Maximal androgen blockade for the treatment of metastatic prostate cancer—a systematic review

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ABSTRACT

Introduction

Maximal androgen blockade (MAB) versus castration alone in patients with metastatic prostate cancer has been extensively evaluated in randomized trials. The inconsistent results have led to the publication of multiple meta-analyses. The present review examines the evidence from meta-analytic reports to determine whether MAB using agents such as flutamide, nilutamide, and cyproterone acetate (CPA) is associated with a survival advantage.

Methods

We conducted a systematic review of the literature (MEDLINE, EMBASE, and the Cochrane Library through July 2004; CANCERLIT through October 2002) for meta-analyses that compared MAB with castration alone in previously untreated men with metastatic prostate cancer (D1 or D2, N+/M0 or M1). Two reviewers selected papers for eligibility; disagreement was resolved by all the authors through consensus.

Results

The literature search identified six meta-analyses that met the eligibility criteria of the review. Two of those reports were based on individual patient data (IPD), and four were based on data from the published literature. All six meta-analyses pooled data on overall survival.

The best evidence came from the largest meta-analysis, conducted by the Prostate Cancer Trialists Collaborative Group and based on IPD (8725 patients) from 27 trials. That analysis detected no difference in overall survival between MAB and castration alone at 2 or 5 years. However, a subgroup analysis showed that MAB with nonsteroidal anti-androgens (NSAAs) was associated with a statistically significant improvement in 5-year survival over castration alone (27.6% vs. 24.7%; $p = 0.005$). The combination of MAB with CPA, a steroidal anti-androgen, was associated with a statistically significant increased risk of death (15.4% vs. 18.1%; $p = 0.04$). Compared with castration alone, MAB was associated with more side effects (that is, gastrointestinal, endocrine function) and reduced quality of life in domains related to treatment symptoms and emotional functioning.

Conclusions

The small survival benefit conferred by MAB with NSAA is of questionable clinical significance given the added toxicity and concomitant decline in quality of life observed in patients treated with MAB. Therefore, combined treatment with flutamide or nilutamide should not be routinely offered to patients with metastatic prostate cancer beyond the purpose of blocking testosterone flare. Monotherapy, consisting of orchiectomy or the administration of a luteinizing hormone–releasing hormone agonist is recommended as standard treatment.

KEY WORDS

Prostatic neoplasms, androgen antagonists, hormonal anti-neoplastic agents

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1. INTRODUCTION

Prostate cancer is currently the most prevalent form of male cancer in Canada [1]. At diagnosis, 20%–30% of patients will present with advanced or metastatic disease. Of those men, approximately 25% will die from their disease within 2 years [2]. Therapeutic interventions seek not only to increase survival in those patients, but also to improve quality of life (QOL) [3].

The mainstay of treatment for advanced or metastatic prostate cancer is to inhibit the biosynthesis of androgens, the hormones responsible for prostate cancer cell growth. Androgen suppression can be achieved through surgical (bilateral orchiectomy) or medical castration. Medical castration involves the long-term use of luteinizing hormone–releasing hormone (LHRH) agonists. The two methods of castration appear equally effective in removing testicular androgens [4].

The testes are the major locale for testosterone production; however, the adrenal glands also produce a small but measurable quantity of androgens. It has been hypothesized that removing all circulating androgens—by blocking adrenal androgens in addition to inhibiting testicular androgen production—might be beneficial to patients. Combination treatment, in the form of surgical or medical castration plus administration of an anti-androgen [for example, flutamide, nilutamide, or cyproterone acetate (CPA)] is called "maximal androgen blockade" (MAB).

The use of MAB was first introduced in the early 1980s [5]. Since then, a large number of randomized controlled trials have been conducted to evaluate the efficacy of MAB as compared with castration alone. The trials yielded inconsistent results. Most failed to provide convincing evidence of improved survival with MAB; however, a few of the larger trials detected survival benefits with combined treatment [6–8]. Low statistical power, study immaturity, compliance to treatment, and imbalances in prognostic indicators between study arms of individual trials were implicated as potential sources of discrepancy [9–13].

Recent attempts to determine the treatment efficacy of MAB have involved meta-analyses of the trials [14]. To determine whether MAB is associated with a survival advantage, the present review systematically examines the results of the meta-analyses comparing MAB with castration alone in patients with metastatic prostate cancer.

2. MATERIALS AND METHODS

The present systematic review was originally completed in the context of developing a clinical practice guideline for Cancer Care Ontario's Program in Evidence-Based Care (PEBC), using the methodology of the Practice Guidelines Development Cycle [15]. The literature was searched by one member of PEBC's Genitourinary Cancer Disease Site Group. Evidence was reviewed and selected by two members, and disagreements pertaining to eligibility were handled through consensus involving the five members of the writing group. Two reviewers assessed eligible reports for important aspects of methodologic quality as expressed in the Quorom statement [16] (Appendix A).

2.1 Literature Search Strategy

We conducted a systematic search of MEDLINE (1980 through July 2004), EMBASE (1980 through 2004 wk 27), CANCERLIT (1980 through October 2002), and the Cochrane Library (2004, Issue 2) databases. In each database, subject headings were combined with disease-specific, treatment-specific, and design-specific search terms (Appendix B). The reference lists of all articles found, including reviews and articles held in personal files, were reviewed for additional citations. The search was restricted to reports published in the English language.

2.2 Eligibility Criteria

Published reports or abstracts of meta-analyses comparing MAB (orchiectomy or LHRH agonist plus administration of an anti-androgen) with castration alone (orchiectomy or LHRH agonist) in previously untreated men with metastatic prostate cancer (D1 or D2, N+/M0 or M1) were eligible for inclusion. Papers were required to report overall mortality or disease progression-related outcomes, or both. Adverse effects and QOL were also outcomes of interest.

3. RESULTS

3.1 Literature Search Results

We identified eleven reports representing seven unique meta-analyses [17–27]. One meta-analysis was excluded based on language [27], leaving six analyses eligible for inclusion in the review [18,20,22–24,26] (Table I). Two meta-analyses pooled individual patient data (IPD) [18,26], and four pooled summary data from published trial reports (literature-based) [20,22–24].

3.1.2 IPD Meta-analyses

Bertagna *et al.* [25] published the first IPD meta-analysis in 1994. That analysis was limited to seven double-blind, placebo-controlled trials of MAB with nilutamide (1056 patients). An update published in abstract form by Debruyne *et al.* [26] provided extended follow-up data on survival and disease progression.

