# Current Status of Monoclonal Antibodies-Based Therapies in Castration-Resistant Prostate Cancer: A Systematic Review and Meta-Analysis of Clinical Trials

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## Abstract

### Background

Multiple patients with prostate cancer become resistant to castration therapies, which is termed castration-resistant prostate cancer (CRPC).

### Purpose

The purpose of this review is to assess the status of efficacy (≥50% decline in prostate-specific antigen (PSA), progression-free survival (PFS), and overall survival (OS)) and safety (grade 3-4 adverse effects) of monoclonal antibodies in CRPC.

### Data source

We searched databases including PubMed, Embase, Cochrane, Web of Science, and ClinicalTrials.gov.

### Results

Hazard ratios of PFS and OS were 0.77 (95% CI = 0.69-0.87, $I^2$ = 53%) and 0.98 (95% CI = 0.86-1.11, $I^2$ = 40%), respectively, in the favor of monoclonal antibodies as compared to placebo. Risk ratio (RR) of >50% decline in PSA was 1.99 (95% CI = 0.97-4.08, $I^2$ = 53%) in favor of monoclonal antibodies. Pooled incidence of >50% decline in PSA levels was 15% (95% CI = 0.1-0.23, $I^2$ = 83%), 29% (95% CI = 0.14-0.51, $I^2$ = 93%), 63% (95% CI = 0.49-0.76, $I^2$ = 77%), and 88% (95% CI = 0.81-0.93, $I^2$ = 0%) in single, two, three, and four-drug regimens, respectively.

### Conclusion

Monoclonal antibodies are well tolerated and showed better PFS as compared to placebo. However, OS was only improved with ipilimumab. Denosumab delayed skeletal-related adverse events as compared to zoledronic acid. More multicenter double-blind clinical trials may be needed to confirm these results.

## Introduction

Prostate cancer is the second most common cause of cancer deaths in men after lung cancer in the United States with both aggressive and slow-growing types identified. More than 20% of the newly diagnosed cases of cancer are prostate cancer [1]. The new cases and estimated deaths for prostate cancer reported in the US in 2019 were 174,650 and 31,620, respectively, with an increase in the trend seen in 2020 with 191,930 new cases and 33,330 estimated deaths [1,2]. Globally, 1,276,106 new cases were estimated in 2018. Developed countries have higher incidence probably due to better use of diagnostic testing [3].

The various modalities that continue to be the mainstay of treatment for prostate cancer are surgical

(prostatectomy), hormonal (gonadotropin-releasing hormone agonist or antagonist, androgen deprivation), and radiation (external beam radiotherapy, brachytherapy) [4-6]. However, surgical/chemical castration is required for most patients with metastatic disease. The progression of the carcinoma with or without metastasis despite castration therapy (androgen deprivation therapy) is termed as castrate-resistant or hormone-resistant cancer and is characterized by rising prostate-specific antigen (PSA) levels with castrate range of testosterone (<50 ng/dl or <1.7 nmol/l) [6-9].

Chemotherapy agents including taxanes, bisphosphonates, immunotherapy agents, and poly (ADP-ribose) polymerase-1 inhibitors have shown anti-tumor activity in patients with castration-resistant prostate cancer (CRPC). Taxane with prednisone is the most common treatment used for CRPC. Despite these treatment options, the prognosis and quality of life of these patients are very poor. There is still room for more combination therapies for the treatment of CRPC, especially for patients who do not tolerate and/or are refractory to first-line therapies [10-13].

In recent years, monoclonal antibodies have shown promising results in clinical trials. Monoclonal antibodies have been evaluated for their efficacy in CRPC due to their targeted action on various tumor factors that help control cancer progression [4]. The most common antibodies studied include bevacizumab (anti-vascular endothelial growth factor (VEGF)), which decreases angiogenesis and improves vessel penetration of cytotoxic agents like taxanes when used in combination [10,11]. Cixutumumab and ramucirumab act against insulin-like growth factor-1 receptor (IGF-1R)/vascular endothelial growth factor receptor (VEGFR) and can prevent tumor growth. Other monoclonal antibodies, including siltuximab, abituzumab, trastuzumab, and cetuximab, bind to interleukin-6, integrin alpha-V, human epidermal growth factor receptor 2 (HER2), and epidermal growth factor receptor (EGFR), respectively [12-15]. Checkpoint inhibitors including nivolumab (anti-programmed cell death protein 1 (PD-1)), pembrolizumab (anti-PD-1), and ipilimumab (anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4)) are also tested in clinical trials for anti-tumor activity against CRPC [16,17]. While several of these immunotherapies are under evaluation in clinical trials, denosumab is the major monoclonal antibody approved by the FDA for metastatic bone lesions in CRPC [18].

The aim of this systematic review and meta-analysis is to assess the efficacy and safety of monoclonal antibodies alone or in combination with chemotherapy drugs in CRPC.

# Materials And Methods

In conducting this systematic review and meta-analysis, we followed a prespecified protocol registered on the International Prospective Register of Systematic Reviews (PROSPERO) (registration number: CRD42021230102). The protocol was made according to the guidelines established by Cochrane [19] and PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) [20].

## Search strategy

A literature search was performed on PubMed, Embase, Web of Science, Cochrane Library, and ClinicalTrials.gov with Medical Subject Heading (MeSH) and Emtree terms "monoclonal antibodies" and "castration-resistant prostate cancer." The search was made from the inception of literature till March 20, 2021, by following the PICO framework (Appendix) [21].

## Inclusion and exclusion criteria

We included all clinical trials that provided safety and efficacy data in clinical terms, i.e., objective response (OR), complete response (CR), partial response (PR), ≥50% decline in PSA, progression-free survival (PFS), overall survival (OS), and grade 3-4 adverse effects. We excluded all preclinical studies, case reports, meta-analyses, review articles, observation studies, and clinical studies irrelevant to the study question.

## Study selection

Two researchers (WA and TAT) independently reviewed the articles identified through initial search and screened them based on inclusion and exclusion criteria. The differences were addressed by a third researcher (MAA).

## Data extraction

Data were extracted by two authors (MS and MYA). The data were extracted for the characteristics of the study, baseline characteristics of participants, treatment drugs, efficacy measures, and toxicity (grade ≥ 3 adverse effects).

## Risk of bias assessment

Two researchers (SR and SFB) assessed the risk of bias in randomized clinical trials (RCTs) selected for final inclusion by using the Risk of Bias 2 (RoB 2) tool for risk of bias assessment in RCTs [22]. The third researcher (MAA) addressed the differences.

