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Evidence-Based Series #3-15 Version 2 REQUIRES UPDATING

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Systemic Therapy in Men with Metastatic Castration-Resistant Prostate Cancer

The CCO-ASCO Joint Castration Resistant Prostate Cancer Expert Panel and the CCO Genitourinary Cancer Disease Site Group

Original Report Date: November 1, 2005
Current Report Date: March 18. 2021

Evidence-based Series (EBS) 3-15v2 was reviewed in 2021 and determined to REQUIRE UPDATING. It is still appropriate for this document to be available while this updating process unfolds. See Section 4: Document Assessment and Review for details.

EBS 5-15v3 is comprised of 4 sections. You can access the summary and full report here: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/431

Section 1:	Guideline Recommendations
Section 2A:	Updated Evidence Summary 2012
Section 2B:	Original Evidence Summary 2005
Section 3:	EBS Development Methods, Recommendations Development, and External Review Process
Section 4:	Document Assessment and Review

For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at: Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775 E-mail: ccopgi@mcmaster.ca

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PUBLICATIONS RELATED TO THIS REPORT

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Loblaw DA, Walker-Dilks C, Winquist E, Hotte SJ; on behalf of the Genitourinary Cancer Disease Site Group of Cancer Care Ontario's Program in Evidence-based Care. Systemic therapy in men with metastatic castration-resistant prostate cancer: a systematic review. Clin Oncol (R Coll Radiol). 2013 Jul;25(7):406-30.

Winquist E, Waldron T, Berry S, Ernst DS, Hotte S, Lukka H. Non-hormonal systemic therapy in men with hormone-refractory prostate cancer and metastases: a systematic review from the Cancer Care Ontario Program in Evidence-based Care's Genitourinary Cancer Disease Site Group. BMC Cancer. 2006 May;6:112.

Evidence-Based Series #3-15 Version 3

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Systemic Therapy in Men with Metastatic Castration-Resistant Prostate Cancer

Guideline Report History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES and KEY CHANGES
	Search Dates	Data		
Original Nov 2005	1966 to Feb2005	Full Report	Peer review publication Web publication	Not Applicable
Version 2 Sep 2014	2003 to Jun 2012	New data added to original Full Report: Section 2A	Peer review publications Updated web publication	Search updated in Jun 2012 (systematic review) and Jun 2014 (clinical practice guideline); scope broadened
Version 2 reviewed March 2021	July 2012 to December 2021	New data found in Section 4	Updated Web pulication	2014 Recommendations REQUIRE UPDATING

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A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Systemic Therapy in Men with Metastatic Castration-Resistant Prostate Cancer: Guideline Recommendations

E. Basch, D.A. Loblaw, T.K. Oliver, C. Bennett, M. Carducci, R. Chen, J. Frame, K. Garrels, S. Hotte, M. Kattan, R. Nam, D. Raghavan, F. Saad, M.E. Taplin, C. Walker-Dilks, J. Williams, E. Winquist, T. Wooten, K. Virgo (The CCO-ASCO Joint Castration Resistant Prostate Cancer Expert Panel), and the CCO Genitourinary Cancer Disease Site Group

Report Date: September 8, 2014

The 2014 guideline recommendations

REQUIRE UPDATING

It is still appropriate for this document to be available while this updating process unfolds. See Section 4 for details.

The guideline recommendations from the CCO-ASCO Joint Castration-Resistant Prostate Cancer Expert Panel are found in the accompanying document entitled:

Systemic Therapy in Men with Metastatic Castration-Resistant Prostate Cancer (CRPC): American Society of Clinical Oncology and Cancer Care Ontario Clinical Practice Guideline

can be found here: www.asco.org/guidelines/mCRPC

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Evidence-Based Series #3-15 Version 2: Section 2A

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Systemic Therapy in Men with Metastatic Castration-Resistant Prostate Cancer: Updated Evidence Summary 2012

D.A. Loblaw, C. Walker-Dilks, E. Winquist, S.J. Hotte, and the Genitourinary Cancer Disease Site Group

The 2014 guideline recommendations

REQUIRE UPDATING

It is still appropriate for this document to be available while this updating process unfolds.

Report Date: September 8, 2014

QUESTION

In men with metastatic castration-resistant prostate cancer (mCRPC), which systemic therapies improve cancer- or patient-related outcomes?

INTRODUCTION

Androgen deprivation therapy (ADT) is commonly prescribed for men with recurrent, progressive, or metastatic prostate cancer that is androgen sensitive (1). Many men with androgen-sensitive disease on ADT will have biochemical, radiographic, and/or symptomatic progression despite conventionally defined castrate levels of testosterone (<50 ng/ml or <1.7 nmol/L) (2,3). This state is now referred to as castration-resistant prostate cancer (CRPC) (4).

Up to 20% of men with a biochemical relapse (5), and most men with advanced disease will eventually develop castration resistance (6). Patients are, therefore, generally divided into two groups: those with biochemical recurrence and no radiographic evidence of metastases (bCRPC), and those with metastatic disease. The latter group is often differentiated into asymptomatic (M1a CRPC) and symptomatic metastatic disease (M1s CRPC), because the onset of symptoms frequently prompts consideration of chemotherapy. This document addresses interventions for patients with M1a and M1s disease, while bCRPC is the topic of a separate American Society of Clinical Oncology (ASCO) guideline (7).

Before docetaxel is administered, various hormonal manipulations can be done (7). These manoeuvres result in a biochemical response in the minority of patients and do not

improve overall survival. The median overall survival in men with bCRPC is approximately 4 years (8).

Docetaxel has become the mainstay of treatment for men with symptomatic metastatic disease, although several other systemic agents have been used or recommended. A systematic review and accompanying practice guideline was produced by the PEBC Genitourinary Cancer Disease Site Group (GU DSG) in 2005 (9) to evaluate the benefit of non-hormonal systemic therapy in men with mCRPC. Up to that time, treatment for men with mCRPC had been primarily palliative. Emerging evidence was examined from randomized controlled trials (RCTs) that evaluated chemotherapy and other nonhormonal agents for mCRPC. The review identified 28 eligible RCTs published between 1979 and 2004. The drugs studied included docetaxel, estramustine, vinorelbine, mitoxantrone, doxorubicin and epirubicin, and other cytotoxic and noncytotoxic agents. The review concluded that docetaxel administered every three weeks improved overall survival (median overall survival improved from approximately 16 to 19 months). Mitoxantrone-prednisone and weekly docetaxel-prednisone improved symptom palliation and disease control without affecting survival and were considered alternatives to three-weekly docetaxel. The use of estramustine was not endorsed, as it was associated with increased risk of toxicity without clear evidence of incremental benefits. An endorsement of the practice guideline was published by ASCO (10).

Since the approval of docetaxel in the United States in 2004 (2005 in Canada) for patients with mCRPC, most efforts in clinical trial design have focused on treatment prior to docetaxel administration, treatment to replace or supplement docetaxel, or treatment options following docetaxel use. Median overall survival for untreated CRPC post-docetaxel is approximately 11 months (11). Recently published RCTs of new agents have prompted the GU DSG to conduct an updated search of the literature and expand the treatments of interest beyond classic cytotoxic chemotherapy to include targeted hormonal therapies and immunotherapy. A systematic review of the new evidence published since the earlier report was released is presented.

METHODS

The EBS guidelines developed by Cancer Care Ontario's PEBC use the methods of the Practice Guidelines Development Cycle (12). For this project, the core methodology used to develop the evidentiary base was the systematic review. Evidence was selected and reviewed by the working group authors, which included three members of the PEBC Genitourinary Cancer DSG and one methodologist (Appendices 1 and 2).

The body of evidence in this review is primarily comprised of mature RCT data. That evidence forms the basis of the recommendations developed by the CCO-ASCO Guideline Panel – Management of Advanced Prostate Cancer, a joint committee of CCO and ASCO clinician representatives (Appendix 3). The systematic review and companion recommendations are intended to promote evidence-based practice. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from the Ministry of Health and Long-Term Care.

Literature Search Strategy

The literature search was designed to identify relevant studies published since the completion of the 2005 version of this guideline. Searches were run from 2003 to June 2012 in MEDLINE (Ovid MEDLINE[R] In-Process & Other Non-Indexed Citations and Ovid MEDLINE[R]) and EMBASE. The Cochrane Library was searched for systematic reviews and technology assessments. The annual meeting proceedings of ASCO and the American Urological

Association were searched for relevant abstracts in from 2009 to 2012. Other literature sources were reference lists of relevant articles and experts' suggestions.

The literature searches in MEDLINE and EMBASE combined methods terms for meta-analyses, systematic reviews, practice guidelines, and RCTs with terms describing castration-resistant prostate cancer and systemic therapy interventions (Appendix 4).

An internet search of Canadian and international websites was also conducted to identify existing clinical practice guidelines, health technology assessments, and systematic reviews relevant to the topic of systemic therapy of mCRPC that were not retrieved in the database searches. The clinical trials registry of the National Institutes of Health (clinicaltrials.gov) was searched and relevant recently begun or ongoing trials are listed at the end of the document.

Study Selection Criteria

Articles were eligible for inclusion if they had the following components:

- They were reports from RCTs, systematic reviews of RCTs with or without meta-analysis, or clinical practice guidelines with a systematic review.
- The intervention was systemic therapy or combination (excluding primary or secondary androgen deprivation therapy, bone protective agents, or radionuclides) compared with placebo or other drug regimens.
- RCTs contained ≥50 patients per study arm.
- The study population consisted of men with mCRPC. In mixed populations, ≥90% of men were required to have metastases.
- The outcomes of interest were any of the following: overall survival, disease control (i.e., progression-free survival, time-to-progression, time-to-treatment failure, objective tumour response, and PSA response), palliative or symptomatic response, quality of life, or toxicity.

Synthesizing the Evidence

When clinically homogenous results from two or more trials were available, a meta-analysis would be conducted using the Review Manager software (13) provided by the Cochrane Collaboration. For time-to-event outcomes, the hazard ratio (HR), rather than the number of events at a certain time point, was the preferred statistic for meta-analysis, and would be used as reported. For all outcomes, the generic inverse variance model with random effects, or other appropriate random effects models in Review Manager would be used.

Statistical heterogeneity would be calculated using the chi-squared test for heterogeneity and the I^2 percentage. A probability level for the chi-squared statistic less than or equal to 10% ($p \leq 0.10$) and/or an I^2 greater than 50% would be considered indicative of statistical heterogeneity. All ratio outcomes (e.g., HR, relative risk [RR]) are reported such that a ratio of less than 1 favours the study drug and a ratio of greater than 1 favours the placebo or control drug.

RESULTS

Literature Search Results

1586 citations were retrieved by the MEDLINE and EMBASE searches. Following detailed abstract and full-text review of 156 citations, 35 citations met the inclusion criteria. From the searches of the Cochrane Library, the ASCO and AUA websites, and other sources, 17 more articles were identified and retained bringing the total number of relevant articles to 52 (Appendix 5): one practice guideline, five health technology assessment/systematic review and 46 RCTs. Twenty-one of the RCTs were secondary publications or older reports that have

been superseded by newer ones, and with three exceptions, are not considered further: one had unique data in the older report only, and two conference abstracts provided updated results to earlier full-text publications.

Clinical Practice Guidelines

One clinical practice guideline on prostate cancer was identified from the European Association of Urology (EAU) that included a chapter on CRPC (14). A summary of this chapter was also published in a separate journal article (15). Of the studies included in the CRPC chapter, 27 did not meet our criteria, five were included in the original version of this guideline, and six were published since the original guideline. These six studies were identified in our search and three have been superseded by new reports. The EAU guideline did not make detailed recommendations on the use of agents in the newer studies and therefore it will not be discussed further.

Systematic Reviews

Several health technology assessments were identified in the database and internet search. All but one was excluded because the methods for developing them were non-systematic, the studies identified did not meet our inclusion criteria, or the studies identified were included in the 2005 version of this guideline. One health technology assessment and one systematic review evaluated sipuleucel-T therapy for mCRPC (16,17). Mark et al included two studies identified in our search and citations of seven studies for off-label indications for sipuleucel-T that did not meet our inclusion criteria. The two relevant studies will be discussed with the individual RCTs. Apart from the IMPACT trial (18), Sonpavde et al did not include any additional studies meeting our criteria.

Two systematic reviews with meta-analyses examined docetaxel-based therapies. Serpa Neto and colleagues combined results from 12 RCTs comparing docetaxel-based therapies with docetaxel alone (19). Qi and colleagues evaluated docetaxel-based therapies with or without estramustine with data from four RCTs (20). Both reviews included studies with <50 patients per study group in their meta-analyses: seven studies in Serpa Neto et al and three of the four studies in Qi et al. As those studies did not meet our inclusion criteria, we excluded the reviews from our analysis. The studies with >50 patients per group were identified in our search and are analyzed with the individual RCTs.

One systematic review evaluated vaccination strategies for prostate cancer in 13 RCTs (21). The intervention vaccines included sipuleucel-T, GVAX, PROSTVAC-VF and MVA-MUC1-IL2 vaccine. One trial of sipuleucel-T and two trials of GVAX were identified in our search (18,22,23). The other trials did not meet our inclusion criteria.

Thus, data from 25 RCTs were extracted, synthesized, and interpreted, and served as the foundation for this systematic review.

Randomized Controlled Trials

The 25 eligible RCTs included in this guideline were published between 2006 and 2012. The study characteristics are shown in Table 1.

Table 1. Eligible Trials.

Study reference	Number of patients (number evaluable)	Patient symptoms	Study comparisons (patients/group)	Dosage schedule	Outcome measures*
Pre-docetaxel					
Targeted Therapy					
Carducci2007 (24) Phase III	809 (809)	Free of disease-related pain requiring opioids and Karnofsky score 70	Atrasentan (408) Placebo (401)	10 mg, once daily po	**TTP**, OS, time to PSA progression, toxicity

		to 100			
James2010 (25) Phase II	312 (312)	Free of disease-related pain requiring opioids	Zibotentan 10 mg (107) Zibotentan 15 mg (98) Placebo (107)	Once daily po	**TTP**, OS, time to PSA progression, objective response, toxicity
Pili2011 (26) Phase II	206 (201)	Minimally symptomatic: Karnofsky score 70 to 100 and VAS pain ≥3 on 0 to 10 scale	Tasquinimod (134) Placebo (67)	1.0 mg, once daily po	**Disease progression**, PFS, toxicity
Nelson2011Ab (27) Phase III	594	Pain free or mildly symptomatic for pain	Zibotentan (299) Placebo (295)	10 mg, once daily po	**OS**, time to pain progression, toxicity
Immunotherapy					
Kantoff2010 (18) (IMPACT) Phase III	512 (512)	Asymptomatic to minimally symptomatic; ECOG performance status <2	Sipuleucel-T (341) Placebo (171)	IV administered over 60 min every 2 wk for total 3 infusions	**OS**, TTP, PSA response, objective response, toxicity
Hypercastration					
Ryan2012Ab (28) (COU-AA-302) Phase III	1088	Asymptomatic to minimally symptomatic	Prednisone/abiraterone acetate (546) Prednisone/placebo (542)	Prednisone, 5 mg Abiraterone, 1 g twice daily	**OS, PFS**, time to PSA progression, toxicity
Docetaxel Alone or in Combination					
Docetaxel with/without Estramustine					
Berry2006 (29) (SWOG 99-16) Phase III	770 (629)	SWOG performance status ≤2; 3 if due to bone pain	Estramustine/docetaxel /dexamethasone (318) Mitoxantrone/prednisone (311)	Estramustine, 280 mg 3 times daily po, day 1 to 5 Docetaxel, 60 mg/m^2 IV on day 2, every 21 days Dexamethasone, 60 mg po in 3 doses Mitoxantrone, 12 mg/m^2 IV, every 21 days Prednisone, 5 mg twice daily po	**QOL**
Fossa2007 (30) (TIPC) Phase II	134 (104 @ 6 wk, 97 @ 12 wk)	ECOG performance status ≤2	Docetaxel/prednisolone (71) Prednisolone (63)	Docetaxel, 30 mg/m^2 IV days 1, 8, 15, 22, 29 Prednisolone, 5 mg twice daily po for 6 6-wk cycles	**PSA response**, OS, PFS, toxicity, QOL
Berthold2008 (31) (TAX 327) Phase III	1006 (1006)	Karnofsky score ≥70	Docetaxel 75 mg /prednisone (335) Docetaxel 30 mg /prednisone (334) Mitoxantrone 12 mg /prednisone† (337)	Docetaxel, 75 mg/m^2 IV every 21 days Docetaxel, 30 mg/m^2 IV days 1, 8, 15, 22, 29 Mitoxantrone, 12 mg/m^2 IV every 21 days Prednisone, 5 mg twice daily po	**OS**
Machiels2008 (32) Phase III	150 (149)	ECOG performance status ≤2	Docetaxel/estramustine /prednisone (75) Docetaxel/prednisone† (75)	Docetaxel, 35 mg/m^2 days 2 & 9 every 21 days Estramustine, 280 mg 3 times daily po days 1 to 5 and 8 to 12 every 21 days Prednisone, 10 mg daily po	**PSA response**, time to PSA progression, PFS, OS, objective response, toxicity
Kellokumpu2011Ab (33) Phase III	361 (346)	WHO performance status ≤2	Docetaxel every 2 wk Docetaxel every 3 wk	50 mg/m^2 IV days 1 and 14 every 28 days 75 mg/m^2 every 21 days Prednisolone, 10 mg daily po	**Time to treatment failure**, PSA response, OS, toxicity
Docetaxel plus Targeted Therapy					
Mathew2007 (34) Phase II	116 (116)	ECOG performance status ≤2	Docetaxel/imatinib (57) Docetaxel/placebo‡ (59)	Docetaxel, 30 mg/m^2 IV days 1, 8, 15, 22 every 42 days Imatinib, 600 mg daily po	**TTP**, OS, PSA response, objective response, toxicity
Sternberg2009b (35)	115 (111)	WHO performance status ≤2	Docetaxel/oblimersen (58)	Oblimersen, 7 mg/kg daily IV days 1 to 7 + docetaxel,	TTP, **PSA response**, objective response,

(EORTC) Phase II			Docetaxel (57)	75 mg/m^2 IV day 5 Docetaxel, 75 mg/m^2 IV day 1 Every 21 days for ≤12 cycles	**toxicity**
Kelly2012 (36) (CALGB 90401) Phase III	1050 (1050)	ECOG performance status ≤2	Docetaxel/prednisone/ bevacizumab (524) Docetaxel/prednisone/ placebo (526)	Docetaxel, 75 mg/m^2 IV day 1 every 21 days Prednisone, 5 mg daily po Bevacizumab, 15 mg/kg IV every 21 days	**OS**, PFS, PSA response, objective response, toxicity
Sonpavde2011Ab (37) Phase II	221	ECOG performance status ≤2	Docetaxel/prednisone/ AT-101 Docetaxel/prednisone/ placebo	Docetaxel, 75 mg/m^2 IV day 1 Prednisone, 5 mg twice daily po AT-101 40 mg twice daily days 1 to 3 Every 21 days	**OS**, PFS, PSA response, toxicity
Quinn2012Ab (38) (SWOG S0421) Phase III	991	Zubrod performance status ≤2; 3 if due to pain secondary to bone metastases	Docetaxel/atrasentan Docetaxel/placebo	Docetaxel IV day 1 Atrasentan once daily po days 1 to 21 Every 21 days for ≤12 cycles	**OS, PFS**, objective response, PSA response, toxicity
Docetaxel plus Immunotherapy					
Higano2009Ab (22) Phase III	626	Free of disease-related pain requiring opioids	GVAX Docetaxel/prednisone	GVAX 500 million cells prime/300 million cells boost every 2 weeks for 13 doses followed by maintenance immunotherapy every 4 weeks Docetaxel, 75 mg/m^2 every 3 weeks for 9 cycles Prednisone, 10 mg daily po	**OS**, toxicity
Small2009Ab (23) Phase III	408	Pain requiring opioids	GVAX/docetaxel Docetaxel/prednisone	Docetaxel, 75 mg/m^2 IV every 21 days GVAX 500 million cells prime/300 million cells boost 2 days after docetaxel infusion followed by maintenance immunotherapy alone every 4 weeks Prednisone, 10 mg daily po Every 21 days for 10 cycles	**OS**, toxicity
Hypercastration					
No trials identified					
Docetaxel plus Calcitriol					
Beer2007 (39) (ASCENT) Phase II	250 (250)	ECOG performance status ≤2	Calcitriol/docetaxel/dexamethasone (125) Placebo/docetaxel/dexamethasone (125)	Calcitriol, 45 µg po day 1 Docetaxel, 36 mg/m^2 IV day 2 Dexamethasone, 4 mg po 12 hour & 1 hour before & 12 hours after docetaxel Weekly for 3 weeks of a 4 week cycle	OS, **PSA response**, time to PSA response, PSA PFS, objective response, toxicity
Scher2011 (40) (ASCENT-2) Phase III	953 (953)	ECOG performance status ≤2	Calcitriol/docetaxel/dexamethasone wkly for 3 of every 4 wk (477) Prednisone/docetaxel/ dexamethasone every 3 wk† (476)	Calcitriol, 45 µg po day 1, 8, 15 Docetaxel, 36 mg/m^2 IV days 2, 9, 16 Dexamethasone, 8 mg po 12, 3, and 1 hour before	**OS**, thromboembolic events, toxicity

				docetaxel Prednisone, 5 mg twice daily po Docetaxel, 75 mg/m^2 day 2 Dexamethasone, 8 mg po 12, 3, and 1 hour before docetaxel	
Post-docetaxel					
Cytotoxic Drugs					
Sternberg2009 (43) (SPARC) Phase III	950 (950)	ECOG performance status ≤2	Prednisone/satraplatin (635) Prednisone/placebo (315)	Satraplatin, 80 mg/m^2 once daily po days 1 to 5 every 35 days Prednisone, 5 mg twice daily po	**OS, PFS**, PSA response, time to pain progression, tumour response, pain response, toxicity
deBono2010 (44) (TROPIC) Phase III	755 (755)	ECOG performance status ≤2	Prednisone/cabazitaxel (378) Prednisone/mitoxantrone (377)	Prednisone, 10 mg daily po Cabazitaxel, 25 mg/m^2 IV day 1 every 21 days Mitoxantrone, 12 mg/m^2 IV day 1 every 21 days	**OS**, PFS, TTP, PSA response, time to PSA progression, time to pain progression, objective response, toxicity
Targeted Therapy					
Ou2011Ab (45) Phase III	873	ECOG performance status ≤1	Prednisone/sunitinib (584) Prednisone/placebo (289)	Prednisone, 5 mg twice daily po Sunitinib, 37.5 mg once daily po	**OS**, PFS, objective response, toxicity
Immunotherapy					
No trials identified					
Hypercastration					
de Bono2011 (11) (COU-AA-301) Phase III	1195 (1195)	ECOG performance status ≤2	Prednisone/abiraterone acetate (797) Prednisone/placebo (398)	Abiraterone, 1 g once daily po Prednisone, 5 mg twice daily po Every 28 days	**OS**, PFS, PSA response, time to PSA progression, objective response, toxicity
de Bono2012Ab (46) (AFFIRM) Phase III	1199	ECOG performance status ≤2	Enzalutamide (800) Placebo (399)	Enzalutamide, 160 mg daily po	**OS**, PFS, PSA response, objective response, toxicity

*Main outcome measures are in bold.
†Patients could have previously received estramustine.
‡Patients could have previously received other taxane-based therapies.
Ab = abstract; ASCENT = AIPC Study of Calcitriol Enhancing Taxotere; CALGB = Cancer and Leukemia Group B; EORTC = European Organisation for Research and Treatment of Cancer; IMPACT = Immunotherapy for Prostate Adenocarcinoma Treatment; IV = intravenous; OS = overall survival; PFS = progression-free survival; po = per os (oral administration); PSA = prostate specific antigen; QOL = quality of life; SPARC = Satraplatin and Prednisone Against Refractory Cancer; SWOG = Southwest Oncology Group; TAX = taxotere; TIPC = Taxotere in Prostate Cancer; TROPIC = Treatment of Hormone-Refractory Metastatic Prostate Cancer; TTP = time to progression; wk = week.

Study Design and Quality

Eighteen of the included RCTs were described as phase III studies and seven as phase II. Fifteen trials were placebo-controlled. The reports of nine trials were available only as conference abstracts. Across the studies, a total of 15,644 men were randomized, with the number per trial ranging from 115 to 1199.

Six trials dealt with interventions in chemotherapy-naïve patients (pre-docetaxel) (18,24-28). Of these, four trials evaluated targeted therapies (24-27), one evaluated sipuleucel-T, a form of immunotherapy (18), and one evaluated abiraterone acetate, a hypercastrative agent (28).

Fourteen trials dealt with interventions in patients receiving docetaxel alone or in combination (22,23,29-40). Of these, five trials evaluated docetaxel with or without estramustine (29-33), five trials evaluated targeted therapies (34-38), two trials evaluated noncytotoxic immunotherapies (22,23), and two trials evaluated calcitriol (39,40). Beer et al was placebo-controlled (39), while Scher et al compared calcitriol plus docetaxel combination therapy with prednisone plus docetaxel combination therapy (40). Berry et al (29) reported quality-of-life outcomes for the SWOG 99-16 trial (41) and Berthold et al (31) reported updated results for the TAX 327 study (42), both included in the 2005 version of the guideline.

Five trials dealt with interventions in patients who had experienced disease progression on or after cytotoxic chemotherapy (post-docetaxel) (11,43-46). Of these, two trials evaluated cytotoxic agents (43,44), one trial evaluated a targeted therapy (45), and two trials evaluated hypercastrative drugs (11,46).

Details of the methodological characteristics of the trials are in Appendix 6. Sixteen trials were blinded. Sixteen trials described the methods for randomizing patients. Allocation to study arms was concealed in six trials. Thirteen trials performed statistical analyses according to intention to treat. Eighteen trials reported that treatment arms were balanced for important baseline characteristics. Twenty trials included a power statement. Seven trials were terminated early.

Outcomes

Individual study data for overall survival (24 trials), progression-free survival or time to progression (19 trials), PSA response (13 trials), and objective tumour response (11 trials) are in Tables 2 to 6.

Pre-docetaxel

Targeted Therapy

Four trials evaluated targeted therapies in pre-docetaxel, chemotherapy-naïve patients (24-27). Three of these trials evaluated endothelin-A receptor inhibitors (24,25,27). Of these, one trial compared atrasentan, 10 mg with placebo in 809 men with mCRPC (24) in a follow-up of the study reported in a meeting abstract in the previous version of this guideline; one trial was a final safety and efficacy analysis of zibotentan, 10 or 15 mg, compared with placebo in 312 men (25); and one trial compared zibotentan, 10 mg/day with placebo in 594 men (27). All three trials assessed overall survival, and none reported a statistically significant difference between the study drug and placebo. Neither of the two trials assessing disease progression showed a difference between groups (24,25). Carducci et al was stopped early, because it was unlikely to achieve statistical significance for time to progression despite enrolling sufficient patients to achieve the prespecified number of outcome events (24).

These three trials (24,25,27) were similar enough in patient characteristics and intervention (drug class) to permit pooling of data for overall survival. The 10-mg zibotentan arm in James et al (25) was used in the meta-analysis with Carducci et al (24) and Nelson et

al (27), which used 10 mg of atrasentan and zibotentan, respectively. The 80% CIs in James et al and the 95.2% CIs in Nelson et al were converted to 95% CIs before pooling. Meta-analysis of the three trials showed a nonsignificant improvement in overall survival favouring endothelin-A receptor inhibitors (HR 0.91, 95% CI 0.80 to 1.04) (Figure 1). A sensitivity analysis using the 15 mg zibotentan arm from James et al gave a similar result (HR 0.90, 95% CI 0.79 to 1.03; I^2=0%, Chi^2 test of heterogeneity p=0.42).

The two trials reporting time to progression (24,25) were not pooled as the definitions of time to progression used in the two trials were too dissimilar. In one trial, the outcome included skeletal-related events (and most progression events were the result of new lesions identified on scheduled bone scans) (24), whereas in the other trial, the number or appearance of bone lesions did not count as progression events (25). Carducci et al also included intervention for urinary tract obstruction in time to progression (24), while James et al excluded transurethral resection in the definition (25). The hazard ratio (HR) for atrasentan versus placebo was 0.89 (95% CI 0.76 to 1.04, p=0.136) (24). The HR for zibotentan, 10 mg versus placebo was 1.06 (80% CI 0.89 to 1.27, p=0.673) and for zibotentan, 15 mg versus placebo was 0.86 (80% CI 0.72 to 1.04, p=0.309) (25).

Time to PSA progression was assessed in the same two trials (with data for zibotentan from the James et al 2009 report [47]), and neither showed a significant difference between groups. The HR for atrasentan compared with placebo was 0.84 (95% CI 0.70 to 1.01, p=0.366) (24) and the HRs for zibotentan 15 mg and 10 mg compared with placebo were 0.82 (80% CI 0.65 to 1.03, p=0.273) and 0.95 (80% CI 0.76 to 1.18, p=0.743), respectively (47). With respect to tumour response, James et al reported no responders in any treatment group (25).

Another pre-docetaxel targeted therapy trial compared tasquinimod with placebo in 206 men (26). Tasquinimod was administered at a dose of 1.0 mg/day after a titration phase of 0.25 mg/day for 2 weeks followed by 0.5 mg/day for 2 weeks. This phase II trial showed improved progression-free survival, with 69% of patients who received tasquinimod being progression-free at 6 months compared with 37% of patients who received placebo, and median progression-free survival improved from 3.3 months to 7.6 months (p=0.0042). In an exploratory multivariate model of known prognostic factors, a recent conference abstract reported an adjusted HR for progression-free survival of 0.54 (95% CI 0.37 to 0.81) and for overall survival of 0.72 (95% CI 0.46 to 1.12) (48). Tasquinimod had an acceptable toxicity profile, but was less well tolerated in older (>75 years) men. Gastrointestinal events, muscle and joint pain, and fatigue were the most common adverse events. Cardiovascular events were also seen in the tasquinimod group, which could be associated with the older age of the patients. Most adverse events in the tasquinimod group (89%) were grade 1 and 2 (26).

Immunotherapy

One trial evaluated sipuleucel-T mainly in pre-docetaxel, chemotherapy-naïve patients (18% had prior chemotherapy) (18). Overall survival favoured sipuleucel-T with an HR of 0.78 (95% CI 0.61 to 0.98, p=0.03), but there was no improvement in time to progression. A PSA reduction of ≥50% was observed in 2.6% of patients who received sipuleucel-T compared with 1.3% of patients who received placebo (p=0.378). One patient in the sipuleucel-T group had an objective partial response. Sipuleucel-T was associated with more chills, fever, headache, influenza-like illness, myalgia, hypertension, hyperhidrosis, and groin pain than was placebo. These effects generally resolved within 1 to 2 days after infusion. Adverse events of grade 3 or more occurred in 6.8% of sipuleucel group patients compared with 1.8% of placebo group patients.

Hypercastration

The COU-AA-302 trial evaluated prednisone and the hypercastrative drug abiraterone acetate versus prednisone alone in chemotherapy-naive patients with asymptomatic or mildly symptomatic mCRPC (28). With planned follow-up of 60 months and a median follow-up of 22.2 months, a pre-defined interim analysis detected statistically significant differences with abiraterone for radiographic progression-free survival, and all secondary endpoints. With a prespecified alpha level of 0.0008, a trend to increased overall survival was observed but did not reach statistical significance (p=0.0097). Abiraterone had an acceptable tolerability and safety profile: grade 3 to 4 adverse events were hypertension (3.9% vs. 3.0%), hypokalemia (2.4% vs. 1.9%), elevated alanine aminotransferase (5.4% vs. 0.7%), and elevated aspartate aminotransferase (3.0% vs. 0.9%). The Independent Data Monitoring Committee unanimously recommended halting the trial and crossing over the placebo group of patients to receive abiraterone.

In summary, among chemotherapy-naïve patients, no survival benefit was conferred from targeted therapy, with the exception of tasquinimod, which improved progression-free survival. Immunotherapy with sipueucel-T prolonged overall survival and was well tolerated, but had no effect on objective disease progression. Hypercastration with abiraterone delayed signs and symptoms of disease progression; overall survival was improved although not statistically proven.

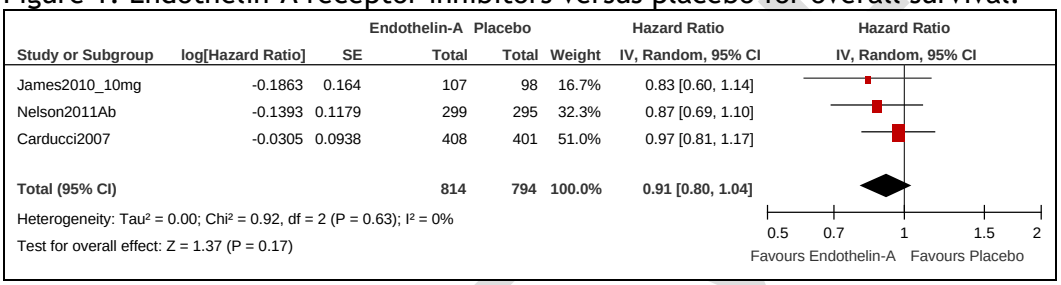
Table 2. Pre-docetaxel therapies: Survival outcomes

Study reference	Treatment arms (patients/group or total number)	OS (median)	PFS or TTP (median)	Disease progression
Targeted Therapy				
Carducci2007 (24)	Atrasentan (408) vs. placebo (401)	20.5 vs. 20.3 mo, HR 0.97 (95% CI 0.81 to 1.17), p=0.775	TTP: HR 0.89 (95% CI 0.76 to 1.04), p=0.136	Proportion with disease progression: 73.3% vs. 77.6%
James2010 (25)	Zibotentan 15 mg (98) vs. placebo (107)	23.9 vs. 19.9 mo, HR 0.76 (80% CI 0.61 to 0.94)*, p=0.103	TTP: 3.8 vs. 3.7 mo, HR 0.86 (80% CI 0.72 to 1.04), p=0.309	
	Zibotentan 10 mg (107) vs. placebo (107)	23.5 vs. 19.9 mo, HR 0.83 (80% CI 0.67 to 1.02)*, p=0.254	TTP: 4.6 vs. 3.7 mo, HR 1.06 (80% CI 0.89 to 1.27), p=0.673	
Pili2011 (26)	Tasquinimod (134) vs. placebo (67)		PFS: 7.6 vs. 3.3 mo, HR 0.57 (95% CI 0.39 to 0.85), p=0.0042	Proportion free of disease progression: 69% vs. 37%, RR 0.49 (95% CI 0.36 to 0.67), p<0.001
Nelson2011Ab (27)	Zibotentan (299) vs. placebo (295)	24.5 vs. 22.5 mo, HR 0.87 (95.2% CI 0.69 to 1.10)*, p=0.240		
Immunotherapy				
Kantoff2010 (18) (IMPACT)	Sipuleucel-T (341) vs. placebo (171)	25.8 vs. 21.7 mo, HR 0.78 (95% CI 0.61 to 0.98), p=0.03	Time to objective disease progression: 3.7 vs. 3.6 mo, HR 0.95 (95% CI 0.77 to 1.17), p=0.63 Time to clinical disease progression: HR 0.92 (95% CI	

Study reference	Treatment arms (patients/group or total number)	OS (median)	PFS or TTP (median)	Disease progression
			0.75 to 1.12), p=0.40	
Hypercastration				
Ryan2012Ab (28) (COU-AA-302)	Prednisone/abiraterone acetate vs. prednisone (n=1088)	Survival time not attained vs. 27.2 mo, HR 0.75 (95% CI 0.61 to 0.93), p=0.0097	PFS time not attained vs. 8.3 mo, HR 0.43 (95% CI 0.35 to 0.52), p<0.0001	

Ab = abstract; CI = confidence interval; HR = hazard ratio; mo = month; IMPACT = Immunotherapy for Prostate Adenocarcinoma Treatment; OS = overall survival; PFS = progression free survival; RR = relative risk; TTP = time to progression.
*The 80% CIs in James et al and the 95.2% CIs in Nelson et al were converted to 95% CIs before pooling (Fig 1).

Figure 1. Endothelin-A receptor inhibitors versus placebo for overall survival.



Docetaxel Alone or in Combination

Docetaxel with or without Estramustine

Five articles reported on trials that evaluated docetaxel alone or in combination with estramustine (29-33). One publication reported QOL outcomes of the SWOG 99-16 trial reported in the 2005 version of this guideline that compared estramustine, 280 mg three times/day; docetaxel, 60 mg/m^2; and dexamethasone, 60 mg with mitoxantrone, 12 mg/m^2 and prednisone, 5 mg two times/day (29). No significant differences in pain response were observed between the estramustine/docetaxel/dexamethasone group compared with the mitoxantrone/prednisone group (21% vs 24%, p=0.12), nor did the groups differ in global QOL scores.