In 1995, the Prostate Cancer Trialists' Collaborative Group (PCTCG) published an IPD meta-analysis that included 22 MAB trials (5710 patients) [17]. All randomized trials that compared castration alone to MAB, both published and unpublished, were sought for

TABLE I Meta-analyses identified by the literature search—descriptions

Meta-analysis	*Trials included in meta-analysis: MAB with*		
	Flutamide	*Nilutamide*	*CPA*
Individual patient data (IPD) meta-analyses			
PCTCG 2000 [18]	Bono (ILG), 1998 [28]	Dijkman (IASG), 1997 [8]	De Voogt (EORTC), 1998 [44]
31 RCTs included in review	Denis (EORTC), 1998 [7]	Bertagna, 1994 [25]	Theiss, 1996 [45]
27 RCTs provided IPD for meta-analysis	Eisenberger (NCI/SWOG), 1998 [29]	Béland (CASG), 1990 [38]	Thorpe, 1996 [46]
12 flutamide trials	Ferrari (Italy), 1996 [30]	Crawford, 1990 [39]	Robinson (EORTC), 1995 [47]
8 nilutamide trials	Zalcberg (Australia), 1996 [31]	Namer, 1990 [40]	Jorgensen (SPCG), 1993 [48]
7 CPA trials	Boccardo (PONCAP), 1993 [32]	Knonagel, 1989 [41]	DiSilverio (Italy), 1990 [49]
88% of patients staged "metastatic";	Fourcade (France), 1993 [33]	Brisset, 1987 [42]	
12% staged "locally advanced"	Iversen (DAPROCA), 1993 [34]	Navratil, 1987 [43]	
	Tyrrell (IPCSG), 1993 [35]		
	Crawford (NCI), 1989 [6]		
	Schulze (WPSG), 1988 [36]		
	Delaere, 1987 [37]		
Bertagna 1994 [25], Debruyne 1996 [26]	None	Bertagna, 1994 [25]	None
Included 7 double-blind RCTs		Janknegt (IASG), 1993 [50]	
7 nilutamide trials		Brisset, 1990 [51]	
% of patients staged D not reported		Namer, 1990 [40]	
		Knonagel, 1989 [41]	
		Béland (CASG), 1988 [52]	
Literature-based meta-analyses			
Schmitt 2003 [22]	Bono (ILG), 1998 [28]	Dijkman (IASG), 1997 [8]	None
20 RCTs included in review	Eisenberger (NCI/SWOG/INT-1015), 1998 [29]	Béland (CASG), 1990 [38]	
14 RCTs provided data for meta-analysis [a]	Zalcberg (Australia), 1996 [31]	Crawford, 1990 [39]	
9 flutamide trials	Boccardo (PONCAP), 1993 [32]	Namer (France), 1990 [40]	
5 nilutamide trials	Denis (EORTC), 1993 [53]	Brisset, 1987 [42]	
96% of patients were stage D2 or M1		Tyrrell (IPCSG), 1991 [54]	
		Fourcade (France), 1990 [55]	
		Iversen (DAPROCA), 1990 [56]	
		Crawford (NCI), 1989 [6]	
Aronson 1999 [20]	Same as above	Same as above	Robinson (EORTC), 1995 [47]
27 RCTs included in review			Jorgensen (SPCG), 1993 [48]
20 RCTs provided data for meta-analysis			DeVoogt (EORTC), 1990 [57]
9 flutamide trials			DiSilverio (Italy), 1990 [49]
5 nilutamide trials			Williams (U.K.), 1990 [58]
6 CPA trials			Klosterhalfen, 1987 [59]
93% of patients were stage D2			
Bennet 1999 [23]	Eisenberger (NCI/SWOG), 1998 [29]	None	None
9 RCTs included in review	Zalcberg (Australia), 1996 [31]		
9 RCTs provided data for meta-analysis	Boccardo (PONCAP), 1993 [32]		
9 flutamide trials	Denis (EORTC), 1993 [4]		
98% of patients were stage D	Fourcade (France), 1993 [33]		
	Tyrrell (IPCSG), 1991 [54]		
	Iversen (DAPROCA), 1990 [56]		
	Crawford (NCI), 1989 [6]		
	Schulze (WPSG), 1988 [36]		
Caubet 1997 [24]	Boccardo (PONCAP), 1993 [32]	Janknegt (IASG), 1993 [50]	None
13 RCTs included in review	Denis (EORTC), 1993 [4]	Béland (CASG), 1991 [38]	
9 RCTs provided data for meta-analysis	Iversen (DAPROCA), 1993 [34]	Navratil, 1987 [43]	
6 flutamide trials	Tyrrell (IPCSG), 1993 [35]		
3 nilutamide trials	Crawford (NCI), 1989 [6]		
57%–100% of patients staged D2	Schulze (WPSG), 1988 [36]		

[a] The 14 trials listed in Table I contributed to the pooled analysis of 2-year survival data. Thirteen trials [6,8,28,29,31,32,34,38,40,42,53–55] and seven trials [6,8,28,29,34,53,54] contributed to the pooled analysis of 1-year and 5-year survival data, respectively.

MAB = maximal androgen blockade; CPA = cyproterone acetate; PCTCG = Prostate Cancer Trialists' Collaborative Group; RCTS = randomized controlled trials; ILG = Italian Leuprorelin Group; EORTC = European Organization for Research and Treatment of Cancer; NCI = National Cancer Institute; SWOG = Southwest Oncology Group; PONCAP = Italian Prostatic Cancer Project; DAPROCA = Danish Prostatic Cancer Group; IPCSG = International Prostate Cancer Study Group; WPSG = Westfälische Prostatakarzinom Study Group; IASG = International Anandron Study Group; CASG = Canadian Anandron Study Group; SPCG = Scandinavian Prostatic Cancer Group.

inclusion. The main limitations of the report include the absence of explicitly defined eligibility criteria, a description of the methods used to identify and select trials, an appraisal of trial quality and its influence on the pooled results, and an indication of whether subgroup analyses were planned *a priori* (Appendix A). The report is also limited by the fact that overall mortality was the only outcome analyzed; other important endpoints, including toxicity and QOL were not examined. The meta-analysis was updated in 2000 [18] to include a total of twenty-seven trials: twelve used flutamide, eight used nilutamide, and seven used CPA as the anti-androgen. In combining data on 8725 patients, this updated report represents the most extensive quantitative analysis of MAB trials conducted to date.

3.1.3 Literature-based Meta-analyses

The number of trials included in the four literature-based meta-analyses ranged from nine (1978 patients) to twenty (6745 patients; Table I). The largest analysis was conducted for the Agency for Health Care Policy Research (AHCPR) by Aronson *et al.* [20]. The review was well conducted, with trials systematically identified through a prospectively designed protocol that specified the objectives, literature search strategy, eligibility criteria, method of assessing trial quality, and subgroup and sensitivity analyses, including an assessment of publication bias (Appendix A). Twenty-seven MAB trials were identified, including twelve using flutamide, eight using nilutamide, and seven using CPA. Overall mortality was the only outcome for which data were statistically pooled, but data on disease progression, QOL, and adverse effects were also summarized.

The three other literature-based meta-analyses were restricted in scope, analyzing trials that compared castration with MAB using nonsteroidal anti-androgens (NSAA) [22–24]. The largest of those analyses, carried out by Schmitt *et al.* [22] for the Cochrane Prostatic Diseases and Urologic Cancers Group, included twenty trials and pooled data on overall mortality, progression-free survival (PFS), and cancer-specific survival. Bennett *et al.* [23] and Caubet *et al.* [24] both included nine trials and pooled data on overall mortality [23,24] and PFS [24].