## Statistical analysis

The meta-analysis was performed using the "R" programming language. We used the "meta" package in R for our data analysis [23]. A random-effects model was used, irrespective of the heterogeneity, to keep our results consistent and applicable. All analyses used the DerSimonian-Laird estimator to calculate between-study variance. The risk ratios were pooled using the Mantel-Haenszel method. For studies with zero events in any of the arms, a continuity correction of 0.5 was used. Standard errors and other calculations were done using a 95% confidence interval. For pooling of the results, all the studies were included even if they have zero events in both arms. To estimate the heterogeneity, $I^2$ was used.

## Results

A total of 3,069 articles were identified with 424 articles from PubMed, 2,427 articles from Embase, 49 articles from Web of Science, 60 articles from Cochrane, and 109 articles from ClinicalTrials.gov. These articles were analyzed by the researchers and 416 articles were removed as duplicates. A total of 2,221 articles were excluded in the first screening based on exclusion criteria. Full texts of 432 articles were reviewed. Eight RCTs (N = 6,227) [13,24-30] and 18 non-randomized clinical trials (NRCTs, N = 920) [10,15,31-41] were included based on prespecified inclusion criteria (Figure 1).
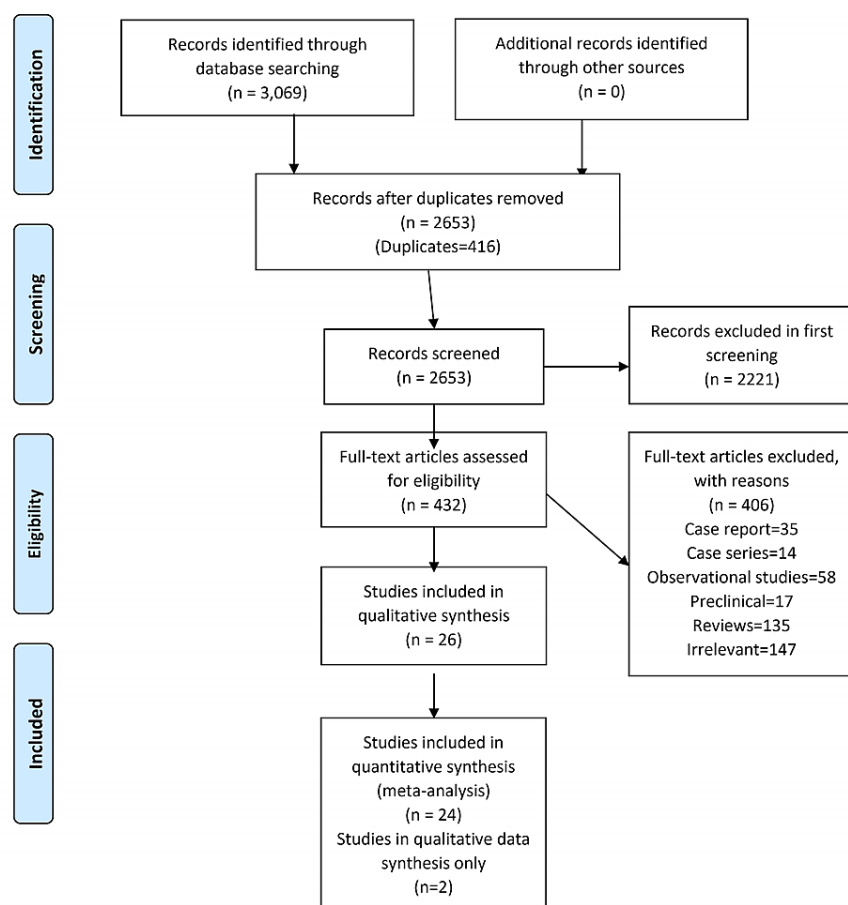


**FIGURE 1: Flow chart of literature search.**

## Risk of bias

The risk of bias was low in double-blinded RCTs except for open-label RCT conducted by Hussain et al. (2015) [30] (Figure 2).

**Risk of bias domains**

| Study | D1 | D2 | D3 | D4 | D5 | Overall |
|---|---|---|---|---|---|---|
| Beer et al. 2017 | + | + | + | + | + | + |
| Smith et al. 2012 | + | + | + | + | + | + |
| Fizazi et al. 2011 | + | + | + | + | + | + |
| Heidenreich et al. 2013 | + | + | + | + | + | + |
| Kwon et al. 2014 | + | + | + | + | + | + |
| Kelly et al. 2012 | + | + | + | + | + | + |
| Hussain et al. 2015 | + | X | + | + | + | X |
| Hussain et al. 2016 | + | + | + | + | + | + |

Domains:
D1: Bias arising from the randomization process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.

Judgement
X High
+ Low

Bias arising from the randomization process
Bias due to deviations from intended interventions
Bias due to missing outcome data
Bias in measurement of the outcome
Bias in selection of the reported result
**Overall risk of bias**

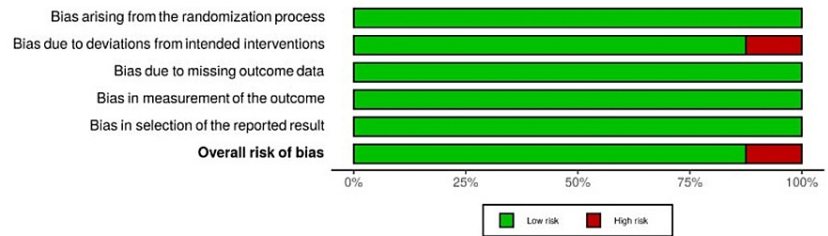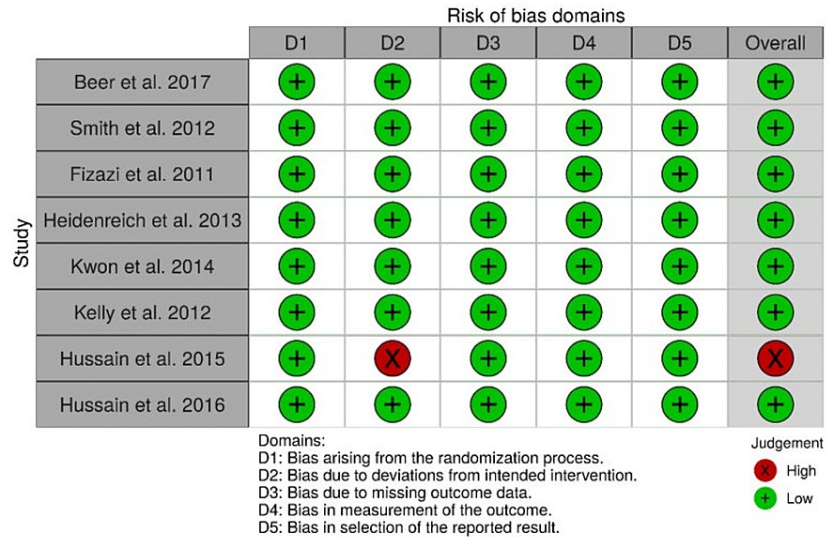0%   25%   50%   75%   100%

Low risk | High risk

**FIGURE 2: Risk of bias assessment with Risk of Bias 2 (RoB 2) tool.**

Studies [12,13,24-30].