The key outcomes of the remaining four articles are summarized in Table 3. Berthold et al reported an updated survival analysis of the TAX 327 study that compared docetaxel, 75 mg/m^2 every three weeks or docetaxel, 30 mg/m^2 weekly with mitoxantrone, 12 mg/m^2 every three weeks (all patients received prednisone, 5 mg twice daily) (31). Docetaxel/prednisone given every three weeks significantly increased overall survival, while no survival benefit was observed with docetaxel-prednisone given on a weekly schedule. These results were consistent with those of the earlier analysis. The TIPC study compared docetaxel, 30 mg/m^2 plus prednisolone, 5 mg twice daily with prednisolone alone (30). The publication of the SWOG 99-16 and TAX 327 trials established the effectiveness of docetaxel and prompted the refusal of clinicians to use prednisolone monotherapy in mCRPC patients. Recruitment to the TIPC study thus stopped early and proposed sample sizes were not reached. Statistical comparisons between groups were not done, but overall survival, progression free survival,

and PSA response were consistent with the TAX 327 and SWOG 99-16 results favouring the docetaxel group.

Two trials compared docetaxel-based chemotherapy regimens (32,33). One trial compared docetaxel, 35 mg/m^2 and estramustine, 280 mg three times/day with docetaxel alone (32). The groups did not differ for overall or disease-free survival, or for PSA or objective response. The median time to PSA progression for the docetaxel/estramustine group was 6.9 months compared with 7.3 months in the docetaxel alone group (p=0.954). Another trial, reported in a conference abstract, compared docetaxel, 50 mg/m^2 every two weeks with docetaxel, 75 mg/m^2 every three weeks (all patients received prednisolone, 10 mg/day) (33). The primary outcome of median time to treatment failure was longer in the group receiving treatment every two weeks. Overall survival and PSA response did not differ between the groups. Adverse events considered serious were more common in the standard three-weekly group (p=0.002).

Docetaxel plus Targeted Therapy

Five trials evaluated noncytotoxic targeted therapies in patients receiving docetaxel (34-38). A phase II trial compared docetaxel, 30 mg/m^2 weekly plus oral imatinib mesylate, 600 mg/d with docetaxel plus placebo (34). Interim analyses indicated a significant treatment difference would be unlikely if the trial continued to its planned accrual of 144 patients and the trial was terminated early. Among the 116 patients accrued, the groups showed no difference between groups in overall or disease-free survival or PSA or objective response. The EORTC performed a phase II trial comparing docetaxel, 75 mg/m^2 plus oblimersen, 7 mg/kg/day with docetaxel alone (35). The study was designed to determine whether docetaxel plus oblimersen could improve on results achieved with docetaxel alone. A treatment was deemed active and safe if the 80% exact CI around the PSA response excluded 30% and the CI around the major toxic event rate excluded 45%. A confirmed PSA response >30% was not reached with docetaxel plus oblimersen. Kelly et al evaluated the addition of bevacizumab, 15 mg/kg to docetaxel, 75 mg/m^2 plus prednisone, 5 mg twice per day (36). Patients receiving bevacizumab showed an improvement in progression-free survival, PSA response, and objective response; however, no difference in overall survival was observed. Bevacizumab was associated with significantly more maximum hematologic and nonhematologic adverse effects (75.4% vs 56.2%, p<0.001) and more treatment-related deaths (4.0% vs. 1.2%, p=0.005). These included neutropenia, fatigue, leukopenia, hypertension, gastrointestinal perforation and hemorrhage, mucositis, and pneumonitis. Sonpavde et al evaluated the addition of the Bcl-2 inhibitor AT-101, 40 mg twice per day to docetaxel, 75 mg/m^2 plus prednisone, 5 mg twice per day compared with docetaxel plus prednisone alone (37). The groups did not differ for overall or progression free survival, or PSA response. Quinn et al evaluated the addition of atrasentan to docetaxel for 12 three-week cycles. No differences were observed between the atrasentan and placebo groups for overall or progression-free survival or response (38).

Docetaxel plus Immunotherapy

Two phase III trials, reported in meeting abstracts, evaluated GVAX immunotherapy in patients receiving docetaxel (22,23). In Higano et al, patients were allocated to CG1940/CG8711, 500 million cells prime/300 million cells boost doses every two weeks for 13 cycles followed by maintenance GVAX immunotherapy every four weeks or docetaxel, 75 mg/m^2 every three weeks for nine cycles plus prednisone, 10 mg/d (22). After accrual of 626 patients the trial was terminated early because a futility analysis deemed it had a <30% chance of meeting the predefined primary endpoint of improvement in overall survival. Overall survival did not differ between the groups. Adverse events grade 3 or higher were less

common with GVAX than with docetaxel (8.8% vs 4.3%). In Small et al, patients were allocated to docetaxel, 75 mg/m^2 every three weeks for 10 cycles plus CG1940/CG8711, 500 million cells prime/300 million cells boost doses every three weeks for 10 cycles followed by maintenance immunotherapy alone or docetaxel, 75 mg/m^2 plus prednisone, 10 mg/day (23). The trial was terminated early after accrual of 408 patients because of an imbalance in deaths (67 in the GVAX + docetaxel group vs. 47 in the docetaxel + prednisone group). Overall survival favoured the docetaxel plus prednisone group, and the difference was statistically significant. The increase in mortality could not be explained by excessive toxicities.

Docetaxel plus Calcitriol

Two trials evaluated calcitriol in patients receiving docetaxel (39,40). The ASCENT trial allocated patients to calcitriol (DN-101), 45 µg administered on day one plus docetaxel, 36 mg/m^2 on day 2 and dexamethasone, 4 mg (12 hours and 1 hour before and 12 hours after docetaxel) or to placebo plus the same docetaxel/dexamethasone regimen (39). Both regimens were administered weekly for three consecutive weeks of a 4-week cycle. The primary endpoint of PSA decline of >50% within six months did not differ between groups. Median overall survival had not been reached in the calcitriol group but was estimated to be 24.5 months, showing an improvement over the placebo group median survival of 16.4 months. The calcitriol and placebo groups did not differ for objective response or PSA progression free survival (median 7.9 vs. 7.6 mo, p=0.7). The addition of calcitriol to docetaxel did not lead to an increase in toxicity. Several adverse events were reduced in the calcitriol group and serious adverse events leading to hospitalization were significantly rarer (27% vs. 41%, p=0.023). The incidence of grade 3 or higher adverse events was 58% in the calcitriol group and 70% in the placebo group (39). ASCENT-2 was a phase III trial designed to verify the observed survival benefit of the previous ASCENT trial (40). Patients were allocated to a 28-day dosing cycle of calcitriol (DN-101), 45 µg (days 1, 8, and 15) plus docetaxel, 36 mg/m^2 (30-minute infusion on days 2, 9, and 16) and dexamethasone, 8 mg (12, 3, and 1 hour before docetaxel) or to a 21-day dosing cycle of prednisone, 5 mg twice daily plus docetaxel, 75 mg/m^2 (1-hour infusion on day 2) and dexamethasone, 8 mg (12, 3, and 1 hour before docetaxel). The trial was terminated early because of a greater number of deaths in the calcitriol group than in the control (prednisone) group. At final assessment six months after the study was terminated, 174 patients (36.5%) had died in the calcitriol group and 138 (29%) had died in the control group. Prostate cancer was the primary cause of death in 142 patients (81.6%) in the calcitriol group and in 108 patients (78.3%) in the control group. The median overall survival rate was statistically significantly lower in the calcitriol group. The mortality increase was not explained by calcitriol-related toxicity. Treatment discontinuations were due to disease progression and docetaxel toxicity and prostate cancer progression was the primary cause of death for most patients.

The control groups in the two ASCENT trials were too dissimilar to permit statistical pooling. One trial used an identical dose and schedule of docetaxel without prednisone in the control arm (39), while the other used docetaxel given every three weeks with prednisone in the control arm (40).

In summary, updated reports and trials of docetaxel alone confirm the survival benefit seen in previous studies. The benefits of adding estramustine to docetaxel remain unestablished. Trials of combining therapies with docetaxel generally did not extend survival and, in the cases of GVAX and calcitriol, were harmful. The addition of bevacizumab improved progression-free survival but not overall survival and was associated with substantial adverse effects.

Table 3. Docetaxel alone or in combination: Survival outcomes

Study reference	Treatment arms	OS (median)	PFS or TTP (median)	Disease progression
Docetaxel with/without Estramustine				
Fossa2007 (30) (TIPC) *	Docetaxel/prednisolone (71) vs. prednisolone (63)	27 vs. 18 mo	PFS: 11 vs. 4 mo*	
Berthold2008 (31) (TAX 327)	Docetaxel 75 mg/prednisone (335) vs. mitoxantrone/prednisone (337)	19.2 vs. 16.3 mo, HR 0.79 (95% CI 0.67 to 0.93), p=0.004		
	Docetaxel 30 mg/prednisone (334) vs. mitoxantrone/prednisone (337)	17.8 vs. 16.3 mo, HR 0.87 (95% CI 0.74 to 1.02), p=0.086		
Machiels2008 (32)	Docetaxel/estramustine/prednisone (75) vs. docetaxel/prednisone (75)	19.3 vs. 21.0 mo, p=0.526	PFS: 6.3 vs. 6.6 mo, p=0.747	
Kellokumpu2011Ab (33)	Docetaxel q 2 wk vs. docetaxel q 3 wk (n=361)	11.2 vs. 11.8 mo, p=0.164	Time to treatment failure: 5.6 vs. 4.9 mo, p=0.016	
Docetaxel plus Targeted Therapy				
Mathew2007 (34)	Docetaxel/imatinib (57) vs. docetaxel (59)	20.9 mo vs. survival time not attained (95% CI 16.9 to upper limit not attained), p=0.23	TTP: 4.2 vs. 4.2 mo, p=0.58	Proportion with disease progression: 75% vs. 78%
Sternberg2009b (35) (EORTC)	Docetaxel/oblimersen (58) vs. docetaxel (57)		TTP: 4.4 vs. 6.2 mo	
Kelly2012 (36) (CALGB 90401)	Docetaxel/prednisone/bevacizumab (524) vs. docetaxel/prednisone (526)	22.6 vs. 21.5 mo, HR 0.91 (95% CI 0.78 to 1.05), p=0.181	PFS: 9.9 vs. 7.5 mo, HR 0.80 (95% CI 0.71 to 0.91), p<0.001	
Sonpavde2011Ab (37)	Docetaxel/prednisone/AT-101 vs. docetaxel/prednisone (n=221)	17.8 vs. 17.5 mo, HR 1.06 (95% CI 0.72 to 1.55)	PFS: 11.0 vs. 10.3 mo, HR 0.88 (95% CI 0.63 to 1.22)	
Quinn2012Ab (38)	Docetaxel/atrasentan vs. Docetaxel/placebo (n=991)	18 vs. 17 mo, HR 1.01 (95% CI 0.87 to 1.18), p=0.88	PFS: 10 vs. 10 mo, HR 1.03 (95% CI 0.90 to 1.19), p=0.64	
Docetaxel plus Immunotherapy				
Higano2009Ab (22)	GVAX vs. docetaxel/prednisone (n=626)	20.7 vs. 21.7 mo, HR 1.03 (95% CI 0.83 to 1.28), p=0.78		
Small2009Ab (23)	GVAX/docetaxel vs. docetaxel/prednisone (n=408)	12.2 vs. 14.1 mo, HR 1.70 (95% CI 1.15 to 2.53), p=0.0076†		
Docetaxel plus Calcitriol				
Beer2007 (39) (ASCENT)	Calcitriol/docetaxel/dexamethasone (125) vs. docetaxel/dexamethasone (125)	24.5 (estimated) vs. 16.4 mo, adjusted HR 0.67 (95% CI 0.45 to 0.97), p=0.04		
Scher2011 (40) (ASCENT-2)	Calcitriol/docetaxel/dexamethasone (477) vs. prednisone/docetaxel/dexamethasone (476)	17.8 v.s 20.2 mo, univariate HR 1.42, P=0.0021; multivariate HR 1.33, p=0.019†		

*As a phase II study, response rates in comparable patients were established, but not statistical intergroup comparisons.
†Favours control group.
Ab = abstract; ASCENT = AIPC Study of Calcitriol Enhancing Taxotere; CALGB = Cancer and Leukemia Group B; CI = confidence interval; EORTC = European Organisation for Research and Treatment of Cancer; HR = hazard ratio; mo = month; OS = overall survival; PFS = progression free survival; TAX = taxotere; TIPC = Taxotere in Prostate Cancer; TTP = time to progression.

Table 4. Docetaxel alone or in combination: PSA and objective tumour response

Study reference	Treatment arms	PSA response	Objective response

Study reference	Treatment arms	PSA response	Objective response
Docetaxel with/without Estramustine			
Fossa2007 (30) (TIPC)*	Docetaxel/prednisolone (71) vs. prednisolone (63)	PSA decline ≥50% at 6 wk, 54% vs. 26% At 12 wk, 69% vs 35%	
Machiels2008 (32)	Docetaxel/estramustine/prednisone (75) vs. docetaxel/prednisone (75)	PSA decline ≥50% at ≥4 wk, 73% vs. 69%, p=0.302	26% vs. 23%, p>0.99
Kellokumpu2011Ab (33)	Docetaxel q 2 wk vs. docetaxel q 3 wk (n=361)	23% vs. 23%	
Docetaxel plus Targeted Therapy			
Mathew2007 (34)	Docetaxel/imatinib (57) vs. docetaxel (59)	PSA decline ≥50% at any time, 28% vs. 37%, p=0.37	8% vs. 13%, p=0.64
Sternberg2009b (35) (EORTC)	Docetaxel/oblimersen (58) vs. docetaxel (57)	37% vs. 46%	24% vs. 18%
Kelly2012 (36) (CALGB 90401)	Docetaxel/prednisone/bevacizumab (524) vs. docetaxel/prednisone (526)	PSA decline ≥50%, 69.5% vs. 57.9%, p=0.0002	49.4% vs. 35.5%, p=0.0113
Sonpavde2011Ab (37)	Docetaxel/prednisone/AT-101 vs. docetaxel/prednisone (n=221)	PSA decline ≥50%, 54% vs. 46%	
Quinn2012Ab (38)	Docetaxel/atrasentan vs. Docetaxel/placebo (n=991)	40% vs. 41%, p=0.88	14% vs. 14%, p=1.0
Docetaxel plus Calcitriol			
Beer2007 (39) (ASCENT)	Calcitriol/docetaxel/dexamethasone (125) vs. docetaxel/dexamethasone (125)	PSA decline >50% within 6 mo of enrolment, 58% vs. 49%, p=0.16 PSA decline >50% at any time, 63% vs. 52%, p=0.07 Time to PSA response: Median 2.9 vs. 5.3 mo, p=0.06	29% vs. 24%, p=0.51

*As a phase II study, response rates in comparable patients were established, but not statistical intergroup comparisons.
Ab = abstract; ASCENT = AIPC Study of Calcitriol Enhancing Taxotere; CALGB = Cancer and Leukemia Group B; EORTC = European Organisation for Research and Treatment of Cancer; mo = month; PSA = prostate specific antigen; TIPC = Taxotere in Prostate Cancer; wk = week.

Post-docetaxel

Cytotoxic Drugs

Two trials evaluated cytotoxic drugs in patients with progressive disease after docetaxel (43,44). In the SPARC trial, patients with progressive disease during or after previous chemotherapy (51% had received docetaxel) received satraplatin, 80 mg/m^2 once daily or placebo in addition to prednisone, 5 mg twice daily (43). Satraplatin recipients also received antiemetic prophylaxis (granisetron, 1 mg twice daily). The primary endpoint of progression free survival was greater in the satraplatin group, but the groups did not differ for the other *a priori* primary endpoint of overall survival. There was a longer time to pain progression (secondary endpoint) in the satraplatin group than in the placebo group (median 66.1 vs. 22.3 wk, HR 0.64, 95% CI 0.51 to 0.79, p<0.001). The prespecified exploratory endpoints of PSA response and tumour response also favoured the satraplatin group. Health-related quality of life and palliative response rates were not reported. Satraplatin was associated with higher rates of hematologic toxicities (p<0.05) and gastrointestinal disorders (p<0.001) than was placebo. Serious adverse effects of all grades and those of grade 3 or higher were also more common with satraplatin.

The TROPIC trial allocated patients who had progressive disease during or after previous docetaxel to cabazitaxel, 25 mg/m^2 or mitoxantrone, 12 mg/m^2 in addition to prednisone, 10 mg daily (44). The primary endpoint of overall survival was statistically significantly longer in the cabazitaxel group (HR 0.70, 95% CI 0.59 to 0.83, p<0.0001). The secondary endpoints of progression free survival, PSA response, and objective tumour response also favoured cabazitaxel. The median time to PSA progression was longer in the

cabazitaxel group (6.4 vs 3.1 mo, HR 0.75, 95% CI 0.63 to 0.90, p=0.001). There was no statistically significant difference between groups in time to pain progression (HR 0.91, 95% CI 0.69 to 1.19, p=0.52). Cabazitaxel was associated with more hematological and gastrointestinal adverse effects than was mitoxantrone. Eighteen patients (5%) receiving cabazitaxel died within 30 days of the last infusion, seven as a result of neutropenia and its consequences.

Targeted Therapy

One trial evaluated targeted therapy in post-docetaxel patients (45). Patients were allocated to prednisone, 5 mg twice daily plus sunitinib, 37.5 mg once daily or prednisone and placebo. The study was terminated early at the second planned interim analysis for futility, because high rates of disease progression, adverse events, and withdrawal of consent were observed. The primary endpoint of overall survival was not improved with sunitinib. Progression free survival and objective response both favoured sunitinib. The occurrence of adverse effects in patients receiving sunitinib was one of the reasons for early termination of the trial (21.4% compared with 5.9% in the placebo group). The most common grade 3 or higher adverse effects were fatigue (18.8% vs 7.3%) and anemia (6.2% vs 5.5%).

Hypercastration

Two trials evaluated hypercastrative agents in post-docetaxel patients (11,46). The COU-AA-301 trial evaluated a CYP17 inhibitor, abiraterone, in post-docetaxel patients who had previously received docetaxel (11). Patients were allocated to abiraterone acetate, 1 g once daily or placebo in addition to prednisone, 5 mg twice daily. At the preplanned interim analysis, the primary endpoint of overall survival was statistically significantly longer in the abiraterone group (14.8 vs. 10.9 mo, HR 0.65 [95% CI 0.54 to 0.77], p<0.001) (11). At a median of 20.2 months, the superiority of abiraterone was sustained (49). The secondary endpoints of PFS, PSA response, and objective response also favoured abiraterone. The median time to PSA progression was longer in the abiraterone group than the placebo group (10.2 vs. 6.6 mo, HR 0.58, [95% CI 0.46 to 0.73], p<0.001). Abiraterone acetate had a favourable safety profile, and was associated with a low rate of drug discontinuation or dose reduction (11). It was associated with higher incidence of urinary tract infection, edema, and hypokalemia (p≤0.02), but these were primarily grade 1 or 2 events. The most common adverse effects were fatigue, back pain, nausea, constipation, bone pain, and arthralgia, and these occurred at a similar rate in the two groups.

The AFFIRM trial compared the androgen receptor signalling inhibitor enzalutamide (MDV3100) with placebo in 1199 men with mCRPC who had received ≤2 regimens of docetaxel-based chemotherapy (46). The results at a planned interim analysis of 520 death events showed a statistically significant improvement in overall survival with enzalutamide, reducing the risk of death by 37% (median overall survival 18.4 vs. 13.6 mo, p<0.0001). Radiographic progression-free survival, PSA response, and objective response were also improved. Time to PSA progression was 8.3 months in the enzalutamide group and 3.0 months in the placebo group (HR 0.25, 95% CI 0.20 to 0.30, p<0.0001). The study has been unblinded and the placebo group patients offered enzalutamide. Enzalutamide was associated with higher incidence of fatigue, diarrhea, and hot flashes than was placebo (46). Adverse events greater than grade 3 were cardiac disorders (0.9% vs. 2%), fatigue (6% vs. 7%), seizure (0.6% vs. 0%), and liver function abnormalities (0.4% vs. 0.8%).

Among the trials of systemic therapies after docetaxel therapy, favorable survival outcomes were observed with cabazitaxel, abiraterone, and enzalutamide. Cabazitaxel was associated with greater toxicity, while abiraterone and enzalutamide had less severe adverse

effects. Satraplatin and sunitinib both extended progression-free survival but did not improve overall survival.

Table 5. Post-docetaxel therapies: Survival outcomes

Study reference	Treatment arms	OS (median)	PFS (median)
Cytotoxic Drugs			
Sternberg2009 (43) (SPARC)	Prednisone/satraplatin (635) vs. prednisone (315)	61.3 vs. 61.4 wk, HR 0.98 (95% CI 0.84 to 1.15), p=0.80	PFS: 11.1 vs. 9.7 wk, HR 0.67 (95% CI 0.57 to 0.77), p<0.001
de Bono2010 (44) (TROPIC)	Prednisone/cabazitaxel (378) vs. prednisone/mitoxantrone (377)	15.1 vs. 12.7 mo, HR 0.70 (95% CI 0.59 to 0.83), p<0.0001	PFS: 2.8 vs. 1.4 mo, HR 0.74 (95% CI 0.64 to 0.86), p<0.0001 Time to tumour progression: Median 8.8 vs. 5.4 mo, HR 0.61 (95% CI 0.49 to 0.76), p<0.0001
Targeted Therapy			
Ou2011Ab (45)	Prednisone/sunitinib (584) vs. prednisone (289)	13.1 vs. 12.8 mo, HR 1.03 (95% CI 0.80 to 1.32), p=0.5813	PFS: 5.6 vs. 3.7 mo, HR 0.76 (95% CI 0.61 to 0.95), p=0.0077
Hypercastration			
de Bono2011 (11) Fizazi2011Ab (49) (COU-AA-301)*	Prednisone/abiraterone acetate (797) vs. prednisone (398)	15.8 vs. 11.2 mo, HR 0.74 (95% CI 0.64 to 0.86), p<0.0001	PFS 5.6 vs. 3.6, HR 0.67 (95% CI 0.59 to 0.78), p<0.001
de Bono2012Ab (46) (AFFIRM)	Enzalutamide (800) vs. placebo (399)	18.4 vs. 13.6 mo, HR 0.63 (95% CI 0.53 to 0.75), p<0.0001	8.3 vs. 2.9 mo, HR 0.40 (95% CI 0.35 to 0.47), p<0.0001

*Overall survival results from Fizazi2011Ab (49); PFS results from deBono2011 (11).
Ab = abstract; CI = confidence interval; HR = hazard ratio; mo = month; OS = overall survival; PFS = progression free survival; SPARC = Satraplatin and Prednisone Against Refractory Cancer; TROPIC = Treatment of Hormone-Refractory Metastatic Prostate Cancer; wk = week.

Table 6. Post-docetaxel therapies: PSA and objective tumour response

Study reference	Treatment arms	PSA response	Objective response
Cytotoxic Drugs			
Sternberg2009 (43) (SPARC)	Prednisone/satraplatin (635) vs prednisone (315)	25.4% vs 12.4%, P<0.001 (exploratory endpoint)	8.0% vs 0.7%, P=0.002 (exploratory endpoint)
deBono2010 (44) (TROPIC)	Prednisone/cabazitaxel (378) vs prednisone/mitoxantrone (377)	PSA decline ≥50% at ≥3 wk, 39.2% vs 17.8%, P=0.0002	14.4% vs 4.4%, P=0.0005
Targeted Therapy			
Ou2011Ab (45)	Prednisone/sunitinib (584) vs prednisone (289)		5.5% vs 1.9%, P=0.0495
Hypercastration			
de Bono2011 (11) (COU-AA-301)	Prednisone/abiraterone acetate (797) vs prednisone (398)	PSA decline ≥50% at ≥4 wk, 29.1% vs 5.5%, P<0.001	14.0% vs 2.8%, P<0.001
deBono2012Ab (46) (AFFIRM)	Enzalutamide (800) vs placebo (399)	54% vs 1.5%, P<0.0001	PR+CR: 25.1%+3.8% vs 2.9%+1.0%, P<0.0001

Ab=abstract; CR=complete response; PR=partial response; PSA=prostate specific antigen; SPARC=Satraplatin and Prednisone Against Refractory Cancer; TROPIC=Treatment of Hormone-Refractory Metastatic Prostate Cancer.

ONGOING TRIALS

Investigator	Sponsor	Title	Identifier	Status
Arlen PM	National Cancer Institute	Vaccine therapy with or without docetaxel in treating patients with metastatic prostate cancer (Phase II)	NCT00045227	Completed
Gulley JL Kantoff P BN	ImmunoTherapeutics, Inc	A Phase 3 Efficacy Study of a Recombinant Vaccinia Virus Vaccine to Treat Metastatic Prostate Cancer (Prospect) (Phase III - PROSTVAC-V/F-TRICOM +/- GM-CSF)	NCT01322490	Recruiting
	Bristol-Myers Squibb	Phase 3 study of immunotherapy to treat advanced prostate cancer (Phase III – ipilimumab vs placebo)	NCT01057810	Ongoing, not recruiting
	Bristol-Myers Squibb	Study of immunotherapy to treat advanced prostate cancer (Phase III – ipilimumab vs placebo)	NCT00861614	Ongoing, not recruiting
Fizazi K Institut Gustave Roussy	AstraZeneca	A phase III trial of ZD4054 (zibotentan) (endothelin A antagonist) and docetaxel in metastatic hormone resistant prostate cancer (ENTHUSE M1C) (Phase III)	NCT00617669	Completed
	Bristol-Myers Squibb	Randomized study comparing docetaxel plus dasatinib to docetaxel plus placebo in castration-resistant prostate cancer (READY) (Phase III)	NCT00744497	Ongoing, not recruiting
Carducci MA Johns Hopkins Kimmel Cancer Center	Active Biotech	A study of tasquinimod in men with metastatic castrate resistant prostate cancer (Phase III – tasquinimod vs placebo)	NCT01234311	Ongoing, not recruiting
Barton D	Celgene Corporation	Study to evaluate safety and effectiveness of lenalidomide in combination with docetaxel and prednisone for patients with castrate-resistant prostate cancer (Mainsail) (Phase III)	NCT00988208	Ongoing, not recruiting
	Sanofi-Aventis	Aflibercept in combination with docetaxel in metastatic androgen independent prostate cancer (VENICE)	NCT00519285	Completed

		(Phase III – aflibercept vs placebo)		
Beer TM Oregon Health and Science University	OncoGenex Technologies Teva Pharmaceuticals	A study evaluating the pain palliation benefit of adding custirsen to docetaxel retreatment or cabazitaxel as second line therapy in men with metastatic castrate resistant prostate cancer (SATURN) (Phase III – custirsen vs placebo)	NCT01083615	Ongoing, not recruiting
Higano C Seattle Cancer Care Alliance	OncoGenex Technologies Teva Pharmaceuticals	Comparison of docetaxel/prednisone to docetaxel/prednisone in combination with OGX-011 in men with prostate cancer (SYNERGY) (Phase III – docetaxel/prednisone +/- custirsen)	NCT01188187	Ongoing, not recruiting
	Medivation, Inc	A safety and efficacy study of oral MDV3100 in chemotherapy-naive patients with progressive metastatic prostate cancer (PREVAIL) (Phase III – MDV3100 vs placebo)	NCT01212991	Ongoing, not recruiting
	Millennium Pharmaceuticals, Inc	Study comparing orteronel plus prednisone in patients with chemotherapy-naive metastatic castration-resistant prostate cancer (Phase III – prednisone +/- orteronel)	NCT01193244	Ongoing, not recruiting
	Millennium Pharmaceuticals, Inc	Study comparing orteronel plus prednisone in patients with metastatic castration-resistant prostate cancer (Phase III – prednisone +/- orteronel)	NCT01193257	Completed

DISCUSSION

This systematic review updates a previous systematic review evaluating nonhormonal systemic therapies for mCRPC (9). That earlier review identified 28 RCTs published between 1979 and 2004, and established docetaxel-based chemotherapy as the only treatment to extend overall survival in men with mCRPC. Two large RCTs reported improvement in overall survival with docetaxel given every 3 weeks compared with mitoxantrone-prednisone, and docetaxel was also associated with improved health-related quality of life and pain response (9).

In 2012, docetaxel is still considered the reference systemic therapy for patients with mCRPC, with investigational efforts occurring in pre-docetaxel, docetaxel combination, and post-docetaxel therapeutic domains. Among pre-docetaxel targeted therapy regimens for

mCRPC, no clear benefits with endothelin-A inhibitors atrasentan or zibotentan were observed. Tasquinimod, a new antitumour agent, showed promising improvement in median progression-free survival (26), but these results will require confirmation in a phase III trial currently recruiting patients with a planned sample size of 1200 participants. The IMPACT study, a phase III placebo-controlled trial evaluating sipuleucel-T immunotherapy, showed a 4.1-month improvement in median overall survival (18). However, no significant differences in radiographic disease progression or PSA response rates were observed between the two groups. These observations, uncertainty about mechanism of action, and concerns about increased mortality due to the effects of immunodepletion in the control arm of the trial (50), have created skepticism about the clinical value of sipuleucel-T.

A trial of abiraterone acetate in pre-docetaxel patients was presented at a recent scientific symposium (the COU-AA-302 study [28]). Differences were observed in radiographic progression-free survival, overall survival, and secondary endpoints that constitute evidence of clinical benefit as well as continued evidence of favorable safety in patients receiving abiraterone acetate plus prednisone compared with those receiving placebo plus prednisone.

An updated survival analysis of the TAX 327 study confirmed the survival advantage associated with docetaxel, 75 mg/m^2 over mitoxantrone (31). Subsequent RCTs assessing docetaxel scheduling with and without the addition of estramustine have not shown any clinically significant advantages. In the 2005 systematic review, of the six RCTs that studied estramustine, either alone or combined with another agent, none showed an improvement in overall survival, and only one showed a longer time to progression with combination estramustine/vinblastine (51). A recent meta-analysis addressed whether the addition of estramustine to docetaxel-based chemotherapy conferred a benefit (20). No significant difference in overall survival was found, but an improvement in PSA response rate confirmed the results of the earlier studies. With respect to toxicity, the risk for grade 3 or 4 neutropenia, anemia, thrombocytopenia, diarrhea, nausea, mucositis, and vomiting was similar between the two groups.

Studies of combination therapy with docetaxel have been disappointing. The addition of bevacizumab to docetaxel did not extend survival (36). The addition of calcitriol looked promising in a phase II trial (39), but was associated with shorter overall survival in a recent phase III trial (40). The addition of GVAX also had a negative effect on survival (23). Phase III trials with docetaxel plus aflibercept, dasatinib, zibotentan, atrasentan, and lenalidomide are ongoing.

Among post-docetaxel therapies, the cytotoxic drug cabazitaxel (44), the hypercastrative drugs abiraterone acetate (11), and the androgen receptor signal inhibitor enzalutamide (46) all extended overall and progression-free survival. In fully assessing these results, one needs to acknowledge that cabazitaxel was compared with mitoxantrone, a cytotoxic agent with known activity in men with CRPC, while abiraterone and enzalutamide were compared with placebo, plus or minus low-dose prednisone. Notwithstanding these considerations, the cabazitaxel survival benefit was associated with increased toxicity and an apparent lack of improvement in pain response. Very favourable toxicity profiles were reported with both abiraterone and enzalutamide, and improved time to pain and fatigue progression reported with abiraterone.

CONCLUSIONS

In men with mCRPC who have minimal metastatic burden and symptoms, no therapy with unequivocal effectiveness has yet been reported. Promising results with tasquinimod support further investigation but not routine clinical use. Despite regulatory approval, recent questions raised about sipuleucel-T suggest a need for further evaluation in well-designed,

pragmatic trials before routine adoption into clinical practice. Abiraterone acetate administered prior to docetaxel chemotherapy showed a statistically significant improvement in progression-free survival over placebo and a trend towards improvement in overall survival. However, the magnitude of overall survival benefit will remain unknown, as the trial was unblinded early and placebo group patients allowed to cross over to abiraterone.

In men with mCRPC who are candidates for docetaxel chemotherapy, the conclusion of the current review remains unchanged from 2005. No RCT results reported to date support the routine addition of agents other than low-dose prednisone to docetaxel chemotherapy for the purpose of improving effectiveness.

Cabazitaxel, abiraterone acetate, and enzalutamide have all been shown to improve overall survival in men who progress on or after docetaxel. None of these agents have been compared with each other. Abiraterone and enzalutamide are oral agents that have shown the most favourable toxicity profiles. To date, abiraterone has reported the most favourable data with regard to palliative effects in this population and, on this basis, would be considered the agent of first choice for most patients. However, more data about the palliative effects of enzalutamide are expected and are likely to show similar results as observed with abiraterone. Not all patients respond to either abiraterone or enzalutamide, and all patients eventually progress when treated with these agents. For these patients who have an adequate performance status and marrow function, cabazitaxel should be considered. Further research to determine the optimal choice, sequence, or even combination of these agents is necessary. As always, patients should be encouraged to participate in clinical trials.

CONFLICT OF INTEREST

In accordance with the PEBC Conflict of Interest Policy, the authors were asked to disclose potential conflicts of interest.

- DAL reported he has received $5000.00 or more in a single year in advisory boards and travel grants from Janssen and Sanofi-Aventis. He has also received research grants as a principal or co-investigator from Sanofi-Aventis.
- EW reported he has received $5000.00 or more in a single year from Sanofi-Aventis for consultant and speaker honoraria.
- SJH reported he has received $5000.00 or more in a single year from Janssen for speaker honoraria. He has also been involved as a local principal investigator or local co-investigator in clinical trials of abiraterone and enzalutamide.

A waiver of the PEBC Conflict of Interest policy was obtained from the PEBC director for the three aforementioned authors, because the authorship was determined before the latest revisions to the policy.

- CWD declared no conflict of interest.

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Appendix 4. Search Strategy.

Methods terms
Publication types, MeSH terms, text words for meta-analyses, systematic reviews, practice guidelines, and RCTs

AND

Terms for castration-resistant prostate cancer
Prostatic neoplasms or prostate carcinoma or prostate cancer
Prostat:.tw. and (cancer or carcinoma or adenocarcinoma or neoplasm: or tumo?r:.tw.)
AND
(castrat: or hormone: or androgen or endocrin:).tw. AND (resist: or refract: or independent).tw.
(CRPC or AIPC or HRPC).tw.

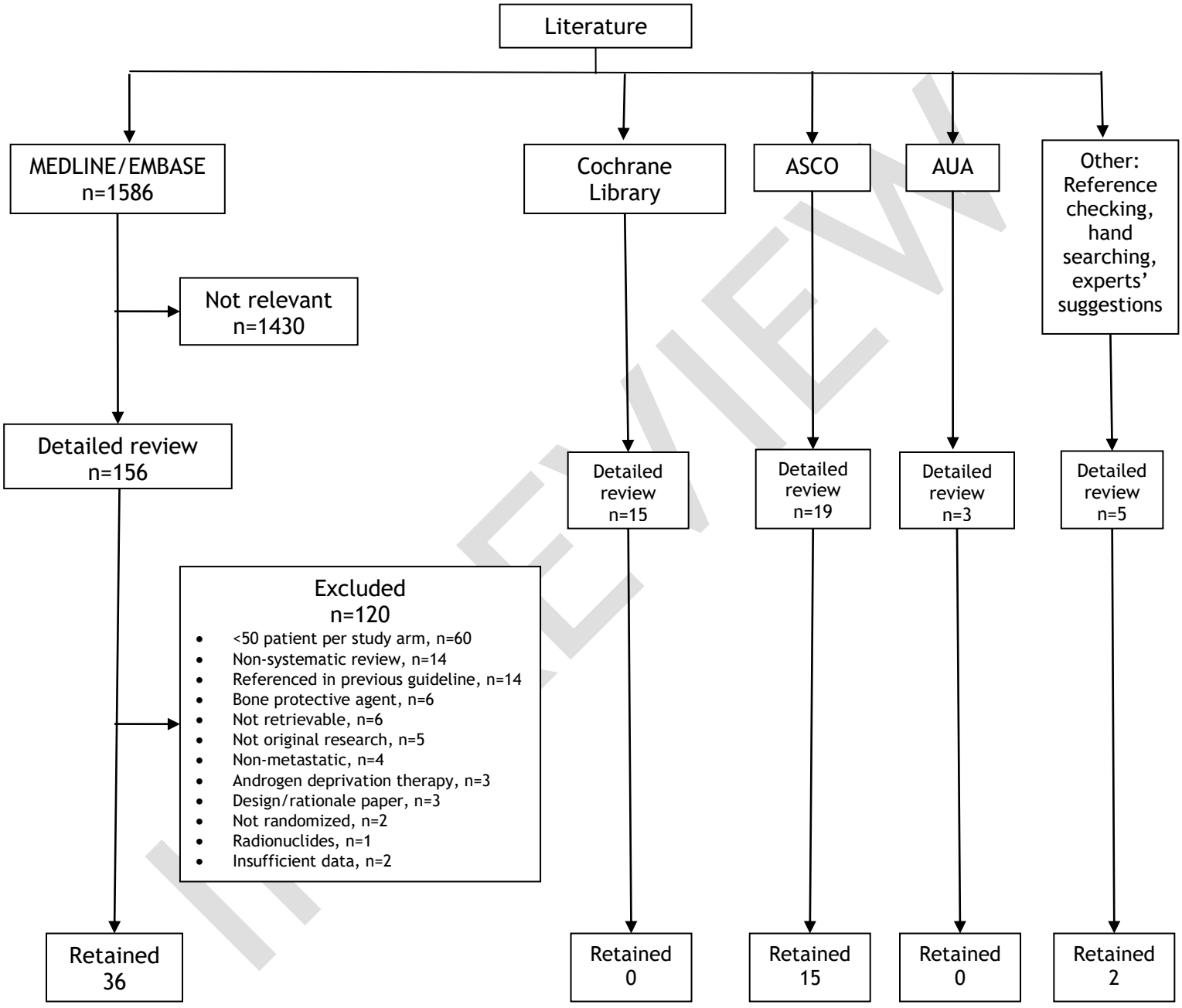
AND

Terms for drug interventions
Antineoplastic agent or cancer combination chemotherapy or drug therapy, combination
(hormon: or nonhormon: or non-hormon:).tw.
systemic.tw.
abiraterone
sipuleucel-T or sipuleucel
provenge
cabazitaxel
jevtana

AND

2003 to 2012
English only

Appendix 5. Literature Search Results.