3.2 Outcomes

3.2.1 Overall Survival

IPD Meta-analyses Results from the original PCTCG overview showed a small survival benefit with MAB that was not statistically significant (5-year survival: 22.8% vs. 26.2%; $p > 0.1$) [17]. In the updated meta-analysis (2000), the PCTCG reported a nonsignificant overall hazard ratio (HR) of 0.96 [95% confidence interval (CI): 0.91–1.01; $p = 0.11$], where ratios less than 1 favoured MAB [18] (Table II). Further analyses at different follow-up periods also showed no difference in mortality and suggested an absolute 5-year survival difference of approximately 2% in favour of MAB. Subgroup analyses were performed by method of androgen suppression (orchiectomy vs. LHRH agonist), type of anti-androgen, patient age, stage of disease (metastases vs. no metastases), and non–prostate cancer mortality. With the exception of type of anti-androgen, no significant differences in treatment effect were observed within any of those subgroups. A small and statistically significant survival benefit was detected for MAB with flutamide (HR = 0.92; 95% CI: 0.86–0.98; $p = 0.02$), and a similar but nonsignificant result was observed for nilutamide. MAB with CPA was associated with a significantly worse survival outcome than castration alone (HR = 1.13; 95% CI: 1.01–1.25; $p = 0.04$). Treatment with MAB containing either of the NSAAs increased 5-year survival over castration alone by 3% (27.6% vs. 24.7%, $p = 0.005$).

Debruyne *et al.* [26] reported a reduction in the odds of death in patients treated with nilutamide-containing MAB; MAB was associated with a 16% reduction in mortality as compared with castration alone [odds ratio (OR) = 0.84; 95% CI: 0.71–0.99; $p = 0.038$].

Literature-based Meta-analyses Table III summarizes the results for overall mortality from the four literature-based meta-analyses. Aronson *et al.* [20] detected no significant difference in overall mortality at 2 years, although at 5 years, overall mortality was significantly improved with MAB (HR = 0.87; 95% CI: 0.81–0.94). However, the 5-year estimate was based on half the trials (10 trials, 66% of patients) that contributed to the 2-year estimate. No differences in treatment effect were detected in any of the subgroup analyses performed (method of androgen suppression, stage of disease, type of anti-androgen, or trial quality).

Schmitt *et al.* [22] reported no difference in mortality at 1 or 2 years between NSAA MAB and castration-only arms, but 5-year mortality was better with MAB (OR = 1.29; 95% CI: 1.11–1.50; $p = 0.0009$). The two other literature-based reports examining NSAA MAB detected significant reductions in the risk for mortality with MAB that ranged between 10% and 22% [23,24].

3.2.2 Disease Progression

Pooled analyses of disease progression data were available from three of the six meta-analyses [22,24,26]; however, those analyses are limited by the inclusion of a small proportion of MAB trials. Each of those reports combined data from trials of MAB using NSAA. Debruyne *et al.* [26] reported that, among seven trials, the odds of progression were reduced by 17% by MAB with nilutamide (OR = 0.83; 95% CI: 0.70–0.98; $p = 0.031$). Schmitt *et al.* [22] pooled published PFS data at 1 (seven trials), 2 (five trials), and 5 years (two trials); the odds of progression were significantly

TABLE II Results (mortality for maximal androgen blockade vs. castration alone [a]) from the 2000 Prostate Cancer Trialists' Collaborative Group individual patient data meta-analysis

	Estimated HR (95% CI), p *value*
Overall mortality (*n*=8725)	0.96 (0.91–1.01), 0.11
By years since randomization:	
Year 0	1.01 (0.91–1.11), NR
Years 1–2	0.93 (0.85–1.01), NR
Years 3–4	0.97 (0.85–1.09), NR
Year 5 onward	0.94 (0.76–1.12), NR
	5-Year survival estimates: 25.4% vs. 23.6%, $p>0.1$
Subgroup analyses	
Age	
<65 (*n*=1641)	0.90 (0.78–1.02), NR
65–74 (*n*=3094)	0.96 (0.88–1.04), NR
≥75 (*n*=2487)	0.95 (0.85–1.05), NR
Stage of disease	
Definite metastases (*n*=7190)	0.95 (0.89–1.01), NR
No metastases (*n*=1025)	1.06 (0.86–1.30), NR
Non-prostate cancer mortality (*n*=4876)	1.04 (0.88–1.20), 0.7
Type of anti-androgen	
Flutamide (*n*=4803)	0.92 (0.86–0.98), 0.02
Nilutamide (*n*=1751)	0.92 (0.80–1.04), >0.1
CPA (*n*=1661)	1.13 (1.01–1.25), 0.04
Class of anti-androgen	5-Year survival estimates:
Non-steroidal (flutamide + nilutamide; *n*=6500)	27.6% vs. 24.7%, $p=0.005$
Steroidal (CPA; *n*=1800)	15.4% vs. 18.1%, $p=0.04$

HR = hazard ratio; CI = confidence interval; NR = not reported; CPA = cyproterone acetate.

TABLE III Results from literature-based meta-analyses of maximal androgen blockade (MAB)

Meta-analysis	*Mortality results [estimated HR (95% CI)*, p *value]*		
MAB with any anti-androgen vs. castration alone [a]			
Aronson 1999 [20]		2-year (20 trials, 6745 patients) 0.97 (0.87–1.09), NR	5-year (10 trials, 4443 patients) 0.87 (0.81–0.94), NR
MAB with non-steroidal anti-androgens vs. castration alone [a]			
Schmitt 2003 [22]	1-year (13 trials, 4970 patients) 1.03 [b] (0.85–1.25), 0.7	2-year (14 trials, 5286 patients) 1.14 [b] (1.00–1.31), 0.06	5-year (7 trials, 3550 patients) 1.29 [b] (1.11–1.50), 0.0009
Bennet 1999 [23]	Overall (9 trials, 4128 patients) 0.90 (0.79–1.00), NR		
Caubet 1997 [24]	Overall: Method 1 [c] (7 trials, 1978 patients) 0.78 (0.67–0.90), <0.001		
	Overall: Method 2 [c] (7 trials, 2592 patients) 0.84 (0.76–0.93), <0.001		

[a] Unless otherwise specified, summary statistic values less than 1 favour MAB and values greater than 1 favour castration alone.
[b] Odds ratio. A ratio greater than 1 favours MAB; a ratio less than 1 favours castration alone.
[c] Method 1: Hazard ratios were derived by reconstructing annual life tables from survival curves and fitting discrete proportional hazard models. Method 2: Hazard ratios were derived from reported *p* values and numbers of deaths.
HR = hazard ratio; CI = confidence interval; NR = not reported.

reduced with MAB at 1 year (OR = 1.38; 95% CI: 1.15–1.67; $p = 0.0006$), but not at 2 or 5 years. Caubet *et al.* [24] reported a 23%–26% reduction in the risk for progression with MAB depending on the type of meta-analytic method used [relative risk (RR) = 0.74, $p < 0.001$ among seven trials; RR = 0.77, $p < 0.001$ among seven trials].

A more representative presentation of disease progression data was provided by Aronson *et al.* [20]. They summarized twenty-three trials [6,8,29,30,32,36,38–40,42,43,46–49,53–58,60] reporting those data. Nineteen of the trials reported no significant difference between MAB and castration alone on those measures [29,30,32,36,38–40,42,43,46–49,54–58,60]. Among six trials reporting

PFS [6,8,29,32,36,47], two reported a statistically significant longer progression-free interval with MAB [6,8]. Both of those trials used an NSAA in the MAB arm. One trial compared orchiectomy plus placebo with orchiectomy plus nilutamide (median PFS: 15 months vs. 21 months; $p = 0.002$) [8], and the other compared leuprolide plus placebo with leuprolide plus flutamide (median PFS: 14 months vs. 17 months; $p = 0.039$) [6]. Of the seventeen trials that reported on time-to-disease progression (TTP) [4,30,38–40,42,43,46,48,49, 54–56,58,60], one trial comparing orchiectomy with goserelin plus flutamide detected a significantly longer TTP interval with MAB (median TTP: 18 months vs. 12 months; $p = 0.002$) [4].

