of the results. There was a lack of clarity surrounding the inclusion and exclusion criteria for the NMA, with some

criteria not clearly defined. Furthermore, there was clinical heterogeneity between the included studies (e.g. variations in patient inclusion/exclusion criteria, pre-treatment allowance, performance status, Gleason Grade, PSA, age range, and disease stage), which makes the comparability of the trials challenging (i.e., different ADT treatments in the trials, disease stage and previous treatments allowed). Additionally, 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. These limitations should be considered when interpreting the results of this NMA.

8 COMPARISON WITH OTHER LITERATURE

The pCODR Clinical Guidance Panel and the pCODR Method Team did not identify other relevant literature proving supporting information for this review.

9 ABOUT THIS DOCUMENT

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

pCODR 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 pCODR Disclosure of Information Guidelines. The manufacturer, 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. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

The Clinical Guidance Panel is comprised of three clinical oncologists.The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the CADTH website (www.cadth.ca/pcodr). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY AND DETAILED METHODOLOGY

1. Literature search via Ovid platform

Database(s): Cochrane Central Register of Controlled Trials (CENTRAL); Embase (1974 to present); MEDLINE All (1946 to present)

#	Searches	Results
1	(Erleada* or apalutamide* or Erlyand* or arn-509 or arn509 or JNJ 56021927 or JNJ56021927 or JNJ-927 or JNJ927 or 4T36H88UA7).ti,ab,ot,kf,kw,hw,nm,rn.	719
2	1 use cctr	77
3	1 use medall	131
4	*apalutamide/	126
5	(Erleada* or apalutamide* or Erlyand* or arn-509 or arn509 or JNJ 56021927 or JNJ56021927 or JNJ-927 or JNJ927).ti,ab,kw,dq.	535
6	or/4-5	544
7	6 use oemezd	348
8	7 not (conference review or conference abstract).pt.	216
9	3 or 8	347
10	limit 9 to english language	326
11	2 or 10	403
12	remove duplicates from 11	284
13	7 and (conference review or conference abstract).pt.	132
14	limit 13 to english language	132
15	limit 14 to yr="2014 -Current"	120
16	12 or 15	404

2. Literature search via PubMed

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

Search	Query	Items Found
#3	Search #1 AND #2 AND publisher[sb] Filters: English	12
#2	Search publisher[sb]	400880
#1	Search apalutamide [Supplementary Concept] OR 4T36H88UA7[rn] OR Erleada*[tiab] OR apalutamide*[tiab] OR Erlyand* OR arn-509[tiab] OR arn509[tiab] OR JNJ 56021927[tiab] OR JNJ56021927[tiab] OR JNJ-927[tiab] OR JNJ927[tiab]	130

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/

World Health Organization
http://apps.who.int/trialsearch/

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

Search: Erleada/apalutamide, metastatic castration sensitive 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: Erleada/apalutamide, metastatic castration sensitive 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: Erleada/apalutamide, metastatic castration sensitive prostate cancer — last five years

Detailed Methodology

The literature search for clinical studies was performed by an information specialist from the pCODR 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).[37]

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 concept was Elreada (apalutamide).

No filters were applied to limit the retrieval by study type. The search was also limited to English-language documents but not limited by publication year.

The search is considered up to date as of February 20, 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).[38] 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 pCODR Review Team.

Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

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 pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

Data Analysis

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

Writing of the Review Report

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

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

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