Appendix 6. Methodological Quality of Included RCTs.

Study reference	Generation of allocation sequence reported	Allocation concealment	Blinding	Intention to treat	Withdrawals described	Industry funding	Statistical power and target sample size	Loss to follow-up	Baseline characteristics balanced	Terminated early
Pre-docetaxel										
Targeted Therapy										
Carducci2007 (24) Phase III	Not reported	Not reported	Yes	Yes	Not reported	Yes	An estimated 650 events would be needed to achieve 90% power at the two-sided 0.05 level of significance to detect a treatment difference.	Not reported	Yes	Yes
James2010 (25) Phase II	Yes	Not reported	Yes	Yes	Yes	Yes	To detect a 50% difference in median time to progression, equivalent to detecting an HR of 0.67 at the 20% significance level (two-sided) with 80% power, a total of 165 progression events were required.	0	Yes, except for greater number of bone metastases in zibotentan 15 mg group	No
Pili2011 (26) Phase II	Yes	Not reported	Yes	Yes	Not reported	Not reported	Sample size was determined using a null hypothesis for progression-free proportion (PFP) at 6 months in the placebo arm of 10% and hypothesized PFP of 30% in the experimental arm, with assumptions of 90% power and two-sided α error of 0.05. Assuming a 5% dropout rate, the planned sample size was 67 in the placebo arm and 133 in the TASQ arm.	5	No, an imbalance of several baseline criteria favoured placebo	No
Nelson2011Ab (27) Phase III	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	At least 263 deaths were required for formal analysis. If the true HR for zibotentan vs placebo was 0.67, the analysis would have 90% power to show a statistically significant effect in OS at the 5% level.	Not reported	Yes	No
Immunotherapy										
Kantoff2010 (18) (IMPACT) Phase III	Yes	Not reported	Yes	Yes	Yes	Yes	500 pts needed enrolled to analyze 304 deaths, providing a power of at least 88% to detect a relative risk reduction for death of 31% in the	6	Yes	No

Study reference	Generation of allocation sequence reported	Allocation concealment	Blinding	Intention to treat	Withdrawals described	Industry funding	Statistical power and target sample size	Loss to follow-up	Baseline characteristics balanced	Terminated early
							sipuleucel-T group compared with placebo (HR 0.69) with the use of a two-sided α of 0.05.			
Ryan2012Ab (28) (COU-AA-302) Phase III	Not reported	Not reported	Yes	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	No
Docetaxel Alone or in Combination										
Docetaxel with/without Estramustine										
Berry2006 (29) (SWOG 99-16) Phase III	Yes	Not reported	No	Yes	Yes	In part	The study had 80% power to detect an improvement of 33% in median survival in the docetaxel/estramustine group compared with mitoxantrone/prednisone, with the use of a one-sided log-rank test at a P value of 0.025.	0	Yes	No
Fossa2007 (30) (TIPC) Phase II	Not reported	Not reported	No	No	Yes	Yes	91 pts in each arm were required to document a difference in biochemical response between arm A (expected response: 40%) and arm B (expected response: 20%; α=0.05, ß=0.20).	25 pts deemed ineligible 5 pts deemed inevaluable	Yes	Yes
Berthold2008 (31) (TAX 327) Phase III	Yes	Yes	No	Yes	Yes	Yes	The study had 90% power to detect an HR of 0.75 for death in the docetaxel groups compared with mitoxantrone, with a two-sided type I error of 0.05 analyzed by intention to treat.	111	Yes	No
Machiels2008 (32) Phase III	Yes	Not reported	No	No	Yes	Yes	The study was powered to determine whether the addition of estramustine to docetaxel would improve the PSA response rate by 25%, assuming a PSA response rate of 40% in docetaxel and 65% in docetaxel/estramustine. PSA response was defined as a PSA decline of ≥50%. Using a two-sided test with a type I error rate of 5% and a statistical power of 80%, 136 pts were	3	Yes	No

Study reference	Generation of allocation sequence reported	Allocation concealment	Blinding	Intention to treat	Withdrawals described	Industry funding	Statistical power and target sample size	Loss to follow-up	Baseline characteristics balanced	Terminated early
							needed.			
Kellokumpu2011Ab (33) Phase III	Yes	Yes	No	Not reported	Not reported	Not reported	Planned sample size of 348 pts.	Not reported	Yes	No
Docetaxel plus Targeted Therapy										
Mathew2007 (34) Phase II	Yes	Not reported	Yes	Yes	Yes	Yes	The study had 80% power to detect improvement in median PFS from 4.5 to 7.5 mo.	Not reported	Not reported	Yes
Sternberg2009b (35) (EORTC) Phase II	Yes	Yes	No	No	Yes	Yes	The sample size was determined to ensure 90% power of rejecting the null hypothesis that, within the docetaxel-oblimersen group, either the PSA response rate was ≤30% or the major toxic event rate was ≥45% at the one-sided 10% significance level, under the alternative that the PSA response rate was ≥50% and the toxicity rate was ≤25%. A treatment arm was declared sufficiently active and safe if the 80% exact CI around the PSA response rate excluded 30% and that around the major toxic event rate excluded 45%.	Not reported	No	No
Kelly2012 (36) (CALGB 90401) Phase III	Yes	Yes	Yes	Yes	Yes	No	The trial was designed with 86% power to detect a 21% decrease in the hazard rate of death (equivalent to an increase in median OS from 19 mo to 24 mo) assuming a two-sided significance level of 0.05.	0	Yes	No
Sonpavde2011Ab (37) Phase II	Not reported	Not reported	Yes	Not reported	Not reported	Not reported	221 pts were planned for 110 events (80% power).	Not reported	Yes	No
Quinn2012Ab (38) Phase III	Yes	Not reported	Yes	Not reported	Not reported	Not reported	930 patients were needed to detect a 25% increase in median OS with docetaxel/atrasentan (1-sided log-rank, α=0.025, 87% power)	Not reported	Not reported	No

Study reference	Generation of allocation sequence reported	Allocation concealment	Blinding	Intention to treat	Withdrawals described	Industry funding	Statistical power and target sample size	Loss to follow-up	Baseline characteristics balanced	Terminated early
Docetaxel plus Immunotherapy										
Higano2009Ab (22) Phase III	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Yes	Yes
Small2009Ab (23) Phase III	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Yes	Yes
Docetaxel plus Calcitriol										
Beer2007 (39) (ASCENT) Phase II	Yes	Not reported	Yes	Yes	No withdrawals	Yes	A sample size of at least 116 pts per treatment group was expected to provide 85% power to detect a 20% absolute increase in the PSA response rate (from 45% to 65%) with a two-sided significance level of 0.045.	0	Yes	No
Scher2011 (40) (ASCENT-2) Phase III	Yes	Yes	Yes	Yes	Yes	Yes	Planned enrollment was amended from 900 to 1200 pts in April 2007 to increase the power from 0.85 to 0.90. The final enrollment target was based on the assumption of a median survival of 18.9 mo in the control group and an HR for mortality of ≤0.78 using a two-sided significance level of 0.05, with a power of 90%.	6	Yes	Yes
Post-docetaxel										
Cytotoxic Drugs										
Sternberg2009 (43) (SPARC) Phase III	Yes	Not reported	Yes	Yes	Yes	Yes	The trial was designed to have 90% power to detect a 30% increase in time to median OS of 12 mo in the placebo arm at a two-sided significance level of 0.05. 912 pts were to be accrued to observe 700 OS events within the 36-mo study period. Similarly, 694 events were required for the PFS end point to provide a 30% improvement in HR at two-sided significance level of 0.05 and 90% power.	1	Yes	No
de Bono2010 (44)	Yes	Yes	Yes	Yes	Yes	Yes	The study required an	2	Yes	No

Study reference	Generation of allocation sequence reported	Allocation concealment	Blinding	Intention to treat	Withdrawals described	Industry funding	Statistical power and target sample size	Loss to follow-up	Baseline characteristics balanced	Terminated early
(TROPIC) Phase III							estimated sample size of 720 pts (360 per group) to detect a 25% reduction in the HR for death in the cabazitaxel group relative to the mitoxantrone group with 90% power, with a two-sided log-rank test at a significance level of 0.05 and on the assumption of 8 mo median OS in the mitoxantrone group.			
Targeted Therapy										
Ou2011Ab (45) Phase III	Not reported	Not reported	Yes	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Yes
Hypercastration										
de Bono2011 (11) (COU-AA-301) Phase III	Yes	Not reported	Yes	Yes	Yes	Yes	The planned sample of approximately 1158 pts provided 85% power to detect an HR of 0.80 for death in the group receiving abiraterone acetate plus prednisone as compared with the group receiving placebo plus prednisone.	0	Yes	No
de Bono2012Ab (46) (AFFIRM)	Not reported	Not reported	Yes	Not reported	Not reported	Yes	Not reported	Not reported	Not reported	No

Ab=abstract; ASCENT=AIPC Study of Calcitriol Enhancing Taxotere; CALGB=Cancer and Leukemia Group B; EORTC=European Organisation for Research and Treatment of Cancer; HR=hazard ratio; IMPACT=Immunotherapy for Prostate Adenocarcinoma Treatment; mo=month; OS=overall survival; PFS=progression free survival; PSA=prostate specific antigen; pts=patients; SPARC=Satraplatin and Prednisone Against Refractory Cancer; SWOG=Southwest Oncology Group; TAX=taxotere; TIPC=Taxotere in Prostate Cancer; TROPIC=Treatment of Hormone-Refractory Metastatic Prostate Cancer; TTP=time to progression.

Evidence-based Series #3-15 Version 2: Section 2B

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Non-Hormonal Systemic Therapy in Men with Metastatic Hormone-Refractory Prostate Cancer: Original Evidence Summary 2005

E. Winquist, T. Waldron, S. Berry, D.S. Ernst, S. Hotte, H. Lukka, and members of the Genitourinary Cancer Disease Site Group

The systematic review that makes up Section 2B of this Evidence-Based Series was originally completed in November 2005 and contains the relevant data on the topic as of that time. Section 2A of this Evidence-Based Series is a systematic review of the relevant data up to June 2012.

Report Date: November 1, 2005

QUESTION

Which non-hormonal systemic therapies are most beneficial and should be recommended for the treatment of hormone-refractory prostate cancer (HRPC)? First-line cytotoxic and non-cytotoxic systemic therapies are the agents of interest. The use of bisphosphonates and radiopharmaceuticals are addressed in separate guideline reports and therefore are not considered further here. Overall survival, disease control (as assessed by measures such as progression-free survival, time-to-progression, time-to-treatment failure, and objective and prostatic-specific antigen [PSA] response rates), palliative response rate, quality of life, and toxicity are the outcomes of interest.

INTRODUCTION

Prostate cancer is the most frequently diagnosed cancer in Ontario. It is the fourth most common cause of cancer death in Ontario and the third most common cause of cancer death in men (1). One in four men diagnosed with prostate cancer eventually dies from the disease. Men with prostate cancer that has recurred after local therapy or disseminated distantly usually respond to androgen deprivation therapy (ADT). However, despite this treatment, most patients eventually experience disease progression within a median of 18 to 24 months (2).

Androgen independence is defined by disease progression despite ADT and may present as a continuous rise in serum PSA levels, the progression of pre-existing disease, and/or the appearance of new metastases. The prognosis of HRPC is associated with several factors, including performance status, presence of bone pain, extent of disease on bone scan, and

serum alkaline phosphatase levels (3). Bone metastases will occur in 90% of men with HRPC (4) and can produce significant morbidity, including pain, pathologic fractures, spinal cord compression, and bone marrow failure. Paraneoplastic effects are also common, including anemia, weight loss, fatigue, hypercoagulability, and increased susceptibility to infection. Thus, HRPC presents a spectrum of disease ranging from patients without metastases or symptoms with rising PSA levels despite ADT, to patients with metastases and significant debilitation due to cancer symptoms.

Historically, clinical management has been primarily palliative, with a focus on expectant management when possible and palliative interventions such as radiotherapy, radioisotopes, and chemotherapy when necessary. Mitoxantrone-prednisone chemotherapy is currently standard palliative treatment for men with HRPC symptomatic with pain, but this regimen is not associated with improvements in overall survival. New data emerging from large clinical trials of systemic therapy (i.e., docetaxel) provided the impetus for a guideline reviewing the value of chemotherapy and other non-hormonal agents in HRPC.

METHODS

This systematic review was developed by Cancer Care Ontario's Program in Evidence-based Care (PEBC). Evidence was selected and reviewed by five members of the PEBC Genitourinary Cancer Disease Site Group (GU DSG) and methodologists.

This systematic review is a convenient and up-to-date source of the best available evidence on non-hormonal systemic therapy for HRPC. The body of evidence in this review is primarily comprised of mature randomized controlled trial data. That evidence forms the basis of a clinical practice guideline developed by the GU DSG. The systematic review and companion practice guideline are intended to promote evidence-based practice in Ontario, Canada. The PEBC is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

Literature Search Strategy

MEDLINE (1966 through February week 2 2005) and EMBASE (1980 through 2005, week 8) databases were searched for relevant papers. MEDLINE was searched using the following medical subject headings: "prostatic neoplasms", "drug therapy", "antineoplastic agents", and "drug therapy, combination"; EMBASE was searched using the following Excerpta Medica tree terms: "prostate tumour", "prostate cancer", "drug therapy", "antineoplastic agent", "drug combination", and "combination chemotherapy". In each database those subject headings were combined with the following disease and treatment-specific text words: "prostat: cancer", "prostat: tumo?r", "prostat: carcinoma", and "chemotherapy". Those terms were then combined with search terms for the following publication types and study designs: practice guidelines, systematic reviews, meta-analyses, reviews, randomized controlled trials, and controlled clinical trials.

In addition, the Cochrane Library databases (2004, Issue 4) and the conference proceedings of the American Society of Clinical Oncology (1999 through 2004) were searched for abstracts of relevant trials. The Canadian Medical Association Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp) and the National Guidelines Clearinghouse (http://www.guideline.gov/index.asp) were also searched for existing evidence-based practice guidelines.

Relevant articles and abstracts were selected and reviewed by five reviewers, and the reference lists from those sources were searched for additional trials, as were the reference lists from relevant review articles.

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they met the following criteria:

1. They were published reports or abstracts of randomized controlled trials (RCTs) or meta-analyses comparing a non-hormonal systemic therapy or combination (i.e., first-line cytotoxic and non-cytotoxic agents excluding bisphosphonates and radiopharmaceuticals) with either placebo or other drug regimens.
2. They included patients with HRPC and metastases, where HRPC was defined as clinical progression (either symptomatically, radiologically, or biochemically) in the presence of a castrate testosterone level.
3. They included a minimum of 50 patients per trial arm.
4. They reported on at least one of the following outcomes: overall survival, disease control (i.e., progression-free survival [PFS], time-to-progression [TTP], time-to-treatment failure [TTF], and objective tumour and PSA response), palliative or symptomatic response, quality of life, or toxicity.

or

5. They were published reports of systematic reviews or evidence-based guidelines that addressed the guideline question.

Synthesizing the Evidence

Reports of RCTs of systemic therapy in HRPC date back 30 years and are highly heterogeneous in terms of patient populations, interventions, and design. Many different drug interventions have been tested, including a variety of single-agent and combination chemotherapy regimens such as estramustine phosphate (EMP) and non-cytotoxic drugs such as liarazole, suramin, and atrasentan. What constitutes standard therapy in the control arms of trials has been controversial and has included placebo, corticosteroids, EMP, and cytotoxics. On the basis of those observations, quantitative statistical pooling of RCT data was felt inappropriate, and an interpretive summary of the data was planned with more weight given to RCTs that were adequately powered.

Although valuable for identifying potential anti-tumour activity, it is well recognized that small RCTs report less reliable results and that studies with positive results are more likely to be subsequently reported and published (5). Theoretically, the results of such trials require confirmation by larger pragmatic RCTs, but this does not always occur. After considering the endpoints of interest for this guideline, the GU DSG chose a minimum sample size of 50 patients per trial arm. The statistical justification for this is a minimum requirement for an RCT to be powered to reliably detect a difference between a response rate of 10% versus 30% with one-tailed α=0.05 and β=0.20 (i.e., power of 80%). RCTs without the ability to provide at least this level of discrimination were considered underpowered and their results potentially misleading with regard to the endpoints of interest. Because the natural history and management of HRPC has changed in the last three decades, more contemporary studies were emphasized in this guideline to provide clinicians with the most reliable evidence relevant to their current practice. Furthermore, more emphasis on the results of RCTs demonstrating internally consistent benefits in survival, palliation, and quality of life outcomes was planned. Statistical pooling of tumour response rates for docetaxel-based regimens was performed using Review Manager 4.2.3, available through the Cochrane Collaboration (6), because individual trials were inadequately powered to detect differences.

RESULTS

Literature Search Results

The literature search identified 83 unique RCTs that compared non-hormonal systemic treatments in HRPC. Fifty-five of those trials randomized less than 50 patients per arm and were considered ineligible (7-61) (Appendix 1). The remaining 28 trials were eligible for inclusion in the guideline (4,62-88) (Table 1). Twenty-four of those trials were published as full reports (4,62-79,81,82,84,86,87), and four were available only in abstract or poster presentation form (80,83,85,88). There were 22 two-arm and six three-arm trials, and two trials were labelled as randomized phase II reports (64,81). No published systematic reviews or evidence-based guidelines were identified.

Trial Characteristics

The 28 RCTs that form the basis of this guideline were published between 1979 and 2004 (Table 1). Across those trials, a total of 7627 eligible men were randomized, with the number of randomized patients per RCT ranging from 102 to 1006. Six trials were placebo-controlled (66,80,81,83,85,86), and four of those were also double-blind (66,80,81,86). Thirteen trials described the methods used to randomize patients (4,62,63,65,66,71,73-75,81,82,84,87), and 21 reported that treatment arms were balanced for important baseline prognostic factors (4,62,63,65-68,70-74,76-79,81,84-87). Twelve trials performed statistical analyses according to intent-to-treat (4,62,63,71,72,75,80,81,83,84,86,87). A minority of trials reported whether patients underwent antiandrogen withdrawal (AAWD) (62-65,70-72,81,84,87) and the percentage of patients who continued to receive luteinizing hormone-releasing hormone (LHRH) agonist during the study period (4,62,63,65,70-72,84,86,87). Twenty trials studied cytotoxic and eight studied non-cytotoxic drug interventions. Two cytotoxic trials studied agents belonging to multiple drug classes (76,88). For clarity, the cytotoxic trials are separated into the following drug classes: antimicrotubule-based regimens (nine trials), anthracendedione/anthracycline-based regimens (nine trials), and other chemotherapy (four trials). Trial descriptions (i.e., information on sample size, treatments arms, and the dosing, scheduling, and duration of treatment) are available in Appendices 2 through 5.

Table 1: Eligible trials contained in this practice guideline report.

References	No. of patients	Trial comparisons
Antimicrotubule-based chemotherapy (9 trials)		
Tannock, 2004 (4)	1006	docetaxel (75mg/m^2)/prednisone vs. docetaxel (30mg/m^2)/prednisone vs. mitoxantrone/prednisone
Petrylak, 2004 (62)	666	docetaxel/ EMP/dexamethasone vs. mitoxantrone/prednisone
Abratt, 2004 (63)	414	vinorelbine/hydrocortisone ± AGM vs. hydrocortisone ± AGM
Berry, 2004 (64)	166	paclitaxel/EMP vs. paclitaxel
Hudes, 1999 (65)	193	vinblastine/EMP vs. vinblastine
Iversen, 1997 (66)	129	EMP vs. placebo
Johansson, 1991 (67)	102	high-dose MPA vs. EMP
De Kernion, 1988 (68)	203	EMP vs. flutamide
Murphy, 1979 (69)	116	EMP/prednimustine vs. prednimustine
Anthracenedione/anthracycline-based chemotherapy (9 trials)		
Berry, 2002 (70)	119	mitoxantrone/prednisone vs. prednisone
Kantoff, 1999 (71)	242	mitoxantrone/hydrocortisone vs. hydrocortisone
Tannock, 1996 (72,89)	161	mitoxantrone/prednisone vs. prednisone
Weissbach, 1998 (88)*	175	epirubicin vs. EMP vs. mitomycin C
Anderström, 1995 (73)	145	epirubicin/MPA vs. EMP
Laurie, 1992 (74)	142	5-FU/doxorubicin/mitomycin C (combined) vs. 5-FU/doxorubicin/mitomycin C (sequential)
Saxman, 1992 (75)	103	cyclophosphamide vs. cyclophosphamide/doxorubicin/MTX
Murphy, 1988 (76)*	152	MTX vs. doxorubicin/cyclophosphamide vs. cisplatin/5-FU/cyclophosphamide
Stephens, 1984 (77)	137	doxorubicin/cyclophosphamide vs. hydroxyurea
Other chemotherapy (4 trials)†		
Newling, 1993 (78)	171	mitomycin C vs. EMP
Loening, 1983 (79)	189	EMP vs. MTX vs. cisplatin
Non-cytotoxic trials (8 trials)		
Carducci, 2004 (80)	809	atrasentan vs. placebo
Carducci, 2003 (81)	288	atrasentan (2.5mg) vs. atrasentan (10mg) vs. placebo
Leaf, 2003 (82)	150	doxorubicin/DES vs. doxorubicin
Small, 2003 (83)	127	APC8015 vs. placebo
Small, 2002 (84)	390	suramin (3.192g/m^2) vs. suramin (5.320g/ m^2) vs. suramin (7.661 g/m^2)
Ahmann, 2001 (85)	406	prinomastat (5mg)/mitoxantrone/prednisone vs. prinomastat (10mg)/mitoxantrone/prednisone vs. placebo/mitoxantrone/prednisone
Small, 2000 (86)	458	suramin/hydrocortisone vs. placebo/hydrocortisone
Debruyne, 1998 (87)	321	liarozole vs. CPA

Abbreviations: AMG – aminoglutethimide; CPA – cyproterone acetate; DES – diethylstilbestrol diphosphate; EMP – estramustine phosphate; g – grams; 5-FU – 5-fluorouracil; mg – milligrams; MPA – medroxyprogesterone acetate; m^2 – metres squared; MTX – methotrexate; No. – number; vs. - versus.

*This trial evaluates regimens from two different drug classes: anthracenedione/anthracycline and other chemotherapy; †the total number of trials studying other chemotherapy is four, including Murphy 1988 and Weissbach 1998.

Antimicrotubule-based chemotherapy (9 trials, Tables 2 and 3)

Docetaxel

Docetaxel is a taxane drug that induces polymerization of microtubules and phosphorylation of bcl-2 protein. Two large RCTs comparing docetaxel-based chemotherapy to mitoxantrone-prednisone have recently been published (Appendix 2). Tannock et al (4), randomized 1006 patients to one of three treatment arms: docetaxel (75 mg/m^2 intravenously every [q] three weeks), docetaxel (30 mg/m^2 five-times weekly for five of six weeks), or control therapy with mitoxantrone. All patients also received prednisone. Petrylak et al (62) reported on 666 eligible patients randomized to docetaxel and EMP or mitoxantrone-prednisone. In addition to dexamethasone premedication, patients in the docetaxel arm also received warfarin and/or acetylsalicylic acid (ASA) as thrombosis prophylaxis during the course of the trial. Men in both trials had clinical evidence of metastases with or without symptoms and had undergone AAWD. Overall survival was the primary endpoint in both trials.

Tannock et al (4) reported improved survival with docetaxel-prednisone (q third week) compared with mitoxantrone-prednisone (median survival, 18.9 versus 16.5 months; hazard ratio [HR]=0.76 [95% confidence interval [CI], 0.62-0.94], two-sided p=0.009) (Table 2). No overall survival benefit was observed with docetaxel-prednisone given on a weekly schedule when compared with mitoxantrone-prednisone. Petrylak et al (62) reported longer survival time with docetaxel-EMP compared with mitoxantrone-prednisone (median survival, 17.5 versus 15.6 months; HR=0.80 [95% CI, 0.67-0.97], two-sided p=0.02). That trial also reported a median progression-free interval of 6.3 versus 3.2 months (two-sided p<0.0001) favouring docetaxel-EMP versus mitoxantrone-prednisone.

Pain response was assessed in both trials. Tannock et al (4) measured pain response as a two-point or greater reduction in the Present Pain Intensity scale (PPI) compared with baseline scores with no concomitant increase in analgesic use (or ≥50% decrease in analgesia without a concomitant increase in PPI). Significantly more patients treated with docetaxel-prednisone (q third week) achieved a pain response compared with patients receiving mitoxantrone-prednisone (35% [53/153] versus 22% [34/157], p=0.01). A trend towards improved pain response was observed with weekly docetaxel-prednisone versus mitoxantrone-prednisone (31% [48/154] versus 22%, p=0.08). Quality of life response was defined as a sustained 16-point or greater improvement from baseline on two consecutive measurements and was higher with docetaxel given every three weeks (22% [61/278] versus 13% [35/267], p=0.009) or weekly (23% [62/270] versus 13%, p=0.005) compared with mitoxantrone. Petrylak et al (62) reported no difference in patient reported pain relief between arms in their trial and did not assess quality of life.

Both trials assessed tumour and PSA response (Table 3). In the Tannock et al trial (4), 27% of patients had measurable disease, and the objective response rates for docetaxel-prednisone (q three weeks) and mitoxantrone-prednisone were 12% versus 7%, respectively. Petrylak et al (62) reported objective response rates of 17% and 11% favouring docetaxel-EMP compared with mitoxantrone-prednisone in the 29% of patients with measurable disease. Although those differences were not statistically significant in either trial, when response rates from both trials are pooled (docetaxel q third week versus mitoxantrone) the rates are 14.3% versus 8.3% (p<0.05) favouring the docetaxel-based regimens. In both trials, PSA response rates were also statistically higher with docetaxel compared to mitoxantrone (Table 3).

In the Tannock et al trial (4), more grade 3-4 neutropenia (32% and 22% versus 1.5%) and neutropenic infection (3% and 0.9% versus 0%) were observed with docetaxel-prednisone (q third week) compared with mitoxantrone-prednisone and docetaxel-prednisone given weekly, respectively. However, only two septic deaths occurred, one each in the

mitoxantrone and weekly docetaxel arms. Grade 3-4 non-hematological toxicities were infrequent and similar in the docetaxel and mitoxantrone arms. Mild to moderate alopecia, fatigue, diarrhea, nail changes, stomatitis, peripheral edema, anorexia, and dyspnea were more common with docetaxel. Docetaxel (q third week) was associated with more mild to moderate neurosensory changes and constipation, while tearing, vomiting, and epistaxis were more common with docetaxel given weekly. In the Petrylak et al trial (62), more grade 3-4 toxicity (54% versus 34%) was associated with docetaxel-EMP compared with mitoxantrone-prednisone, primarily due to higher rates of gastrointestinal and cardiovascular events. The protocol was amended to add oral coumadin (2 mg daily) and oral ASA (325 mg daily) to the docetaxel arm, due to the observation of an increased number of thrombotic events with that regimen in a phase II study, but a post hoc analysis suggested prophylactic anticoagulation had little effect on the rate of thromboembolic events in the trial. Docetaxel-EMP was also associated with statistically significantly higher rates of metabolic disturbances (6% versus 1%) and neurologic events (7% versus 2%) compared to mitoxantrone. Eight (2%) versus four (1%) toxic deaths occurred in the docetaxel and mitoxantrone arms, respectively.

Estramustine

EMP is a nor-nitrogen mustard carbamate derivative of estradiol-17β-phosphate with estrogenic and antimicrotubule effects (90). It is unclear how much of this agent's activity in HRPC is due to its hormonal versus its cytotoxic effects. Six RCTs directly examined the efficacy of EMP in HRPC (Appendix 2); three studied EMP either by comparing it to a placebo or an oral antiandrogen (66-68) and three added EMP to a cytotoxic agent and compared this combination to the cytotoxic agent alone (64,65,69). One other large RCT comparing docetaxel-EMP to mitoxantrone-prednisone indirectly addressed the value of EMP (see *Docetaxel* above) (62).

All six trials reported on overall survival; five detected no improvements in survival with EMP, and one detected a survival benefit that was of borderline statistical significance (64) (Table 2). Five trials reported TTP or PFS results; of those, one trial comparing EMP-vinblastine to vinblastine alone reported longer TTP with the combination (median, 3.7 versus 2.2 months, one-sided $p<0.0004$) (65). EMP was not associated with improved pain, performance status or subjective response rate in two trials reporting those data (66,69). Hudes et al (65) reported improved pain frequency with EMP, however, less than 50% of patients with pain completed pain questionnaires. Quality of life data were also collected in that trial but did not allow for comparative assessment. Berry et al (64) assessed quality of life and reported no differences in global quality of life and all subscales between paclitaxel-EMP and paclitaxel alone. Three of the trials reported on objective response (65,68,69), and none of those showed improved tumour response with EMP (Table 3). The three trials reporting on PSA response (64-66) all showed higher PSA response with EMP (Table 3).

Compared with flutamide, EMP was associated with statistically significant higher rates and severity of nausea and vomiting and edema (68). Increased gastrointestinal side effects were seen in 19% of patients receiving EMP in comparison to medroxyprogesterone acetate (MPA) (67), and 10% discontinued treatment because of this in another trial (66). EMP caused more gastrointestinal toxicity (including nausea and vomiting, diarrhea, and dyspepsia), breast tenderness/gynecomastia, and cardiovascular deaths (6.8% versus 1.5%) in a placebo-controlled trial (66). When EMP was added to prednimustine and compared with prednimustine alone, a trend towards increased nausea and vomiting and reduced severe neutropenia were observed with the combination (69). EMP-vinblastine was associated with more nausea, leg edema, thrombosis, and less severe neutropenia (8% versus 27%, $p<0.0001$) compared with vinblastine alone (65). Similarly, a higher incidence of gastrointestinal

toxicity and thrombosis, and a lower incidence of severe neutropenia was reported with EMP-paclitaxel compared with paclitaxel alone (64).

Vinorelbine

Vinorelbine is a semi-synthetic vinca alkaloid with single-agent activity in HRPC. Abratt et al (63) randomized 414 men treated with hydrocortisone with or without aminoglutethimide to vinorelbine or no chemotherapy (Appendix 2). The primary endpoint of that trial was PFS (Table 2). A statistically significant longer progression-free interval was reported with vinorelbine after adjustment for predetermined prognostic factors (median, 3.7 versus 2.8 months; HR=0.71, unadjusted two-sided p=0.055, adjusted two-sided p=0.005). No difference in overall survival was detected between trial arms. Clinical benefit response (defined as improved pain, analgesic score, or performance status for greater than nine weeks) was improved with vinorelbine compared with the control arm (30.6% versus 19.2%, p=0.008). Quality–of-life data were also collected in the trial but are limited due to poor patient compliance and use of a general rather than a specific prostate cancer quality of life instrument; the analysis of those data showed no benefit with vinorelbine on either global quality of life or functional subscales. Thirty-four percent of patients (n=142) in the trial had measurable disease, and response rates of 5.9% (partial only) and 0% were reported for vinorelbine versus control, but no statistical comparison of those data was provided (Table 3). PSA response rates were higher with vinorelbine (Table 3). Significantly more frequent severe neutropenia (26%), neutropenic infection (3%), anemia (6.5%), and constipation (3%) were observed with the addition of vinorelbine to hydrocortisone with or without aminoglutethimide.

Table 2: Antimicrotubule trials: survival outcomes.

Trial	Treatment arms	Overall survival			Progression-free survival or TTP		
		N	Median (mo)	Statistical comparison	N	Median (mo)	Statistical comparison
Tannock, 2004 (4)	docetaxel q 3 wks prednisone	335	18.9	HR=0.76 (95% CI, 0.62-0.94), p=0.009	NR		
	docetaxel q wk prednisone	334	17.4	HR=0.91 (95% CI, 0.75-1.11) p=0.36			
	mitoxantrone prednisone	337	16.5	NA			
Petrylak, 2004 (62)	docetaxel EMP	338	17.5	HR=0.80 (95% CI, 0.67-0.97) p=0.02	324	6.3	p<0.001 (TTP)
	mitoxantrone prednisone	336	15.6		324	3.2	
Abratt, 2004 (63)	vinorelbine hydrocortisone ± AGM	206	14.7	p=0.95	206	3.7	HR=0.71 p=0.055 (unadjusted) p=0.005 (adjusted)*
	hydrocortisone ± AGM	208	15.2		208	2.8	
Berry, 2004 (64)	paclitaxel EMP	163	16.1	p=0.05	163	5.5	p=0.1
	paclitaxel		13.1			4.3	
Hudes, 1999 (65)	vinblastine EMP	95	11.9	p=0.08†	98	3.7	p<0.0004† (TTP)
	vinblastine	98	9.2		95	2.2	
Iversen, 1997 (66)	EMP	61	9.4	p=0.9	60	4.6	p=0.72 (TTP)
	placebo	68	6.1		67	5.0	
Johansson, 1991 (67)	EMP	51	NR	p=0.23	51	NR	p=0.28
	MPA	51			51		
De Kernion, 1988 (68)	EMP	102	NR	p=NS	102	NR	p=NS
	flutamide	101			101		
Murphy, 1979 (69)	EMP prednimustine	54	9.3	p=NS	NR		
	prednimustine	62	9.0				

Abbreviations: AGM – aminoglutethimide; CI – confidence interval; EMP – estramustine phosphate; HR – hazard ratio; mo – months; MPA – medroxyprogesterone acetate; N – number; NA – not applicable; NR – not reported; NS – non-significant; q – every; TTP – time-to-progression; wk(s) – week(s).

*Adjusted for age, baseline hemoglobin, performance status, and alkaline phosphatase, and number of prior hormonal manipulations; †based on one-sided significance testing.

Table 3: Antimicrotubule trials: PSA and tumour response.

Trial	Treatment arms	PSA response*			Tumour response		
		N	Response rate %	Statistical comparison	N	Objective response rate %	Statistical comparison
Tannock, 2004 (4)	docetaxel q 3 wks prednisone	291	45	p<0.001	141	12	p=0.1
	docetaxel q wk prednisone	282	48	p<0.001	134	8	p=0.6
	mitoxantrone prednisone	300	32	NA	137	7	NA
Petrylak, 2004 (62)	docetaxel EMP	309	50	p<0.001	103	17	p=0.30
	mitoxantrone prednisone	303	27		93	11	
Abratt, 2004 (63)	vinorelbine hydrocortisone ± AGM	206	30.1	p=0.01	68	5.9 (PR)	NR
	hydrocortisone ± AGM	208	19.2		74	0	
Berry, 2004 (64)	paclitaxel EMP	161	47	p<0.01	NR		
	paclitaxel		27				
Hudes, 1999 (65)	vinblastine EMP	87	25.2	p<0.0001	30	20 (PR)	p=0.13
	vinblastine	94	3.2		33	6 (PR)	
Iversen, 1997 (66)	EMP	43	37.2	p=0.001	NR		
	placebo	51	2.0				
Johansson, 1991 (67)	EMP	NR			NR		
	MPA						
De Kernion, 1988 (68)	EMP	NR			102	0	p=NS
	flutamide				101	1.0 (PR)	
Murphy, 1979 (69)	EMP prednimustine	NR			54	1.9 (PR)	p=NS
	prednimustine				62	0	

Abbreviations: AGM – aminoglutethimide; EMP – estramustine phosphate; MPA – medroxyprogesterone acetate; N – number; NA – not applicable; NR – not reported; NS – non-significant; PR – partial response; PSA – prostatic-specific-antigen; q – every; wk(s) – week(s).

*PSA response was defined as ≥50 decrease in PSA compared with baseline.

Anthracenedione/anthracycline-based chemotherapy (9 trials, Tables 4 and 5)

Mitoxantrone

Mitoxantrone is an anthracenedione drug with mechanisms of activity similar to anthracyclines and a modest toxicity profile. Three RCTs compared mitoxantrone combined with low-dose corticosteroid to the same low-dose corticosteroid alone without placebo (70-72) (Appendix 3). In the largest trial, Kantoff et al (71) randomized 242 patients with evidence of metastatic HRPC who had undergone AAWD to either mitoxantrone and hydrocortisone or hydrocortisone alone. The primary endpoint of the trial was overall

survival. Tannock et al (72) compared mitoxantrone plus prednisone to prednisone alone in 161 men with HRPC who were symptomatic with pain. Pain relief was the primary endpoint of the trial, defined by patient self-reported pain intensity and analgesic use as recorded in an analgesic diary. Patients in that trial were permitted to crossover to the mitoxantrone arm at the time of cancer progression, confounding the analysis of overall survival. Berry et al (70) evaluated the same treatment regimens as Tannock et al but randomized 120 men with HRPC and asymptomatic progression and designated TTF/progression as the primary endpoint.