## Monoclonal antibodies vs. placebo

In six clinical trials (N = 4,194) [13,24-30], monoclonal antibodies were given to 2,225 participants while placebo was given to 1,969 participants. Standard of care (SOC) including luteinizing hormone-releasing hormone agonist/antagonist was given to 180 patients in the study by Hussain et al. [30]. The median ages of participants were ≥65 years in RCTs. Baseline characteristics of participants are given in Table 1.

| Author, year | Phase | Trial NCT | Follow-up | N | Age | Treatment | ECOG score | Metastasis | Prior systemic therapy | Gleason score | Bone lesion | Median PSA |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Randomized clinical trials | | | | | | | | | | | | |
| Beer et al. (2017) [24] | III | NCT01057810 | 2-4 years | 400 | 70 (44-91) | Ipilimumab (anti-CTLA-4, 10 mg/Kg) | 0 = 75%, 1 = 25% | Bone = 78% | N/A | ≤7 = 47%, ≥8 = 48% | Yes = 78%, no = 21% | 41.2 (0.05-4,956) |
| | | | | 202 | 69 (42-92) | Placebo | 0 = 75%, 1 = 25% | Bone = 79% | N/A | ≤7 = 51%, ≥8 = 45% | Yes = 79%, no = 19% | 49.5 (0.01-9,297) |
| Smith et al. (2012) [25] | III | NCT00286091 | N/A | 716 | 74·0 (67-80) | Denosumab (targets RANKL) (120 mg) | 0 = 71%, 1 = 29% | Non-metastatic | N/A | ≤7 = 60%, 8-10 = 30% | N/A | 12·2 (4·7-27·5) |
| | | | | 716 | 74·0 (67-80) | Placebo | 0 = 72%, 1 = 28% | Non-metastatic | N/A | ≤7 = 56%, 8-10 = 33% | N/A | 12·5 (4·9-28·5) |

| Study | Phase | NCT | Follow-up | N | Age | Intervention | Performance status | Metastasis | Prior treatment | Gleason | Skeletal | PSA |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Fizazi et al. (2011) [26] | III | NCT00321620 | 12.2 month | 950 | 71 (64-77) | Denosumab (targets RANKL) | 0-1 = 93% | Visceral metastasis = 17% | Recent chemotherapy = 14% | 2-6 = 18%, 7 = 29%, 8-10 = 41% | Skeletal event = 24% | 58·5 (18·2-225·6) |
| | | | 11.2 month | 951 | 71 (66-77) | Zoledronic acid | 0-1 = 93% | Visceral metastasis = 19% | Recent chemotherapy = 14% | 2-6 = 19%, 7 = 29%, 8-10 = 43% | Skeletal event = 24% | 60·0 (19·8-202·2) |
| Heidenreich et al. (2013) [27] | II | N/A | 24 months | 66 | 68 (41, 83) | Docetaxel + prednisone + intetumumab (integrin α-V, 10 mg/kg) | 0 = 34, 1 = 30, 2 = 2 | Metastatic cancer | 57/66 | <7 = 31, >7 = 22 | N/A | N/A |
| | | | 24 months | 65 | 68 (46, 82) | Docetaxel + prednisone + placebo | 0 = 31, 1 = 32, 2 = 2 | Metastatic cancer | 62/65 | <7 = 26, >7 = 25 | N/A | N/A |
| Kwon et al. (2014) [28] | III | NCT00861614 | 9.9 months | 399 | 69·0 (47-86) | Ipilimumab group (anti-CTLA-4, 10 mg/kg) | 0 = 168, 1 = 216, 2 = 3 | Bone events <5 = 276, >5 = 103 | N/A | <7 = 174, >7 = 192 | Bone <5 = 276, >5 = 103 | 138·5 (0-4576) |
| | | | 9.3 months | 400 | 67·5 (45-86) | Placebo | 0 = 170, 1 = 220 | Bone events <5 = 253, >5 = 111 | N/A | <7 = 190, >7 = 187 | Bone <5 = 253, >5 = 111 | 176·5 (0-13768) |
| Kelly et al. (2012) [29] | III | N/A | 8 cycles | 524 | 68.8 | Bevacizumab (anti-VEGF-A, 15 mg/kg) + docetaxel | 0 = 57, 1 = 39, 2 = 4 | Metastatic cancer | N/A | N/A | N/A | N/A |
| | | | | 526 | 69.3 | Docetaxel | 0 = 55, 1 = 40, 2 = 5 | Metastatic cancer | N/A | N/A | N/A | N/A |
| Hussain et al. (2015) [30] | II | NCT00683475 | N/A | 66 | 65 (48-88) | Cixutumumab (anti-IGF, 6 mg/kg) + M + P | 0 = 23, 1 = 38, 2 = 5 | Metastatic cancer | Docetaxel-pretreated | N/A | N/A | 133.45 (0.1-5530.0) |
| | | | | 66 | 68 (46-86) | Ramucirumab (VEGFR, 6 mg/kg) + M + P | 0 = 19, 1 = 41, 2 =6 | Metastatic cancer | Docetaxel-pretreated | N/A | N/A | 107.30 (2.2-5826.4) |
| Hussain et al. (2016) [13] | II | NCT01360840 | 4.1 months | 60 | 69.5 (54-84) | Abituzumab (anti-CD-51, 750 mg) and SOC | 0 = 39, 1 = 18 | Metastasis = 57 | N/A | N/A | N/A | N/A |
| | | | 4.2 months | 60 | 71.0 (53-88) | Abituzumab 1,500 mg and SOC | 0 = 34, 1 = 22 | Metastasis = 59 | N/A | N/A | N/A | N/A |
| | | | 4.2 months | 60 | 71.0 (46-88) | Placebo and SOC | 0 = 32, 1 = 25 | Metastasis = 59 | N/A | N/A | N/A | N/A |
| Non-randomized clinical trials | | | | | | | | | | | | |
| Vaishampayan et al. (2015) [31] | I | N/A | 4 weeks | 7 | 66-85 | Anti-CD3 x anti-HER2 bispecific antibody | 0-2 = 100% | Metastatic cancer | Hormones = 7, docetaxel = 1 | 6-9 | Present | N/A |
| Picus et al. (2011) [33] | II | N/A | 24 months | 77 | 69 (48-88) | Estramustine, docetaxel, and bevacizumab ( anti-VEGF-A) | 0-2 = 100% | Metastatic cancer | N/A | N/A | 86% | 123 ng/ml |
| Vaishampayan et al. (2014) [32] | II | N/A | 24 months | 30 | 67 (50-85) | Bevacizumab and satraplatin | N/A | Metastatic cancer | Docetaxel = 100% | 6 = 6%, 7 = 26%, 8-10 = 65% | 21 (68%) | 180.7 ng/ml (4.7-1,432.8 ng/ml) |
| McNeel et al. | | | | 73 | | Anti-tumor vaccine | | Metastatic | | <7 = 8%, 7 = | | 24 (3- |