3.2.3 QOL and Adverse Effects

Aronson *et al.* [20] wrote the only report that reviewed QOL and adverse effects. Among the 27 randomized controlled trials that those authors reviewed, only one formally assessed QOL. The authors summarized two reports [61,62] of the large National Cancer Institute (NCI) INT-0105 Southwest Oncology Group/Eastern Cooperative Oncology Group trial [29], which compared orchiectomy plus flutamide with orchiectomy plus placebo. Measures of QOL included three treatment-related symptoms (diarrhea, gas pain, and body image), physical functioning, and emotional functioning; all were assessed at 1, 3, and 6 months after the start of treatment. Patients treated with MAB experienced significantly more diarrhea at 3 months ($p < 0.001$) and worse emotional functioning at 3 and 6 months ($p < 0.003$) than did patients treated with castration alone. Nonsignificant trends toward poor scores on measures of physical functioning, fatigue, abdominal gas, overall pain, and body image were also observed with MAB.

Major limitations were present in the reporting of adverse effects in the MAB trials. Because of those limitations, data on adverse effects were supplemented with similar data from package inserts that accompany therapeutic agents marketed in the United States and from phase II studies. Tables IV and V summarize the adverse effects data contained in the Aronson *et al.* report [20]. Compared with castration alone, treatment with MAB that included NSAA appeared to produce more gastrointestinal-related problems and more frequent withdrawal from treatment. When MAB contained CPA, treatment was associated with more complications related to endocrine function, but a withdrawal pattern similar to that in patients receiving monotherapy was demonstrated.

4. DISCUSSION

Six meta-analyses form the evidence base of the present review [17,18,20,22–25]. Evidence from those analyses suggests that patient outcomes depend on the type of anti-androgen used with MAB. The PCTCG meta-analysis [18] showed that MAB was not associated with a statistically significant improvement in overall survival. However, when outcomes were analyzed by type of anti-androgen, varying treatment efficacies among the agents were evident. Small but statistically significant survival benefits in the range of 3% at 5 years were detected among trials that used MAB with an NSAA (as compared with castration alone). Compared with castration alone, MAB with CPA (a steroidal anti-androgen) was associated with an approximate 3% increased risk of death.

Variability in the magnitude of outcome among meta-analyses may arise from a number of factors, including the number and size of the trials contributing to the pooled estimate, the type of anti-androgens being evaluated, and the use of published summary data or IPD for the analyses. The four literature-based meta-analyses [20,22–24] included fewer trials (and fewer patients) than did the PCTCG meta-analysis, but the resulting pooled estimates were of greater magnitude (in favour of MAB) than were those generated using IPD [18]. In meta-analyses based on published data, publication bias is more likely to exaggerate treatment effects [63]. Only one of the four literature-based meta-analyses assessed the influence of publication status on the overall pooled result [20]. With IPD, many of the problems associated with published data that introduce bias are eliminated by the ability to incorporate all trial data (published and unpublished), to check the integrity of patient randomization, and to perform proper time-to-event analyses (as compared with fixed time point) by intent-to-treat [64,65]. Further, because of greater patient numbers, IPD often provides greater statistical power to properly perform subgroup analyses [65]. The methodologic weaknesses of the PCTCG have been identified, but the advantages of using IPD currently make the PCTCG meta-analysis the most reliable evidence comparing MAB with castration alone.

To decide whether MAB should be the preferred treatment for patients, the small survival benefit and the additional adverse effects of combined treatment must be balanced. The clinical significance of a statistically significant 3% improvement in survival with NSAA MAB is questionable, especially when the toxicity of MAB is considered. Data on adverse effects and QOL are limited, but they suggest increased toxicity and a concomitant decline in QOL in MAB-treated patients. In addition, data on disease progression provide further evidence that MAB does not provide superior treatment efficacy over castration alone [20].

Based on the evidence reviewed, MAB should not be routinely offered to patients with metastatic prostate cancer. Monotherapy, consisting of orchiectomy or the administration of an LHRH agonist, should be recommended as standard treatment.

It is important to distinguish between MAB as long-term treatment and short-term use of MAB in the prevention of testosterone flare. In patients treated with

TABLE IV Adverse effects by category, combined results

Adverse effect	*Castration only*		*MAB: Castration + NSAA*		*MAB: Castration + CPA*		*Any MAB*	
	Patients [n (%)]	*Studies (n)*	*Patients [n (%)]*	*Studies (n)*	*Patients [n (%)]*	*Studies (n)*	*Patients [n (%)]*	*Studies (n)*
Cardiovascular								
Cardiovascular, not specified	570 (4)	4	387 (4.9)	3	175 (1.7)	1	562 (3.9)	4
Edema	569 (3.2)	3	293 (2)	1	277 (6.5)	2	570 (4.2)	3
Endocrine								
Hot flashes	2594 (40.1)	16	2789 (40)	12	488 (52.7)	4	3277 (41.9)	16
Gynecomastia	1441 (9.4)	10	1987 (7)	9	257 (17.5)	2	2244 (8.2)	11
Breast tenderness or pain	649 (7.7)	5	1206 (5.1)	5	257 (6.6)	2	1463 (5.4)	7
Impotence	515 (71.1)	5	362 (66)	4	156 (82.1)	1	518 (70.8)	5
Decreased libido	519 (70.1)	5	367 (65.4)	4	156 (78.8)	1	523 (69.4)	5
Gastrointestinal (GI)								
GI, not specified	959 (2.3)	7	768 (10.3)	6	175 (0.6)	1	943 (8.5)	7
Nausea or vomiting	1872 (3.2–7.1)	8	1851 (5.6–9.2)	8	0 (0)	0	1851 (5.6–9.2)	8
Diarrhea	1464 (2.2)	6	1458 (8.2)	6	0 (0)	0	1458 (8.2)	6
GI pain	124 (1.6)	2	122 (7.4)	2	0 (0)	0	122 (7.4)	2
Hepatic								
Hepatic, not specified	1197 (1.3)	4	2004 (5)	6	0 (0)	0		
Increased liver enzymes	483 (2.7)	3	474 (6.8)	3	0 (0)	0	NR	
Ophthalmologic	*Orchiectomy*		*Orchiectomy + nilutamide*					
Ophthalmologic, not specified	407 (5.4)	3	396 (29)	3	NR		NR	

MAB = maximal androgen blockade; NSAA = nonsteroidal anti-androgen; CPA = cyproterone acetate; NR = not reported. Adapted, with permission, from Aronson *et al.* [20], Appendix II, Tables II-6 to II-10.