All three RCTs reported on overall survival, but none detected an improvement in survival with mitoxantrone (Table 4). Berry et al (70) and Kantoff et al (71) both reported longer median TTP with mitoxantrone versus control (8.1 versus 4.1 months [p=0.018], and 3.7 versus 2.3 months [p=0.02], respectively).

Pain was assessed in one trial. Tannock et al (72) rigorously assessed palliative response through self-reported pain scores and analgesic consumption. In the mitoxantrone-prednisone treatment arm, 29% (23/80) of patients had a two-point reduction in pain intensity (or complete elimination of pain) on the six-point McGill-Melzack Pain Questionnaire maintained for at least three weeks apart without an increase in analgesic use, compared with 12% (10/81) of patients treated with prednisone alone (p=0.01). The median duration of pain response was 43 versus 18 weeks, favouring mitoxantrone (p<0.0001). An additional seven patients in each arm had a decrease of ≥ 50% in analgesic score without an increase in pain; thus, 38% (30/80) of patients treated with mitoxantrone-prednisone had palliative benefit compared with 21% (17/81) with prednisone alone (p=0.025).

Two of the trials reported quality-of-life data (71,72). Tannock et al (72) reported improved quality of life with mitoxantrone-prednisone over prednisone alone in domains related to pain, physical activity or function, constipation, and mood with the Prostate Cancer Specific Quality of Life Instrument (PROSQOLI) and European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Cancer (QLQ-C)30 instruments. Patients meeting criteria for palliative response had improvements in most quality of life domains including overall wellbeing. Kantoff et al (71) also reported improved quality of life favouring mitoxantrone in the Functional Living Index-Cancer (FLIC) emotional state and family disruption subscales.

Objective response rates were reported in two trials (70,71), with no difference observed between arms (Table 5). All three trials reported PSA response rates, which were significantly higher with mitoxantrone in one trial (70) (Table 5).

Grade 3-4 neutropenia occurred in 45% of cycles, and 63% and 48% of patients, respectively (70-72). Neutropenic sepsis occurred in 6.9% and 2% of patients (70,72). Severe symptomatic non-hematological toxicities were rare: for example, severe nausea and vomiting occurred in 0.5% of cycles (72). Cardiac dysfunction, either symptomatic or detected by reduced LVEF, was observed in 3.8% and 5% of patients (70,72). No toxic deaths were observed with mitoxantrone in any of those trials.

Doxorubicin and Epirubicin

Anthracyclines are believed to exert their cytotoxic effects primarily through the inhibition of topoisomerase-II activity. Six RCTs examined anthracycline combinations (73-77,88) (Appendix 3). Four performed in the pre-PSA era compared doxorubicin-based cytotoxic chemotherapy regimens to non-doxorubicin-based regimens or single agents (75-77) or compared combined versus sequential 5-flourouracil–doxorubicin–mitomycin-C (FAM) (74). Two trials compared anthracyclines to EMP (73,88). The primary endpoints of those trials were tumour response and survival (74-77), TTP (73), and unspecified in one trial (88).

Five of the RCTs reported comparative overall survival data (73-77) (Table 4). Only one of those trials reported improved survival with chemotherapy (74). Laurie et al (74) randomized 142 patients to either combination chemotherapy with FAM or sequential chemotherapy with the same drugs (mitomycin C followed by doxorubicin followed by 5-fluorouracil). Although response rates were similar between the two arms and hematological toxicity was greater with FAM administered in combination, overall survival favoured the combined FAM regimen (median survival, 8.7 versus 7.1 months, p=0.025). Three trials provided comparative data on disease progression; two reported on TTP (73,75) and one reported on PFS (76). Only one of those trials reported a statistically significant difference between arms; improved TTP was detected with epirubicin and MPA compared with EMP (median, 7.6 versus 4.3 months, p=0.013) (73).

Two of the trials assessed a pain or palliative endpoint (77,88). Stephens et al (77) reported that the symptomatic response rate (a composite endpoint comprising of worsening symptoms and analgesic use) was higher with doxorubicin plus cyclophosphamide compared with hydoxyurea [26% (18/68) versus 13% (9/69), p=0.048), but the duration of this response was not significantly different between the two groups (p=0.62). The second trial by Weissbach et al (88) reported comparable rates of pain relief (undefined) among patients treated with epirubicin [49% (30/61)], mitomycin C (48%), and EMP (42%), but no statistical comparisons were provided. None of the six trials reported quality-of-life data.

Five trials reported on objective response (74-77,88) (Table 5). Only two of the trials provided statistical comparisons of those data; one detected no difference in response rates between trial arms (76), and the other reported higher response rates with combined doxorubicin-cyclophosphamide chemotherapy (32%) versus hydroxyurea (4%) that was of borderline statistical significance (p=0.05) (77).

More frequent severe leucopenia was observed with hydroxyurea compared with doxorubicin-cyclophosphamide (77), and FAM compared with mitomycin C (74). Heart failure or pulmonary edema occurred in 12% of patients, whether treated with epirubicin plus MPA or EMP (73). In that trial, alopecia and leucopenia were more common in the epirubicin arm.

Table 4: Mitoxantrone and anthracycline trials: survival outcomes.

Trial	Treatment arms	Overall survival			Progression-free survival or TTP		
		N	Median (mo)	Statistical comparison	N	Median (mo)	Statistical comparison
Berry, 2002 (70)	mitoxantrone prednisone	56	23	p=0.48	56	8.1	p=0.018 (TTP)
	prednisone	63	19		63	4.1	
Kantoff, 1999 (71)	mitoxantrone hydrocortisone	119	12.3	p=0.77	119	3.7	p=0.02 (TTP)
	hydrocortisone	123	12.6		123	2.3	
Tannock, 1996 (72)	mitoxantrone prednisone	80	NR	p=0.27	NR		
	prednisone	81					
Weissbach, 1998 (88)	epirubicin	61	NR by treatment group		61	NR by treatment group	"TTF was longer with mitomycin C vs. EMP (p=0.037); and vs. epirubicin (p=0.039)
	EMP	54			54		
	mitomycin C	60			60		
Anderström, 1995 (73)	epiribucin MPA	73	11.5	p=NS	73	7.6	p=0.013 (TTP)
	EMP	72	9.5		72	4.3	
Laurie, 1992 (74)	5-FU doxorubicin mitomycin C (combined)	70	8.7	p=0.025	NR		
	5-FU doxorubicin mitomycin C (sequential)	72	7.1				
Saxman, 1992 (75)	cyclophosphamide doxorubicin methotrexate	26 high PS 24 low PS	9.5 6	p=0.93 p=0.51	50	6.2*	p=0.07 (TTP)
	cyclophosphamide	26 high PS 27 low PS	9 5	p=0.7 (unstratified)	53	4.4*	
Murphy, 1988 (76)	doxorubicin cyclophosphamide	54	NR	p=NS	54	NR	p=NS
	cisplatin 5-FU cyclophosphamide	46			46		
	methotrexate	52			52		
Stephens, 1984 (77)	doxorubicin cyclophosphamide	68	6.8	p=NS	NR		
	hydroxyurea	69	7				

Abbreviations: 5-FU – 5- fluorouracil; EMP – estramustine phosphate; mo – months; MPA – medroxyprogesterone; N – number; NR – not reported; NS – non-significant; PS – performance status; TTF – time-to-treatment failure; TTP – time-to-progression; vs. – versus.

*Median values include only patients with partial response or stable disease (n was not reported).

Table 5: Mitoxantrone and anthracycline trials: PSA and tumour response.

Trial	Treatment arms	PSA response*			Tumour response		
		N	Response rate %	Statistical comparison	N	Objective response rate %	Statistical comparison
Berry, 2002 (70)	mitoxantrone prednisone	56	48†	p=0.007	8	25 (PR)	p=NR
	prednisone	63	24†		9	22 (PR)	
Kantoff, 1999 (71)	mitoxantrone hydrocortisone	96	18.7	p=0.41	116	7 (PR)	p=0.38
	hydrocortisone	91	14.3		118	4 (PR)	
Tannock, 1996 (72)	mitoxantrone prednisone	57	33	p=0.11	NR		
	prednisone	54	22				
Weissbach, 1998 (88)	mitomycin C	NR			60	22	NR
	epirubicin				61	11	
	EMP				55	9	
Laurie, 1992 (74)	5-FU doxorubicin mitomycin C (combined)	NR			70	14	NR
	5-FU doxorubicin mitomycin C (sequential)				72	18	
Saxman, 1992 (75)	cyclophosphamide doxorubicin methotrexate	NR			16	18.8 (PR)	NR
	cyclophosphamide				16	6 (PR)	
Murphy, 1988 (76)	doxorubicin cyclophosphamide	NR			54	1 (PR)	p=NS
	cisplatin 5-FU cyclophosphamide				46	0	
	methotrexate				52	0	
Stephens, 1984 (77)	doxorubicin cyclophosphamide	NR			19	32	p=0.05
	hydroxyurea				24	4	

Abbreviations: 5-FU – 5-fluorouracil; EMP – estramustine phosphate; N – number; NR – not reported; NS – non-significant; PR – partial response; PSA – prostatic-specific antigen.

*PSA response was defined as ≥50% decrease in PSA compared with baseline; †PSA response with stabilization or improvement of performance status for at least 2 weeks.

Other cytotoxic agents (4 trials, Tables 6 and 7)

Four trials studied other chemotherapy agents (76,78,79,88) (Appendix 4). The National Prostatic Cancer Project (NPCP) randomized 189 men with clinically progressing HRPC to either single-agent cisplatin, methotrexate, or EMP (79). In a successor RCT, 180 patients were randomized to either single-agent methotrexate, combination cyclophosphamide–5-fluorouracil–cisplatin or cyclophosphamide-doxorubicin (76). Objective response by NPCP criteria was the primary endpoint of both trials. Newling et al (78) compared mitomycin C with EMP in 171 randomized patients with TTP and overall survival as

primary endpoints. All three trials were completed during the pre-PSA era. Weissbach et al (88) randomized 175 patients to mitomycin C, epirubicin, or EMP.

All four trials reported data on overall survival (Table 6), but only three provided comparative data (76,78,79); none of those trials reported differences between trial arms. Two trials reported on disease progression (76,78) (Table 6), and no differences in PFS (76) or TTP (78) were detected between treatment arms in either trial. Weissbach et al (88) reported improved TTF with mitomycin C compared with epirubicin (p=0.039) and EMP (p=0.037).

Two trials provided data on symptomatic or pain response (79,88). Loening et al (79) reported improved performance status in 12% (7/58) of men treated with methotrexate, 10% (5/50) treated with cisplatin, and 2% (1/50) with EMP (79), and pain was improved with methotrexate (19% [11/58]) and cisplatin (22% [11/50]) compared with EMP (6% [3/50]); however, none of those differences reached statistical significance. As previously noted, comparable rates of pain improvement were seen in the Weissbach et al trial (88). One trial collected quality-of-life data; however, it is of limited value due to missing data (78).

Three trials reported tumour response data (76,79,88) (Table 7), but only two provided statistical comparisons (76,79); no differences in response rates were observed between arms in either trial. None of the trials reported on PSA response.

More severe stomatitis and mild to moderate stomatitis were seen with methotrexate compared with EMP and cisplatin, but with methotrexate less mild to moderate nausea/vomiting and anorexia were observed (79). Renal toxicity and leucopenia were more frequent with methotrexate and cisplatin. More patients had leucopenia, nausea/vomiting, and anorexia, and fewer had stomatitis with cyclophosphamide–5-fluorouracil–cisplatin than with methotrexate (p<0.05) (76). Myelosuppression was more frequent with mitomycin C compared with EMP and resulted in 22% of patients discontinuing treatment. Nausea and anorexia occurred in 44% and 42% of patients, respectively (78). EMP was associated with gastrointestinal toxicity (nausea, anorexia, vomiting, and diarrhea), resulting in 25% of patients discontinuing treatment in that trial.

Table 6: Other chemotherapy trials: survival.

Trial	Treatment arms	Overall survival			Progression-free survival or TTP		
		N	Median (mo)	Statistical comparison	N	Median (mo)	Statistical comparison
Weissbach, 1998 (88)	epirubicin	61	NR by treatment group		61	NR by treatment group	"TTF was longer with mitomycin C vs. EMP (p=0.037); and vs. epirubicin (p=0.039)
	EMP	54			54		
	mitomycin C	60			60		
Newling, 1993 (78)	mitomycin C	79	10	p=0.60	79	5	p=0.46 (TTP)
	EMP	82	10		82	5	
Murphy, 1988 (76)	doxorubicin cyclophosphamide	54	NR	p=NS	54	NR	p=NS
	cisplatin 5-FU cyclophosphamide	46			46		
	methotrexate	52			52		
Loening, 1983 (79)	methotrexate	58	11.5	p=NS	NR		
	cisplatin	50	10				
	EMP	50	10				

Abbreviations: 5-FU – 5-fluorouracil; EMP – estramustine phosphate; mo – months; N – number; NR – not reported; NS – non-significant; TTF – time-to-treatment failure; TTP – time-to-progression; vs. – versus.

Table 7: Other chemotherapy trials: tumour response.

Trial	Treatment arms	Tumour response		
		N	objective response rate %	Statistical comparison
Weissbach, 1998 (88)	epirubicin	60	22	NR
	EMP	61	11	
	mitomycin C	55	9	
Newling, 1993 (78)	mitomycin C	NR		
	EMP			
Murphy, 1988 (76)	doxorubicin cyclophosphamide	54	1 (PR)	p=NS
	cisplatin 5-FU cyclophosphamide	46	0	
	methotrexate	52	0	
Loening, 1983 (79)	methotrexate	58	5	p=NS for all comparisons
	cisplatin	50	4 (PR)	
	EMP	50	2 (PR)	

Abbreviations: 5-FU -5-fluorouracil; EMP – estramustine phosphate; N – number; NR – not reported; NS – non-significant; PR – partial response.

Non-cytotoxic agents (8 trials, Tables 8 and 9)

Six non-cytotoxic agents, including estrogen diethylstilbestrol (DES), liarozole, suramin, atrasentan, prinomastat, and APC8015 have been investigated in RCTs in HRPC (Appendix 5). Leaf et al (82) evaluated the estrogen DES alone or combined with doxorubicin in an RCT involving 150 patients. Liarozole is thought to promote the differentiation of malignant cells by increasing intracellular levels of retinoic acid. Debruyne et al (87) randomized 321 patients to either liarozole or cyproterone acetate. Suramin is a highly charged polysulfonated napthylurea with antineoplastic activity of uncertain mechanisms and adrenolytic effects. Two recent, large RCTs have studied suramin in men with HRPC. In a placebo-controlled trial, Small et al (86) studied the effects of suramin plus hydrocortisone to hydrocortisone alone in men with HRPC and pain requiring opioid analgesics. The primary endpoint was pain response. A subsequent RCT compared three different doses of suramin and evaluated PSA response as the primary endpoint (84). Atrasentan is an orally bioavailable endothelin A antagonist. Two large RCTs have studied atrasentan in comparison to placebo in men with HRPC (80,81). The matrix metalloprotease inhibitor prinomastat has been combined with mitoxantrone-prednisone and compared with placebo (85). APC8015 is a cellular therapy consisting of autologous peripheral blood mononuclear cells enriched for dendritic cells and pulsed with a prostatic acid phosphatase-GM-CSF construct. APC8015 has also been compared with placebo in men with HRPC (83).

Five of the eight trials of non-cytotoxic agents reported overall survival results (82,84-87) (Table 8), and none reported differences in overall survival between treatment arms. Reduced mortality was reported with liarozole in comparison with cyproterone acetate after adjustment for prognostic factors by Cox multivariate regression analysis (HR=0.74 [95% CI, 0.56-0.99], p=0.039) (87). All eight trials reported on a disease-progression outcome (Table 8); four trials reported TTP (80,81,83,86), three reported on PFS (84,85,87), and one reported failure-free survival data (82). Of those trials, two detected statistically significant

differences favouring the experimental treatment (82,86). Failure-free survival was improved with DES-doxorubicin compared with doxorubicin alone (3.2 versus 2.6 months, two-sided p=0.012) (82). TTP was improved with suramin-hydrocortisone compared with placebo-hydrocortisone [RR=1.51 (95% CI, 1.22-1.85), two-sided p=0.0003) (86), but was not affected by suramin schedule in another trial (84).

Five trials reported pain or symptomatic response data (82,83,86,87,91). No difference in clinical response (defined as improved performance status, bone pain, body weight, or hemoglobin) was observed with DES-doxorubicin compared with doxorubicin (82). Mean best change in pain and analgesic-use score compared with baseline was improved with liarozole compared with cyproterone acetate (mean reduction 0.4 versus 0.2, p=0.026) (87). Small et al (86) assessed palliative response to suramin with self-reported pain scores and opioid analgesic use, using two methods. For the first method, average worst pain scores (during the previous 24 hours) measured with the Brief Pain Inventory (BPI) and opioid analgesic consumption were assessed in each treatment group and compared with baseline at six weeks and at the end of treatment. Suramin was superior to placebo for pain reduction at both six weeks and at the end of study; no statistically significant differences in narcotic analgesic consumption were observed. For the second method, pain response was measured and defined by either a three-point reduction (or complete elimination) of worst pain on the BPI (maintained for at least three weeks) with a <16% increase in opioid analgesic use, or by a ≥33% (minimum 5 mg) reduction in opioid analgesic use with a two-point or less increase in pain. More patients in the suramin group had pain response compared with placebo (43% versus 28%, p=0.001), and the duration of pain response was significantly higher (median 240 versus 69 days, two-sided p=0.0027). Performance status measured by the Revised Rand Functional Limitations Scale was not improved with suramin compared with placebo. There were no group differences in BPI changes from baseline in the three-dose suramin trial (91).

Four trials assessed quality of life outcomes (81,86,87,91). No differences in the Functional Assessment of Cancer Therapy-Prostate (FACT-P) or EORTC QLQ-C30 scores were seen with atrasentan compared with placebo (81). Suramin was not superior to placebo in any of the five FACT-G domains (86). Compared with intermediate- and high-dose suramin, low-dose suramin was associated with significant improvements in overall FACT-G and FACT-Treatment Outcome Index scores, as well as all subscales (emotional, physical, and functional wellbeing, and prostate additional concerns) and depression, during but not after treatment (91). No statistically significant differences in total FLIC scores were observed between liarozole and cyproterone acetate (87). Tumour response data were reported in three trials (82,84,86) (Table 9). Only one trial detected significant differences between trial arms (82). PSA response rates were reported in seven trials (80,81,83-87) (Table 9); four of those detected statistically significantly higher response rates with the experimental therapy (80,81,86,87).

Liarozole was associated with increased rates of skin toxicity, nausea and vomiting, and fatigue (87). Severe, life-threatening, and lethal cardiac toxicity was higher with DES added to doxorubicin than doxorubicin alone (13.5 % versus 1.3%, p=0.0041), and rates of thrombosis were also higher (8.2% versus 0%). In comparison to placebo, suramin was associated with more frequent mild to moderate rash (57% versus 13%) and severe edema and anemia (both <5%) (86). Higher rates of severe toxicities were seen with high-dose suramin including neutropenia, anorexia, cardiac dysrhythmias, and neuromotor toxicity (84). Prinomastat was associated with increased rates of mild to moderate musculoskeletal effects including arthralgia, joint stiffness and swelling, and, rarely, contracture compared with placebo (85). Atrasentan was associated with increased rates of mild to moderate peripheral edema, rhinitis, headache, hypotension, anemia, and weight gain compared with placebo (81).

Table 8: Non-cytotoxic trials: survival outcomes.

Trial	Treatment arms	Overall survival			Progression-free survival or TTP or FFS		
		N	Median (mo)	Statistical comparison	N	Median (mo)	Statistical comparison
Carducci, 2004 (80)	atrasentan	NR			408	NR	HR for TTP=1.14 (95% CI, 0.98-1.34) p=0.091
	placebo				401		
Carducci, 2003 (81)	atrasentan 10mg	NR			89	6.5	p=0.13 (TTP)
	atrasentan 2.5mg				95	6.4	p=0.29 (TTP)
	placebo				104	4.9	NA
Leaf, 2003 (82)	doxorubicin DES	74	8.5	p=0.37	74	3.2	p=0.012 (FFS)
	doxorubicin	76	7.7		76	2.6	
Small, 2003 (83)	APC8015	NR			82	NR	HR for TTP=1.39 (95% CI, 0.95-2.04) p=0.085
	placebo				45		
Small, 2002 (84)	suramin (3.192g/m^2)	128	16	p=0.49	128	NR	p=NS
	suramin (5.320g/m^2)	124	14		124		
	suramin (7.661g/m^2)	120	13		120		
Ahmann, 2001 (85)	prinomastat (5mg) mitoxantrone prednisone	134	15.1	p=NS	134	6	p=NS
	prinomastat (10mg) mitoxantrone prednisone	134	14.7		134	4.7	
	mitoxantrone prednisone placebo	138	14.8		138	6	
Small, 2000 (86)	suramin hydrocortisone	228	10.2	p=NS	228	NR	RR for TTP=1.51 (95% CI, 1.22-1.85) p=0.0003
	placebo hydrocortisone	230	10		230		
Debruyne, 1998 (87)	liarozole	160	10.3	p=0.519 (unadjusted)	160	4.9	p=NS
	CPA	161	10.3	HR=0.74 (95% CI, 0.56-0.99) p=0.039* (adjusted)	161	4.6	

Abbreviations: CI – confidence interval; CPA – cyproterone acetate; DES – diethylstilbestrol; FFS – failure-free survival; HR – hazard ratio; m^2 – meters squared; mg – milligrams; mo – months; N – number; NA – not applicable; NR – not reported; NS – non-significant; RR– relative risk; TTP – time-to-progression.

*adjusted for performance status, hemoglobin, baseline PSA, alkaline phosphatase, and duration of response.

Table 9: Non-cytotoxic trials: PSA and tumour response.

Trial	Treatment arms	PSA response*			Tumour response		
		N	Response rate %, unless otherwise specified	Statistical comparison	N	Objective response rate %	Statistical comparison
Carducci, 2004 (80)	atrasentan	408	"smaller mean ↑ with atrasentan vs. placebo"	p=0.025	NR		
	placebo	401					
Carducci, 2003 (81)		median time-to-PSA progression:			NR		
	atrasentan 10mg	89	5.5 mo	p=0.002			
	atrasentan 2.5mg	95	5 mo	p=0.055			
	placebo	104	2.5 mo	NA			
Leaf, 2003 (82)	doxorubicin	NR			30	27‡	p=0.04
	DES				71	12.7§	p>0.99
	doxorubicin				32	6.3‡	
					73	12.3§	
Small, 2003 (83)	APC8015	82	4.9	NR	NR		
	placebo	45	0				
Small, 2002 (84)	suramin (3.192g/m^2)	128	24	p=0.08 (test for trend)	128	9	p=0.104 (test for trend)
	suramin (5.320g/m^2)	124	28		124	7	
	suramin (7.661g/m^2)	120	34		120	15	
Ahmann, 2001 (85)	prinomastat (5mg) mitoxantrone prednisone	134	17†	p=NS	NR		
	prinomastat (10mg) mitoxantrone prednisone	134	18†				
	mitoxantrone prednisone placebo	138	14†				
Small, 2000 (86)	suramin hydrocortisone	228	33	p=0.01	76	4 (PR)	NR
	placebo hydrocortisone	230	16		80	0	
Debruyne, 1998 (87)	liarozole	160	20	p<0.001	NR		
	CPA	161	4				

Abbreviations: CPA – cyproterone acetate; DES – diethylstilbestrol; g – grams; m^2 – meters squared; mg – milligrams; mo – months; N – number; NA – not applicable; NR – not reported; NS – non-significant; PR – partial response; PSA – prostatic-specific-antigen; vs. – versus.

*PSA response was defined as ≥50% decrease in PSA compared with baseline; †75% reduction in PSA for 3 weeks; ‡non-osseous tumour response; §osseous tumour response.

DISCUSSION

In evaluating the evidence for benefits of non-hormonal systemic therapy in HRPC, the GU DSG was aware of a number of important factors critical to the interpretation of clinical trial data in this area. Those factors are listed below and were considered in the weighting of the evidence provided by the clinical trials.

1. Generalizability: The diagnosis and clinical management of HRPC has undergone radical change over the past decade, along with the design and methodology of clinical trials. Over this time, a stage migration has occurred in HRPC due to the ability of PSA testing to detect the biochemical emergence of androgen independence before symptoms or signs become apparent. In the pre-PSA era, men with HRPC treated in RCTs were often quite symptomatic and extensively pre-treated with palliative radiotherapy. This implies that care must be taken in generalizing the results of trials to current practice, particularly if the trials were completed prior to 1990.
2. Hormonal therapy: Although HRPC is by definition androgen independent, androgen levels may still influence tumour growth. Differences or lack of control of ADT used in trial subjects may affect outcomes. LHRH-agonist use has become much more prevalent over the past decade, replacing estrogens and reducing the use of bilateral orchiectomy; opinions about the value of maintaining ADT during chemotherapy have also varied. As well, the AAWD syndrome has been identified as a potential confounder of clinical and biochemical response in HRPC (92). While the value of maintaining ADT after the development of HRPC has not been validated in prospective randomized trials, entry onto current RCTs of new agents, including chemotherapies, require that ADT be continued. Certainly, maintenance of ADT was required for entry onto the largest clinical trials (4,62,71,72) discussed in this guideline.
3. Trial endpoints: The determination of valid endpoints for clinical trials in HRPC presents a challenge. Typically, men with HRPC have skeletal metastases that cannot be conventionally assessed for objective response to anticancer therapy. As a result, trials have used a number of different primary endpoints. The identification of definitive benefits from non-hormonal drug therapy has only become clear over the past decade with the emergence of validated symptom and quality of life instruments, the availability of PSA as a tumour marker, and the ability to conduct randomized trials large enough to adequately assess survival benefits. As the purpose of this guideline is to inform clinical practice, endpoints unequivocally associated with patient benefit or harm were emphasized.

Antimicrotubule-based Chemotherapy

Docetaxel

Improvement in overall survival has been reported with docetaxel-based chemotherapy given every three weeks in comparison with mitoxantrone-prednisone in two large, well-conducted RCTs (4,62). Docetaxel-prednisone given on a weekly schedule was not associated with an overall survival benefit in one of those trials (4). Comparison of both trials provided indirect evidence of similar efficacy but increased toxicity with the addition of EMP to docetaxel given every third week. Docetaxel-prednisone was associated with more frequent mild toxicities, similar rates of serious toxicities, and better quality of life than mitoxantrone-prednisone. Palliative and objective response rates were also improved with docetaxel-prednisone over mitoxantrone-prednisone. Based on that evidence, the GU DSG recommends that docetaxel given every third week with daily prednisone be offered to men

with HRPC and metastases. Weekly docetaxel is a treatment alternative, with clinical benefits that do not include improved overall survival.

Other Antimicrotubule Agents

One trial reported improved TTP with the addition of EMP to vinblastine compared with vinblastine alone, with equivocal improvement in pain frequency (65); another trial reported a marginal survival benefit with combination EMP-paclitaxel over paclitaxel alone (64). Improved PFS was seen with vinorelbine compared with placebo (63) after adjustment for predetermined prognostic factors associated with a modest benefit in clinical benefit response. In addition to gastrointestinal side effects, four of six trials studying EMP reported higher rates of thrombosis or cardiovascular toxicity with that agent compared with control therapies. Based on the evidence above, the GU DSG recommends that docetaxel given every third week be administered without EMP.

Anthracenedione/Anthracycline-based Chemotherapy

Early RCTs studying doxorubicin- or epirubicin-based combinations compared with single-agent chemotherapy controls suggested anti-tumour activity generally accompanied by toxicity. Interpretation of the results of those trials is limited by small sample sizes and a lack of validated psychometric tools to ascertain treatment benefits. Tannock et al (72) established mitoxantrone-prednisone as a standard palliative therapy for men with HRPC symptomatic with pain. Two trials (70,71) subsequently confirmed that mitoxantrone also improved TTP compared to initial corticosteroid therapy alone. The lack of toxicity in those trials was notable, with no toxic deaths and few serious hematological and non-hematological side effects. Cardiomyopathy is a chronic toxicity of concern with mitoxantrone and was observed in ≤5% of patients in those trials. Based on that evidence, the GU DSG considers mitoxantrone a less efficacious alternative to docetaxel with clinical benefits that do not include improved overall survival.

Other Agents

Cytotoxic Agents

Early RCTs studying several single-agent and combination chemotherapy regimens compared with other single-agent chemotherapy controls showed hints of anti-tumour activity generally accompanied by toxicity. Interpretation of the results of those trials is limited by their sample sizes and lack of validated psychometric tools to ascertain treatment benefits.

Non-cytotoxic Agents

A number of agents with novel mechanisms of anti-tumour activity have been studied in HRPC. Liarozole was reported to improve survival compared with cyproterone acetate after multivariate analysis (87). However, liarazole was associated with toxicity and was not associated with improvement in other endpoints. As well, cyproterone is known to be associated with increased mortality when added to ADT as a primary therapy in prostate cancer (93). When added to doxorubicin, DES was associated with improved failure-free survival but was also associated with serious cardiac toxicity and thrombosis. TTP and pain response were improved with suramin-hydrocortisone compared with placebo-hydrocortisone; however, suramin was also associated with rash, edema, and anemia, and no improvement in quality of life was observed. No statistically significant improvements in survival or disease control were reported with prinomastat, atrasentan, or APC8015. Based on that evidence, the GU DSG recommends that those agents not be used routinely.

ONGOING TRIALS

The National Cancer Institute's clinical trials database on the Internet (http://www.cancer.gov/search/clinical_trials/) was searched for reports of new or ongoing trials. The GU DSG will monitor the progress of the following trials and review reported results when they become available.

Protocol ID(s)	Title and details of trial
G-0029 NCT00089856	GVAX® prostate cancer vaccine vs. docetaxel and prednisone in patients with metastatic hormone-refractory prostate cancer. Treatment groups: GVAX® vs. docetaxel/prednisone Target accrual: unknown Date trial summary last modified: June 3, 2005 Status: active
ECOG-E1899 CALGB-E1899, SWOG-E1899	Phase III randomized study of second-line hormonal therapy versus combination chemotherapy in asymptomatic patients with prostate cancer and a rising PSA after androgen suppression. Treatment groups: ketoconazole/hydrocortisone vs. docetaxel/EMP Target accrual: 590 within 4 years Date trial summary last modified: February 3, 2005 Status: closed
GPC SAT3-03-01 NCT00069745	Satraplatin in hormone-refractory prostate cancer patients previously treated with one cytotoxic chemotherapy regimen (phase III). Treatment groups: satraplatin/prednisone vs. prednisone alone Target accrual: unknown Date trial summary last revised: June 1, 2005 Status: active
UCLA-0307121-01 DEN-D9902B	Phase III randomized study of APC8015 (Provenge®) in patients with asymptomatic metastatic androgen-independent adenocarcinoma of the prostate. Treatment groups: APC8015 vs. placebo Target accrual: 275 patients within 1 year Date trial summary last revised: September 2, 2004 Status: active
MDA-ID-030008 DFCI-03187, MSKCC-03132, Novartis-MDA-ID-030008	Phase II randomized study of docetaxel with versus without imatinib mesylate in patients with androgen-independent prostate cancer and bone metastases. Treatment groups: docetaxel plus imatinib vs. docetaxel plus placebo Target accrual: 144 patients within 2 years Date trial summary last revised: June 18, 2004 Status: active
EORTC-30021 AVENTIS-AVE3139E/2501	Phase II randomized study of docetaxel with or without oblimersen in patients with hormone-refractory adenocarcinoma of the prostate. Treatment groups: docetaxel/oblimersen vs. docetaxel Target accrual: 102 patients Date trial summary last revised: March 8, 2005 Status: active
CALGB-90401 NCT00110214	Phase III randomized study of docetaxel and prednisone with versus without bevacizumab in patients with hormone-refractory metastatic adenocarcinoma of the prostate. Treatment groups: docetaxel/prednisone vs. docetaxel/prednisone/bevacizumab Target accrual: 1020 patients over 3 years Date trial summary last revised: April 23, 2005 Status: active

CONCLUSIONS

Docetaxel-based chemotherapy is the only treatment that has demonstrated an overall survival benefit in men with HRPC. The timing of docetaxel therapy in men without symptoms and only biochemical evidence of progression should be discussed with patients and individualized based on their clinical status and preferences. In the largest randomized trials, the men enrolled continued on gonadal androgen suppression and discontinued the use of antiandrogens. Those manoeuvres are recommended for men with HRPC who receive chemotherapy, in addition to symptom control. Use of EMP in combination with other cytotoxic agents is not recommended due to the increased risk of clinically important toxicities without evidence of improved survival or palliation. There is less evidence of a clinical benefit for EMP plus vinblastine, suramin plus hydrocortisone, and vinorelbine plus hydrocortisone; the routine use of those regimens is not recommended. Non-cytotoxic therapies studied in randomized trials including liarozole, atrasentan, and APC8015 should not be used outside the setting of a clinical trial. Expectant management, trials of secondary hormonal manipulations, and/or participation in clinical trials may be reasonable alternatives for patients on an individualized basis. Use of bisphosphonates and radioisotopes may also be an option for patients with HRPC.

CONFLICT OF INTEREST

The members of the GU DSG disclosed potential conflicts of interest relating to this practice guideline. Three of the guideline authors were co-investigators for the recent Tannock et al trial (4), and one of those authors was also an investigator for three other trials (72,84,87). Two authors reported involvement with the pharmaceutical company that manufactures the chemotherapy agent recommended in the guideline, including advisory boards and receipt of honoraria.

JOURNAL REFERENCE

Winquist E, Waldron T, Berry S, Ernst DS, Hotte S, Lukka H. Non-hormonal systemic therapy in men with hormone-refractory prostate cancer and metastases: a systematic review from the Cancer Care Ontario Program in Evidence-based Care's Genitourinary Cancer Disease Site Group. BMC Cancer. 2006 May 2;6:112. Available from: http://www.biomedcentral.com/content/pdf/1471-2407-6-112.pdf

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Appendix 1: Ineligible randomized trials.