| Study | Phase | NCT | Follow-up | N | Age | Treatment | ECOG | Cancer type | Prior therapies | Gleason score | Metastasis | PSA |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (2018) [34] | II | N/A | N/A | 26 | (56-85) | (+pembrolizumab-PD-1 inhibitor in 13) | <2 | cancer | Radiation, chemo, abiraterone, enzalutamide | 19%, 8 = 19%, 9 = 54% | N/A | 165) |
| Gross et al. (2017) [11] | Ib | NCT00574769 | 12 cycles + maintenance | 43 | 65 (50-79) | Docetaxel, bevacizumab, and everolimus | N/A | Bone = 88%, nodes = 44%, viscera = 19% | Abiraterone = 26%, orteronel = 7%, enzalutamide = 5% | N/A | Bone metastasis = 88% | 76.6 (0-1847) |
| Cathomas et al. (2012) [15] | II | NCT00728663 | 25.4 months | 38 | 68 (45-82) | Docetaxel + cetuximab (EGFR inhibitor, 400 mg/m2) | N/A | Bone = 89%, node = 63%, visceral = 34% | 1 regimen = 65%, 2 regimens = 26%, 3 regimens = 9% (docetaxel regimens) | N/A | Bone metastasis = 89% | 212 ng/ml (4.4-8,898) |
| Batra et al. (2020) [35] | I | NCT00916123 | N/A | 15 | 69 (49-80) | Docetaxel + J591 (177Lu-J591) | 0 = 40%, 1 = 53.3%, 2 = 6.7% | Bone = 93.3%, node = 60%, lung = 6.7% | Primary radiotherapy = 40%, salvage radiotherapy = 13.3%, prostatectomy = 46.7% | 6 = 13.3%, 7 = 40%, 8-10 = 40% | Bone metastasis = 93.3% | 84.32 ng/ml (17.2-776) |
| Madan et al. (2016) [36] | II | NCT00942578 | 47.5 months | 63 | 65.6 (51-82) | Lenalidomide with bevacizumab, docetaxel, and prednisone | 0 = 10, 1 = 50, 2 = 3 | Bone = 24, bone + nodes = 27, bone + visceral = 7 | N/A | ≤6 = 4, 7 = 15, 8 = 15, 9 = 23, 10 = 6 | Bone = 24 | 90.36 (0.14-3 520) |
| Slovin et al. (2013) [37] | I/II | NCT00323882 | N/A | 16 | 65 (53-76) | Ipilimumab (anti-CTLA-4, 10 mg/kg) | 0 = 10, 1 = 6, 2 = 0 | Metastatic cancer | 6 (38%) | N/A | 2.5 (1-12) | 132 (13-2581) |
| | | | | 34 | 66 (50-83) | Ipilimumab = 10 mg/kg + XRT | 0 = 9, 1 = 22, 2 = 0 | Metastatic cancer | 21 (62%) | N/A | 8 (1-15) | 120 (8-1314) |
| Barata et al. (2019) [38] | I/II | NCT01083368 | N/A | 21 | 64 (53-82) | Temsirolimus and bevacizumab | 0 = 19%, 1 = 62%, 2 = 14% | Metastatic cancer | Docetaxel = 86%, mitoxantrone = 29%, ketoconazole = 24%, cabazitaxel = 10%, gemcitabine = 10% | <7 = 33%, >= 8 = 43% | 21 (100%) | 205.3 (11.1-1801.0) |
| Autio et al. (2020) [39] | I | NCT02265536 | N/A | 12 | 58-84 | LY3022855 | 0 = 33%, 1 = 58.3%, 2 = 8% | Metastatic cancer | Chemotherapy = 42% Abiraterone acetate/enzalutamide = 100% | N/A | 10/12 (83%) | N/A |
| Di Lorenzo et al. (2008) [40] | II | N/A | N/A | 20 | 66 (49-73) | Bevacizumab + docetaxel | N/A | Metastatic cancer | Docetaxel = 100%, mitoxantrone = 100%, vinorelbine = 65% | <7 = 8, >7 = 12 | Bone metastasis = 100% | 260 |
| Graff et al. (2020) [42] | II | NCT02312557 | 37 months | 28 | 72 (61-90) | Pembrolizumab (anti-PD-1, 200mg) + enzalutamide | 0 = 39%, 1 = 61% | Metastatic cancer | Docetaxel = 4, abiraterone = 10, enzalutamide = 28 | <7 = 1, 7 = 9, >7 =1 4 | Bone only = 13, bone and lymph nodes = 9 | 26.61 ng/ml (3.03-2502.75) |
| Francini et al. (2011) [43] | II | N/A | 11.3 months | 43 | 74 (58-82) | Docetaxel + bevacizumab + prednisone | 0 = 20.9%, 1-2 = 79% | Metastatic cancer | w-epirubicin + w-docetaxel = 21 3-w, docetaxel + prednisone = 15, w-docetaxel + prednisone = 7 | N/A | N/A | 78 (47-374) |
| Ning et al. (2010) [44] | II | N/A | 34 months | 60 | 66 (44-79) | Docetaxel, bevacizumab, thalidomide, prednisone | 0 = 13%, 1 = 80%, 2 = 7% | Metastatic cancer | N/A | <7 = 20 (33%), >8 = 39 (65%) | N/A | 99 (0.9-4,399) |
| Hudes et al. (2013) [41] | I | N/A | N/A | 39 | 66 (43, 82) | Docetaxel 75 mg/m2 + siltuximab (anti-IL-6, 6-12 mg/kg) | N/A | Metastatic cancer | N/A | 8 (5,10) | N/A | 57 (12, 1430) |
| Sharma et al. (2020) [16] | II | NCT02985957 | 11.9 months | 45 | 69 (48-85) | Nivolumab (anti-PD-1, 1 mg/kg) + ipilimumab (anti-CTLA-4, 3 mg/kg) | 0 = 26 (57.8%), 1 = 19 (42.2%) | M0 = 28 (62.2%), MI = 15 (33.3%) | Abiraterone = 66.7%, enzalutamide = 57.8%, bicalutamide = 55.6%, leuprolide = 60%, docetaxel = 11.1% | <7 = 35.5%, >7 = 60% | 0 = 20%, <4 = 13.3%, >4 = 66.7% | 59.5 ng/ml (93.3-1045) |
| | | | 13.5 months | 45 | 65 (46-84) | Nivolumab 1 mg/kg + ipilimumab (3 mg/kg) | 0 = 25 (55.6) 1 = 20 (44.4%) | M0 = 22 (48.9%), MI = 20 (44.4%) | Abiraterone = 71.1%, enzalutamide = 62.2%, bicalutamide = 64.4%, leuprolide = 53.3%, docetaxel = 86.7%, cabazitaxel = 46.7% | 7 or less = 42.2%, 8 or more = 51.1% | 0 = 6.7%, <4 = 2.2%, >4 = 91.1% | 158.9 ng/ml (1.8-1348.7) |