TABLE V Adverse effects leading to withdrawal from treatment, combined results

Treatment	*Studies (n)*	*Treatment group (n)*	*Withdrawals from treatment [n (%)]*
Leuprolide (1 daily)	1	268	0 (0)
Goserelin (3.6, 1-month)	11	1679	33 (2)
Goserelin (10.8, 3-month)	2	77	1 (1.3)
Buserelin (0.4)	1	72	3 (4.2)
Orchiectomy + nilutamide (150)	2	271	38 (14)
Orchiectomy + nilutamide (300)	3	209	24 (11.5)
Orchiectomy + CPA (150)	1	102	3 (2.9)
Orchiectomy + CPA (300)	1	20	2 (10)
Orchiectomy or LHRH agonist or both	28	4275	82 (1.9)
Goserelin (3.6, 1-month) + flutamide (750)	5	846	94 (11.1)
Orchiectomy or LHRH agonist + flutamide (750) or both	9	2804	233 (8.3)
Orchiectomy or LHRH agonist + bicalutamide (50) or both	1	401	41 (10.2)
Orchiectomy or LHRH agonist + nilutamide (150 or 300) or both	5	480	62 (12.9)
Orchiectomy or LHRH agonist + CPA (150 or 300) or both	2	122	5 (4.1)

CPA = cyproterone acetate; LHRH = luteinizing hormone–releasing hormone. From Aronson *et al.* [20], Appendix II, Table II-11. Used with permission.

medical castration, initial treatment with an LHRH agonist is accompanied by a surge in serum testosterone during the first week or weeks of therapy, followed by a decline. That surge may exacerbate existing metastatic disease [66,67,68], therefore short-term use of an anti-androgen is indicated to prevent or block the flare phenomenon [68]. Administration of an anti-androgen is reasonable for a period of 2–4 weeks when treatment with an LHRH agonist is initiated.

Because of the small survival improvement observed with MAB, some clinicians may still choose MAB over monotherapy for individual patients. If MAB is administered with this intent, MAB containing a NSAA is suggested. Given its higher mortality, MAB with CPA should be avoided as compared with castration alone [18].

The present review did not identify any meta-analyses that included trials evaluating MAB with the newer anti-androgen bicalutamide. Bicalutamide-

based MAB has been compared in a randomized trial only with combination flutamide [69]. A castration-only control arm was deemed unethical at the time the bicalutamide trial was designed because MAB was considered standard care (over monotherapy). The trial compared bicalutamide plus an LHRH agonist with flutamide plus an LHRH agonist and detected a survival improvement with bicalutamide that was not statistically significant (median survival: 180 weeks vs. 148 weeks; HR = 0.87; 95% CI: 0.72–1.05; p = 0.15) [69]. With the exception of a higher incidence of hematuria, bicalutamide appeared less toxic than flutamide. Klotz *et al.* [70] recently re-analyzed the data from the bicalutamide trial [69] and the PCTCG meta-analysis (subgroup of trials comparing MAB with flutamide versus castration alone) [18] to calculate an estimate of the likely benefit of MAB with bicalutamide relative to castration alone. They reported an estimated HR of 0.80 (95% CI: 0.66–0.98) for bicalutamide-based MAB versus castration alone, which equates to a 20% relative reduction in the risk of death with bicalutamide. On the basis of those data, use of bicalutamide in patients who are offered MAB would also be reasonable. A randomized trial comparing MAB with bicalutamide to castration alone is ongoing, but that trial is assessing bicalutamide at a dose of 80 mg [71]. Before beginning MAB, selected patients should be advised of the magnitude of the survival benefit and on possible adverse effects and their potential impact on QOL.

Progressive prostate cancer is usually detected through a rise in prostate-specific antigen (PSA), which usually predates clinical or radiologic evidence of metastases. Most patients included in MAB trials had documented metastases (stage D2), and whether results from those trials are generalizable to patients with a rising PSA without evidence of metastatic disease is unknown. Only a handful of trials have analyzed outcomes by extent of metastatic involvement [4,6,11,29,34]. Most of those have not shown a benefit of MAB in patients with minimal disease, although the subgroup analyses included small numbers of patients. Only 12% of patients (approximately 1000) in the PCTCG meta-analysis [18] had documented non-metastatic prostate cancer. An analysis of those patients showed slightly worse survival with MAB, although the difference did not reach statistical significance. Prospective randomized trials to investigate the efficacy of MAB in that subgroup of patients are warranted.

5. CONCLUSIONS

The small survival benefit conferred by MAB with NSAA is of questionable clinical significance given the added toxicity and concomitant decline in QOL observed in patients treated with MAB. Therefore, combined treatment with flutamide or nilutamide should not be routinely offered to patients with metastatic prostate cancer (beyond the purpose of blocking testosterone flare). Monotherapy consisting of orchiectomy or the administration of a LHRH agonist is recommended as standard treatment.

6. REFERENCES

1. Canada, National Cancer Institute (NCI). *Canadian Cancer Statistics 2001.* Toronto: NCI; 2001.
2. Crawford ED, Nabors WL. Total androgen ablation: American experience. *Urol Clin North Am* 1991;18:55–63.
3. van Tinteren H, Dalesio O. Systematic overview (metaanalysis) of all randomized trials of treatment of prostate cancer. *Cancer* 1993;72(suppl):3847–50.
4. Denis LJ, Murphy GP. Overview of phase III trials on combined androgen treatment in patients with metastatic prostate cancer. *Cancer* 1993;72(suppl):3888–95.
5. Labrie F, Dupont A, Belanger A, *et al.* New hormonal therapy in prostatic carcinoma: combined treatment with an LHRH agonist and an antiandrogen. *Clin Invest Med* 1982;5:267–75.
6. Crawford ED, Eisenberger MA, McLeod DG, *et al.* A controlled trial of leuprolide with and without flutamide in prostatic carcinoma. *N Engl J Med* 1989;321:419–24. [Erratum in: *N Engl J Med* 1989;321:1420]
7. Denis LJ, Keuppens F, Smith PH, *et al.* Maximal androgen blockade: final analysis of EORTC phase III trial 30853. EORTC Genito-Urinary Tract Cancer Cooperative Group and the EORTC Data Center. *Eur Urol* 1998; 33: 144–51.
8. Dijkman GA, Janknegt RA, De Reijke TM, Debruyne FM. Long-term efficacy and safety of nilutamide plus castration in advanced prostate cancer, and the significance of early prostate specific antigen normalization. International Anandron Study Group. *J Urol* 1997;158:160–3.
9. Blumenstein BA. Some statistical considerations for the interpretation of trials of combined androgen therapy. *Cancer* 1993; 72(suppl):3834–40.
10. Schellhammer PF. Combined androgen blockade for the treatment of metastatic cancer of the prostate. *Urology* 1996;47: 622–8.
11. Sylvester RJ, Denis L, de Voogt HJ. The importance of prognostic factors in the interpretation of two EORTC metastatic prostate cancer trials. European Organization for Research and Treatment of Cancer (EORTC) Genito-Urinary Tract Cancer Cooperative Group. *Eur Urol* 1998;33:134–43.
12. Laufer M, Denmeade SR, Sinibaldi VJ, Carducci MA, Eisenberger MA. Complete androgen blockade for prostate cancer: what went wrong? *J Urol* 2000;164:3–9.
13. Collette L, Studer UE, Schroder FH, Denis L, Sylvester RJ. Why phase III trials of maximal androgen blockade versus castration in M1 prostate cancer rarely show statistically significant differences. *Prostate* 2001;48:29–39.
14. Klotz LH. Combined androgen blockade in prostate cancer: meta-analyses and associated issues. *BJU Int* 2001;87:806–13.
15. Browman GP, Levine MN, Mohide EA, *et al.* The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. *J Clin Oncol* 1995;13:502–12.
16. Moher D, Cook DJ, Eastwood S, Ingram O, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of