Trial	N	Treatment arms
Eagen, 1976 (7)	26	doxorubicin 5-FU + cyclophosphamide
Kvols, 1977 (8)	16	melphalan ICRF-159 hydroxyurea
Murphy, 1977 (9)	125	EMP streptozotocin standard treatment
Scott, 1977 (10)	110	5-FU cyclophosphamide standard treatment
Tejada, 1977 (11)	18	5-FU CCNU
Chlebowski, 1978 (12)	27	cyclophosphamide cyclophosphamide + 5-FU + doxorubicin
Schmidt, 1979 (13)	129	cyclophosphamide DTIC procarbazine
Loening, 1981 (14)	123	hydroxyurea cyclophosphamide CCNU
Muss, 1981 (15)	32	cyclophosphamide cyclophosphamide + MTX + 5-FU
Smalley, 1981 (16)	71	cyclophosphamide + doxorubicin + 5-FU 5-FU
Soloway, 1981 (17)	90	EMP EMP + vincristine vincristine
Herr, 1982 (18)	40	cyclophosphamide + MTX + 5-FU CCNU
DeWys, 1983 (19)	99	doxorubicin 5-FU
Soloway, 1983 (20)	124	EMP cisplatin EMP + cisplatin
Kasimis, 1985 (21)	30	cyclophosphamide 5-FU + doxorubicin + mitomycin C
Page, 1985 (22)	47	doxorubicin + lomustine cyclophosphamide + 5-FU
Torti, 1985 (23)	37	doxorubicin + cisplatin doxorubicin
Graham, 1986 (24)	58	mephalan + MTX + vincristine + 5-FU + prednisone cyclophosphamide + 5-FU + MTX + prednisone
Akaza, 1988 (25)	26	EMP + peplomycin + doxorubicin 5-FU + peplomycin + doxorubicin
Kitahara, 1988 (26)	22	ifosfamide + 5-FU + cisplatin ifosfamide
Manni, 1988 (27)	85	androgen priming [AGM + hcort + cyclophosphamide + 5-FU + doxorubicin, then MTX, fluorouracil] no priming [AGM + hcort + cyclophosphamide + 5-FU + doxorubicin, then MTX, fluorouracil]
McLeod, 1988 (28)	86	megace megace + DES stilphostrol streptozotocin
Benson, 1989 (29)	60	EMP

Trial	N (subgroup)	Treatment arms DES
Papdopoulos, 1989 (30)	30	cisplatin + epirubicin cisplatin + epirubicin + factor AF2
Ruff, 1989 (31)	57	MPA chlorambucil cyclophosphamide + doxorubicin + 5-FU
Shafik, 1990 (32)	36	MTX per annum MTX iv
Tveter, 1990 (33)	79	EMP epirubicin + MPA epirubicin + placebo
Elomaa, 1991 (34)	41	EMP epirubicin (low dose)
Rangel, 1992 (35)	52	doxorubicin + prednisone prednisone
Francini, 1993 (36)	72	epirubicin doxorubicin
Daliani, 1995 (37)	51	5-FU + interferon-alpha 5-FU
Breul, 1997 (38)	49	5-FU 5-FU + folinic acid
Brune, 1998 (39)	82	pirarubicin AGM + hcort
van Andel, 2000 (40)	28	epirubicin + MPA epirubicin
Figg, 2001(41)	63	thalidomide (low dose, 200mg) thalidomide (high dose, 1200mg)
Millikan, 2001 (42)	89	ketoconazole + doxorubicin ketoconazole
Culine, 2002 (43) Tombal, 2003 (94)	61	irofulven + prednisone irofulven
Hervonen, 2002 (44)	30	ifosfamide (24hr infusion d1) ifosfamide (3hr infusion d1-4)
Oudard, 2002 (45,95)	130	docetaxel (70mg/m^2 d2) + EMP + prednisone docetaxel (35mg/m^2 d2, d8) + EMP + prednisone mitoxantrone + prednisone
Tolcher, 2002 (46)	30	antisense oligonucleotide ISIS 3521 antisense oligonucleotide ISIS 5132
Droz, 2003 (47)	42	oxaliplatin + 5-FU oxaliplatin
Kelly, 2003 (48) Kelly, 2004 (96)	43	epothilone B analogue BMS-247550 + EMP epothilone B analogue BMS-247550
Millikan, 2003 (49)	71	ketoconazole + doxorubicin + vinblastine + EMP paclitaxel + EMP + etoposide
Salimichokami, 2003 (50)	55	docetaxel + thalidomide docetaxel
Sternberg, 2003 (51)	50	satraplatin + prednisone prednisone
van Andel, 2003 (52)	79	epirubicin weekly epirubicin q 4 wks
Albrecht, 2004 (53)	90	EMP + vinblastine EMP
Birch, 2004 (54)	62	docetaxel (36mg/m^2) + EMP docetaxel (70mg/m^2) + EMP
Dahut, 2004 (55)	75	docetaxel + thalidomide docetaxel
Dimopoulos, 2004 (56)	38	EMP + etoposide LHRH analogue + somatostatin analogue (lanreotide) + dexamethasone
Eymard, 2004 (57)	92	docetaxel + EMP

Trial	N	Treatment arms
		docetaxel
Heidenreich, 2004 (58)	48	pegylated liposomal doxorubicin (25mg/m^2) pegylated liposomal doxorubicin (50mg/m^2)
Lara, 2004 (59)	80	MMPI BMS-275291 (1200mg) MMPI BMS-275291 (2400mg)
Millikan, 2004 (60)	150	ketoconazole + doxorubicin alternating with vinblastine + EMP cyclophosphamide + vincristine + dexamethasone paclitaxel + EMP + etoposide paclitaxel + EMP + carboplatin
Stadler, 2004 (61)	36	SU5416 + dexamethasone dexamethasone

Abbreviations: 5-FU – 5-fluorouracil; AGM - aminoglutethimide; CCNU – lomustine; d – day; DES – diethylstilbestrol; DTIC – dacarbazine; EMP – estramustine phosphate; hcort – hydrocortisone; hr – hour; iv – intravenously; LHRH – luteinizing hormone-releasing hormone; m^2 – meters squared; mg – milligrams; MMPI – matrix metalloproteinase inhibitor; MPA – medroxyprogresterone; MTX – methotrexate; N – number; q – every; wks – weeks.

Appendix 2: Antimicrotubule trials – descriptions.

Trial	N randomized/ evaluable	Treatment arms (dose) and schedule	Duration
Tannock, 2004 (4)	1006/1006	docetaxel (75mg/m^2) iv q 3 wks prednisone (5mg) po twice daily dexamethasone (8mg) at 12, 3, and 1hr(s) prior to infusion	10 cycles
		docetaxel (30mg/m^2) iv q wk for 5wks prednisone (5mg) po twice daily dexamethasone (8mg) at 1hr prior to infusion	5 cycles
		mitoxantrone (12mg/m^2) iv q 3 wks prednisone (5mg) po twice daily	10 cycles
Petrylak, 2004 (62)	770/666	docetaxel (60mg/m^2)* iv q 3 wks EMP (280mg) po thrice daily q 3 wks dexamethasone (20mg) po thrice daily q 3 wks	12 cycles
		mitoxantrone (12mg/m^2)* iv q 3 wks prednisone (5mg) po twice daily q 3 wks	
Abratt, 2004 (63)	451/414	vinorelbine (30mg/m^2) iv q 3 wks hydrocortisone (40mg) ± AGM (1000mg)† daily	to progression
		hydrocortisone (40mg) ± AGM (1000mg)† daily	
Berry, 2004 (64)	166/163	paclitaxel‡ (100mg/m^2) iv q 4 wks EMP (280mg) po thrice daily	to progression or intolerable toxicity
		paclitaxel‡ (100mg/m^2) iv q 4 wks	
Hudes, 1999 (65)	201/193	vinblastine (4mg/m^2) iv q wk for 6 of 8 wks EMP (600mg/m^2) po daily (2 or 3 divided doses)	to progression
		vinblastine (4mg/m^2) iv q wk for 6 of 8 wks	
Iversen, 1997 (66)	131/129	EMP (560mg) po daily (2 divided doses)	as long as tolerated by patient
		placebo po daily	
Johansson, 1991 (67)	105/102	MPA (1000mg) im daily (d1-15), then im weekly	to progression
		EMP (280mg) po twice daily	
De Kernion, 1988 (68)	220/203	EMP (600mg/m^2) po (3 divided doses)	NR
		flutamide (0.25gm) po thrice daily	
Murphy, 1979 (69)	135/116	EMP (600mg/m^2) po daily (3 divided doses) prednimustine (30mg) po daily (3 divided doses) q wk	to progression
		prednimustine (30mg) po daily (3 divided doses) q wk	

Abbreviations: AGM – aminoglutethimide; d – day; EMP – estramustine phosphate; hr – hour; im – intra muscular; iv – intravenous; m^2 – meters squared; mg – milligrams; MPA – medroxyprogesterone acetate; N – number; NR – not reported; po – per oral; q – every. wk(s) – week (s).

*Docetaxel could be increased to 70mg/m^2 and mitoxantrone could be increased to 14mg/m^2 if no grade 3 or 4 toxicities were observed in cycle 1
†Decision to use AGM was at the discretion of participating centres
‡Before treatment with paclitaxel, all patients were premedicated with a regimen of dexamethasone (20mg po), diphenhydramine (50mg iv), and cimetidine (300mg iv) or ranitidine (50mg iv).

Appendix 3: Mitoxantrone and anthracycline trials.

Trial	N randomized/ evaluable	Treatment arms (dose) and schedule	Duration
Berry, 2002 (70)	120/119	mitoxantrone (12mg/m^2) iv q 3 wks prednisone (5mg) po twice daily prednisone (5mg) po twice daily	6 cycles
Kantoff, 1999 (71)	242/242	mitoxantrone (14mg/m^2) iv q 3 wks hydrocortisone (40mg) po daily (two divided doses) hydrocortisone (40mg) po daily (two divided doses)	hydrocortisone to progression or treatment failure
Tannock, 1996 (72)	161/161	mitoxantrone (12mg/m^2) iv q 3 wks prednisone (5mg) po twice daily prednisone (5mg) po twice daily	mitoxantrone to dose of 140mg/m^2, continuing on prednisone
Weissbach, 1998 (88)	NR/175	epirubicin (25 mg/m^2) iv q mo EMP (560mg) daily mitomycin C (10mg/m^2) iv q mo	NR
Anderström, 1995 (73)	149/145	epirubicin (20mg/m^2) iv q wk MPA (500mg) po twice daily EMP (12mg/kg) po daily (two divided doses)	epirubicin to dose of 1000mg/m^2, MPA to progression
Laurie, 1992* (74)	145/142	In combination: 5-FU (600mg/m^2) iv q 4-5 wks doxorubicin (30mg/m^2) iv q 4-5 wks mitomycin-C (10mg/m^2) iv q 4-5 wks† In sequence: 5-FU (500mg/m^2) iv q 5 wk doxorubicin (50mg/m^2) iv q 3-4 wk mitomycin-C (12.5mg/m^2) iv q 4 wk	to progression
Saxman, 1992 (75)	103/103	cyclophosphamide (500mg/m^2)‡ iv q 3 wks doxorubicin (50mg/m^2)‡ iv q 3 wks methotrexate (40mg/m^2)‡ iv q 3 wks cyclophosphamide (1000mg/m^2)§ iv q 3 wks	to progression, doxorubicin not to exceed dose of 450mg/m^2
Murphy, 1988 (76)	180/152	doxorubicin (50mg/m^2) iv q 3 wks cyclophosphamide (500mg/m^2) iv q 3 wks cisplatin (50mg/m^2) iv q 3 wks 5-FU (500mg/m^2) iv q 3 wks cyclophosphamide (500mg/m^2) iv q 3 wks methotrexate (100mg/m^2) iv (2 divided doses) q 2 wks	to progression
Stephens, 1984 (77)	158/137	doxorubicin (40mg/m^2)¶ iv q 3 wks cyclophosphamide (200mg/m^2)¶ iv q 3 wks hydroxyurea (3600mg/m^2) po twice q wk	doxorubicin to dose of 450mg/m^2, continuing on cyclophosphamide or hydroxyurea to progression

Abbreviations: 5-FU – 5- fluorouracil; EMP – estramustine phosphate; iv – intravenous; m^2 – meters squared; mg – milligrams; mo – month; MPA – medroxyprogesterone; N – number; NR – not reported; po – per oral; q – every; wk(s) – week(s).

*This trial was terminated early due to declining patient accrual
†after three courses, mitomycin-C was only given with every other course
‡patients who had received prior radiation therapy were give cyclophosphamide, doxorubicin, and methotrexate at doses

of 400mg/m^2, 40mg/m^2, and 32mg/m^2, respectively
§patients who had received prior radiation therapy were given cyclophosphamide at a dose of 800mg/m^2
¶patients older than 65 years and with prior bone irradiation and marrow invasion with tumour were deemed poor risk and were randomized to a reduced dose of doxorubicin (20mg/m^2) and cyclophosphamide (100mg/m^2)

Appendix 4: Other chemotherapy trials.

Trial	N randomized/ evaluable	Treatments (dose) and schedule	Duration
Weissbach, 1998 (88)	NR/175	epirubicin (25 mg/m^2) iv q mo EMP (560mg) daily mitomycin C (10mg/m^2) iv q mo	NR
Newling, 1993 (78)	171/161	mitomycin-C (15mg/m^2) iv q 6 wks EMP (560 to 700mg)* po daily	to progression
Murphy, 1988 (76)	180/152	doxorubicin (50mg/m^2) iv q 3 wks cyclophosphamide (500mg/m^2) iv q 3 wks cisplatin (50mg/m^2) iv q 3 wks 5-FU (500mg/m^2) iv q 3 wks cyclophosphamide (500mg/m^2) iv q 3 wks methotrexate (100mg/m^2) iv (2 divided doses) q 2 wks	to progression
Loening, 1983 (79)	189/158	methotrexate (100mg/m^2) iv (two divided doses) q wk cisplatin (60mg/m^2) iv (d1,4,21,24), then once monthly EMP (600mg/m^2) po daily (3 divided doses)	12 wks

Abbreviations: 5-FU – 5- fluorouracil; d – day; EMP – estramustine phosphate; iv – intravenous; m^2 – meters squared; mg – milligrams; mo – month; N – number; NR – not reported; po – per oral; q – every; wk(s) – week (s).

*Dose of estramustine escalated to 700mg if 560mg dose was tolerated for two weeks.

Appendix 5: Non-cytotoxic trials.

Trial	N randomized/ evaluable	Treatments (dose) and schedule	Duration
Carducci, 2004 (80)	809/809	atrasentan po (10mg) placebo	NR
Carducci, 2003 (81)	288/288	atrasentan (2.5mg) po daily atrasentan (10mg) po daily placebo	to progression
Leaf, 2003 (82)	188/150	doxorubicin (50mg/m^2) iv q 3 wks DES (1g) iv daily for 5d, then twice q wk doxorubicin (50mg/m^2) iv q 3 wks	12 wks, then until doxorubicin cumulative dose of 500mg/m^2 or progression
Small, 2003 (83)	127/127	APC8015 iv q 2 wks x 3 placebo	to progression
Small, 2002 (84)	390/390	suramin (3.192mg/m^2)* iv suramin (5.320mg/m^2)* iv suramin (7.661mg/m^2)* iv	3 cycles (12 weeks)
Ahmann, 2001 (85)	553/406†	prinomastat (5mg) po twice daily mitoxantrone (12mg/m^2) iv q 3 wks prednisone (5mg) po twice daily prinomastat (10mg) po twice daily mitoxantrone (12mg/m^2) iv q 3 wks prednisone (5mg) po twice daily mitoxantrone (12mg/m^2) iv q 3 wks prednisone (5mg) po twice daily placebo	NR
Small, 2000 (86)	460/458	suramin d1: 1000mg/m^2 2-hr iv d2-5: 400 mg/m^2, 300 mg/m^2, 250 mg/m^2, and 200 mg/m^2 iv, respectively d8,11,15,19: 275mg/m^2 iv for 2 wks d22,29,36,43,50,57,64,71,78: 275mg/m^2 iv wks 4-12 hydrocortisone (40mg) po daily hydrocortisone po daily placebo	to progression or unacceptable toxicity
Debruyne, 1998 (87)	321/321	liarozole (300mg) twice daily CPA (100mg) twice daily	to progression or unacceptable toxicity

Abbreviations: CPA – cyproterone acetate; d – day; DES – diethylstilbestrol diphosphate; g – grams; hr – hour; iv – intravenous; m^2 – meters squared; mg – milligram; N – number; NR – not reported; po – per oral; q – every; wk(s) – week(s); x – times.

*Doses of suramin decreased over 10 weeks; all patients received hydrocortisone at a dose of 25mg orally each morning and 15mg orally each evening; †interim results available for 406/553 patients.

Evidence-Based Series 3-15 Version 2: Section 3

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Systemic Therapy in Men with Metastatic Castration-Resistant Prostate Cancer: Development Methods, Recommendations Development and External Review Process

D.A. Loblaw, C. Walker-Dilks, E. Winquist, S.J. Hotte, and the Genitourinary Cancer Disease Site Group

Report Date: September 8, 2014

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, termed Disease Site Groups (DSGs), as well as other groups or panels called together for a specific topic, all mandated to develop the PEBC products. These panels are comprised of clinicians, other health care providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based guidelines, known as Evidence-Based Series (EBS) reports, using the methods of the Practice Guidelines Development Cycle (1,2). The EBS report consists of an evidentiary base (typically a systematic review), an interpretation of and consensus agreement on that evidence by our Groups or Panels, the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each document, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original guideline information.

The Evidence-Based Series

Each EBS is comprised of three sections:

- *Section 1: Guideline Recommendations*. Contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the Group or Panel involved and a formalized external review by review participants.

- *Section 2: Evidentiary Base.* Presents the comprehensive evidentiary/systematic review of the clinical and scientific research on the topic and the conclusions reached by the Group or Panel.

- *Section 3: EBS Development Methods, Recommendations Development, and External Review Process.* Summarizes the EBS development process and the results of the formal external review of the draft version of the EBS.

DEVELOPMENT OF THE ORIGINAL EVIDENCE-BASED SERIES – VERSION 1.2005

The original EBS was developed by the GU DSG of CCO's PEBC. The series was a convenient and up-to-date source of the best available evidence on non-hormonal systemic therapy for hormone-refractory prostate cancer, developed through systematic review, evidence synthesis, and input from practitioners in Ontario. The guideline was completed in 2005. A summary of the development and review process of that guideline document follows.

External Review by Ontario Clinicians

Following review and discussion of sections 1 and 2 of this evidence-based series, the GU DSG circulated the clinical practice guideline and systematic review to clinicians in Ontario for review and feedback. Box 1 summarizes the draft clinical recommendations developed by the panel.

BOX 1:
DRAFT RECOMMENDATIONS (approved for external review March 9, 2005)

Target Population

- Men with progressive hormone-refractory prostate cancer and evidence of metastases.

Recommendation

- For men with clinical or biochemical evidence of progression and evidence of metastases, treatment with docetaxel 75 mg/m^2 administered intravenously every three weeks with 5mg oral prednisone twice daily should be offered to improve overall survival, disease control, symptom palliation, and quality of life.

- Alternative therapies that have not demonstrated improvement in overall survival but can provide disease control, palliation, and improve quality of life include weekly docetaxel plus prednisone, and mitoxantrone plus prednisone (or hydrocortisone).

Qualifying Statements

- Docetaxel-based chemotherapy is the only treatment that has demonstrated an overall survival benefit in men with hormone-refractory prostate cancer.

- The timing of docetaxel therapy in men with evidence of metastases but without symptoms should be discussed with patients and individualized based on their clinical status and preferences.

- In the largest randomized trials reviewed for this guideline, the men enrolled continued on gonadal androgen suppression and discontinued the use of antiandrogens. These manoeuvres are recommended for men with hormone-refractory prostate cancer who

receive chemotherapy.

- Men with hormone-refractory prostate cancer should have symptom control optimized.
- Use of estramustine in combination with other cytotoxic agents is not recommended due to the increased risk of clinically important toxicities without evidence of improved survival or palliation.

Clinician Feedback

Methods

Clinician feedback was obtained through a mailed survey of 105 clinicians in Ontario (11 medical oncologists, 19 radiation oncologists, and 75 urologists). The survey consisted of 23 items evaluating the methods, results, and interpretation used to inform the draft recommendations and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again).

Results

Key results of the clinician feedback survey are summarized in Table 1. Sixty-four (61%) surveys were returned. Of the clinicians who responded, 54 (84%) indicated that the report was relevant to their clinical practice, and they completed the survey.

Table 1. Clinician responses to eight items on the practitioner feedback survey.

Item	Number (%)		
	Strongly agree or agree	Neither agree nor disagree	Strongly disagree or disagree
The rationale for developing a clinical practice guideline, as stated in the "Choice of Topic" section of the report, is clear.	52 (96.3)	2 (3.7)	0
There is a need for a clinical practice guideline on this topic.	50 (92.6)	3 (5.6)	1 (1.9)
The literature search is relevant and complete.	47 (88.7)	6 (11.3)	0
The results of the trials described in the report are interpreted according to my understanding of the data.	53 (98.1)	1 (1.9)	0
The draft recommendations in this report are clear.	53 (98.2)	0	1 (1.9)
I agree with the draft recommendations as stated.	51 (94.4)	2 (3.7)	1 (1.9)
This report should be approved as a practice guideline.	46 (85.2)	4 (7.4)	4 (7.4)
If this report were to become a practice guideline, how likely would you be to make use of it in your own practice?	Very likely or likely	Unsure	Not at all likely or unlikely
	45 (83.3)	5 (9.3)	4 (7.4)

Summary of Written Comments

Fourteen respondents (26%) provided written comments. The main points contained in the written comments were:

1. Several clinicians raised concerns over the modest survival benefit (i.e., two months) associated with docetaxel and the expensive cost of this chemotherapy. Those clinicians predict the cost implications of recommending this drug will be huge given the large size of this patient population. One clinician commented, "have you proven

that the patients receiving expensive new chemotherapy and surviving an additional two months had improved quality of life?" This clinician requested information on the cost for a quality of life year before subjecting patients to this form of chemotherapy. Another clinician was sceptical that a two-month survival benefit was clinically significant, and suggested the benefit be weighed against the improved quality of life of less toxic regimens. It was also suggested that the recommendations stress the need for symptom relief and options for medications, and not just the survival benefit.

2. A number of clinicians voiced uncertainty over when to introduce treatment with docetaxel.

3. One clinician commented that it is not clear if the recommendations apply to symptomatic or asymptomatic patients.

4. Four clinicians thought the review was a good summary of the evidence, the recommendations were appropriate, and there is a need for a guideline on this topic.

Modifications/Actions

1. The GU DSG acknowledges the importance of cost and funding issues; however, the mandate of the GU DSG is to examine the evidence on the clinical effectiveness of treatment, and assess this aspect in relation to impacts on quality of life and adverse effects. This guideline has been forwarded to the Drug Quality and Therapeutics Committee-CCO Subcommittee for funding consideration (see below); there, pharmaco-economics are considered. Regarding the comments on the magnitude of the survival benefit and improvements in quality of life – the Tannock et al (3) trial shows improved quality of life response, pain response, and PSA response, and the Petrylak et al (4) trial shows improved PFS, with docetaxel-based regimens. Although modest, the survival benefit is accompanied by unequivocal benefits in palliation and disease control.

2. The optimal time to introduce treatment with docetaxel cannot be determined from the docetaxel trials reviewed in this report. For asymptomatic or minimally symptomatic patients, the trials did show improved overall survival, and PFS, providing a basis for offering docetaxel for disease control if patients have signs of progression (e.g., rising PSA).

3. Presence of symptoms was not required for entry into both docetaxel trials, but evidence of metastases and disease progression were required. Therefore, docetaxel should be considered a treatment option in patients with significant cancer symptoms in the setting of progressive disease.

After carefully reviewing the written comments provided by clinicians, the GU DSG decided not to modify the recommendations.

Report Approval Panel

The final practice guideline report was reviewed by one member of the PEBC Report Approval Panel and was approved with minor editorial changes.

POLICY REVIEW

This practice guideline report was requested by the former Policy Advisory Committee in June 2004. The report was forwarded to the new drug funding body, the Drug Quality and Therapeutics Committee-CCO Subcommittee, for a funding request for docetaxel (75 mg/m^2 administered intravenously every three weeks) plus prednisone (5 mg administered orally twice daily) for men with progressive HRPC and evidence of metastases.

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4. Petrylak DP, Tangen CM, Maha PH, Hussain HA, Lara PH, Jones JA, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. N Engl J Med. 2004;351:1513-20.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES – VERSION 2.2013

This EBS was a joint collaboration between CCO and the American Society of Clinical Oncology (ASCO). The series is a convenient and up-to-date source of the best available evidence on systemic therapy in men with mCRPC, developed through review of the evidentiary base, evidence synthesis, and input from external review participants in Canada and the United States.

The guideline recommendations were developed by an Expert Panel composed of representatives of CCO and ASCO. The format of the guideline recommendations followed the structure of an ASCO clinical practice guideline.

The systematic review providing the evidentiary base for the guideline recommendations was produced by three CCO clinicians who were also members of the Expert Panel and a CCO-PEBC research coordinator.

The systematic review was completed in 2012 and submitted for publication. Because the guideline recommendations were formulated in the ensuing months, the guideline portion of this EBS has some updated references and incorporates some changes to the text.

FORMATION OF THE GUIDELINE DEVELOPMENT/WORKING GROUP

The ASCO Clinical Practice Guidelines Committee and CCO Program in Evidence-Based Care convened an Expert Panel with multidisciplinary representation in medical oncology, urologic oncology, radiation oncology, community oncology, patient representation, health services and implementation research and guideline methodology. The Expert Panel was led by a Chair who had the primary responsibility for the development and timely completion of the guideline. For this guideline, the Chair selected an additional member from the Expert Panel to form a Steering Group to assist in the development and review of the guideline drafts. The Expert Panel members are listed in Appendix 1.

The Expert Panel met on several occasions and corresponded frequently through email; work on the guideline was completed primarily through a steering group along with ASCO staff. The purpose of the Panel meetings was for members to contribute content, provide critical review, and finalize the guideline recommendations based upon the consideration of the evidence. All members of the Expert Panel participated in the preparation of the draft guideline document, which was submitted to the Journal of Clinical Oncology (JCO) for peer review. All ASCO guidelines are reviewed and approved by the ASCO Clinical Practice Guideline Committee prior to publication. All CCO guidelines are reviewed and approved by a Report Approval Panel and a topic-specific disease site group: in this instance, the CCO Genitourinary Disease Site Group (GU DSG). The document was also disseminated to physicians with relevant expertise in Canada and the United States for external review.

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Management Procedures for Clinical Practice Guidelines ("Procedures," summarized at http://www.asco.org/guidelinescoi) and in accordance with CCO's Conflict of Interest Policy. Members of the Panel completed ASCO's and CCO's disclosure forms, which requires disclosure of financial and other interests that are relevant to the subject matter of the guideline, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as the result of promulgation of the guideline. Categories for disclosure include employment relationships, consulting arrangements, stock ownership, honoraria, research funding, and expert testimony. In accordance with the Procedures, the majority of the members of the Panel did not disclose any such relationships.

INTERNAL REVIEW

Report Approval Panel, ASCO Clinical Practice Guideline Committee, and GU DSG Review

Prior to the submission of this EBS draft report for External Review, the report was reviewed and approved by the PEBC Report Approval Panel, a panel that includes oncologists and whose members have clinical and methodological expertise; the ASCO Clinical Practice Guideline Committee; and members of the GU DSG.

Report Approval Panel

The CCO Report Approval Panel reviewed the guideline and was supplied with the systematic review for additional information. The Panel approved the guideline unconditionally. The main comments pertained to the presentation of the recommendations, for example, the use of imperatives (should, should not).

Response

Concerns about the wording of the recommendations were considered and the wording was revised.

A comment was also made about inconsistencies in the interpretation of the data between recommendations in the guideline portion and conclusions in the systematic review regarding the use of mitoxantrone.

Response

The text on the use of mitoxantrone was revised to reflect that it may be suitable for select patients depending on clinical circumstances or patient preferences.

ASCO Clinical Practice Guideline Committee

The ASCO Clinical Practice Guideline Committee reviewed the guideline. The Committee approved the guideline unconditionally.

Some suggestions were made to improve the clarity of the document:

An updated interim analysis of the COU-AA-302 study was presented at the ASCO GU Symposium after the cut-off of the guideline search with results showing a 47% reduction in risk of disease progression and a 21% decrease in risk of death.

Response

The reference to the full publication (Ryan2013) replaced the 2012 abstract in the guideline.

It was asked whether any validated tools, such as GRADE, were used for assessment and rating of study quality.

Response

Much of the GRADE framework is incorporated into the quality assessment, as are elements from the AHRQ and Cochrane Collaboration. Since the GRADE framework is still evolving and can be confusing to readers, we thought that a blend of approaches would best suit our guideline development needs.

GU DSG

The GU DSG reviewed the guideline and was supplied with the systematic review for additional information. The GU DSG approved the guideline with minor suggestions. Comments were similar to those of the Report Approval Panel with suggestions to rephrase the recommendations and the Clinical Practice Guidelines Committee, which noted that some updated references were available in full publications to replace abstracts.

Response

These comments were addressed.

EXTERNAL REVIEW

Canadian and U.S. Content Experts

Following the review and discussion of Section 1: Recommendations and Section 2: Evidence Summary of this EBS and the review and approval of the report by the PEBC Report Approval Panel and the ASCO Clinical Practice Guideline Committee, the guideline was disseminated to external review participants in Canada and the United States for review and feedback. The reviewers also had access to the systematic review. Box 1 summarizes the draft recommendations and supporting evidence developed by the Expert Panel.

BOX 1:
DRAFT RECOMMENDATIONS (approved for external review July 18, 2013)

Recommendations

The following recommendations are informed by RCTs and are evidence-based. There are no data on the optimum sequence of therapy, hence sequencing recommendations cannot be offered at this time. Ratings for benefits, harms, evidence quality and recommendation strength are provided.

Pre-Docetaxel Containing Systemic Therapy

For men with metastatic CRPC being considered for systemic therapy prior to chemotherapy, it is recommended that Oncology Clinicians:

- **should** offer abiraterone acetate and prednisone
  (Benefits: high; Harms: low; Evidence quality: moderate; Recommendation strength: moderate)
- **should** offer sipuleucel-T

  (Benefits: high [modest survival benefits]; Harms: low; Evidence quality: weak; Recommendation strength: weak)

The optimum time to start systemic therapy is unknown; reasonable alternatives include observation or participation in clinical trials. No recommendation can be made on the use of tasquinamod or enzalutamide at this time; results from phase III trials are pending. Results from phase III trials on atrasentan or zibotentan were negative and these agents are not recommended.

Docetaxel-Containing Systemic Therapy

For men with metastatic CRPC being considered for chemotherapy, it is recommended that oncology clinicians:

- **should** offer docetaxel and prednisone
  (Benefits: high; Harms: moderate; Evidence quality: strong; Recommendation strength: strong)
- **may** offer mitoxantrone and prednisone
  (Benefits: moderate; Harms: moderate; Evidence quality: moderate; Recommendation strength: moderate)
- **should not** offer bevacizumab in addition to docetaxel and prednisone
  (Benefits: moderate; Harms: high; Evidence quality: strong; Recommendation strength: moderate against).

No recommendations can be made on the use of prednisolone, AT-101, oblimersen, or imatinib at this time. Results from small RCTs on these agents are considered exploratory. Results from phase III trials on atrasentan, GVAX, and calcitriol were negative and these agents are not recommended. A meta-analysis of 5 phase II/III trials of estramustine (N=605) detected significant clinical benefit with increased toxicity while a subsequent phase II trial (N=150) was negative with increased toxicity.

On the basis of the evidence to date, the use of estramustine is not recommended.

Post-Docetaxel Systemic Therapy

For men with metastatic CRPC who are being considered for post-chemotherapy systemic therapy, it is recommended that oncology clinicians:

- **should** offer one of the following:
  - abiraterone and prednisone
    (Benefits: high; Harms: low; Evidence quality: strong; Recommendation strength: strong)
  - enzalutamide
    (Benefits: high; Harms: low; Evidence quality: strong; Recommendation strength: strong)
  - cabazitaxel and prednisone
    (Benefits: high; Harms: moderate; Evidence quality: strong; Recommendation strength: strong)
- **may** offer mitoxantrone plus prednisone
  (Benefits: low; Harms: moderate; Evidence quality: weak to moderate; Recommendation strength: moderate)
- **should not** offer sunitinib
  (Benefit: moderate; Harms: moderate; Evidence quality: moderate; Recommendation strength: moderate against)

Based on the results from a phase III trial on satraplatin (N=950), the harms from adverse events were seen to outweigh the clinical benefit and this agent is not recommended. No recommendations can be made on the use of cabozantinib at this time; results from ongoing phase III trials are pending.

See Appendix II for details of how the above recommendations fit in the greater context of care for men who develop CRPC.

Qualifying Statements

In the setting of metastatic CRPC, the intent of treatment is palliation with delay of clinical decline and optimization of quality of life; modest improvements in overall survival are also now being observed with many interventions but many patients will place a higher importance on quality rather than length of life. The objective and choice of treatment is highly dependent upon patient treatment preferences and clinicians should balance patient preferences with the expected tolerability of treatment choice. Patients may opt for a less efficacious treatment if the trade-off involves less toxicity or includes other meaningful benefits. This may be in spite of limited evidence and/or an uncertain balance between benefits and harms for a given agent or course of action. There could also be drug cost or availability considerations that may influence treatment decisions. In addition, the evidence informing recommendations is from RCTs that selected medically fit patients to participate in the trials. Therefore, the choice of treatments for patients with lower or poor performance status is less clearly informed by the evidence.

The categorization of benefits or harms (high, moderate, or low) is intended to indicate the overall assessment of impact to the patient and the quality of evidence supporting that assessment. In the absence of benefits, harms were not considered and are labeled as not applicable.

Methods

Professional Consultation: Feedback was obtained through a brief online survey of health care professionals who are the intended users of the guideline. A mix of Canadian and American physicians was surveyed as this guideline is a collaborative project between CCO and ASCO. Participants were asked to rate the overall quality of the guideline and whether they would use and/or recommend it. Written comments were invited. Participants were contacted by email and directed to the survey website where they were provided with access to the survey, the guideline recommendations, and the evidentiary base. The notification email was sent on July 18, 2013. The consultation period ended on August 19, 2013. The Expert Panel reviewed the results of the survey.

Results

Professional Consultation: Fourteen responses were received. Key results of the feedback survey are summarized in Table 1.

Table 1. Responses to four items on the professional consultation survey.

	Number (%)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.				9	5
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.			1	4	9
3. I would recommend this guideline for use in practice.			1	3	10

4. What are the barriers or enablers to the implementation of this guideline report?

- Difficulties of providing new agents to eligible patients with diverse drug coverage.
- Ongoing lag between practice guideline recommendation publication and ODB coverage.
- Cost and uncertainty around availability and funding of agents.
- Funding policies that may directly influence choice of therapy where more than one option is appropriate and may prevent full access to the range of effective therapies, depending on the sequence of therapies given to an individual.
- Recommendations are not Canadian-centric enough. The inclusion of sipuleucel-T as a standard option is not warranted as it is not available in Canada.
- The evidence supporting the recommendation of sipuleucel-T is flawed, and it should not be recommended. The fact that patient selection criteria were altered as the trial progressed and the primary endpoints were changed from PFS and time to disease-related pain to overall survival invalidates this trial, and we are left with a treatment that apparently improves overall survival without any effect on PSA response or delay in disease progression. The likely explanation of the difference in overall survival is worse survival in the control group patients due to harm caused by leukapheresis in older patients rather than benefit of the treatment. There should be a stronger recommendation in favour of abiraterone or enzalutamide post-chemotherapy.

- Timing of initiation of additional therapies in nonmetastatic and metastatic CRPC unavoidably remains ambiguous for the practitioner. Rising PSA values, sometimes without documented evidence of objective worsening of metastatic disease or symptoms, prompt increasing anxiety in the patient and physician and engender pressure to do something.

Summary of Written Comments

The main points contained in the written comments were:

The comments revealed controversy surrounding the use of sipuleucel-T. One respondent urged the removal of sipuleucel-T from the recommendations, or at least separation of the CCO and ASCO recommendations regarding sipuleucel-T. Another respondent suggested emphasizing the potential for additive benefit with sequencing sipuleucel-T and abiraterone acetate, although the optimal sequence in the chemo-naïve setting is not currently known. One respondent mentioned that the new oral agents abiraterone and enzalutamide will likely be used sequentially despite little evidence available to quantify response rates, durability, or optimal sequencing.

Modifications/Actions

In response to the external review suggestions and comments, the recommendations were restructured to allow for greater consideration of healthcare setting and drug availability. Also, further discussion about sipuleucel-T with supporting references was provided.

Peer Review Feedback

Clinical Oncology

The systematic review portion of the EBS was submitted to Clinical Oncology in September 2012. Peer review feedback included requests to add more information on the reporting structure (PRISMA flow diagram, forest plot to summarize meta-analysis data, and methodological details of the studies) and a clearer statement of the objectives. Although these items were present in the online version of the document, they were added to the journal version and it was resubmitted in January 2013.

Journal of Clinical Oncology

The clinical practice guideline portion of the EBS was submitted to JCO in April 2013. JCO reviewer comments included the following:

- Concern was expressed about the planned omission of androgen deprivation therapies, bone targeted agents, and radionuclides from the document given the role of these agents in treating metastatic prostate cancer.
    - Although these topics were beyond the scope of the guideline parameters, they were addressed through the use of existing guidelines. The National Comprehensive Cancer Network and American Urology Association (AUA) guideline recommendations were summarized in the text, and recommendations from the AUA, which were based on a systematic literature review, were presented in an appendix. In addition, reference to a companion ASCO guideline that discusses whether these agents have a role in mCRPC now that abiraterone acetate and enzalutamide are approved was added.

- Concern was expressed about the tepid recommendation for sipuleucel-T despite the improvement in overall survival while other agents, particularly abiraterone acetate, were recommended, despite not showing a significant increase in survival in the pre-chemotherapy setting.
    - The recommendation was revised to recommend offering sipuleucel-T as treatment option.
- Concern was expressed about the lack of advice on the optimal sequence of available therapies for mCRPC.
    - Although the Expert Panel tried to formulate an optimal sequence strategy, it was unable to come to a consensus on these aspects of care, and the existing guidelines did not provide recommendations. These uses were addressed by indicating in the recommendations that due to lack of data, no recommendations can currently be made on the optimum sequence of therapy.

CONFLICT OF INTEREST

In accordance with the PEBC and ASCO Conflict of Interest Policy, the Expert Panel, GU DSG members, and internal reviewers were asked to disclose potential conflicts of interest.