| Author | Phase | NCT | Duration | N/PD-L1 | Age | Drug | ECOG | Cancer | Previous chemotherapy | Prior treatment | PSA (bone) | PSA |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 9.5 months | 133 PD-L1+ | 68 (48-85) | | | | | | | 115.5 (0.1-5000) |
| Antonarakis et al. (2020) [17] | II | NCT02787005 | 7.9 months | 66 PD-L1- | 68 (53-84) | Pembrolizumab 200 mg | 0 = 36%, 1 = 53.4%, 2 = 10% | Metastatic cancer | No. of previous chemotherapy regimens: 1 = 183 (71%), 2 or more = 75 (29%) | 7 or less = 31.7%, 8 or more = 62%, unknown = 6.2% | Bone predominant = 59 | 116.1 (1.0-3583.0) |
| | | | 14.1 months | 59 | 71 (53-90) | | | | | | | 43.3 (0.1-2539.0) |

**TABLE 1: Baseline characteristics of trials.**

NCT = National Clinical Trial; ECOG = Eastern Cooperative Oncology Group; PSA = prostate-specific antigen; CTLA-4 = cytotoxic T-lymphocyte-associated antigen-4; RANKL = receptor activator of nuclear factor kappa-B ligand; M = mitoxantrone; P = prednisone; XRT= radiation therapy; SOC = standard of care; VEGFR = vascular endothelial growth factor receptor; EGFR = epidermal growth factor receptor; PD-1 = programmed cell death protein 1; IL-6 = interleukin 6; IGF = insulin-like growth factor; HER2 = human epidermal growth factor receptor 2; VEGF-A = vascular endothelial growth factor A.

### Efficacy

In RCTs with ipilimumab, denosumab, bevacizumab, and abituzumab (N = 4,063), pooled hazard ratio (HR) of PFS was 0.77 (95% CI = 0.69-0.87, $I^2$ = 53) in favor of monoclonal antibodies as compared to placebo. HR of PFS for trial on intetumumab (N = 131) was 1.73 (95% CI = 1.11-2.69) in favor of placebo as compared to monoclonal antibodies (Figure 3A).

In RCTs with ipilimumab and bevacizumab (N = 2,254), the risk ratio (RR) of ≥50% decline in PSA was 1.99 (95% CI = 0.97-4.08, $I^2$ = 53%) in favor of monoclonal antibodies as compared to placebo. While in the RCT with intetumumab, RR of ≥50% decline in PSA was 0.62 (95% CI = 0.44-0.87) in favor of placebo as compared to monoclonal antibodies (Figure 3B).

In RCTs with ipilimumab, denosumab, bevacizumab, and intetumumab (N = 4014), HR of overall survival was similar in monoclonal antibodies groups vs. placebo, i.e., 0.98 (95% CI = 0.86-1.11, $I^2$ = 40%) (Figure 3C).
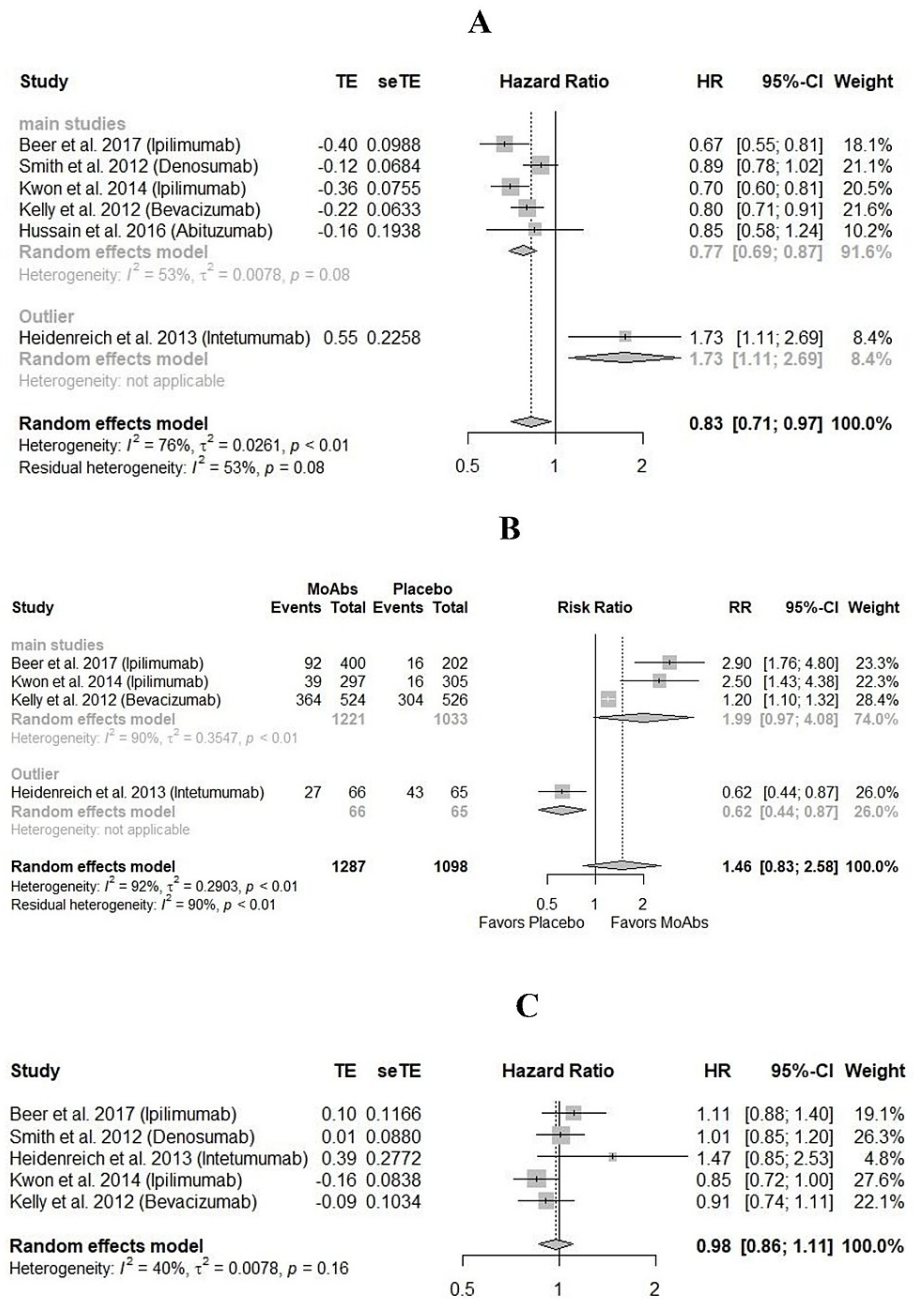
**A**