randomised controlled trials: the Quorom statement. *Lancet* 1999;354:1896–900.
17. Prostate Cancer Trialists' Collaborative Group. Maximum androgen blockade in advanced prostate cancer: an overview of 22 randomized trials with 3283 deaths in 5710 patients. *Lancet* 1995;346:265–9.
18. Prostate Cancer Trialists' Collaborative Group. Maximum androgen blockade in advanced prostate cancer: an overview of the randomised trials. *Lancet* 2000;355:1491–8.
19. Samson DJ, Seidenfeld J, Schmitt B, *et al.* Systematic review and meta-analysis of monotherapy compared with combined androgen blockade for patients with advanced prostate carcinoma. *Cancer* 2002;95:361–76.
20. Aronson N, Seidenfeld J, Samson DJ, *et al.* Relative effectiveness and cost-effectiveness of methods of androgen suppression in the treatment of advanced prostate cancer. Evidence report/technology assessment. No. 4. Rockville, MD: Agency for Health Care Policy and Research (AHCPR); 1999. [AHCPR Publication No. 99-E0012]
21. Schmitt B, Wilt TJ, Schellhammer PF, *et al.* Combined androgen blockade with nonsteroidal antiandrogens for advanced prostate cancer: a systematic review. *Urology* 2001;57:727–32.
22. Schmitt B, Bennett C, Seidenfeld J, Samson D, Wilt T. Maximal androgen blockade for advanced prostate cancer [Cochrane Review]. In: *The Cochrane Database of Systematic Reviews*, Issue 2. Chichester, U.K.: John Wiley & Sons; 2006.
23. Bennett CL, Tosteson TD, Schmitt B, Weinberg PD, Ernstoff MS, Ross SD. Maximum androgen-blockade with medical or surgical castration in advanced prostate cancer: a meta-analysis of nine published randomized controlled trials and 4128 patients using flutamide. *Prostate Cancer Prostatic Dis* 1999; 2:4–8.
24. Caubet JF, Tosteson TD, Dong EW, *et al.* Maximum androgen blockade in advanced prostate cancer: a meta-analysis of published randomized controlled trials using nonsteroidal antiandrogens. *Urology* 1997;49:71–8.
25. Bertagna C, De Géry A, Hucher M, Francois JP, Zanirato J. Efficacy of the combination of nilutamide plus orchidectomy in patients with metastatic prostate cancer. A meta-analysis of seven randomized double-blind trials (1056 patients). *Br J Urol* 1994;73:396–402.
26. Debruyne FMJ, De Géry A, Hucher M, Godfroid N. Maximum androgen blockade with nilutamide combined with orchidectomy in advanced prostate cancer: an updated meta-analysis of 7 randomised, placebo-controlled trials (1191 patients) [abstract]. *Eur Urol* 1996;30(suppl 2):264.
27. Shiina H, Igawa M. Change of endocrine therapy for advanced prostate cancer: results of meta-analysis [Japanese]. *Nishinihon J Urol* 1999;61:389–94.
28. Bono AV, Di Silverio F, Robustelli della Cuna G, *et al.* Complete androgen blockade versus chemical castration in advanced prostatic cancer: analysis of an Italian multicentre study. Italian Leuprorelin Group. *Urol Int* 1998;60:18–24.
29. Eisenberger MA, Blumenstein BA, Crawford ED, *et al.* Bilateral orchiectomy with or without flutamide for metastatic prostate cancer. *N Engl J Med* 1998;339:1036–42.
30. Ferrari P, Castagnetti G, Ferrari G, Baisi B, Dotti A. Combination treatment versus LHRH alone in advanced prostatic cancer. *Urol Int* 1996;56:13–17.
31. Zalcberg JR, Raghavan D, Marshall V, Thompson PJ. Bilateral orchidectomy and flutamide versus orchidectomy alone in newly diagnosed patients with metastatic carcinoma of the prostate—an Australian multicentre trial. *Br J Urol* 1996;77: 865–9.
32. Boccardo F, Pace M, Rubagotti A, *et al.* Goserelin acetate with or without flutamide in the treatment of patients with locally advanced or metastatic prostate cancer. The Italian Prostatic Cancer Project (PONCAP) Study Group. *Eur J Cancer* 1993;29A: 1088–93.
33. Fourcade RO, Colombel P, Mangin M. Zoladex plus flutamide versus Zoladex plus placebo in advanced prostatic carcinoma: extended follow-up of the French multicentre study. In: Murphy G, Khoury S, Chatelain C, Denis L, eds. Proceedings of the 3rd International Symposium on Recent Advances in Urological Cancer Diagnosis and Treatment; June 17–19, 1992; Paris, France. Paris: Scientific Communication International; 1993: 102–6.
34. Iversen P, Rasmussen F, Klarskov P, Christensen IJ. Long-term results of Danish Prostatic Group trial 86. Goserelin acetate plus flutamide versus orchiectomy in advanced prostate cancer. *Cancer* 1993;72(suppl):3851–4.
35. Tyrrell CJ, Altwein JE, Klippel F, *et al.* Multicenter randomized trial comparing Zoladex with Zoladex plus flutamide in the treatment of advanced prostate cancer. International Prostate Cancer Study Group. *Cancer* 1993;72(suppl):3878–9.
36. Schulze H, Kaldenhoff H, Senge T. Evaluation of total versus partial androgen blockade in the treatment of advanced prostatic cancer. *Urol Int* 1988;43:193–7.
37. Delaere KP, Boccon–Gibod L, Corrado F. Randomized, double-blind, parallel group study of flutamide and orchidectomy versus placebo and orchidectomy in men with D2 adenocarcinoma of the prostate [abstract]. *Proc Eur Conf Clin Oncol* 1987;68.
38. Béland G, Elhilali M, Fradet Y, *et al.* A controlled trial of castration with and without nilutamide in metastatic prostatic carcinoma. *Cancer* 1990;66(suppl):1074–9.
39. Crawford ED, Kasimis BS, Gandara D, *et al.* A randomized, controlled clinical trial of leuprolide and Anandron (LA) vs. leuprolide and placebo (LP) for advanced prostate cancer (D2cap) [abstract]. *Proc Am Soc Clin Oncol* 1990;9:A523.
40. Namer M, Toubol J, Caty A, *et al.* A randomized double-blind study evaluating Anandron associated with orchiectomy in stage D prostate cancer. *J Steroid Biochem Mol Biol* 1990;37: 909–15.
41. Knonagel H, Bolle JF, Hering F, *et al.* Therapy of metastatic prostatic cancer by orchiectomy plus Anandron versus orchiectomy plus placebo. Initial results of a randomized multicenter study [German]. *Helv Chir Acta* 1989;56:343–5.
42. Brisset JM, Boccon–Gibod L, Botto H, *et al.* Anandron (RU 23908) associated to surgical castration in previously untreated stage D prostate cancer: a multicenter comparative study of two doses of the drug and of a placebo. *Prog Clin Biol Res* 1987;243A:411–22.
43. Navratil H. Double-blind study of Anandron versus placebo in stage D2 prostate cancer patients receiving buserelin. Results on 49 cases from a multicentre study. *Prog Clin Biol Res* 1987;243A:401–10.
44. de Voogt HJ, Studer U, Schroder FH, Klijn JG, de Pauw M,

Sylvester R. Maximum androgen blockade using LHRH agonist buserelin in combination with short-term (two weeks) or long-term (continuous) cyproterone acetate is not superior to standard androgen deprivation in the treatment of advanced prostate cancer. Final analysis of EORTC GU Group Trial 30843. European Organization for Research and Treatment of Cancer (EROTC) Genito-Urinary Tract Cancer Cooperative Group. *Eur Urol* 1998;33:152–8.