Name	Role	Declared interests
Michael Carducci	Author/Expert Panel Member	Financial interests: Consultant or advisory role for Medivation and Sanofi.
Sebastien Hotte		Financial interests: Consultant or advisory role for Pfizer. Professional interests: Research funding from Medivation and Pfizer.
Michael Katton		Financial interests: Consultant or advisory role for Dendreon. Professional interests: Research funding from Dendreon.
Andrew Loblaw		Financial interests: Consultant or advisory role for AstraZeneca, Roche, and Sanofi-Aventis; honoraria from AstraZeneca and Sanofi-Aventis. Professional interests: Research funding from Sanofi-Aventis.
Derek Raghavan		Financial interests: Consultant or advisory role for Sanofi.
Fred Saad		Financial interests: Consultant or advisory role for Centocor Ortho, Dendreon, Medivation, and Sanofi; honoraria from Sanofi. Professional interests: Research funding from Genentech and Medivation.
Mary-Ellen Taplin		Financial interests: Consultant or advisory role for Sanofi. Professional interests: Research funding from

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Ethan Basch		No interests declared
Charles Bennett		
Ronald Chen		
James Frame		
Kristina Garrells		
Robert Nam		
Katherine Virgo		
James Williams		
Eric Winquist		
Ted Wootton		
Thomas Oliver	Author/ASCO Staff	
Cindy Walker-Dilks	Author/CCO Staff	
Glenn Bauman	GU DSG Member	Professional interests: Grant support from Sanofi-Aventis; managerial responsibility for a department that has received $5,000 or more in a single year from a relevant business entity (Chair of Department of Oncology, University of Western Ontario).
Christina Canil		Financial interests: $5,000 or more in a single year from consulting fees, honoraria, or other support from Sanofi-Aventis. Professional interests: Local principal investigator or co-investigator in trials of enzalutamide, abiraterone acetate, and cabazitaxel.
Charles Catton		Financial interests: Radiation oncology practice is incorporated.
Urban Emmenegger		Financial interests: $5,000 or more in a single year from consulting fees, honoraria, or other support from Sanofi-Aventis. Professional interests: Local principal investigator in clinical trials of cabazitaxel and enzalutamide.
Himu Lukka		Financial interests: Radiation oncology practice is incorporated. Professional interests: Funding from AstraZeneca, Abbot Labs, and Sanofi-Aventis as sponsorship for Genitourinary Radiation Oncologists of Canada meeting (co-ordinator).
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UPDATING

This document will be reviewed in three years time to determine if it is still relevant to current practice and to ensure that the recommendations are based on the best available evidence. The outcome of the review will be posted on the CCO website. If new evidence that will result in changes to these recommendations becomes available before three years have elapsed, an update will be initiated as soon as possible.

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Ontario Health
Cancer Care Ontario

Evidence-based Series 3-15 Version 2: Section 4

Systemic Therapy in Men with Metastatic Castration-Resistant Prostate Cancer

Document Review Summary

M. Smoragiewicz, N. Coakley and Members of the Genitourinary Guideline Development Group

Review Date: March 18, 2021

The 2014 guideline recommendations

REQUIRE UPDATING

This means that the recommendations require additional evidence but are are relevant for decision making.

OVERVIEW

The original version of this evidence summary was released by the OH (CCO) Program in Evidence-based Care on November 1, 2005. In January 2019, this document was assessed in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. As part of the review, a PEBC methodologist conducted an updated search of the literature in December 2020. Clinicians from the Genitourinary Guideline Development Group determined that the recommendations should be updated. The recommendations may still be used for decision making.

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Research Question

In men with metastatic castration-resistant prostate cancer (mCRPC), which systemic therapies improve cancer- or patient-related outcomes?

Target Population
Men with metastatic castration-resistant prostate cancer.

Study Selection Criteria
Articles were eligible for inclusion if they had the following components:

- They were reports from RCTs, systematic reviews of RCTs with or without meta-analysis, or clinical practice guidelines with a systematic review.
- The intervention was systemic therapy or combination (excluding primary or secondary androgen deprivation therapy, bone protective agents, or radionuclides) compared with placebo or other drug regimens.
- RCTs contained ≥50 patients per study arm.
- The study population consisted of men with mCRPC. In mixed populations, ≥90% of men were required to have metastases.
- The outcomes of interest were any of the following: overall survival, disease control (i.e., progression-free survival, time-to-progression, time-to-treatment failure, objective tumour response, and PSA response), palliative or symptomatic response, quality of life, or toxicity.

Search details

- July 2021 to December 2020 (Cochrane Database of Systematic Reviews)
- July 2021 to December 2020 (Medline and Embase)
- July 2021 to December 2020 (Medline and Embase)

Summary of New Evidence
6082 articles we found in the search from 2013 to November 26 2020. Of these 839 underwent full text review. 89 were kept and are listed below in the table. There were 11 guidelines 28, systematic reviews and 50 RCTs. See the evidence table for the results.

Document Assessment and Review tool

1. Does any of the newly identified evidence contradict the current recommendations? (i.e., the current recommendations may cause harm or lead to unnecessary or improper treatment if followed)	The newly identified evidence does not *per se* contradict the current recommendations, except perhaps some data regarding sequencing of therapies as described below (CARD trial for example).
2. Does the newly identified evidence support the existing recommendations?	To a large extent, they still do.
3. Do the current recommendations cover all relevant subjects addressed by the evidence? (i.e., no new recommendations are necessary)	There are a number of updates and novel agents that should be updated in the recommendations: - PARP inhibitors - Pembrolizumab for dMMR/MSI high. The study is not identified below, probably due to the search strategy but probably should be discussed in the updated recommendations. - Sequencing of therapies based on CARD trial - The non-mestastatic CRPC space has a number of novel indications. While technically not considered mCRPC, most of these patients probably have metastatic disease based on novel imaging with PSMA PET, and this may need to be at least mentioned in an updated recommendation. - Many of the agents currently recommended for use in the mCRPC are now being offered in the metastatic hormone sensitive space. Therefore, this may have implications on the available choices in mCRPC. This should be mentioned in a recommendation update.
Review Outcome as recommended by the Clinical Expert	Update
If outcome is UPDATE, are you aware of trials now underway (not yet published) that could affect the recommendations?	The phase III VISION clinical trial (NCT03511664) is anticipated to report this year. This is evaluating a novel class of agent (177Lu-PSMA-617) in the 3rd line+ for mCRPC, and has very encouraging phase II data.
DSG/Expert Panel Commentary	None

Evidence Tables

Guidelines

Study reference	Type of study	Summary of recommendations
So 2020	Canadian Urological Association-Canadian Urologic Oncology Group guideline on metastatic castration-naive and castration-sensitive prostate cancer	Docetaxel (75 mg/m2 every three weeks for six cycles) plus ADT is an option for men with mCNPC/mCSPC with good performance status and high-volume metastatic disease, defined as: presence of visceral metastases, or four or more bone lesions with at least one beyond the vertebral bodies and pelvis (Level 1, Strong recommendation). Docetaxel plus ADT may also be an option in patients with mCNPC/mCSPC with good performance status with low-volume disease (Level 2, Weak recommendation) . "High risk" mCNPC/mCSPC patients (defined as at least two of: Gleason score of 8–10, visceral metastases, and three or more bone metastases) with good performance status can also be considered for docetaxel chemotherapy (Level 1, Strong recommendation) Abiraterone acetate (1000 mg daily) with prednisone (5 mg daily) plus ADT is an option for mCNPC patients with at least two of the three: Gleason score of ≥8, presence of three or more lesions on bone scan, or presence of measurable visceral metastasis (Level of evidence 1, Strong recommendation). Abiraterone acetate (1000 mg daily) with prednisone (5 mg daily) plus ADT may be considered for patients with low-volume mCNPC(Level of evidence 3, Weak recommendation). Enzalutamide (160 mg/day) is a treatment option for mCNPC/mCSPC regardless of volume of disease (Level of evidence 1, Strong recommendation). Enzalutamide should not be used in combination (concurrent use) with docetaxel to treat mCNPC/mCSPC (Level of evidence 2, Strong recommendation). Enzalutamide may be considered in mCSPC patients pre-iously treated with docetaxel chemotherapy (sequential use) (Level of evidence 1, Weak recommendation). Apalutamide (240 mg) is a treatment option for men with mCNPC/mCSPC regardless

Study reference	Type of study	Summary of recommendations
		of volume of disease (Level of evidence 1, Strong recommendation).
Saad 2020	Consensus GL used Modified Delphi process	For most asymptomatic or minimally symptomatic men with mCRPC who did not receive docetaxel or abiraterone acetate + prednisone in the castrationsensitive setting, abiraterone acetate + prednisone or enzalutamide is the preferred first-line treatment for mCRPC. 100% Chemotherapy used after initial ARAT therapy is not felt to restore sensitivity to further ARAT use. 74.1% In the mCRPC setting, fatigue related to enzalutamide was treated with a dose reduction of enzalutamide. 88.9
Puente 2020	Consensus recommendation on on the management of patients with metastatic castration-resistant prostate cancer who progress after CHAARTED or LATITUDE Used Delphi process	1. In patients with mCRPC who have progressed after ADT+DOC treatment (1st line) and present a time-to-progression up to 6 months from the last DOC cycle, the panel considers CAB to be preferable 2. In patients with mCRPC who have progressed during treatment with ADT+DOC (1st line), the panel considers CAB to be preferable 3. In patients with mCRPC who have progressed after ADT+DOC treatment (1st line) and only present biochemical progression, the panel considers either ABI or ENZ to be preferable 4. In patients with mCRPC who have progressed after ADT+DOC treatment (1st line) and present clinical or radiographic progression, the panel considers it appropriate to analyze other factors before making a final treatment decision 5. In patients with mCRPC who have progressed after ADT+DOC treatment (1st line) and present visceral metastases (hepatic), the panel considers chemotherapy to be preferable 6. In patients with mCRPC who have progressed after ADT+DOC treatment (1st line) and present an ECOG score ⩾2, the panel considers either ABI or ENZ to be preferable 7. In patients with mCRPC who have progressed after ADT+DOC treatment (1st line) and present an ECOG score ⩾2, deemed to be cancer-related, the panel considers chemotherapy to be a potential treatment option 8. In patients with mCRPC who have progressed after ADT+DOC treatment (1st line) and present aggressive disease, the panel considers platinum-based combinations as treatment option 9. In patients with mCRPC who have progressed after ADT+DOC treatment (1st line) and present neuroendocrine variants without aggressive disease criteria, the panel considers that platinum-based combinations are preferable 10. In patients with mCRPC who have progressed after ADT+DOC treatment (1st line) and exhibit poor tolerance to chemotherapy, the panel considers either ABI or

Study reference	Type of study	Summary of recommendations
		ENZ to be preferable 11. In patients with mCRPC who have progressed after ADT+ABI treatment (1st line), the panel considers DOC to be generally preferable 12. Taking into account the new EMA restrictions regarding the use of radium-223 in patients with mCRPC who have progressed after ADT+ DTX treatment, the panel considers radium-223 as an treatment option in patients with symptomatic bone metastases without visceral disease, and with high-volume disease, but only in patients who have previously failed two previous treatments for mCRPC or have no other treatment alternatives 13. In patients with mCRPC who have progressed after ADT+ABI treatment (1st line) and are unfit according to SIOG criteria, the panel considers ENZ to be preferable, taking into account thatradium-223 is restricted to patients who have previously failed in two treatments for mCRPC or have no other cancer treatment alternatives 14. In any treatment decision-making, the panel considers it crucial to take into account the patient's preferences
Parker 2020	**Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up**	• Abiraterone or enzalutamide [ESMO-MCBS v1.1 scores: 4] is recommended for asymptomatic/mildly symptomatic men with ChT-naive mCRPC [I, A]. • Docetaxel [ESMO-MCBS v1.1 score: 4] is recommended for men with mCRPC [I, A]. • In patients with mCRPC in the post-docetaxel setting, abiraterone [ESMO-MCBS v1.1 score: 4], enzalutamide [ESMO-MCBS v1.1 score: 4] and cabazitaxel [ESMO-MCBS v1.1 score: 3] are recommended options [I, A]. • In patients with bone metastases from CRPC at risk for clinically significant skeletal-related events (SREs), a bisphosphonate or denosumab is recommended (see section on palliative care) [I, B]. • ^{223}Ra [ESMO-MCBS v1.1 score: 5] is recommended for men with bone-predominant, symptomatic mCRPC without visceral metastases [I, B]. •^{223}Ra is not recommended in combination with abiraterone and prednisolone [I, E]. •The use of a second AR inhibitor (abiraterone after enzalutamide or vice versa) is not recommended [II, D]
Gillessen 2020	Consensus conference Modified Delphi **Report of the Advanced Prostate Cancer Consensus Conference**	Q74: For patients whose mCRPC is progressing on abiraterone, assuming that there are no regulatory limitations, 14% of panellists voted for switching to enzalutamide in the majority of patients, 63% voted for switching to enzalutamide in a minority of selected patients (eg, response ≥6 mo on treatment with abiraterone), and 23% voted against switching to enzalutamide. There were no abstentions. (No consensus

Study reference	Type of study	Summary of recommendations
	2019	for any given answer option) Q75: For patients whose mCRPC is progressing on enzalutamide, assuming that there are no regulatory limitations, 6% of panellists voted for switching to abiraterone in the majority of patients, 49% voted for switching to abiraterone in a minority of selected patients, and 45% voted against switching to abiraterone. There was one abstention. (No consensus for any given answer option) Q77: In all, 15% of panellists voted for and 85% voted against the use of AR-V7 testing to select candidates for abiraterone after enzalutamide therapy (or vice versa). There was one abstention. (Consensus against the use of AR-V7 testing to identify candidates for treatment with abiraterone or enzalutamide) Q78: When starting abiraterone in patients with mCRPC, 75% of panellists voted for a steroid regimen of prednisone/prednisolone 5 mg twice daily, 5% voted for prednisone/prednisolone 10 mg once daily, 16% voted for prednisone/prednisolone 5 mg once daily, and 4% voted for dexamethasone 0.5–1 mg once daily. There were no abstentions. (Consensus for using prednisone/prednisolone 5 mg twice daily when starting abiraterone in patients with mCRPC) Q76: When discontinuing abiraterone or chemotherapy, 86% of panellists voted to taper steroids over a course of some weeks, 14% voted to stop steroids at the last administration of abiraterone or chemotherapy, and none voted to continue the same dose of steroids. There were no abstentions. (Consensus for tapering steroids over a course of some weeks) Q79: In all, 89% of panellists considered it appropriate to prescribe a lower dose of abiraterone (250 mg) with food for patients with metastatic prostate cancer in the context of limited resources (patient or system), while 11% voted against this practice. There were no abstentions. (Consensus for a lower dose of abiraterone with food in the context of limited resources) Q80: Regarding the use of bicalutamide as sole additional therapy (with ADT) for the management of mCRPC, 49% of panellists voted for this practice only in the context of limited resources, 27% voted for it in a minority of selected patients, 20% voted

Study reference	Type of study	Summary of recommendations
		against it, and 4% voted for it for the majority of patients. There were no abstentions. (No consensus for any given answer option) Q81: Regarding the use of low-dose dexamethasone as sole additional therapy (with ADT) for the management of mCRPC, 44% of panellists voted for this practice only in the context of limited resources, 27% voted for it in a minority of selected patients, 20% voted against it, and 9% voted for it in the majority of patients. There was one abstention. (No consensus for any given answer option)
EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer. Part II—2020	Consensus GL	Ensure that testosterone levels are confirmed to be <50 ng/dl, before diagnosing castration-resistant PCa (CRPC). Counsel, manage, and treat patients with mCRPC in a multidisciplinary team. Treat patients with mCRPC with life-prolonging agents. Base the choice of first-line treatment on the performance status, symptoms, comorbidities, location and extent of disease, patient preference, and previous treatment for HSPC (in alphabetical order: abiraterone, cabazitaxel, docetaxel, enzalutamide, radium-223, sipuleucel-T). Offer docetaxel 75 mg/m^2 every 3 wk to patients with mCRPC who are candidates for cytotoxic therapy. Offer patients with mCRPC and progression following docetaxel chemotherapy further life-prolonging treatment options, which include abiraterone, cabazitaxel, enzalutamide, and radium-223 Base further treatment decisions of mCRPC on pretreatment performance status, response to previous treatment, symptoms, comorbidities, extent of disease, and patient preference. Offer cabazitaxel to patients previously treated with docetaxel and progressing within 12 mo of treatment with abiraterone or enzalutamide.
Gillessen 2019	Consensus Guideline Report of the Advanced Prostate Cancer Consensus Conference 2019 Management of Patients with Advanced Prostate Cancer:	Management of mCRPC Recommended strategy regarding steroid therapy when discontinuing abiraterone or chemotherapy: consensus (86%) for tapering steroids over a course of some weeks The panel was asked whether they recommended AR-V7 testing to select candidates for abiraterone after enzalutamide (or vice versa): consensus (85%) against the use of AR-V7 testing to identify candidates for treatment with abiraterone or enzalutamide The panel voted on the recommended glucocorticoid regimen when starting

Study reference	Type of study	Summary of recommendations
		abiraterone in patients with mCRPC: consensus (75%) for using prednisone/prednisolone 5mg twice daily when starting abiraterone in patients with mCRPC The panel voted on the question whether it was appropriate to prescribe a lower dose of abiraterone (250 mg) given with food for patients with metastatic prostate cancer in the context of limited resources (patient or system): consensus (89%) for a lower dose of abiraterone with food in the context of limited resources The panel voted on the question: Do you recommend that the majority of patients with mCRPC receive cabazitaxel sometime during their disease course? Consensus (75%) for use of cabazitaxel sometime during the disease course
Saad 2019	Canadian Urological Association (CUA)-Canadian Uro Oncology Group (CUOG) guideline Management of castration-resistant prostate cancer (CRPC)	Docetaxel 75 mg/m2 intravenous (IV) every three weeks with 5 mg oral prednisone twice daily is recommended for patients with mCRPC *(Level 1, Strong recommendation)*. Alternative therapies that have not demonstrated improvement in OS but can provide disease control, palliation, and improve quality of life include weekly docetaxel plus prednisone, and mitoxantrone plus prednisone *(Level 2, Weak recommendation)*. The timing of docetaxel therapy in men with evidence of metastases but without symptoms should be discussed with patients, and therapy should be individualized based on patients' clinical status and preferences *(Level 3, Weak recommendation)*. Patients who do not respond to first-line ADT or who progress clinically or radiologically without significant PSA elevations may have neuroendocrine differentiation. Biopsy of accessible lesions should be considered to identify these patients; these patients should then be treated with combination chemotherapy, such as cisplatin/etoposide or carboplatin/etoposide *(Level 3, Weak recommendation)*. Cabazitaxel is recommended for mCRPC patients progressing on or following docetaxel *(Level 1, Strong recommendation)*. For patients who have had a good response to first-line docetaxel, re-treatment with

Study reference	Type of study	Summary of recommendations
		docetaxel can be considered *(Expert opinion, Weak recommendation)*. Mitoxantrone has not shown any survival advantage but may provide symptomatic relief. Mitoxantrone may be considered a therapeutic option in symptomatic patients with mCRPC in the first- or second-line setting *(Expert opinion, Weak recommendation)*.
Mohler 2019	NCCN guideline	Too much information to put here and we don't often use them
Gomez-Caamano 2019	Urological Tumours Working Group (URONCOR) of the Spanish Society of Radiation Oncology Modified delphi consensus	In an asymptomatic/minimally symptomatic M1 CPRC patient, follow-up tests must be performed: Every 3–6 months, regardless of PSA values When the PSA values double In the event of symptoms related to the metastatic disease appearing In a symptomatic M1 CPRC patient, follow-up tests must be performed: Every 3 months, regardless of PSA values Every 6 months, regardless of PSA values When the PSA values double In the event of new symptoms appearing
Foroughi Moghadam 2018	Systematic review of guidelines	The following guidelines were compared. The results are too difficult to list American Urological Association (AUA), National Comprehensive Cancer Network (NCCN), European Association of Urology (EUA), Spanish Oncology Genitourinary Group (SOGG), Asian Oncology Summit, Saudi Oncology Society-Saudi Urology Association combined guideline, National Institute for Health and Care Excellence (NICE) and Canadian Urological Association-Canadian Urologic Oncology Group (CUA-CUOG) were

Systematic Reviews

Study reference	Type of study	Inclusion criteria	Search details	Results
Tan 2020	Meta Analysis to study efficacy and safety of abiraterone acetate (AA)	6 RCTs	Databases including PubMed, EMBASE, and Cochrane library were searched for relevant literature through to September 2019	The pooled analysis reported AAe showed significant efficacy in high-risk prostate cancer patients, including overall survival (OS) [HR 0.66, 95% C), 0.61–0.73, P<0.001], the time to prostate-specific antigen (PSA) progression (HR 0.45, 95% CI, 0.34–0.59, P<0.001), PFS (according to radiographic evidence) (HR 0.55, 95% CI, 0.45–0.68, P<0.001) and PSA response rate (RR 2.49, 95% CI, 1.47–)

Study reference	Type of study	Inclusion criteria	Search details	Results
	in mCRPC			4.22, P<0.001). A subgroup analysis was carried out due to the significant heterogeneity between the studies. The incidence of arthralgia (RR 1.19), hypokalemia (RR 2.47), cardiac disorder (RR 1.48), and hypertension (RR 1.57) in the abiraterone acetate group was moderately higher than the control group.
Riaz Sipra 2020 ASCO Abstract	Meta Analysis of Chemotherapy with Docetaxel (D) or androgen pathway inhibition (API) with Abiraterone Acetate plus prednisone (AAP), Aplautamide (APA) and Enzalutamide(E)	MEDLINE(Ovid), Embase, and Scopus for RCTs of chemotherapy(D) or APIs (AAP, APA, ENZ) that had available hazard ratios (HRs) OS, PFS according to patient's volume of disease	We calculated the pooled overall survival HR and 95% CI by chemotherapy and APIs and by high volume(HVD) and low volume(LVD) using a random effect model, and tested for heterogeneity to assess the null hypothesis that no difference in the survival advantage exists by choice of initial agent and volume of disease.	Of 4456 studies identified in our search, there were 8 eligible randomized controlled trials that were included in the analysis. Both D and APIs significantly improved PFS [HR 0.48; 0.45-0.51] and OS [0.72; 0.64-0.81] when added to ADT, however the latter was associated with significantly higher improvement in PFS(*P < 0.01)* and OS*(P = 0.03)*. In patients treated with D, patients with HVD derive significantly more benefit as compared to LVD(*P = 0.046)* and patients treated with APIs both HVD and LVD patients derive similar benefit(*P = 0.80*)
Chung 2020	to compare oncologic outcomes between the treatment sequences of ABI-ENZA and ENZA-ABI in patients with mCRPC	A literature search of all publications up to July 2019 was conducted using the Embase, PubMed, and Cochrane library databases	A total of five trials on 553 patients were included in this study. Each of the included studies was retrospective	In two studies including both chemo-naïve and post-chemotherapy mCRPC patients, for ABI-ENZA compared with ENZA-ABI, pooled hazard ratios (HRs) for PFS and OS were 0.37 (p<0.0001; 95% confidence intervals (CIs), 0.23–0.60) and 0.64 (p=0.10; 95% CIs,0.37–1.10), respectively. In three studies with chemo-naïve mCRPC patients only, for ABI-ENZA compared with ENZA-ABI, pooled HRs for PFS and OS were 0.57 (p=0.02; 95% CIs, 0.35–0.92) and0.86 (p=0.39; 95% CIs, 0.61–1.21), respectively. The current meta-analysis revealed that ABI-ENZA had a significantly more favorable oncological outcome, but the level of evidence was low.
Abdel-Rahman	This study is	Incidence of	analysis of the control	A total of 1,212 patients were <75 years old and 388

Study reference	Type of study	Inclusion criteria	Search details	Results
2019	a pooled analysis	toxicities between the 2 age groups (<75 years vs. ≥75 years) was assessed through chi-squared testing. Through Kaplan-Meier survival estimates, overall survival was compared between the 2 age groups (<75 years vs. ≥75 years). Multivariate Cox regression analysis was then conducted to evaluate factors potentially affecting overall survival.	arms of 3 prospective studies (NCT00273338; NCT00988208; NCT00519285) which assessed docetaxel/prednisone among patients with mCRPC	patients were ≥75 years old were included in the pooled analysis. Comparing both patient subgroups together, older patients were more likely to have any high-grade adverse event ($P < 0.001$), any fatal adverse events ($P = 0.007$), any-grade anemia ($P < 0.001$), and any-grade neutropenia ($P < 0.001$). Using Kaplan-Meier survival estimates, there was no difference in overall survival between both age groups ($P = 0.084$). Multivariable Cox regression analysis was additionally conducted to further assess the impact of age on overall survival. There was no difference in overall survival according to age (hazard ratio for age < 75 years vs. age ≥ 75 years: 0.883; 0.738–1.057; $P = 0.176$).
Zheng 2019	Systematic Review and Meta Analysis	RCTs to comprehensively assess the efficacy and safety of abiraterone and enzalutamide treatment in mCRPC	PubMed, Embase, and ClinicalTrial.gov were systematically searched	Eight eligible RCTs with 6,490 patients were selected. Pooled HRs were 0.72 for overall survival, 0.45 for radiographic progression-free survival (rPFS), and 0.36 for PSA PFS. abiraterone and enzalutamide could significantly increase the PSA response rate OR = 8.67, 95%CI 4.42–17.04) and any AE occurrence (OR = 1.98, 95%CI 1.46–2.68). The treatment group had more occurrence of fatigue (OR = 1.34, 95%CI 1.20–1.49), back pain (OR = 1.15, 95%CI 1.01–1.15), hot flush (OR = 1.76, 95%CI 1.50–2.06), diarrhea (OR=1.22, 95%CI 1.07–2.40) and arthralgia (OR = 1.34, 95%CI 1.16–1.54). Particularly, AEs of special interest including any grade hypertension (OR = 2.06, 95%CI 1.71–2.47), hypokalemia (OR = 1.80, 95%CI 1.42–2.30) and fluid retention or

Study reference	Type of study	Inclusion criteria	Search details	Results
				edema (OR = 1.38, 95%CI 1.17–1.63) also occurred less in the control group. Moreover, a higher incidence of high-grade hypertension (OR = 2.60, 95%CI 1.79–3.79) and extremity pain (OR = 4.46, 95%CI 2.81–7.07) was observed in the treatment group.
Leaf 2019	Systematic review and Meta analysis	Both randomized and nonrandomized studies were included for qualitative synthesis, only randomized studies were included for meta-analyses	Medline (Ovid), Embase, Lilacs, and the Cochrane Central Register of Controlled Trials from inception to January 2019	We identified 53 studies delivering platinum agents for patients with CRPC. cORR varied from 0 to 82%, while sORR varied from 2% to 100%. Response rates were higher in patients who received combination treatments rather than platinum compounds alone. Pooled data from randomized trials demonstrated a statistically significant increase in both cORR (odds ratio = 5.3; 95% confidence interval, 1.89-14.92) and sORR (odds ratio = 2.07; 95% confidence interval, 1.33-3.22) when adding platinum compounds to chemotherapy. PFS varied from 2.1 to 12 months and OS 4.2 to 28 months with platinum-containing chemotherapy. Nausea and myelosuppression were the most common adverse effects. Toxicity was manageable in most studies.
Chung 2019	Meta analysis	to compare oncologic outcomes between the treatment sequences of ABI-ENZA and ENZA-ABI in patients with mCRPC	up to July 2019 was conducted using the Embase, PubMed, and Cochrane library databases. A total of five trials on 553 patients were included in this study	. Each of the included studies was retrospective. In two studies including both chemo-naïve and post-chemotherapy mCRPC patients, for ABI-ENZA compared with ENZA-ABI, pooled hazard ratios (HRs) for PFS and OS were 0.37 (p < 0.0001; 95% confidence intervals (CIs), 0.23–0.60) and 0.64 (p = 0.10; 95% CIs, 0.37–1.10), respectively. In three studies with chemo-naïve mCRPC patients only, for ABI-ENZA compared with ENZA-ABI, pooled HRs for PFS and OS were 0.57 (p = 0.02; 95% CIs, 0.35–0.92) and 0.86 (p = 0.39; 95% CIs, 0.61–1.21), respectively. The current meta-analysis revealed that ABI-ENZA had a significantly more favorable oncological outcome, but the level of evidence was low. Therefore, large-scale randomized trials may be needed.
Leal 2019	Systematic Review and Meta-Analysis	Prospective clinical studies testing platinum compounds for CRPC. Platinum	Medline (Ovid), Embase, Lilacs, and the Cochrane Central Register of Controlled Trials from	Clinical overall response rate (cORR), varied from 0 to 82%, while sORR varied from 2% to 100%. Response rates were higher in patients who received combination treatments rather than platinum compounds alone. Pooled data from randomized trials demonstrated a statistically significant

Study reference	Type of study	Inclusion criteria	Search details	Results
	Risk of Bias performed none at high risk	compounds could be delivered alone or in combination with other drugs. Both randomized and nonrandomized studies were included for qualitative synthesis, only randomized studies were included for meta-analyses.	inception to January 2019. References from relevant articles were scanned as well as conference reports from ASCO and ESMO. 2075 studies were found, 103 were selected for full text assessment. Of these, 50 were excluded. 53 studies were included for qualitative synthesis	increase in both cORR (odds ratio = 5.3; 95% confidence interval, 1.89-14.92) and sORR (odds ratio = 2.07; 95% confidence interval, 1.33-3.22) when adding platinum compounds to chemotherapy. PFS varied from 2.1 to 12 months and OS 4.2 to 28 months with platinum-containing chemotherapy. Nausea and myelosuppression were the most common adverse effects. Toxicity was manageable in most studies
Zhao 2018	Bayesian network analysis of randomized controlled trials	castrate levels of serum testosterone (<50 ng/dL) failed previous docetaxel-containing chemotherapy; documented progression was based on PSAWG criteria or radiographic progression in soft tissue or bone; Comparator: another active agent, Prednisone plus placebo, placebo, or no	Major electronic databases including PubMed, Web of Science and Embase were searched until Jan 2017. Hazard ratios (HRs) and odds ratios (ORs) with corresponding 95% credible intervals (CrIs) were used to estimate the association	17 Randomized Controlled Trials (RCTs) comprising 14 different interventions with 12347 patients were enrolled. Compared with control arms, Abiraterone Acetate (HR: 0.70, 95%CrI: 0.63-0.79), Cabazitaxel (HR: 0.70, 95%CrI: 0.51-0.95) and Enzalutamide (HR: 0.63, 95%CrI: 0.53-0.75) presented similar benefits in term of OS. Enzalutamide showed superiority over PFS and PSA response with a highest probability to rank 1. Moreover, sensitivity analysis showed that Abiraterone Acetate (HR: 0.71, 95%CrI: 0.63-0.78) exhibited the most efficacious intervention of being rank 1 in term of OS compared with control arms, followed by Cabazitaxel and Cetuximab. On the other hand, Abiraterone Acetate (OR: 0.86, 95%CrI: 0.35-2.03) presented no significant toxicities compared with control arms.

Study reference	Type of study	Inclusion criteria	Search details	Results
		intervention		
Wang 2018	network meta-analysis to assess the effectiveness and tolerability of targeted agents for mCRPC.	(1) RCTs with a blinded design; (2) the studied patients had mCRPC; (3) targeted agents were used for treatment, and the control group received another type of targeted agents or placebo; and (4) the analyzed outcomes included either PFS or OS	literature search through Sep 5, 2017, using electronic databases including MEDLINE, EMBASE, and the Cochrane Library	26 articles assessing a total of 20,314 patients were included in this study. A random-effect analysis showed that targeted agents could significant prolong PFS in mCRPC patients (I^2 = 94.3%; hazard ratio (HR): 0.74; 95% confidence interval (CI): 0.65-0.84; p < 0.001). In addition, the surface under the cumulative ranking curve (SUCRA) ranking from the network analysis showed that enzalutamide was the most effective in improving the PFS of mCRPC patients (100%), followed by abiraterone (90.1%) and tasquinimod (84.2%). Additionally, targeted agents could clearly prolong OS in mCRPC patients (I^2 = 71.6%; HR: 0.91; 95% CI: 0.85-0.97; p < 0.001). Furthermore, based on SUCRA ranking, enzalutamide was the most effective in improving the OS of mCRPC patients (97.2%), followed by abiraterone (91.1%) and zibotentan (65.8%). Intetumumab was associated with the lowest incidence of severe AEs (94.9%), followed by atrasentan (85.1%) and placebo (79.3%).
McCool 2018	Net work Meta Analysis	To estimate the relative effectiveness of enzalutamide in chemotherapy-naive metastatic castration-resistant prostate cancer	RCTs in Medline, EMBASE, PUBMED, Cochrane and others	Ten randomized controlled trials were eligible for the NMA. Enzalutamide was superior to placebo for OS and rPFS (fixed-effects model). NMA results (fixed-effects model) showed no evidence of a difference between enzalutamide and abiraterone/prednisone (HR 0.95 [95% CrI 0.77–1.16]), sipuleucel-T (HR 1.07 [95% CrI 0.84–1.37]), or radium-223 (HR 1.10 [95% CrI 0.87–1.37]) for OS. HRs were similar for the random-effects model. Nevertheless, results (fixed-effects model) suggested that enzalutamide was superior to abiraterone/prednisone (HR 0.59 [95% CrI 0.48–0.72]) and sipuleucel-T (HR 0.32 [95% CrI 0.25–0.42]) for rPFS. Results also suggested superiority of enzalutamide versus placebo, abiraterone/prednisone, or sipuleucel-T for time to chemotherapy.
Marchioni 2018	Meta analysis	To assess the efficacy and safety of treatment with	PUBMED (MEDLINE), Ovid, Scopus, Cochrane Libraries and GoogleScholar.	Within the eight identified studies that fulfilled the criteria, a total of 801 patients were included in the meta-analysis. Baseline PSA ranged between 9.5 and 212.0 ng/ml. Most of the patients had bone metastases. Duration

Study reference	Type of study	Inclusion criteria	Search details	Results
		abiraterone acetate (AA) in chemotherapy-naïve men with mCRPC in the 'real-life' setting.	Controlled clinical trials (phase II and III studies) were excluded. We considered as 'real-life' studies all the observational studies outside the controlled clinical trial setting.	of treatment with AA was longer in the studies with lower baseline PSA levels. The median OS ranged between 14 and 36.4 months. The PFS, assessed according to different definitions, ranged from 3.9 to 18.5 months. A 50% PSA reduction at 12 weeks was reached by a variable percentage of patients ranging from 36.0% to 62.1%. Finally, the rate of grade 3 and higher adverse events was reported in three studies and ranged from 4.4% to 15.5%.
Gong 2018	Meta Analysis	To evaluate the efficacy, safety, and long-term survival for tasquinimod in patients with mCRPC.	PubMed, Embase, and the Cochrane Library A total of 61 studies were found. Upon further screening, 3 studies were selected for the final evaluation	Three RCTs were selected for final evaluation. The pooled results from the 3 studies indicated that tasquinimod was associated with good radiologic progression-free survival (rPFS) in mCRPC. For adverse effects (AEs), the results of meta-analysis indicated that patients with mCRPC who received tasquinimod had obvious anemia (risk ratio (RR) 1.35, 95% confidence interval (CI) 1.06–1.73, P=.02), back pain (RR: 1.57, 95% CI: 1.01–2.47, P=.05), pain in the extremities (RR: 1.90, 95% CI: 1.14–3.17, P=.01), insomnia (RR: 1.50, 95% CI: 1.03–2.17, P=.03), vomiting (RR: 1.52, 95% CI: 1.04–2.21, P=.03), and peripheral edema (RR: 1.52, 95% CI: 1.03–2.23, P=.03).
Fryzek 2018	Network Meta analysis	To examine cabazitaxel, abiraterone and enzalutamide to determine the clinical efficacy and safety of cabazitaxel relative to comparators in the treatment of patients with mCRPC who	MEDLINE ,Embase, and Cochrane CENTRAL were conducted from January 1, 2010 to February 26, 2015 Due to a lack of head-to-head trials, studies with a comparator arm of best supportive care were included in the analysis.	Three of thirteen trials identified for abstraction were relevant for analyses. Median overall survival was not statistically significantly different for abiraterone (HR = 1.04; 95% CI = 0.83-1.28) or enzalutamide (HR = 0.88; 95% CI = 0.69-1.11) when compared to cabazitaxel in the Bayesian analysis. Anaemia (OR = 3.71; 95% CI = 1.01-10.44), diarrhoea (OR = 16.60; 95% CI = 1.41-75.31) and haematuria (OR = 3.88; 95% CI = 1.03-10.09) were more likely to occur in the cabazitaxel group than the abiraterone group, while pyrexia risk was higher in cabazitaxel compared to enzalutamide (OR = 36.23; 95% CI = 1.14-206.40). Frequentist analyses produced similar results.

Study reference	Type of study	Inclusion criteria	Search details	Results
		progress on docetaxel-based therapies		
Clarke 2018	Double blind placebo RCT	mCRPC who had previously received docetaxel and were candidates for abiraterone treatment.	olaparib 300 mg plus oral abiraterone 1000 mg once daily and prednisone or prednisolone 5 mg N= 71 or placebo plus oral abiraterone 1000 mg once daily and prednisone or prednisolone 5 mg. N= 71	Median rPFS was 13·8 months (95% CI 10·8–20·4) with olaparib and abiraterone and 8·2 months (5·5–9·7) with placebo and abiraterone (hazard ratio [HR] 0·65, 95% CI 0·44–0·97, p=0·034). 38 (54%) of 71 patients in the olaparib and abiraterone group and 20 (28%) of 71 patients in the placebo and abiraterone group had grade 3 or worse adverse events, including anaemia (in 15 [21%] of 71 patients *vs* none of 71), pneumonia (four [6%] *vs* three [4%]), and myocardial infarction (four [6%] *vs* none). Serious adverse events were reported by 24 (34%) of 71 patients receiving olaparib and abiraterone (seven of which were related to treatment) and 13 (18%) of 71 patients receiving placebo and abiraterone (one of which was related to treatment). One treatment-related death (pneumonitis) occurred in the olaparib and abiraterone group.
Zheng 2017	**Systematic Review and Indirect Comparison**	(RCTs and phase-3 clinical trials comparing any of the following docetaxel, cabazitaxel, mitoxantrone, abiraterone, enzalutamide, and sipuleucel-T, as initial treatment for mCRPC. Clinical trials that focused on treatment of patients after failed docetaxel	PubMed, Web of Science, Cochrane Collaboration, and ClinicalTrials.gov were searched to identify relevant studies up to June 29, 2017. Reference lists were also searched for related articles. Quality and bias were assessed using the Cochrane RoB tool. A total of 2533 potential articles were identified. After excluding 2510, 23 fulltext articles which	No significant differences in primary outcome (overall survival) were found among initial treatments. However, docetaxel had the highest probability (37.53%) of being the most effective, but at the cost of more adverse events, while enzalutamide was associated with the best secondary outcomes (prostate-specific antigen response, progression-free survival, quality of life, and adverse event profile). Thus, docetaxel is recommended as the first agent used for the chemotherapy of mCRPC, while enzalutamide is recommended as the first non-chemotherapy treatment. Additional clinical trials are needed to confirm these findings and establish the optimal order for multidrug treatment of mCRPC.