| Study | TE | seTE | Hazard Ratio | HR | 95%-CI | Weight |
|---|---|---|---|---|---|---|
| **main studies** | | | | | | |
| Beer et al. 2017 (Ipilimumab) | -0.40 | 0.0988 | | 0.67 | [0.55; 0.81] | 18.1% |
| Smith et al. 2012 (Denosumab) | -0.12 | 0.0684 | | 0.89 | [0.78; 1.02] | 21.1% |
| Kwon et al. 2014 (Ipilimumab) | -0.36 | 0.0755 | | 0.70 | [0.60; 0.81] | 20.5% |
| Kelly et al. 2012 (Bevacizumab) | -0.22 | 0.0633 | | 0.80 | [0.71; 0.91] | 21.6% |
| Hussain et al. 2016 (Abituzumab) | -0.16 | 0.1938 | | 0.85 | [0.58; 1.24] | 10.2% |
| Random effects model | | | | 0.77 | [0.69; 0.87] | 91.6% |
| Heterogeneity: $I^2 = 53\%$, $\tau^2 = 0.0078$, $p = 0.08$ | | | | | | |
| **Outlier** | | | | | | |
| Heidenreich et al. 2013 (Intetumumab) | 0.55 | 0.2258 | | 1.73 | [1.11; 2.69] | 8.4% |
| Random effects model | | | | 1.73 | [1.11; 2.69] | 8.4% |
| Heterogeneity: not applicable | | | | | | |
| **Random effects model** | | | | **0.83** | **[0.71; 0.97]** | **100.0%** |
| Heterogeneity: $I^2 = 76\%$, $\tau^2 = 0.0261$, $p < 0.01$ | | | | | | |
| Residual heterogeneity: $I^2 = 53\%$, $p = 0.08$ | | | 0.5  1  2 | | | |

**B**

| Study | MoAbs Events | Total | Placebo Events | Total | Risk Ratio | RR | 95%-CI | Weight |
|---|---|---|---|---|---|---|---|---|
| **main studies** | | | | | | | | |
| Beer et al. 2017 (Ipilimumab) | 92 | 400 | 16 | 202 | | 2.90 | [1.76; 4.80] | 23.3% |
| Kwon et al. 2014 (Ipilimumab) | 39 | 297 | 16 | 305 | | 2.50 | [1.43; 4.38] | 22.3% |
| Kelly et al. 2012 (Bevacizumab) | 364 | 524 | 304 | 526 | | 1.20 | [1.10; 1.32] | 28.4% |
| Random effects model | | 1221 | | 1033 | | 1.99 | [0.97; 4.08] | 74.0% |
| Heterogeneity: $I^2 = 90\%$, $\tau^2 = 0.3547$, $p < 0.01$ | | | | | | | | |
| **Outlier** | | | | | | | | |
| Heidenreich et al. 2013 (Intetumumab) | 27 | 66 | 43 | 65 | | 0.62 | [0.44; 0.87] | 26.0% |
| Random effects model | | 66 | | 65 | | 0.62 | [0.44; 0.87] | 26.0% |
| Heterogeneity: not applicable | | | | | | | | |
| **Random effects model** | | **1287** | | **1098** | | **1.46** | **[0.83; 2.58]** | **100.0%** |
| Heterogeneity: $I^2 = 92\%$, $\tau^2 = 0.2903$, $p < 0.01$ | | | | | 0.5  1  2 | | | |
| Residual heterogeneity: $I^2 = 90\%$, $p < 0.01$ | | | | | Favors Placebo  Favors MoAbs | | | |

**C**

| Study | TE | seTE | Hazard Ratio | HR | 95%-CI | Weight |
|---|---|---|---|---|---|---|
| Beer et al. 2017 (Ipilimumab) | 0.10 | 0.1166 | | 1.11 | [0.88; 1.40] | 19.1% |
| Smith et al. 2012 (Denosumab) | 0.01 | 0.0880 | | 1.01 | [0.85; 1.20] | 26.3% |
| Heidenreich et al. 2013 (Intetumumab) | 0.39 | 0.2772 | | 1.47 | [0.85; 2.53] | 4.8% |
| Kwon et al. 2014 (Ipilimumab) | -0.16 | 0.0838 | | 0.85 | [0.72; 1.00] | 27.6% |
| Kelly et al. 2012 (Bevacizumab) | -0.09 | 0.1034 | | 0.91 | [0.74; 1.11] | 22.1% |
| **Random effects model** | | | | **0.98** | **[0.86; 1.11]** | **100.0%** |
| Heterogeneity: $I^2 = 40\%$, $\tau^2 = 0.0078$, $p = 0.16$ | | | 0.5  1  2 | | | |

**FIGURE 3: Comparison of efficacy in monoclonal antibodies vs. placebo.**

(A) Hazard ratio of progression-free survival. (B) Risk ratio of ≥50% decline in prostate-specific antigen (PSA). (C) Hazard ratio of overall survival [24-30].

MoAbs = monoclonal antibodies; TE = treatment effect; seTE: standard error of treatment effect.

In RCT with denosumab (N = 1432), HRs of bone metastasis-free survival and first bone metastasis were statistically significant in favor of denosumab. HRs of bone metastasis-free survival and first bone metastasis were 0.85 (95% CI = 0.73-0.98) and 0.84 (95% CI = 0.71-0.98), respectively.