45. Theiss M, Wirth M, Tunn U. Triptorelin–cyproteronacetate versus triptorelin–placebo: multizentrische phase III-studie an 222 patienten met fortgeshrittenem prostata-karzinom [abstract, German]. *Urologe A* 1996;35(suppl 1):S41.
46. Thorpe SC, Azmatullah S, Fellows GJ, Gingell JC, O'Boyle PJ. A prospective, randomised study to compare goserelin acetate (Zoladex) versus cyproterone acetate (Cyprostat) versus a combination of the two in the treatment of metastatic prostatic carcinoma. *Eur Urol* 1996;29:47–54.
47. Robinson MR, Smith PH, Richards B, Newling D, de Pauw M, Sylvester R. The final analysis of the EORTC Genito-Urinary Tract Cancer Co-operative Group phase III clinical trial (protocol 30805) comparing orchidectomy, orchidectomy plus cyproterone acetate and low dose stilboestrol in the management of metastatic carcinoma of the prostate. *Eur Urol* 1995;28: 273–83.
48. Jorgensen T, Tveter KJ, Jorgensen LH. Total androgen suppression: experience from the Scandinavian Prostatic Cancer Group Study No. 2. *Eur Urol* 1993;24:466–70.
49. Di Silverio F, Serio M, D'Eramo G, Sciarra F. Zoladex vs. Zoladex plus cyproterone acetate in the treatment of advanced prostatic cancer: a multicenter Italian study. *Eur Urol* 1990; 18(suppl 3):54–61.
50. Janknegt RA, Abbou CC, Bartoletti R, *et al.* Orchiectomy and nilutamide or placebo as treatment of metastatic prostatic cancer in a multinational double-blind randomized trial. *J Urol* 1993;149:77–82.
51. Brisset JM. Nilutamide (Anandron) in prostatic cancer: review of four clinical trials. In: Khoury S, Chatelain C, Denis L, eds. *Urology, Prostate Cancer.* Paris: Fiis et RGP; 1990: 381–9.
52. Béland G, Elhilali M, Fradet Y, *et al.* Total androgen blockade for metastatic cancer of the prostate. *Am J Clin Oncol* 1988; 11(suppl 2):S187–90.
53. Denis LJ, Carnelro de Moura JL, Bono AV, *et al.* Goserelin acetate and flutamide versus bilateral orchiectomy: a phase III EORTC trial (30853). EORTC GU Group and EORTC Data Center. *Urology* 1993;42:119–29.
54. Tyrrell CJ, Altwein JE, Klippel F, *et al.* A multicenter randomized trial comparing the luteinizing hormone–releasing hormone analogue goserelin acetate alone and with flutamide in the treatment of advanced prostate cancer. The International Prostate Cancer Study Group. *J Urol* 1991;146:1321–6.
55. Fourcade RO, Cariou G, Coloby P, *et al.* Total androgen blockade with Zoladex plus flutamide vs. Zoladex alone in advanced prostatic carcinoma: interim report of a multicenter, double-blind, placebo-controlled study. *Eur Urol* 1990;18(suppl 3): 45–7.
56. Iversen P, Christensen MG, Friis E, *et al.* A phase III trial of Zoladex and flutamide versus orchiectomy in the treatment of patients with advanced carcinoma of the prostate. *Cancer* 1990; 66(suppl):1058–66.
57. de Voogt HJ, Klijn JG, Studer U, Schroder FH, Sylvester R, de Pauw M. Orchidectomy versus buserelin in combination with cyproterone acetate, for 2 weeks or continuously, in the treatment of metastatic prostatic cancer. Preliminary results of EORTC-trial 30843. *J Steroid Biochem Mol Biol* 1990;37:965–9.
58. Williams G, Asopa R, Abel PD, Smith C. Pituitary adrenal and gonadal endocrine suppression for the primary treatment of prostate cancer. *Br J Urol* 1990;65:504–8.
59. Klosterhalfen H, Becker H. 10-Jahres-Ergebnisse einer randomisierten Prospectivstudie beim metastasierten Prostatakarzinom [German]. *Aktuelle Urol* 1987;18:234–6.
60. Periti P, Rizzo M, Mazzei T, Mini E. Depot leuprorelin acetate alone or with nilutamide in the treatment of metastatic prostate carcinoma: interim report of a multicenter, double-blind, placebo-controlled study [abstract]. *Can J Infect* 1995;6(suppl C):292C.
61. Moinpour CM, Savage MJ, Lovato LC, Troxel A, Skeel R, Eisenberger MA. Quality of life (QOL) endpoints in advanced stage prostate cancer: a randomized, double-blind study comparing flutamide to placebo in orchiectomized stage D2 prostate patients (PTS) [abstract]. *Proc Am Soc Clin Oncol* 1997; 16:53a.
62. Moinpour CM, Savage MJ, Troxel A, Lovato LC, *et al.* Quality of life in advanced prostate cancer: results of a randomized therapeutic trial. *J Natl Cancer Inst* 1998;90:1537–44.
63. Egger M, Smith GD. Bias in location and selection of studies. *BMJ* 1998;316:61–6.
64. Stewart LA, Parmar MKB. Meta-analysis of the literature or of individual patient data: is there a difference? *Lancet* 1993; 341:418–22.
65. Stewart LA, Tierney JF. To IPD or not to IPD? Advantages and disadvantages of systematic reviews using individual patient data. *Eval Health Prof* 2002;25:76–97.
66. Sarosdy MF, Schellhammer PF, Sharifi R, *et al.* Comparison of goserelin and leuprolide in combined androgen blockade therapy. *Urology* 1998;52:82–8.
67. Waxman J, Man A, Hendry WF, *et al.* Importance of early tumour exacerbation in patients treated with long acting analogues of gonadotrophin releasing hormone for advanced prostatic cancer. *Br Med J (Clin Res Ed)* 1985;291:1387–8.
68. Thompson IM, Zeidman EJ, Rodriguez FR. Sudden death due to disease flare with luteinizing hormone–releasing hormone agonist therapy for carcinoma of the prostate. *J Urol* 1990;144: 1479–80.
69. Schellhammer PF, Sharifi R, Block NL, *et al.* Clinical benefits of bicalutamide compared with flutamide in combined androgen blockade for patients with advanced prostatic carcinoma: final report of a double-blind, randomized, multicenter trial. Casodex Combination Study Group. *Urology* 1997;50: 330–6.
70. Klotz LH, Schellhammer PF, Carroll K. A re-assessment of the role of combined androgen blockade for advanced prostate cancer. *BJU Int* 2004;93:1177–82.
71. Akaza H, Yamaguchi A, Matsuda T, *et al.* Superior antitumour efficacy of bicalutamide 80 mg in combination with a luteinizing hormone–releasing hormone (LHRH) agonist versus LHRH agonist monotherapy as first-line treatment for advanced prostate cancer: interim results of a randomized study in Japanese patients. *Jpn J Clin Oncol* 2004;34:20–8.