Study reference	Type of study	Inclusion criteria	Search details	Results
		therapy or chemotherapy were excluded.	described 10 CTs, including 3 for docetaxel, 3 for sipuleucel-T, 1 for abiraterone, 1 for enzalutamide, 1 for mitoxantrone, and 1 for cabazitaxel, were included.	
Zhang 2017	Systematic review Indirect comparison	To evaluate the efficacy, tolerability, and sequential administration of abiraterone acetate (AA) and enzalutamide (Enz) for mCRPC	PubMed, Embase, and Web of Science. Reviewed literature included published phase III trials of AA or Enz in mCRPC and studies regarding their sequential administration	Given the difference in control arms in AA (active comparator) and Enz (true placebo) randomized phase III studies, indirect comparisons between AA and Enz in mCRPC showed no statistically significant difference in overall survival in prechemotherapy and postchemotherapy settings (HR: 0.90, 95% CI,0.73–1.11; HR: 0.85, 95% CI, 0.68–1.07). Compared with AA, Enz may better outperform control arms in treating mCRPC both before and after chemotherapy regarding secondary endpoints based on indirect comparisons: time to prostate-specific antigen (PSA)progression (HR: 0.34, 95% CI, 0.28–0.42; HR: 0.40, 95% CI, 0.30–0.53), radiographic progression-free survival (HR: 0.37,95% CI, 0.28–0.48; HR: 0.61, 95% CI, 0.50–0.74), and PSA response rate (OR: 18.29, 95% CI, 11.20–29.88; OR: 10.69,95% CI, 3.92–29.20). With regard to the effectiveness of Enz following AA or AA following Enz, recent retrospective case series reported overall survival and secondary endpoints for patients with mCRPC progression after chemotherapy. However, confirmatory head-to-head trials are necessary to determine the optimal sequencing of these agents.
Summers 2017	Systematic review	To assess published efficacy and safety data for select mCRPC therapies – such as abiraterone, cabazitaxel, and	MEDLINE, Embase, and Cochrane CENTRAL The RCT search resulted in 935 records for initial screening; of these, 13 unique studies were identified	Randomized studies demonstrated significant improvements in median overall survival (OS) outcomes over placebo for abiraterone (15.8 vs. 11.2 months) and enzalutamide (18.4 vs. 13.6 months), and similar significant improvements were noted for cabazitaxel over mitoxantrone (15.1 vs. 12.7 months). Differences in progression-free survival (PFS) were similarly significant,

Study reference	Type of study	Inclusion criteria	Search details	Results
		enzalutamide – in the post-docetaxel setting.	from 31 individual publications	although variance in the criteria for measuring PFS may limit the extent to which these outcomes can be compared between studies. Non-randomized evidence included multiple publications from several early access and compassionate use programs with a primary objective to report safety outcomes. Results from these studies largely reflected the findings in randomized trials.
Poorthuis 2017	Systematic review	To systematically evaluate all available treatment options in chemotherapy-naive patients with mCRPC	PubMed, EMBASE, and the Cochrane libraries up to 1 March 2016 for peer-reviewed publications on RCTs 25 articles, reporting on 10 unique RCTs describing 7 different comparisons.	In one RCT, a prolonged OS and PFS (high quality) were found with abiraterone and prednisone compared to placebo plus prednisone. In one RCT, a prolonged OS and PFS (high quality) were found with enzalutamide compared to placebo. In two RCTs, a prolonged OS (high and moderate quality) was found with 223 radium compared to placebo, but its effect on PFS is unknown. In three RCTs, a prolonged OS (moderate quality) was found with sipuleucel-T compared to placebo, but no prolonged PFS (low quality). In one RCT a prolonged PFS (high quality) was found with orteronel compared to placebo, but no prolonged OS (moderate quality). In one RCT, a prolonged OS (moderate quality) was found with bicalutamide compared to placebo, but its effect on PFS is unknown. In one RCT, a prolonged PFS (high quality) was found with enzalutamide compared to bicalutamide, but its effect on OS is unknown. The best evidence was found for abiraterone and enzalutamide for effective prolongation of OS and PFS to treat chemotherapy-naive patients with mCRPC. However, taking both QoL and AEs into consideration, other treatment modalities could be considered for individual patients
Kang 2017	Network Meta Analysis	abiraterone acetate, enzalutamide, and orteronel in mCRPC	RCTs published before June 2016	Pairwise meta-analysis and network meta-analysis were conducted to obtain direct and indirect evidence, respectively. Notably, enzalutamide and abiraterone were significantly associated with improved OS compared with control arms. Enzalutamide was ranked as the most efficacious agent for improving OS (hazard ratio [HR] = 0.71), and abiraterone appeared to be the second-most efficacious drug for this purpose (HR = 0.78). Enzalutamide

Study reference	Type of study	Inclusion criteria	Search details	Results
				improved PFS in comparison with control groups (HR = 0.36), but abiraterone and orteronel were not significantly associated with PFS improvements. Enzalutamide (HR = 0.20) and abiraterone (HR = 0.56) were significantly associated with prolonged times to PSA progression as compared with control groups. However, only orteronel was associated with an increased risk of AEs as compared with control groups.
Chopra 2017	Indirect Analysis	a comparative effectiveness analyses between enzalutamide and abiraterone acetate in both the pre and post docetaxel settings based on phase III rcts	4 preselected rcts	We found weak evidence that enzalutamide outperforms AA with prednisone in terms of OS in the pre-docetaxel and post-docetaxel settings. However, we found strong evidence that enzalutamide outperforms AA with prednisone in terms of radiographic PFS, time until PSA progression, and PSA response rate in both the pre- and post-docetaxel settings. Rates of grade 3 or worse adverse events were broadly similar between treatment(enzalutamide or AA) and control arms (placebo or placebo with prednisone) in all included rcts.
Cherubini 2017	Network Meta Analysis	Efficacy and safety of Enzalutamide (E) versus abiraterone acetate (AA)	compared using the data of the PREVAIL, AFFIRM, COU-AA-302 and COU-AA-301 trials.	The outcome of 5191 patients were reviewed. 1671 patients had been treated with E, 1339 with AA and 2181 with placebo. Comparing E vs AA no differences were observed for overall survival in the entire population (HR = 0.955, IC95% = 0.796-1.144, p = 0.616), overall survival in chemotherapy-naïve patients (HR = 0.947, IC95% = 0.723-1.24, p = 0.692), overall survival in docetaxel-resistant patients (HR = 0.961, IC95% = 0.753-1.228, p = 0.75), all side effects (OR = 0.414, IC95% = 0.054-3.196, p = 0.463), grade III-IV side effects (OR = 1.36, IC95% = 0.253-7.318, p = 0.72), serious side effects (OR = 0.742, IC95% = 0.137-4.006, p = 0.729), side effects leading to treatment discontinuation (OR = 0.743, IC95% = 0.132-4.193, p = 0.736), and side effects leading to death (OR = 0.572, IC95% = 0.089-3.657, p = 0.556).
Cherubini 2016	Network Meta Analysis	Treatment options in advanced castration-	Not stated	The outcome of 4070 patients were analyzed. 378 were treated with cabazitaxel, 797 with abiraterone, 800 with enzalutamide, 614 with Ra-223, 377 with mitoxantrone and 1104 with placebo. No significant differences were

Study reference	Type of study	Inclusion criteria	Search details	Results
		resistant, docetaxel-resistant prostate cancer (ACRDRPC)		observed for OS in all the indirect comparisons, while a significant improve in favor of enzalutamide was observed in TTP-PSA when compared with abiraterone, cabazitaxel or Ra-223
Shameem 2015	Meta analysis	To study the efficacy and safety of abiraterone in mCRPC patients with and without prior chemotherapy	PubMed and abstracts presented at the American Society of Clinical Oncology meetings up to April 2014	A total of two phase III RCTs were included in our analysis, with metastatic CPRC patients before (n = 1088) and after chemotherapy (n = 1195). Prior chemotherapy did not significantly alter the effect of abiraterone on OS (P = 0.92) and prostate specific antigen (PSA) progression-free survival (P = 0.13), but reduced its effect on radiographic-PFS (P = 0.04), objective response rate (P < 0.001), and PSA response rate (P < 0.001). Prior chemotherapy significantly increased the specific risk of fluid retention and edema (P < 0.001) and hypokalemia (P < 0.001), but decreased the risk of all-grade hypertension (P < 0.001) attributable to abiraterone. There was no significant difference of cardiac disorders associated with abiraterone between the two settings (P= 0.58)
Zhou 2014	Meta Analysis	To evaluate the efficacy and toxicity of abiraterone in the treatment of mCRPC.	Literature was searched from Embase, PubMed, Web of Science, and Cochrane Library up to July, 2013.	Ten trials were included in the systematic review; Data of 2,283 patients (1,343 abiraterone; 940 placebo) from two phase 3 trials: COU-AA-301 and COU-AA-302 were meta-analyzed. Compared with placebo, abiraterone significantly prolonged OS (HR, 0.74; 95% confidence interval [CI], 0.66 to 0.84), RPFS (HR, 0.59; 95% CI, 0.48 to 0.74) and time to PSA progression (HR, 0.55; 95% CI, 0.43 to 0.70); it also significantly increased PSA response rate (RR, 3.63; 95% CI, 1.72 to 7.65) and objective response rate (RR, 3.05; 95% CI, 1.51 to 6.15). This meta-analysis suggested that the adverse events caused by abiraterone are acceptable and can be controlled.
Tan 2014	Indirect comparison	enzalutamide and abiraterone acetate for mCRPC post-docetaxel.	A search for published phase 3 trials was performed with PubMed	There was no statistically significant difference in OS (hazard ratio (HR) 0.85, 95% CI 0.68-1.07). However, there was some evidence that enzalutamide may outperform abiraterone acetate with respect to secondary outcomes: time to PSA progression (HR 0.40, 95% CI 0.30-0.53), radiographic PFS (HR 0.61, 95% CI 0.50-0.74), and PSA

Study reference	Type of study	Inclusion criteria	Search details	Results
				response rates (RRs) (OR 10.69, 95% CI 3.92-29.20).
Chen 2014	Systematic review of docetaxel plus thalidomide vs. docetaxel alone for treating androgen-independent prostate cancer (AIPC)	they were randomized clinical trials and involved patients with AIPC. Studies were excluded for case reports, focusing on other type of prostate cancer, or lack of efficacies and toxities analyzing.	Study selection. A total of 127 articles were identified through searching databases 45 studies underwent full-text review and 3 RCT's were retained	Survival: Generally, the prognosis was more favorable in patients treated with docetaxel plus thalidomide than those treated with docetaxel alone. Dahut et al and Figg et al reported response to therapy based on PSA, an over 50% decline in PSA occurred more frequently in the patients treated with docetaxel plus thalidomide than those treated with docetaxel alone. Dahut et al reported progression-free survival (PFS) and 18 month-OS rate, the results showed the median PFS in the combined group (5.7 months) was higher than that in docetaxel alone group (3.7 months, P 5 0.32), and 18-month survival was 68.2% in the combined group, higher than that in docetaxel alone group (42.9%, P 5 0.11).
Lacovelli 2013	Meta Analysis	patients with CRPC progressed after docetaxel chemotherapy	PubMed was reviewed for phase III randomized trials	A total of 3,149 patients was available for meta-analysis. In the overall population, the experimental treatments decrease the risk of death by 31% (HR=0.69; 95% CI: 0.63–0.76; *P*<0.001). The activity of experimental treatments was similar in 2,859 patients with ECOG-PS=0 or 1 with a reduced risk of death of 31% (HR=0.69; 95% CI: 0.62–0.76). A total of 290 patients (9.2%) had ECOG-PS=2 and experimental treatments decreased the risk of death by 26% (HR=0.74; 95% CI: 0.56–0.98; *P*=0.035) compared with the controls even in this sub-group. When patients were stratified by type of treatment, the reduction of the risk of death was confirmed for hormonal therapies: abiraterone and enzalutamide (HR=0.72; 95% CI: 0.52–0.99; *P*=0.046), but not for chemotherapy (HR=0.81; 95% CI: 0.48–1.37; *P*=0.43).

RCT's

Study reference	Type of study	Study Inclusion criteria	Study comparisons (patients/group)	Results
Saad F	Phase 3	No previous	400 mg orteronel plus 5	Median follow-up for radiographic progression-free survival

Study reference	Type of study	Study Inclusion criteria	Study comparisons (patients/group)	Results
2020 ELM-PC 4	double blind RCT	Chemotherapy 18 years or older with histologically or cytologically confirmed adenocarcinoma of the prostate	mg prednisone twice daily (n=781 placebo plus 5 mg prednisone twice daily orteronel plus prednisone (n=779)	was 8·4 months. Median radiographic PFS was 13·8 months (95% CI 13·1–14·9) with orteronel plus prednisone and 8·7 months (8·3–10·9) with placebo plus prednisone (HR 0·71, 95% CI 0·63–0·80; p<0·0001). After median follow-up of 20·7 months median OS was 31·4 months (95% CI 28·6–not estimable) with orteronel + prednisone and 29·5 months (27·0–not estimable) with placebo + prednisone (HR 0·92, 95% CI 0·79–1·08; p=0·31). The most common grade 3 or worse adverse events were increased lipase (137 [17%] of 784 patients in the orteronel plus prednisone group *vs* 14 [2%] of 770 patients in the placebo + prednisone group), increased amylase (77 [10%] *vs* nine [1%]), fatigue (50 [6%] *vs* 14 [2%]), and pulmonary embolism (40 [5%] *vs* 27 [4%]).
Spetsieris 2020	open-label RCT phase 2 study	Prostate cancer progression documented either by PSA or (mRECIST), while being surgically or medically castrated with testosterone levels ≤ 50 ng/dL (≤2.0 nM). Previous treatment with docetaxel was allowed	AA-Sunitinib (n = 64) or AA-Dasatinib (n = 68) at resistance to AA (as predefined), while continuing treatment with AA. At progression, only 71 patients crossed over to the alternate treatment arm	Median TTF was 5.7 months in the dasatinib group and 5.5 months in the sunitinib group. There was no difference between the two groups in terms of TTF (hazard ratio, 0.85; 95% confidence interval, 0.59-1.22). Median overall survival from study entry was 26.3 months in the dasatinib group and 27.7 months in the sunitinib group (hazard ratio, 1.02; 95% confidence interval, 0.71-1.47). Grade 3 or higher adverse events related to study medication were more frequent with sunitinib (n = 44, 46%) compared to dasatinib (n = 26, 24%). At data cutoff, 7 patients were experiencing a continuous response to AA, with a median duration of treatment of 5.7 years.
Slovin 2020 ASCO abstract	Non-comparative Phase 2 RCT	93 pts were accrued; 81 were randomized. Median age was 68 years and ECOG performance status was 0 or 1.	AA/prednisone (AAP) with and without cabazitaxel (CBZ) in mCRPC patients (pts)	Results of AAP + CBZ (Arm 2) in chemotherapy naïve pts suggest that men may derive benefit from the earlier use of CBZ with acceptable toxicity, supporting further study of this combination in mCRPC pts.

Study reference	Type of study	Study Inclusion criteria	Study comparisons (patients/group)	Results
Kim 2020 ASCO abstract	RCT Phase 2	Men with a minimum of one prior line of systemic therapy for mCRPC	cediranib 30mg po daily plus olaparib 200mg po BID (Arm A) N=45 or olaparib 300mg BID alone (Arm B). N=45 At radiographic progression, patients in Arm B could crossover to Arm A	The median rPFS was 11.1 versus 4.0 months in Arm A and Arm B, respectively (HR 0.54, 95% CI 0.317, 0.928, p=0.026). Trends toward a higher ORR (19% and 12%), Disease Control Rate (Stable Disease + Partial Response) (77% and 64%,) and PSA50 (29% and 17%) were observed in Arm A compared to Arm B, respectively. 13 pts in Arm B crossed over to Arm A. One pt had a PR after crossover. Grade 3/4 adverse events, occurred in 77% and 58% of Arm A and Arm B pts, respectively. G3/4 AEs occurring in >10% of pts were hypertension (32%), fatigue (23%) and diarrhea (11%) in Arm A, and anemia (16%) and lymphopenia (11%) in Arm B.
Hu 2020 Abstract	RCT double Blind Phase 3	men aged ≥18 years who have previously received ADT, with histologically or cytologically confirmed mCRPC were eligible; documented metastases and had PSA progression	abiraterone acetate orally (1000 mg, qd) plus prednisone (5 mg, bid) N= 178 or placebo plus prednisone N= 84	The median follow-up of abiraterone and placebo was 22.8 and 21.5 months. The median time to PSA progression was 11.5 months (95%CI, 10.12-14.0) with abiraterone with 5.65 months (95%CI, 4.60-8.34) with placebo (hazard ratio, 0.57; 95% CI, 0.40 to 0.80; P=0.0011). The PSA response rate was 63.79% in abiraterone and 32.14% in placebo (P<0.0001). And the median OS was 23.95 months (95%CI, 17.18-NR) in abiraterone. Grade 3 or 4 AEs were reported in 18.97% of patients in the abiraterone group versus 19.05% of patients in the placebo group; Most of the occurring AEs included upper respiratory tract infection (13.22%), hypertension (12.64%), nasopharyngitis (12.07%), cough (9.77%), hypokalemia (8.62%), and diarrhea (8.62%)
Duran 2020 ASCO Abstract	Phase 2 RCT	Asymptomatic or minimally symptomatic mCRPC pts with no visceral	Docetaxel 75 mg/m2 q3wk plus abiraterone acetate 1000 mg/d (arm A) N= 46	Median rPFS was 11.4 months (m) in arm A vs 10.5 m in ARM B; 12-m rPFS was 43% vs 45%; Median PSA PFS was 6.2 vs 5.5 m and median OS was 17.3 vs 16.9 m. Twenty four pts (52%) in arm A and 19 (46%) in arm B achieve ≥50% PSA

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		metastases, ECOG PS 0-1, and adequate organ functions were included.	Docetaxel 75 mg/m2 q3wk (arm B), N= 42	response. RR was achieved in 15% vs 7% of pts and disease control rate in 74% in both arms. No statistically significant differences were found in efficacy parameters. Eleven pts discontinued treatment due to non-hematological toxicity, 5 in arm A and 6 in arm B. Most frequent G3-4 toxicities per arm (A/B) were: neutropenia (57%/29%; P=0.027), febrile neutropenia (17%/10%), diarrhea (9%/7%), and asthenia (11%/10%).
De Bono 2020 Abstract PROfound	RCT Open label	Men with mCRPC and disease progression on a prior new hormonal agent (eg enzalutamide or abiraterone)	**Cohort A** Olaparib N= 162 Control N=83 **Overall population** Olaparib N= 256 Control N=131 Pts could crossover to olaparib upon radiographic disease progression	At data cut-off (20 March 2020), median final OS in Cohort A was significantly longer with olaparib than with physician's choice of enzalutamide or abiraterone (HR 0.69; 95% CI 0.50, 0.97; *P*=0.0175), with a trend towards improvement in the overall population (HR 0.79; 95% CI 0.61, 1.03; nominal *P*=0.0515). Of pts in the control arm, 56 (67%) in Cohort A and 86 (66%) in the overall population crossed over to olaparib. Longer follow-up yielded no new safety signals.
De Bono 2020 Abstract LBA4 IPATential150	Phase 3 Double blind RCT	Pts with mCRPC	ipat (400 mg/d) + abi (1000 mg/d) + prednisone (5 mg bid) N= 547 or pbo + abi + prednisone N= 554	Median follow-up was 19 mo. In PTEN loss by IHC pts, median rPFS was 18.5 mo (95% CI: 16.3, 22.1) with ipat and 16.5 mo (95% CI: 13.9, 17.0) with pbo (HR: 0.77; 95% CI: 0.61, 0.98; P = 0.0335); in ITT pts, rPFS was 19.2 mo (95% CI: 16.5, 22.3) with ipat and 16.6 mo (95% CI: 15.6, 19.1) with pbo (HR: 0.84; 95% CI: 0.71, 0.99; P = 0.0431). Secondary endpoints favoured the combination arm. Serious adverse events (AEs) occurred in 40% and 23% of ipat and pbo pts, respectively; AEs leading to discontinuation of ipat/pbo occurred in 21% and 5%.
De Bono 2020 PROfound trial NCT02987543	Phase 3 RCT Open label Physicians choice	Pts with mCRPC	Cohort A Control n=83 Overall population Olaparib n=256 Control n=131	At data cut-off (20 March 2020), median final OS in Cohort A was significantly longer with olaparib than with physician's choice of enzalutamide or abiraterone (HR 0.69; 95% CI 0.50, 0.97; P=0.0175), with a trend towards improvement in the overall population (HR 0.79; 95% CI 0.61, 1.03; nominal P=0.0515). Of pts in the control arm, 56 (67%) in Cohort A and 86 (66%) in the overall population

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				crossed over to olaparib. Longer follow-up yielded no new safety signals.
De Bono 2020 NEJM	Phase 3 RCT Open label	Pts with mCRPC whose disease had progressed during treatment with enzalutamide or abiraterone. Previous taxane chemotherapy was allowed. Men without previous surgical castration were required to continue luteinizing-hormone–releasing hormone analogue therapy.	Cohort A N= N= 245) had at least one alteration in *BRCA1*, *BRCA2*, or *ATM*; Cohort B N=142 had alterations in any of 12 other prespecified genes Patients were randomly assigned (in a 2:1 ratio) to receive olaparib or the physician's choice of enzalutamide or abiraterone (control).	In cohort A, imaging-based progression-free survival was significantly longer in the olaparib group than in the control group (median, 7.4 months vs. 3.6 months; hazard ratio for progression or death, 0.34; 95% confidence interval, 0.25 to 0.47; P<0.001); a significant benefit was also observed with respect to the confirmed objective response rate and the time to pain progression. The median overall survival in cohort A was 18.5 months in the olaparib group and 15.1 months in the control group; 81% of the patients in the control group who had progression crossed over to receive olaparib. A significant benefit for olaparib was also seen for imaging-based progression-free survival in the overall population (cohorts A and B). Anemia and nausea were the main toxic effects in patients who received olaparib.
Khalaf 2019	RCT, open-label, phase 2, crossover trial	patients aged 18 years or older with newly-diagnosed metastatic castration-resistant prostate cancer without neuroendocrine differentiation and Eastern Cooperative Oncology Group performance status 2 or less.	group A abiraterone 1000 mg + prednisone 5 mg orally until confirmed PSA progression They then crossed over to receive enzalutamide 160 mg orally until symptomatic or clinical progression. Patients in group B received the opposite sequence of enzalutamide followed by abiraterone plus prednisone.	Between Oct 21, 2014, and Dec 13, 2016, 202 patients were enrolled and randomly assigned to either group A (n=101) or group B (n=101). At the time of data cutoff, 73 (72%) patients in group A and 75 (74%) patients in group B had crossed over. Time to second PSA progression was longer in group A than in group B (median 19·3 months [95% CI 16·0–30·5] *vs* 15·2 months [95% CI 11·9–19·8] months; hazard ratio 0·66, 95% CI 0·45–0·97, p=0·036), at a median follow-up of 22·8 months (IQR 10·3–33·4). PSA responses to second-line therapy were seen in 26 (36%) of 73 patients for enzalutamide and three (4%) of 75 for abiraterone (x^2 p<0·0001). The most common grade 3–4 adverse events throughout the trial were hypertension (27 [27%] of 101 patients in group A *vs* 18 [18%] of 101 patients in group B) and fatigue (six [10%] *vs* four [4%]). Serious adverse events were reported in 15 (15%) of 101 patients in group A and 20 (20%) of 101 patients in group B. There

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			Baseline Group A N= 101 Group B N= 101 At Crossover Group A N= 73 Group B N= 75	were no treatment-related deaths.
Hussein 2019 ABSTRACT	RCT Open label phase 2	patients (pts) with mCRPC with alterations in any of 15 predefined genes with a direct or indirect role in HRR whose disease had progressed on prior new hormonal agent (NHA) therapy Crossover to ola was allowed after BICR progression.	Cohort A pts with alterations in BRCA1, BRCA2 or ATM; Cohort B pts with any 1 of 12 other HRR alterations (BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D or RAD54L). Pts were randomized (2:1) to olaparib (300 mg bid) or physician's choice (pcNHA) of enzalutamid (160 mg/d) or abiraterone (1000 mg/d + prednisone 5 mg bid).	4425 men were screened; 245 randomized to Cohort A, 142 to Cohort B (65.6% had prior taxane). Efficacy is shown in Table. Most common adverse events (AEs) were anaemia (46.1 v 15.4%), nausea (41.4 v 19.2%), decreased appetite (30.1 v 17.7%) and fatigue (26.2 v 20.8%) for ola vs pcNHA; 16.4 and 8.5% of pts, respectively, discontinued due to AE.
Hakenberg 2019	Phase 2 RCT	patients with (mCRPC) who progressed after docetaxel	olaratumab plus mitoxantrone and prednisone N=63 or mitoxantrone and prednisone alone. N=60	Median PFS was 2.3 months for olaratumab + M/P and 2.4 months for M/P (hazard ratio [HR] = 1.29; 95% confidence interval [CI] = 0.87–1.90). Median OS was 14.2 months for olaratumab + M/P and 12.8 months for M/P (HR = 1.08; 95% CI = 0.72–1.61). Both treatment arms had similar toxicity profiles; neutropenia (24% versus 15%), anaemia (13% versus 14%) and fatigue (11% versus 9%) (olaratumab + M/P versus M/P, respectively) were the most common

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				grade ≥3 events. High CTC count was associated with poorer OS in both arms. Patients with very high cell counts (>37 cells/7.5 ml) exhibited improved OS with olaratumab + M/P (interaction P = 0.043).
De Wit 2019 CARD	RCT	Patients with mCRPC previously treated with ≥ 3 cycles of DOC and progressing ≤ 12 months (mo) on an alternative ART, in any order,	Cabazitaxel (CBZ) + prednisone + G-CSF) vs abiraterone (1000 mg PO + prednisone) N= 129 or enzalutamide (160 mg PO). N=126 Randomization was stratified by ECOG PS (0/1 vs 2), time to progression on prior ART (≤ 6 vs 6–12 mo) and ART timing (before vs after DOC)	After median follow-up of 9.2 months, imaging-based progression or death was reported in 95 of 129 patients (73.6%) in the cabazitaxel group, and in 101 of 126 patients (80.2%) in the group that received an androgen-signaling–targeted inhibitor (HR, 0.54; 95% [CI], 0.40 to 0.73; P<0.001). The median imaging-based PFS was 8.0 months with cabazitaxel and 3.7 months with the androgen-signaling–targeted inhibitor. The median OS was 13.6 months with cabazitaxel and 11.0 months with the androgen-signaling–targeted inhibitor (HR for death, 0.64; 95% CI, 0.46 to 0.89; P=0.008). The median PFS was 4.4 months with cabazitaxel and 2.7 months with an androgen-signaling–targeted inhibitor (HR for progression or death, 0.52; 95% CI, 0.40 to 0.68; P<0.001), a prostate-specific antigen response occurred in 35.7% and 13.5% of the patients, respectively (P<0.001), and tumor response was noted in 36.5% and 11.5% (P=0.004). Adverse events of grade 3 or higher occurred in 56.3% of patients receiving cabazitaxel and in 52.4% of those receiving an androgen-signaling–targeted inhibitor.
Chi 2019 ABSTRACT	Phase 2 RCT	poor prognosis mCRPC	Arm A: cabazitaxel N= 45, Arm B: abiraterone or enzalutamide N= 50	18% had liver mets, 88% early CRPC and 30% had > 3 of 6 poor prognostic criteria. 52% of pts had prior docetaxel, half for castration sensitive disease. Baseline ctDNA fraction > 15% (median) was associated with shorter 1st-line progression-free survival (PFS) (median 2.8 vs 8.4 m, HR = 2.54, P < 0.001) and overall survival (OS) (median 14.0 vs 38.7 m, HR = 2.64, P = 0.001). ctDNA alterations in AR, TP53, PI3K pathway, RB1 and DNA repair were detected in 53%, 45%, 31%, 23%, and 21% of pts. Shorter PFS and OS were associated with AR gain (HR 2.57 (95% CI 1.63-4.06); HR 3.59, (1.9-6.69), respectively) and TP53 defects (HR 2.62 (CI 1.65-4.15); HR 3.33 (CI 1.8-6.14),

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				respectively). Pts with concurrent defects in TP53 and RB1 had a trend for worse PFS/OS than pts with TP53 defect alone. AR rearrangements predicted to disrupt the ligand binding domain were detected in 6% of pts and had a shorter PFS (HR = 2.60 (1.11 - 6.09)) with a trend for shorter OS (HR = 2.27 (0.89 - 5.81)).
Caffo 2019 ABSTRACT CHEIRON study	Phase 2 RCT	mCRPC diagnosis, ECOG PS ≤ 2, adequate renal, hepatic and hematological functions, no prior treatment for mCRPC	docetaxel (D) 75 mg/m2 IV d1 q3w plus prednisone 5 mg PO BID for 8 courses alone N=126 or plus enzalutamide (E) 160 mg PO daily for 24 weeks N=120	The rate of pts without disease progression at 6 mos was significantly higher in DE arm compared to D arm (89.1% vs 72.8%; p = 0.002). Similarly, a higher proportion of DE pts achieved a PSA reduction ≥ 50% compared to the baseline values compared to the D pts (92% vs 69%; p < 0.0001). No differences were observed in terms of objective response rate. Major haematological toxicities consisted of grade 3-4 neutropenia (19 pts DE – 15 pts D); febrile neutropenia was observed in 10 DE pts and in 7 D pts. At a median follow-up of 24 mos, the median progression free survival was 10.1 mos and 9.1 mos in DE and D arm, respectively (p = 0.01). In DE arm the median overall survival was 33.7 mos compared to 29.6 mos of the standard arm (p NS).
Attard 2019	Phase 2 open label RCT	mCRPC	All groups Abiraterone acetate, 1000 mg, once daily + prednisone: 5 mg, twice daily (n = 41), 5 mg once daily (n = 41), 2.5 mg twice daily (n = 40), dexamethasone, 0.5 mg, once daily (n = 42).	Plasma adrenocorticotrophic hormone and urinary mineralocorticoid metabolites after 8 weeks were higher with prednisone, 2.5 mg, twice daily and 5 mg once daily than with 5 mg twice daily or dexamethasone, 0.5 mg, once daily. The level of urinary glucocorticoid metabolites appeared higher in patients who did not meet the primary end point, regardless of glucocorticoid regimen. Total lean body mass decreased in the prednisone groups and total body fat increased in the prednisone, 5 mg, twice daily and dexamethasone groups. In the dexamethasone group, there was an increase in serum insulin and homeostatic model assessment of insulin resistance, while total bone mineral density decreased. In the prednisone, 5 mg, twice daily, 5 mg once daily, 2.5 mg twice daily, and dexamethasone groups, median radiographic progression-free survival was 18.5, 15.3, 12.8, and 26.6 months, respectively.
Armstrong	Phase 2		Enzalutamide 160mg	At the 5 year OS analysis reported here there were 1382

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2019 ABSTRACT PREVAIL	open label RCT with crossover		N= 872 or placebo N-845	deaths (689 in the enzalutamide arm and 693 in the placebo arm). Survival probabilities at 2, 3, and 5 years favored enzalutamide. Enzalutamide reduced the risk of death by 17% (HR, 0.83; 95% CI, 0.75-0.93; P=0.0008). Median OS was 35.5 months (95% CI, 33.5-38.0) in the enzalutamide arm vs 31.4 months (95% CI, 28.9-33.8) in the placebo arm, with a median follow-up time of 69 months. The treatment effect was consistent across all baseline disease specific subgroups. At the data cut off, 70% of patients in the enzalutamide arm and 80% in the placebo arm had received ≥ 1post baseline antineoplastic therapy. The most common subsequent therapy was docetaxel (55% in the enzalutamide arm and 62% in the placebo arm), followed by abiraterone acetate (42% and 51%, respectively). The most common (≥20%) AEs were fatigue (38.2% vs 26.1%), backpain (32.5% vs 22.4%), constipation (25.6%vs17.4%), nausea (24.5% vs 22.7%), arthralgia (23.5% vs 16.2%), and decreased appetite (21.0% vs 16.6%) in the enzalutamide vs placebo arms, respectively
Yachin 2018 (ConCab)	Phase II RCT	patients with mCRPC who had previously received docetaxel and had progressive disease, the appearance of at least one new lesion for nonmeasurable disease or a rising prostate-specific antigen (PSA) on two consecutive occasions at least 1 week apart. ECOG PF of 0 or 1	Arm A, cabazitaxel Q3W, 25 mg/m2 N-52 Or Arm B, Q1W, 10 mg/m2 5 of 6 week sN=49	Median doses of cabazitaxel were 276 mg (45-320) and 257 mg (20-330) in Arms A and B, respectively, at week 18 (p = 0.13). More patients in Arm B stopped treatment because of toxicity. Median PFS in Arms A and B were 6.0 and 6.4 months (hazard ratio [HR] 0.73, 95% confidence interval [CI]: 0.47-1.13, p = 0.156) and for OS, 14.6 and 15.6 months (HR 0.95, CI: 0.58-1.58, p = 0.85), respectively. PSA responses ≥50% were seen in 52% and 46% of patients in Arms A and B, respectively. A higher incidence of febrile neutropenia was observed in the standard arm (10 events versus 1, p < 0.008). A grade V febrile neutropenia occurred in Arm A. Low-grade haematuria was more prevalent with weekly cabazitaxel (15 events versus 5, p Z 0.003). Three patients in Arm B experienced clinically significant inflammation of the ureters. A toxicity is not previously described for cabazitaxel.