## Safety

In RCTs, RRs of any ≥ grade 3 toxicity were 1.41 (CI = 1.10-1.82, $I^2 = 92\%$) in favor of placebo as compared to monoclonal antibodies. RRs of ≥ grade 3 adverse events, i.e., vomiting, rash, pancreatitis, neutropenia, hypertension, hepatitis, fatigue, diarrhea, colitis, and anemia, were 5.30 (95% CI = 0.87-32.36, $I^2 = 0$), 7.50 (95% CI = 0.94-59.46, $I^2 = 0$), 9.21 (95% CI = 4.27-19.85), 1.01 (95% CI = 0.58-1.74, $I^2 = 63.5\%$), 3.98 (95% CI =

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1.23-12.84, $I^2$ = 19.2%), 5.02 (95% CI = 0.58-42.95, $I^2$ = 0), 1.44 (95% CI = 1.00-2.07, $I^2$ = 22.8%), 4.42 (95% CI = 0.25-75.69, $I^2$ = 81.1%), 2.82 (95% CI = 0.01-550.00, $I^2$ = 84.6%), and 1.28 (95% CI = 0.79-2.08, $I^2$ = 8.3%), respectively. Denosumab increased the incidence of ⩾ grade 3 osteonecrosis of jaw in RCT 33/720 vs. 0/705 (Figure 4).
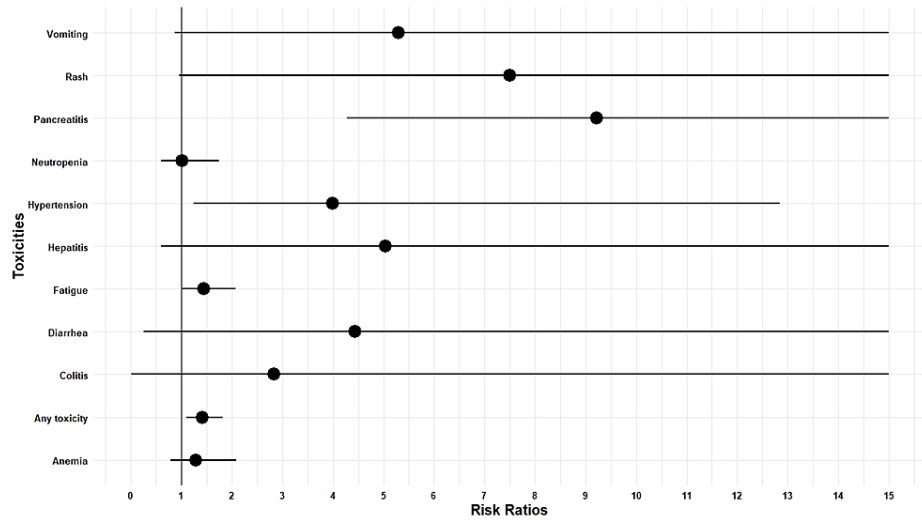


**FIGURE 4: Plot of the risk ratio of ≥ grade 3 adverse events.**

## Denosumab vs. zoledronic acid

Fizazi et al. (2011) [26] compared denosumab vs. zoledronic acid for the treatment of CRPC (N = 1,904). HR of the first skeletal-related adverse event was 0.82 (95% CI = 0.71-0.95) in favor of denosumab as compared to zoledronic acid. The incidence of total skeletal-related events was 36% in the denosumab group vs. 41% in the zoledronic acid group. Radiation to bone was used in 19% of the people in the denosumab group vs. 21% in the zoledronic acid group. The incidence of adverse events was 97% each in both groups. Greater than or equal to grade 3 adverse events were 72% and 66% in denosumab and zoledronic acid groups, respectively. Osteonecrosis of the jaw was 1% in the zoledronic acid group vs. 2% in the denosumab group. Discontinuation of treatment due to adverse events was reported in 15% of participants in the zoledronic acid group and 17% in the denosumab group.

## Cixutumumab vs. ramucirumab

Hussain et al. (2015) [30] compared cixutumumab vs. ramucirumab (N = 132). The median time to radiographic disease progression was 7.5 months (95% CI = 4.8-10.1) for patients on cixutumumab while it was 10.2 months (95% CI = 7.5-12.6) for patients on ramucirumab. Median OS was 10.8 months (95% CI = 6.5-13.0) for patients on cixutumumab while it was 13.0 months (95% CI = 9.5-16.0) for patients on ramucirumab. Decline >50% in PSA occurred in 18.5% of patients in the cixutumumab group and 21.4% of patients in the ramucirumab group. Among ⩾ grade 3 adverse events, fatigue, diarrhea, dehydration, hypertension, neutropenia, and anemia were reported in 16.7% vs. 7.6%, 7.6% vs. 1.5%, 6.1% vs. 1.5%, 1.5% vs. 9.1%, 31.9% vs. 31.8%, and 3% vs. 10.6% of patients, respectively, in cixutumumab vs. ramucirumab groups.

## Single-arm comparison of monoclonal antibody regimens

Ipilimumab, cixutumumab, ramucirumab, anti-CD3 x anti-HER2 bispecific antibody, and pembrolizumab were used as monotherapy in clinical trials (N = 1,129) [17,24,28,30,31]. Pooled incidences of OR and >50% decline in PSA were 8% (95% CI = 0.03-0.22, $I^2$ = 89%) and 15% (95% CI = 0.1-0.23, $I^2$ = 83%), respectively. Individual study results and pooled results are given in Figure 5. Median OS and PFS were 7.4-19.6 months and 2.1 months, respectively (Table 2).

**A**
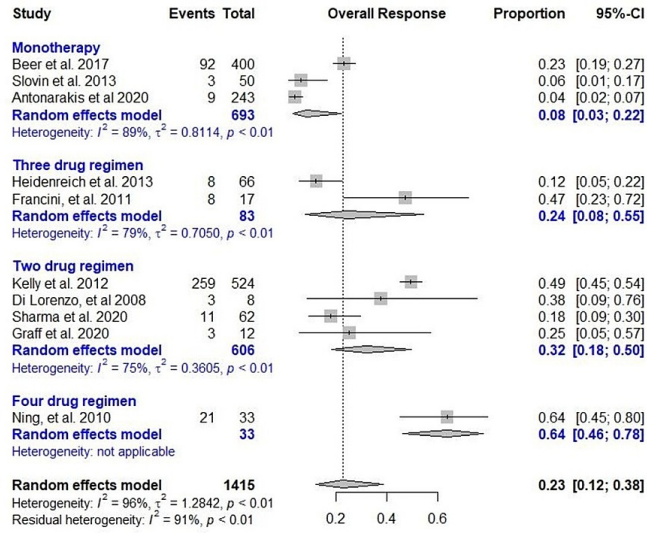


**B**
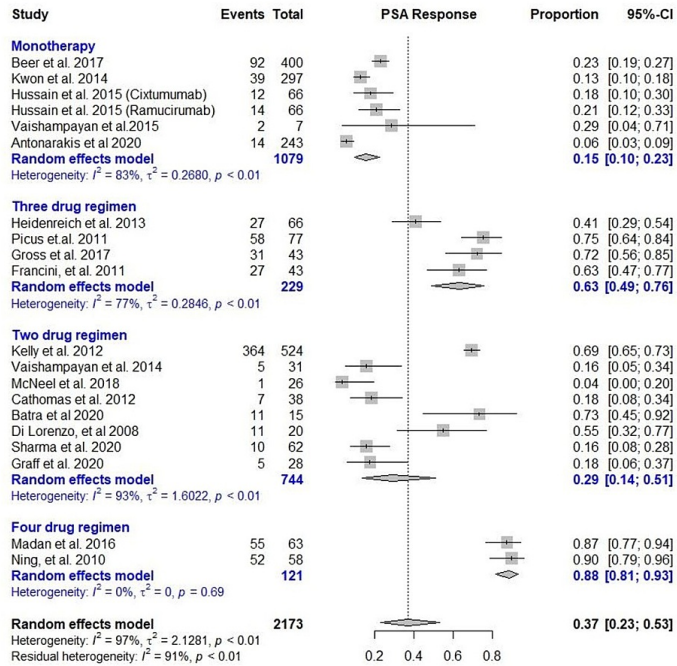


**FIGURE 5: Meta-analysis of efficacy in single arms.**

(A) Pooled overall response. (B) Pooled >50% prostate-specific antigen (PSA) response [10,17,24-35].