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APPENDIX A Meta-analysis quality, as evaluated using the quality of reporting of meta-analyses (Quorom) statement; closed circles denote fully described items, open circles denote partially described items, and dashes denote items not described

Quorom checklist item	*Meta-analyses*					
		IPD		*Literature-based*		
	PCTCG 2000[18], *PCTCG 1995*[17]	*Bertagna 1994*[25], *Debruyne 1996*[26]	*Schmitt 2003*[22]	*Aronson 1999*[20]	*Bennett 1999*[23]	*Caubet 1997*[24]
INTRODUCTION						
Clinical problem	—	—	•	•	•	—
Biologic rationale for treatment	•	•	•	•	•	•
Rationale for review	•	•	•	•	•	•
METHODS						
Searching						
Information sources (e.g., databases, registers)	○	—	•	•	—	•
Restrictions (e.g., years, publication status, language)	○	—	○	•	○	•
Selection						
Inclusion/exclusion criteria (e.g., defining population, intervention, outcomes, and study design)	○	○	•	•	○	•
Validity assessment						
Criteria and process used (e.g., masked conditions, quality assessment, and their findings)	—	—	•	•	—	•
Data abstraction						
Process used (e.g., completed independently or in duplicate)	—	—	•	•	○	•
Study characteristics						
Type of study design	•	•	•	•	—	—
Participants' characteristics	—	•	•	•	—	—
Details of intervention	—	•	•	•	—	—
Outcome definitions	—	•	•	•	○	—
How clinical heterogeneity assessed	—	—	—	•	—	—
Quantitative data synthesis						
Measures of effect (e.g., relative risk, hazard ratio)	•	•	•	•	•	•
Method of combining results (e.g., statistical testing, CIs)	•	•	•	•	•	•
Handling of missing data	—	—	—	•	•	•
How statistical heterogeneity was assessed	—	•	•	•	—	—
Rationale for any *a priori* sub-group and sensitivity analyses	—	—	•	•	—	•
Assessment of publication bias	—	—	—	•	—	—
RESULTS						
Trial flow						
Provide meta-analysis profile summarizing trial flow	—	—	—	—	—	—
Study characteristics						
Present descriptive data for each trial (e.g., age, sample size, intervention, dose, duration, follow-up period)	•	—	•	•	•	•
Quantitative data synthesis						
Report agreement on selection and validity assessment	—	—	•	•	—	•
Present summary results (for each treatment group in trial and each outcome)	•	•	•	•	•	—
Present data needed to calculate effect sizes and CIs in ITT analyses (e.g., 2×2 tables of counts, means, proportions, SDs)	•	•	•	•	—	—
DISCUSSION						
Summarize key findings	•	•	•	•	•	•
Discuss clinical inferences based on internal and external validity	•	○	•	•	•	•
Interpret results in light of the totality of evidence	•	—	○	○	•	•
Describe potential biases in the review process (e.g., publication bias)	•	—	○	○	○	○
Suggest future research agenda	—	—	•	•	—	○

IPD = individual patient data; PCTCG = Prostate Cancer Trialists' Collaborative Group; CIs = confidence intervals; ITT = intent-to-treat; SDs = standard deviations.

APPENDIX B Literature search strategy

MEDLINE	*EMBASE*
1. practice guidelines/	1. exp randomized controlled trial/
2. practice guideline.pt.	2. exp controlled study/
3. practice guideline?.ti,tw.	3. Major Clinical Study/
4. meta-analysis/	4. Clinical trial/
5. metaanal:.ti,tw.	5. or/1–4
6. meta-anal:.ti,tw.	6. random:.ti,tw.
7. metanal:.ti,tw.	7. 5 and 6
8. systematic review?.ti,tw.	8. exp meta-analysis/
9. systematic overview?.ti,tw.	9. meta-analysis.ti,tw.
10. quantitative overview?.ti,tw.	10. (meta-anal: or meta anal:).ti,tw.
11. quantitative synthes#s.ti,tw.	11. (quantitative overview: or quantitative synth:).ti,tw.
12. randomized controlled trials/	12. (systematic review: or systematic overview:).ti,tw.
13. randomized controlled trial.pt.	13. exp practice guideline/
14. random allocation/	14. practice guideline.ti,tw.
15. double-blind method/	15. or/8–14
16. single-blind method/	16. 7 or 15
17. random:.ti,tw.	17. exp prostate tumor/
18. controlled clinical trial.pt.	18. exp prostate cancer/
19. clinical trial, phase iii.pt.	19. (prostat: cancer or prostat: carcinoma: or prostat: tumo?r: or prostat: malignan:).ti,tw.
20. or/1–19	20. *prostate tumor/dt
21. leuprolide.ti,tw.	21. *prostate cancer/dt
22. lupron.ti,tw.	22. or/17–21
23. goserelin.ti,tw.	23. total androgen blockade.ti,tw.
24. zoladex.ti,tw.	24. maximal androgen blockade.ti,tw.
25. buserelin.ti,tw.	25. androgen ablation.ti,tw.
26. suprefact.ti,tw.	26. flutamide.ti,tw.
27. flutamide.ti,tw.	27. eulexin.ti,tw.
28. eulexin.ti,tw.	28. nilutamide.ti,tw.
29. nilutamide.ti,tw.	29. anandron.ti,tw.
30. anandron.ti,tw.	30. nilandron.ti,tw.
31. nilandron.ti,tw.	31. bicalutamide.ti,tw.
32. bicalutamide.ti,tw.	32. casodex.ti,tw.
33. casodex.ti,tw.	33. cyproterone acetate.ti,tw.
34. cyproterone acetate.ti,tw.	34. androcur.ti,tw.
35. androcur.ti,tw.	35. diethylstilbestrol.ti,tw.
36. diethylstilbestrol.ti,tw.	36. des.ti,tw.
37. des.ti,tw.	37. exp gonadorelin/
38. total androgen blockade.ti,tw.	38. exp androgen antagonists/
39. maximal androgen blockade.ti,tw.	39. exp diethylstilbestrol/
40. combined androgen blockade.ti,tw.	40. or/23–39
41. androgen ablation.ti,tw.	41. exp castration/
42. exp gonadorelin/	42. castration.ti,tw.
43. exp androgen antagonists/	43. orchidectomy.ti,tw.
44. exp diethylstilbestrol/	44. orchiectomy.ti,tw.
45. or/21–44	45. monotherapy.ti,tw.
46. exp castration/	46. leuprolide.ti,tw.
47. castration.ti,tw.	47. lupron.ti,tw.
48. orchidectomy.ti,tw.	48. goserelin.ti,tw.
49. orchiectomy.ti,tw.	49. zoladex.ti,tw.
50. monotherapy.ti,tw.	50. buserelin.ti,tw.
51. or/46–50	51. suprefact.ti,tw.
52. prostatic neoplasms/	52. or/41–51
53. prostat: cancer.ti,tw.	53. 22 and 40 and 52
54. *prostatic neoplasms/dt	54. 53 and 16
55. or/52–54	
56. 45 and 51 and 55	
57. 56 and 20	