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		and adequate haematological, renal and liver function.		
Stein 2018 STAAR study	Phase 2 Open label RCT	Men with progressive mCRPC, receiving gonadotropin-releasing hormone agonist or antagonist therapy, and with a serum testosterone level of <50 ng/dl	Abiraterone acetate fine particle (AAFP) formulation 500 mg daily plus 4 mg methylprednisolone N=24 or Original Abiraterone acetate (OAA) 1000 mg daily plus 5 mg prednisone BID N=29	Mean age was 75.1 years and 54.7% had Gleason>7. Over 90% of patients in each group achieved absolute testosterone levels of ≤1 ng/dl during the study. The averaged absolute testosterone levels ≤0.1 ng/dl were achieved in 25% of AAFP-treated patients and 17% of OAA-treated patients. A PSA-50 response was observed in>65% of patients in both groups on days 28, 56, and 84 (*P* = NS, all timepoints). Days 9 and 10 averaged rounded-up least squares (LS) mean (SE) serum testosterone levels were comparable (1.05 ng/dl [0.04], AAFP; 1.02 ng/dl [0.03], OAA; *P* = 0.4703 for LS mean difference). The geometric mean ratio between groups was 1.021 (90% CI: 0.965–1.081); the 90% CI fell within 80.0% to 125.0% equivalence limits. The LS mean differences in abiraterone trough plasma concentrations were not statistically significant at any visit. Adverse event frequency was comparable between arms (75.0%, AAFP; 82.8%, OAA). Musculoskeletal events were more common among OAA-treated patients (37.9% vs. 12.5%).
Small 2018 ABSTRACT	Phase 3 double blind RCT	Pts with nmCRPC and prostate-specific antigen doubling time (PSADT) of ≤ 10 mos	apalutamide (APA) vs Placebo	1207 pts were randomized. Baseline PSADT was < 5 mos in both groups. APA decreased the risk of distant metastasis or death by 72% (HR = 0.28; 95% CI, 0.23-0.35; p < 0.0001), with a median MFS of 40.5 vs 16.2 mos in the PBO group. Secondary end points (TTM, PFS, and SymProg) were all significantly improved. At an interim analysis for OS, there was a trend favoring APA. At a median follow-up of 20.3 mos, 61% of APA and 30% of PBO pts were still on treatment. Rates of discontinuation due to adverse events were low in both groups (10.7% APA, 6.3% PBO). Mean baseline health-related quality of life scores were maintained with treatment, with no difference between groups over time. Of those whose disease progressed, 80%

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				of PBO and 56% of APA pts received therapy for metastatic CRPC. PFS2 was significantly longer for APA vs PBO.
Yu 2018	Phase II RCT	progressive, MCRPC ECOG PS of 0 or 1, no prior chemotherapy for metastatic disease, prior surgical or continuing medical castration therapy (serum testosterone <1.7 nmol/L), any external beam radiation completed ≥28 days before randomization/cross over except single fraction of limitedfield radiotherapy could be ≥7 days prior. Prior corticosteroid therapy was permitted.	intravenous apatorsen (3 loading doses of 600 mg within 5–9 days followed by weekly doses of 1000 mg) with oral prednisone 5 mg twice daily or prednisone alone. (n = 36) prednisone alone (n = 38) Crossover from prednisone alone was allowed after radiographic progression	Twenty-five patients crossed-over to receive apatorsen + prednisone. Apatorsen treated patients received a median of 19 infusions. 50% of apatorsen + prednisone patients (95% CI: 32.9%, 67.1%) compared with 42% of prednisone patients (95% CI: 26.3%, 59.2%) did not have disease progression at week 12 (P = 0.33). A PSA decline of ≥50% was observed in 47% of apatorsen + prednisone and 24% of prednisone patients (P = 0.04), with a median duration of response of 24.1 weeks (95% CI: 12.0, 52) and 14.0 weeks (95% CI: 4.0, 44.4), respectively. A PSA decline of ≥50% was observed in 5 patients (20%) that received cross-over apatorsen. Infusion reactions were the most commonly reported adverse event occurring in 77% of apatorsen-treated patients. Apatorsen + prednisone did not change the proportion of CRPC patients without disease progression at 12 weeks compared to prednisone but was associated with significant PSA declines. Further evaluation of Hsp27 targeting in prostate cancer is warranted.
Clarke 2018	Double blind placebo RCT	mCRPC who had previously received docetaxel and were candidates for abiraterone treatment.	olaparib 300 mg plus oral abiraterone 1000 mg once daily and prednisone or prednisolone 5 mg N= 71 or placebo plus oral abiraterone 1000 mg once daily and	Median rPFS was 13·8 months (95% CI 10·8–20·4) with olaparib and abiraterone and 8·2 months (5·5–9·7) with placebo and abiraterone (hazard ratio [HR] 0·65, 95% CI 0·44–0·97, p=0·034). 38 (54%) of 71 patients in the olaparib and abiraterone group and 20 (28%) of 71 patients in the placebo and abiraterone group had grade 3 or worse adverse events, including anaemia (in 15 [21%] of 71 patients *vs* none of 71), pneumonia (four [6%] *vs* three [4%]), and myocardial infarction (four [6%] *vs* none). Serious adverse events were reported by 24 (34%) of 71

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			prednisone or prednisolone 5 mg. N= 71	patients receiving olaparib and abiraterone (seven of which were related to treatment) and 13 (18%) of 71 patients receiving placebo and abiraterone (one of which was related to treatment). One treatment-related death (pneumonitis) occurred in the olaparib and abiraterone group.
Bouman-Wammes 2018 RECARDO trial	Phase 2 RCT	Patients with mCRPC with a progression-free interval of ≥3 months after initial docetaxel treatment	docetaxel 75 mg/m^2 N=38 docetaxel 60 mg/m^2 plus carboplatin AUC4 N=38	Owing to insufficient recruitment, the study was discontinued early after inclusion of 75 patients (targeted 150) PFS and overall survival (OS) were comparable between both groups (median PFS 12.7 months (95% CI 9.9–17.5 months) with docetaxel monotherapy and 11.7 months (95% CI 8.5–21.0 months) with combination therapy (p = 0.98); OS 18.5 months (95% CI 11.8–24.5 months) versus 18.9 months (95% CI 16.0–23.7 months) (p = 0.79). An interim analysis (SEQTEST) showed that the null hypothesis could already be excepted, and no significant difference between both study arms was expected if inclusion would be completed. The incidence of grade 3–4 infections and gastrointestinal side-effects was numerical higher in the carboplatin arm (p = 0.056).
Attard 2018	Double blind RCT	mCRPC with Rising Prostate-Specific Antigen During Enzalutamide Treatment	abiraterone acetate 1,000 mg daily and prednisone 5 mg twice daily with either enzalutamide or placebo (combination or control group,	251 were randomly assigned in period two. Median progression-free survival was 5.7 months in the combination group and 5.6 months in the control group (hazard ratio, 0.83; 95% CI, 0.61 to 1.12; P = .22). There was no difference in the secondary end points. Grade 3 hypertension (10% v 2%) and increased ALT (6% v 2%) or AST (2% v 0%) were more frequent in the combination than the control group.
Ye 2017	Phase 3 double blind placebo RCT	Adult chemotherapy-naıve patients with confirmed prostate adenocarcinoma, Eastern Cooperative Oncology Group ECOG PS grade 0-1,	abiraterone acetate (1000 mg,QD) + prednisone (5 mg, BID) n = 157 or placebo + prednisone (5 mg, BID), n = 156);	At clinical cut-off (median follow-up time: 3.9 months), 80% patients received treatment (abiraterone: n = 138, prednisone: n = 112). Median time to PSA progression was not reached with abiraterone versus 3.8 months for prednisone, attaining 58% reduction in PSA progression risk (HR = 0.418; p < 0.0001). Abiraterone treated patients had higher confirmed PSA response rate (50% vs. 21%; relative odds = 2.4; p < 0.0001) and were 5 times more likely to

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		ongoing androgen deprivation (serum testosterone <50 ng/dL) with prostate specific antigen (PSA) or radiographic progression		achieve radiographic response than prednisone treated patients (22.9% vs. 4.8%, p = 0.0369). Median survival was not reached. Most common (≥10% abiraterone vs. prednisone-treated) adverse events: bone pain (7% vs. 14%), pain in extremity (6% vs. 12%), arthralgia (10% vs. 8%), back pain (7% vs. 11%), and hypertension (15% vs. 14%).
Oudard 2017 FIRSTANA	Phase III RCT open label	ECOG PS of 0 to 2, evidence of effective castration (serum testosterone ≤0.50 ng/mL), and disease progression	cabazitaxel 20 mg/m2 N= 389 (C20) cabazitaxel 25 mg/m2 N= 388 receiving (C25) docetaxel 75 mg/m2 N=391 (D75)	Median OS was 24.5 months with C20, 25.2 months with C25, and 24.3 months with D75. Hazard ratio for C20 versus D75 was 1.01 (95% CI, 0.85 to 1.20; P = .997), and hazard ratio for C25 versus D75 was 0.97 (95% CI, 0.82 to 1.16; P = .757). Median PFS was 4.4 months with C20, 5.1 months with C25, and 5.3 months with D75, with no significant differences between treatment arms. Radiographic tumor responses were numerically higher for C25 (41.6%) versus D75 (30.9%; nominal P = .037, without multiplicity test adjustment). Rates of grade 3 or 4 treatment-emergent adverse events were 41.2%, 60.1%, and 46.0% for C20, C25, and D75, respectively. Febrile neutropenia, diarrhea, and hematuria were more frequent with C25; peripheral neuropathy, peripheral edema, alopecia, and nail disorders were more frequent with D75.
Fizazi 2017 ABSTRACT CABADOC	Patient Preferences RCT	taxane-naïve mCRPC	docetaxel 75mg/m2/q3w x 4 followed by cabazitaxel 25mg/m2/q3w x 4 (DO-CA) N=Not stated cabazitaxel 25mg/m2/q3w x 4 followed by docetaxel 75mg/m2/q3w x 4 (CA-DO) N= not stated	After adjusting for the treatment period effect, more patients preferred cabazitaxel (43%) vs docetaxel (27%) (p < 0.004); 30% had no preference between taxanes. Fatigue, patient-defined quality of life, hair loss, and pain were the most common factors influencing patient preference. Febrile neutropenia was experienced by 5 (7.1%) men treated with cabazitaxel during the first period who received G-CSF and by 2 (7.1%) of those who did not. No febrile neutropenia was reported with docetaxel in both arms and with cabazitaxel during the 2nd period, irrespectively of the use of G-CSF. The incidence of diarrhea during the first 3-month period was slightly

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				reduced with G-CSF use in men receiving cabazitaxel (32.1% vs 24.3%) but not in those receiving docetaxel (23.8% vs 25%). The median progression-free survival was 9.81 in the DO-CA arm and 9.33 months in the CA-DO arm. The median overall survival was also similar in the two groups (22.64 in the DO-CA arm and 20.73 months in the CA-DO arm.
Eisenberger 2017 PROSELICA study	Phase 3 Open label RCT	mCRPC	Cabazitaxel (20 mg/m^2) N= 590 Cabazitaxel (25 mg/m^2) N = 602	Median OS was 13.4 months for C20 and 14.5 months for C25 (HR, 1.024). The upper boundary of the HR CI was 1.184 (less than the 1.214 noninferiority margin). Significant differences were observed in favor of C25 for PSA response (C20, 29.5%; C25, 42.9%; nominal *P* < .001) and time to PSA progression (median: C20, 5.7 months; C25, 6.8 months; HR for C20 *v* C25, 1.195; 95% CI, 1.025 to 1.393). Health-related quality of life did not differ between cohorts. Rates of grade 3 or 4 treatment-emergent adverse events were 39.7% for C20 and 54.5% for C25.
Chi 2017 ABSTRACT	Phase 2 RCT crossover	treatment-naïve mCRPC	abiraterone + prednisone (ABI) N=101 enzalutamide (ENZ) N = 101	With 1stline therapy for ABI vs ENZ, PSA50 at 12 weeks was 53% vs 73% (P = 0.004), no PSA decline occurred in 21% vs 15% (P = 0.243), and median TTPP was 7.4 vs 8.0 months (HR = 0.88, 95% CI 0.61, 1.27). Baseline ctDNA fraction was >2% in 60% of patients, and associated with worse TTPP (HR 1.80, P=0.005). Baseline pathogenic ctDNA alterations in AR, TP53, RB1, and DNA repair (BRCA2, ATM) genes were associated with a shorter TTPP (univariate analysis: TABLE). On multivariate analysis including clinical factors, TP53 and BRCA2/ATM alterations remained significant (HR = 2.54 (95%CI 1.55-4.19) and HR = 2.68 (1.58-4.54)). Pts with a PSA increase as best response were enriched for alterations in DNA repair (P <0.001), TP53 (P = 0.005), RB1 (P = 0.04), and (in 1 pt) a genomically truncated AR.
Beer 2017	Phase 3 open label RCT	radiographically documented metastatic castration-resistant	Cabazitaxel and prednisone plus custirsen N=317	Median overall survival in all randomly assigned patients did not differ between the two groups (14.1 months [95% CI 12.7-15.9] in the curtisen group vs 13.4 months [12.1-14.9] in the control group; [HR] 0.95 [95% CI 0.80-1.12];

Study reference	Type of study	Study Inclusion criteria	Study comparisons (patients/group)	Results
		prostate cancer that had progressed after docetaxel treatment with a Karnofsky performance status of more than 70% and who were fit for chemotherapy	Cabazitaxel and prednisone N=318	log-rank p=0.53). In the poor prognosis subgroup, median overall survival also did not differ between the two treatment groups (11.0 months [95% CI 9.3-13.3] in the custursin group vs 10.9 months [8.2-12.4] in the control group; HR 0.97 [95% CI 0.80-1.21]; two-sided p=0.80). The most frequently reported grade 3 or worse adverse events in the custirsen versus control groups were neutropenia (70 [22%] of 315 vs 61 [20%] of 312), anaemia (68 [22%] vs 49 [16%]), fatigue (23 [7%] vs 18 [6%]), asthenia (16 [5%] vs 8 [3%]), bone pain (16 [5%] vs 5 [2%]), and febrile neutropenia (16 [5%] vs 9 [3%]). Serious adverse events were reported in 155 (49%) versus 132 (42%). 27 patients died within 30 days of treatment in the cabazitaxel and prednisone plus custirsen group, seven of which were deemed to be treatment related, versus 17 in the cabazitaxel and prednisone group, eight of which were deemed to be treatment related. Of the 21 deaths reported, 15 were reported as complications related to study treatment, either chemotherapy (eight and three, respectively) or study drug (none and four, respectively)
Antonarakis 2017 TAXYNERGY trial	Non-comparative Phase II RCT	chemotherapy-naiive with progressive mCRPC and an ECOG PS of 0 to 2, no prior b isotope therapy, whole pelvic radiotherapy, or radiotherapy to > 30% of bone marrow. Patients with neuropathy grade >2 were excluded. Prior hormonal therapy (including	docetaxel 75 mg/m2 3 weeks plus daily prednisone 10 mg. N=41 or cabazitaxel 25 mg/m2 3 weeks plus daily prednisone 10 mg. N=22 withdrawal of consent.	35 patients (55.6%) had confirmed ≥ 50% PSA responses, exceeding the historical control rate of 45.4% (TAX327). Of 61 treated patients, 33 (54.1%) had ≥ 30% PSA declines by C4 and did not switch taxane, 15 patients (24.6%) who did not achieve ≥ 30% PSA declines by C4 switched taxane, and 13 patients (21.3%) discontinued therapy before or at C4. Of patients switching taxane, 46.7% subsequently achieved ≥ 50% PSA decrease. In 26 CTC-evaluable patients, taxane-induced decrease in %ARNL (cycle 1 day 1 v cycle 1 day 8) was associated with a higher rate of ≥ 50% PSA decrease at C4 (P = .009). Median composite progression-free survival was 9.1 months (95% CI, 4.9 to 11.7 months) Median overall survival was not reached at 14 months.

Study reference	Type of study	Study Inclusion criteria	Study comparisons (patients/group)	Results
		potent CYP17 inhibitors and AR signaling inhibitors) and immunotherapy were allowed.		Common grade 3 or 4 adverse events included fatigue (13.1%) and febrile neutropenia (11.5%).
Sun 2016	Phase 3 double blind RCT	Histologically/cytol ogically confirmed mCRPC were eligible if they had failed previous docetaxel-containing chemotherapy; documented disease progression according to PSAWG criteria or radiographic progression in soft tissue or bone despite castrate levels of serum testosterone (<50 ng/dL); and≤2 ECOG PS score.	Abiraterone acetate 1000 mg once daily plus prednisone 5 mg twice daily N=133 placebo plus prednisone 5 mg twice daily N=67	Abiraterone acetate-prednisone treatment significantly decreased prostate-specific antigen progression risk by 49%, with longer median time to prostate-specific antigen progression of 5.55 months versus 2.76 months in the placebo-prednisone group (hazard ratio 0.506, P = 0.0001, primary end-point). There was a strong trend for improved overall survival in the abiraterone acetate-prednisone group, with a 40% decrease in the risk of death (hazard ratio 0.604, P = 0.0597); however, median survival was not reached in either group because of the short follow-up period (12.9 months) and limited number of observed death events. The prostate-specific antigen response rate was higher in the abiraterone-prednisone group (49.7%) than in the placebo-prednisone group (14.1%). A total of 37.1% patients in this group had pain progression events compared with 50.7% in the placebo-prednisone group. Abiraterone-prednisone significantly decreased the risk of pain progression by 50% (hazard ratio 0.496, P = 0.0014). The incidence of adverse events was similar between the two groups; the most common adverse events being anemia (25.9% for abiraterone-prednisone vs 22.5% for placebo-prednisone), hypokalemia (25.9% and 11.3%), bone pain (23.8% and 21.1%), hypertension (16.1% and 12.7%) and increased aspartate aminotransferase (14.7% and 15.5%), respectively.
Smith 2016 COMET-1	Phase 3 RCT	mCRPC who had bone metastases and disease progression after docetaxel and	cabozantinib 60 mg once per day (n = 682) prednisone 5 mg twice per day (n = 346).	Median OS was 11.0 months with cabozantinib and 9.8 months with prednisone (hazard ratio, 0.90; 95% CI, 0.76 to 1.06; stratified log-rank *P* = .213). BSR at week 12 favored cabozantinib (42% *v* 3%; stratified Cochran-Mantel-Haenszel *P* < .001). rPFS was improved in the cabozantinib group

Study reference	Type of study	Study Inclusion criteria	Study comparisons (patients/group)	Results
		abiraterone acetate and/or enzalutamide. There was no limit on the number of prior anticancer treatments.		(median, 5.6 *v* 2.8 months; hazard ratio, 0.48; 95% CI, 0.40 to 0.57; stratified log-rank *P* < .001). Cabozantinib was associated with improvements in CTC conversion, bone biomarkers, and post–random assignment incidence of SSEs but not PSA outcomes. Grade 3 to 4 adverse events and discontinuations because of adverse events were higher with cabozantinib than with prednisone (71% *v* 56% and 33% *v* 12%, respectively).
Shore 2016 TERRAIN	Phase 2 double blind RCT	histologically confirmed adenocarcinoma of the prostate with documented metastases, testosterone concentration of 1·7 nmol/L (50 ng/dL) or lower, and disease progression on ADT.	enzalutamide 160 mg/day N= 184 bicalutamide 50 mg/day N=191 126 (68%) and 168 (88%) patients, respectively, discontinued their assigned treatment before study end, mainly due to progressive disease.	Median follow-up time was 20·0 months (IQR 15·0–25·6) in the enzalutamide group and 16·7 months (10·2–21·9) in the bicalutamide group. Patients in the enzalutamide group had significantly improved median PFS (15·7 months [95% CI 11·5–19·4]) compared with patients in the bicalutamide group (5·8 months [4·8–8·1]; HR 0·44 [95% CI 0·34–0·57]; p<0·0001). Of The most common grade 3 or worse adverse events in the enzalutamide or bicalutamide treatment groups, respectively, were hypertension (13 [7%] *vs* eight [4%]), hydronephrosis (three [2%] *vs* seven [4%]), back pain (five [3%] *vs* three [2%]), pathological fracture (five [3%] *vs* two [1%]), dyspnoea (four [2%] *vs* one [1%]), bone pain (one [1%] *vs* four [2%]), congestive cardiac failure (four [2%] *vs* two [1%]), myocardial infarction (five [3%] *vs* none), and anaemia (four [2%] *vs* none]). Serious adverse events were reported by 57 (31%) of 183 patients and 44 (23%) of 189 patients in the enzalutamide and bicalutamide groups, respectively. One of the nine deaths in the enzalutamide group was thought to be possibly related to treatment (due to systemic inflammatory response syndrome) compared with none of the three deaths in the bicalutamide group.
James 2016 TRAPEZE	open-label, phase 3 2 × 2 Factorial design	progressive metastatic CRPC, with 1ormore sclerotic bone metastases. Consenting participants had an	Arm A: 3 iv doses of 75mg/m2 docetaxel per week up to 10 cycles N= 191 Arm B, 3 intravenous doses of 4mg docetaxel plus zoledronic acid	Clinical progression-free survival did not reach statistical significance for either Sr89 or ZA. Cox regression analysis adjusted for all stratification variables showed benefit of Sr89 on CPFS (hazard ratio [HR], 0.85; 95%CI, 0.73-0.99; *P* = .03) and confirmed no effect of ZA (HR, 0.98; 95%CI, 0.85-1.14; *P* = .81); ZA had a significant effect on SRE-free interval (HR, 0.78; 95%CI, 0.65-0.95; *P* = .01). For OS,

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	RCT	ECOG score of 0 to 2 and adequate hematological, renal, and hepatic function	(DZA) per week during chemotherapy then 4 doses per week until disease progression N=188 Arm C, 6 cycles of docetaxel (75mg/m2 every 21days) followed by a 150MBq single dose of Sr89 (DSr89) then 4 further cycles of docetaxel N=190 Arm D:docetaxel plus doses of both Sr89 and ZA (DSZ) previously described N=188	there was no effect of either Sr89 (HR, 0.92; 95%CI, 0.79-1.08; *P* = 0.34) or ZA (HR, 0.99; 95%CI, 0.84-1.16; *P* = 0.91).
De Bono 2016 ABSTRCT PROSELICA	Phase 3 open label RCT	mCRPC and ECOG performance status 0–2, who progressed after treatment	cabazitaxel 20 mg/m^2 (C20) N=590 cabazitaxel 25 mg/m^2 (C25) N= 602	The median survival of C20 and C25 did not differ significantly and the HR boundaries (99% confidence level) were within the non-inferiority margins assumptions, therefore meeting the study's non-inferiority endpoint. PSA and RECIST response rates were higher in C25 (see Table). Grade 3–4 adverse events: 39.7% C20; 54.5% C25. Grade 4 laboratory neutropenia: 21.3% C20; 48.6% C25. Neutropenic sepsis/infection: 2.2% C20; 6.1% C25
Ryan 2015 COU-AA-302	Double blind Phase 3 RCT Crossover	asymptomatic or mildly symptomatic patients with chemotherapy-naive prostate cancer stratified by ECOG PS (0 *vs* 1)	abiraterone acetate (1000 mg) plus prednisone (5 mg) N=546 Placebo + prednisone (5 mg) N=542	At a median follow-up of 49·2 months (IQR 47·0–51·8), 741 (96%) of the prespecified 773 death events for the final analysis had been observed: 354 (65%) of 546 patients in the abiraterone acetate group and 387 (71%) of 542 in the placebo group. 238 (44%) patients initially receiving prednisone alone subsequently received abiraterone acetate plus prednisone as crossover per protocol (93 patients) or as subsequent therapy (145 patients). Overall, 365 (67%) patients in the abiraterone acetate group and 435 (80%) in the placebo group received subsequent treatment with one or more approved agents. Median OS was significantly longer in the abiraterone acetate group

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				than in the placebo group (34·7 months [95% CI 32·7–36·8] *vs* 30·3 months [28·7–33·3]; hazard ratio 0·81 [95% CI 0·70–0·93]; p=0·0033). The most common grade 3–4 adverse events of special interest were cardiac disorders (41 [8%] of 542 patients in the abiraterone acetate group *vs* 20 [4%] of 540 patients in the placebo group), increased alanine aminotransferase (32 [6%] *vs* four [<1%]), and hypertension (25 [5%] *vs* 17 [3%]).
Petrylak 2015 MAINSAIL	Double blind Phase 3 RCT	chemotherapy-naive patients with progressive metastatic castration-resistant prostate cancer	docetaxel (75 mg/m^2) and prednisone (5 mg) plus lenalidomide (25 mg) N= 533 docetaxel (75 mg/m^2) and prednisone (5 mg) N=526	At data cutoff (Jan 13, 2012) after a median follow-up of 8 months (IQR 5–12), 221 patients had died: 129 in the lenalidomide group and 92 in the placebo group. Median OS was 17·7 months (95% CI 14·8–18·8) in the lenalidomide group and not reached in the placebo group (HR 1·53, 95% CI 1·17–2·00, p=0·0017). The trial was subsequently closed early due to futility. The number of deaths that occurred during treatment or less than 28 days since the last dose were similar in both groups (18 [3%] of 525 patients in the lenalidomide group *vs* 13 [2%] of 521 patients). 109 (21%) patients in the lenalidomide group and 78 (15%) in the placebo group died more than 28 days from last dose, mainly due to disease progression. At least one grade 3 or higher adverse event was reported in 381 (73%) of 525 patients receiving lenalidomide and 303 (58%) of 521 patients receiving placebo. Grade 3–4 neutropenia (114 [22%] for lenalidomide *vs* 85 [16%] for placebo), febrile neutropenia (62 [12%] *vs* 23 [4%]), diarrhoea (37 [7%] *vs* 12 [2%]), pneumonia (24 [5%] *vs* five [1%]), dyspnoea (22 [4%] *vs* nine [2%]), asthenia (27 [5%] *vs* 17 [3%]), and pulmonary embolism (32 [6%] *vs* seven [1%]) occurred more frequently in the lenalidomide group than in the placebo
Hussain 2015	Non comparative phase 2 RCT	Men with progressive mCRPC during or after docetaxel therapy	Cixutumumab 6 mg/kg N=66 ramucirumab 6 mg/kg N=66	Median cPFS was 4.1 months (95% CI, 2.2–5.6) for cixutumumab and 6.7 months (95% CI, 4.5–8.3) for ramucirumab. Median time to radiographic progression was 7.5 months for cixutumumab and 10.2 months for ramucirumab, with a median OS of 10.8 and 13.0 months, respectively. Fatigue was the most frequent adverse event

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				(AE). Incidence of most non-hematologic grade 3-4 AEs was <10% on both arms. Grade 3 cardiac dysfunction occurred in 7.6% of patients on ramucirumab.
Fizazi 2015 ELM-PC 5	Phase 3 double blind placebo RCT	patients with metastatic castration-resistant prostate cancer that progressed after docetaxel therapy.	orteronel 400 mg plus prednisone 5 mg twice daily or placebo plus prednisone 5 mg	The study was unblinded after crossing a prespecified OS futility boundary. The median OS was 17.0 months versus 15.2 months with orteronel-prednisone versus placebo-prednisone (HR, 0.886; 95% CI, 0.739 to 1.062; *P* _ .190). Improved rPFS was observed with orteronel-prednisone (median, 8.3 *v* 5.7 months; HR, 0.760; 95% CI, 0.653 to 0.885; *P* _ .001). Orteronel-prednisone showed advantages over placebo-prednisone in PSA50 rate (25% *v* 10%, *P* _ .001) and time to PSA progression (median, 5.5 *v* 2.9 months, *P*_.001) but not pain response rate (12% *v* 9%; *P*_.128). Adverse events (all grades) were generally more frequent with orteronel-prednisone, including nausea (42% *v* 26%), vomiting (36% *v* 17%), fatigue (29% *v* 23%), and increased amylase (14% *v* 2%).

Study reference	Type of study	Study Inclusion criteria	Study comparisons (patients/group)	Results
Saad 2015 ELM-PC 4	Phase 3 double blind placebo RCT	with progressive metastatic castration-resistant prostate cancer and no previous chemotherapy	400 mg orteronel plus 5 mg prednisone N=781 placebo plus 5 mg prednisone N=779	Median follow-up for radiographic progression-free survival was 8·4 months (IQR 3·7–16·6). Median radiographic PFS was 13·8 months (95% CI 13·1–14·9) with orteronel plus prednisone and 8·7 months (8·3–10·9) with placebo plus prednisone ([HR] 0·71, 95% CI 0·63–0·80; p<0·0001). After a median follow-up of 20·7 months (IQR 14·2–25·4), median OS was 31·4 months (95% CI 28·6–not estimable) with orteronel plus prednisone and 29·5 months (27·0–not estimable) with placebo plus prednisone (HR 0·92, 95% CI 0·79–1·08; p=0·31). The most common grade 3 or worse adverse events were increased lipase (137 [17%] of 784 patients in the orteronel plus prednisone group *vs* 14 [2%] of 770 patients in the placebo plus prednisone group), increased amylase (77 [10%] *vs* nine [1%]), fatigue (50 [6%] *vs* 14 [2%]), and pulmonary embolism (40 [5%] *vs* 27 [4%]). Serious adverse events were reported in 358 [46%] patients receiving orteronel plus prednisone and in 292 [38%] patients receiving placebo plus prednisone.
Aggarwal 2015	Non-comparative Phase II RCT	mCRPC patients with ≥ 50% prostate-specific antigen (PSA) decline after 6 cycles of D+P	Arm 1 – Observation Arm 2 - GM-CSF 250 mg/m2	Of 125 patients enrolled, 52 (42%) experienced ≥ 50% PSA decline on induction D+P and were randomized to GM-CSF (n = 27) or Obs (n = 25). The median time to PD was 3.3 months (95% confidence interval [CI], 2.4-3.5) and 1.5 months (95% CI, 1.5-2.4) during the initial course of GM-CSF and Obs, respectively. Twelve of 26 (46%) patients responded to a second course of D+P. Eleven randomized patients (21%) experienced PD during chemotherapy, precluding accurate assessment of TTCR. The remaining 41 randomized patients discontinued study for lack of PSA response to chemotherapy (n = 8), patient choice to not restart chemotherapy with PSA PD (n = 13), toxicity (n = 7), or study withdrawal (n = 13).
Michaelson 2014	Phase 3 RCT	Men with progressive mCRPC after docetaxel-based chemotherapy	Sunitinib 37.5 mg/d (n = 584) placebo (n = 289)	The independent data monitoring committee stopped the study for futility after the second interim analysis. After a median overall follow-up of 8.7 months, median OS was 13.1 months and 11.8 months for sunitinib and placebo, respectively (hazard ratio [HR], 0.914; 95% CI, 0.762 to

Study reference	Type of study	Study Inclusion criteria	Study comparisons (patients/group)	Results
				1.097; stratified log-rank test, *P* = .168). PFS was significantly improved in the sunitinib arm (median 5.6 *v* 4.1 months; HR, 0.725; 95% CI, 0.591 to 0.890; stratified log-rank test, *P* < .001). Toxicity and rates of discontinuations because of adverse events (AEs; 27% *v* 7%) were greater with sunitinib than placebo. The most common treatment-related grade 3/4 AEs were fatigue (9% *v* 1%), asthenia (8% *v* 2%), and hand-foot syndrome (7% *v* 0%). Frequent treatment-emergent grade 3/4 hematologic abnormalities were lymphopenia (20% *v* 11%), anemia (9% *v* 8%), and neutropenia (6% *v* < 1%).
Ryan 2013	Phase 3 RCT	mCRPC no prior chemotherapy	(1000 mg) plus prednisone (5 mg twice daily) or placebo plus prednisone	The study was unblinded after a planned interim analysis (IA) at 43% of OS events. Treatment with abiraterone acetate-prednisone resulted in a 57% reduction in the risk of radiographic progression or death (HR, 0.43; 95% confidence interval [CI]: 0.35 to 0.52; P<0.001; 13% OS events IA) and an estimated 25% decrease in the risk of death (HR, 0.75; 95% CI: 0.61 to 0.93; P=0.009; 43% OS events IA). Secondary end points supported superiority of abiraterone acetate-prednisone: time to cytotoxic chemotherapy initiation, opiate use for cancer related pain, prostate-specific antigen progression (all P<0.001) and performance status deterioration (P=0.005). Self-reported time to pain progression and patient functional status degradation favored abiraterone acetate-prednisone (P=0.05 and P=0.003). Grade ¾ mineralocorticoid-related adverse events and liver function test abnormalities were more common with abiraterone acetate-prednisone.
Heidenreich 2013	Phase 2 double blind RCT with crossover	metastatic CRPC without prior systemic nonhormonal therapy	75-mg/m^2 docetaxel (Taxotere) and 5-mg prednisone plus placebo (*N* = 65) 10-mg/kg intetumumab (*N* = 66) q3w.	All efficacy end-points favored placebo over intetumumab, including PFS (median 11.0 versus 7.6 months, *P* = 0.014), tumor response (20% versus 16%, *P* = 0.795), PSA response (68% versus 47%, *P* = 0.018), OS (median 20.6 versus 17.2 months, *P* = 0.163). Common all-grade adverse events (AEs) with placebo and intetumumab were alopecia (43% versus 26%); diarrhea, leukopenia (both 34% versus 27%); neutropenia (35% versus 23%). Grade ≥3 leukopenia (28%

Study reference	Type of study	Study Inclusion criteria	Study comparisons (patients/group)	Results
				versus 17%) and neutropenia (26% versus 18%) occurred more often with placebo than with intetumumab. Intetumumab serum concentrations increased with repeated dosing and did not reach steady-state. Greater decreases in N-telopeptide of type I collagen (NTx), C-telopeptide (CTx) and CTCs occurred with intetumumab than with placebo.
Araujo 2013 READY	Double-blind, randomised, placebo-controlled phase 3 study	Confirmed metastatic prostate cancer that had progressed despite castrate concentrations of serum testosterone (≤1.74 nmol/L [≤50 ng/dL]), and no previous cytotoxic chemotherapy (except for estra mustine). ECOG PS 0-2 and adequate organ function	Docetaxel (75 mg/m2 intravenously every 3 weeks, plus oral prednisone 5 mg twice daily), plus either dasatinib (100 mg orally once daily) N=762 or placebo until disease progression or unacceptable toxicity N=760	At final analysis, median follow-up was 19.0 months (IQR 11.2–25.1) and 914 patients had died. Median overall survival was 21.5 months (95% CI 20.3–22.8) in the dasatinib group and 21.2 months (20.0–23.4) in the placebo group (stratified hazard ratio [HR] 0.99, 95.5% CI 0.87–1.13; p=0.90). The most common grade 3–4 adverse events included diarrhoea (58 [8%] patients in the dasatinib group vs 27 [4%] patients in the placebo group), fatigue (62 [8%] vs 42 [6%]), and asthenia (40 [5%] vs 23 [3%]); grade 3–4 pleural effusions were uncommon (ten [1%] vs three [<1%]).
Bahl 2013 TROPIC	Open label RCT	Histologically or cytologically confirmed adenocarcinoma of the prostate that is refractory to hormone therapy and previously treated with a Taxotere®-containing regimen. Documented progression of disease Surgical or	Prednisone/ 10 mg daily administered by oral route cabazitaxel 25 mg/m^2 administered by intravenous (IV) route over 1 hour on day 1 of each 21-day cycle (378) vs. prednisone/ mitoxantrone (377)	Median follow-up was 25.5 months. After 2 years, more patients remained alive following cabazitaxel than mitoxantrone [odds ratio 2.11; 95% confidence interval (CI) 1.33–3.33]. Treatment with cabazitaxel was prognostic for survival ≥2 years. Demographics/baseline characteristics were balanced between treatment arms irrespective of survival. Pain at baseline and pain response were comparable between treatment groups. Average daily pain performance index was lower for cabazitaxel versus mitoxantrone (all cycles; 95% CI –0.27 to –0.01; P = 0.035) and analgesic scores were similar. Grade ≥3 peripheral neuropathies were uncommon and comparable between treatment groups.

Study reference	Type of study	Study Inclusion criteria	Study comparisons (patients/group)	Results
		hormone-induced castrationLife expectancy > 2 months (ECOG) performance status 0 - 2	12 mg/m^2 administered by intravenous (IV) route over 15-30 minutes on day 1 of each 21-day cycle	
Basch 2013	Double blind Phase II RCT	Patients with mCRPC asymptomatic (score of 0 or 1 on item three of the Brief Pain Inventory Short Form [BPI-SF] questionnaire) or mildly symptomatic (score of 2 or 3) and had not previously received chemotherapy.	oral abiraterone (1 g daily) plus prednisone (5 mg twice daily) N=546 placebo plus prednisone N=542	At the time of 2nd prespecified interim analysis, median follow-up was 22·2 months (IQR 20·2–24·8). Median time to progression of mean pain intensity was longer in patients assigned to experimental group (26·7 months [95% CI 19·3–not estimable]) than in assigned to placebo(18·4 months [14·9–not estimable]; HR 0·82, 95% CI 0·67–1·00; p=0·0490), as was median time to progression of pain interference with daily activities (10·3 months [95% CI 9·3–13·0] vs 7·4 months [6·4–8·6]; HR 0·79, 95% CI 0·67–0·93; p=0·005). Median time to progression of worst pain was also longer with experimental group (26·7 months [95% CI 19·4–not estimable]) than with placebo (19·4 months [16·6–not estimable]), but the difference was not significant (HR 0·85, 95% CI 0·69–1·04; p=0·109).
Dreicer 2013	Double blind Phase II RCT	mCRPC with evidence of disease progression no prior chemotherapy for advanced prostate cancer, ECOG PS of 0–2, adequate organ function, and written informed consent.	Docetaxel (75mg/m2) /prednisone (5 mg) /enzastaurin (loading dose 375-mg dose three times orally followed by 500-mg oral enzastaurin once daily (DPE) arm N=42 docetaxel/prednisone/ placebo (DPP) N=42	There was no difference in the objective response rate between the enzastaurin and placebo arms (placebo: 7 [15.2 %]; enzastaurin: 6 [15.0 %]; P=1.00). The median PFS was 229 days for patients in the enzastaurin arm versus 213 days for the placebo arm (P=0.524). The 1-year overall survival rates were almost identical, with 76.7 % and 75.1 % in the enzastaurin and placebo arms, respectively.
Fizazi 2013	Double blind	confirmed prostate adenocarcinoma,	docetaxel 75 mg/m^2 plus oral zibotentan 10	There was no difference in OS HR, 1.00; 95% CI, 0.84 to 1.18; *P* = .963).

Study reference	Type of study	Study Inclusion criteria	Study comparisons (patients/group)	Results
	Phase 3 RCT	surgically castrated or continuously medically castrated (for ≥ 8 weeks before random assignment) and serum testosterone levels ≤ 2.4 nmol/L (70 ng/dL; lower limit of quantification).	mg N= 524 docetaxel 75 mg/m^2 plus placebo N=528	No significant differences were observed on secondary end points, including time to pain progression (median 9.3 *v* 10.0 months, respectively) or pain response (odds ratio, 0.84; 95% CI, 0.61 to 1.16; *P* = .283). The median time to death was 20.0 and 19.2 months for the zibotentan and placebo groups

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DEFINITIONS OF REVIEW OUTCOMES

1. **ARCHIVE -** ARCHIVE means that a Clinical Expert and/or Expert Panel has reviewed new evidence pertaining to the guideline topic and determined that the guideline is out of date or has become less relevant. The document, however, may still be useful for education or other information purposes. The document is designated archived on the CCO website and each page is watermarked with the words "ARCHIVED."

2. **ENDORSE** – ENDORSE means that a Clinical Expert and/or Expert Panel has reviewed new evidence pertaining to the guideline topic and determined that the guideline is still useful as guidance for clinical decision making. A document may be endorsed because the Expert Panel feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. **UPDATE** – UPDATE means the Clinical Expert and/or Expert Panel recognizes that the new evidence pertaining to the guideline topic makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The Expert Panel advises that an update of the document be initiated. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making, unless the recommendations are considered harmful.