| Author | Median PFS (months) | Median OS (months) | Any ≥ grade 3 | Diarrhea | Hypertension | Anemia | Neutropenia/lymphopenia | Colitis | Hepatitis | Fatigue | Rash | Vomiting |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Monotherapy | | | | | | | | | | | | |
| Vaishampayan et al. (2015) [31] | N/A | N/A | 5/7 | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Antonarakis et al. (2020) [17] | 2.1 (2.1-2.2) | 9.6 (7.9-12.2) | 27 (10%) | 2 (<1%) | N/A | 2 (<1%) | N/A | 3 (1%) | 1 (<1%) | 3 (1%) | 0 | 0 |
| Slovin et al. (2013) [17] | N/A | 17.4 (11.5-24.7) | N/A | 4(8) | N/A | N/A | N/A | 8 (16) | 4 (8) | 3 (6) | 16 (32%) | 3 (6%) |
| Autio et al. (2020) [39] | N/A | N/A | 3 | N/A | N/A | N/A | N/A | N/A | N/A | 2 | N/A | 0 |
| Two-drug regimens | | | | | | | | | | | | |
| Vaishampayan et al. (2014) [32] | 7.0 (4.7-8.5) | 11.2 (9.1-16.4) | N/A | 2/30 | 3/30 | 7/30 | 9/30 | N/A | N/A | 1/30 | N/A | N/A |
| McNeel et al. (2018) [34] | N/A | N/A | N/A | 1/26 | N/A | N/A | N/A | N/A | 1/26 | 1/26 | N/A | N/A |
| Cathomas et al. (2012) [15] | 2.8 (2.4-3.2) | 13.3 (7.3-15.4) | N/A | 1 (3%) | N/A | 1 (3%) | 3 (8%) | N/A | N/A | 4 (11%) | 2 (5%) | N/A |
| Batra et al. (2020) [35] | N/A | 18.4 (16.13-NR) | N/A | N/A | N/A | N/A | 11 (73.3%) | N/A | N/A | 1 (6.66%) | N/A | N/A |
| Di Lorenzo et al. (2008) [40] | 4 (2-6) | 9 (4-12.5) | 11/20 (55%) | N/A | N/A | 1/20 (5%) | 4 (20%) | N/A | N/A | N/A | N/A | 2 (10%) |
| Sharma et al. (2020) [16] | 5.5 (3.5-7.1) and 3.8 (2.1-5.1) | 19 (11.5-NE) and 15.2 (8.4-NE) | 43/85 | 8 | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Graff et al. (2020) [42] | 3.8 (2.8-9.9) | 22.2 (14.7-28.4) | 19/28 (68%) | N/A | 3 (10.7%) | 1 (3.5%) | N/A | 2 (7.1%) | N/A | 1 (3.5%) | N/A | N/A |
| Barata et al. (2019) [38] | N/A | N/A | 9 (43%) | N/A | N/A | N/A | N/A | N/A | N/A | 5 (24%) | N/A | 1 (5%) |
| Hudes et al. (2013) [41] | N/A | N/A | 33/37 | 0 | N/A | 1 | 27/37 (73%) | N/A | N/A | N/A | N/A | N/A |
| Three-drug regimens | | | | | | | | | | | | |
| Francini et al. (2011) [43] | N/A | N/A | 16/43 (37.2%) | N/A | N/A | 6 (13.9%) | 8 (18.6%) | N/A | N/A | 2 (4.6%) | N/A | N/A |
| Picus et al. (2011) [33] | 9.2 (7.5-10.9) | 24 (20.3-26.5) | N/A | N/A | 4/77 (5%) | N/A | 53/77 (69%) | N/A | N/A | 19 (24%) | N/A | N/A |
| Gross et al. (2017) [11] | 8.9 (7.4-10.6) | 21.9 (18.4-30.3) | N/A | N/A | 8 (19%) | N/A | 12 (28%) | N/A | N/A | 3 (7%) | N/A | N/A |
| Four-drug regimens | | | | | | | | | | | | |
| Ning et al. (2010) [44] | 18.3 | 28.2 | N/A | 2/60 (3.33%) | 7/60 (11.6%) | 8/60 (13.3%) | 60/60 (100%) | N/A | N/A | 2/60 (3.33%) | N/A | N/A |
| Madan et al. (2016) [36] | 18.2 | 24.6 | N/A | 6 (10%) | N/A | 20 (32%) | 61 | N/A | N/A | 6 (11%) | N/A | N/A |

**TABLE 2: Survival rates and ≥ grade 3 adverse events in early phase trials.**

PFS = progression-free survival; OS = overall survival.

Bevacizumab + docetaxel, bevacizumab + satraplatin, anti-tumor vaccine + pembrolizumab, docetaxel + cetuximab, docetaxel + J591, bevacizumab + docetaxel, nivolumab + ipilimumab, and pembrolizumab + enzalutamide were two drug combination regimens used in clinical trials to treat CRPC (N = 744) [15,16,32,34,40,41]. Pooled incidences of OR and >50% decline in PSA were 32% (95% CI = 0.18-0.50, $I^2$ = 75%) and 29% (95% CI = 0.14-0.51, $I^2$ = 93%), respectively (Figure 5). Median OS and PFS were 9-19 months and 2.8-7 months, respectively (Table 2).

Intetumumab + docetaxel + prednisone, estramustine + docetaxel + bevacizumab, docetaxel + bevacizumab + everolimus, and docetaxel + bevacizumab + prednisone were the three-drug regimens used in clinical trials (N = 229) [10,27,33,40,43]. Pooled incidences of OR and >50% decline in PSA were 24% (95% CI = 0.08-0.55, $I^2$ = 79%) and 63% (95% CI = 0.49-0.76, $I^2$ = 77%), respectively (Figure 5). Median OS and PFS were 21.9-24 months and 9.2-8.9 months, respectively (Table 2).

Lenalidomide + bevacizumab + docetaxel + prednisone and docetaxel + bevacizumab + thalidomide + prednisone were the four-drug regimens used in clinical trials (N = 121) [36,44]. Pooled incidences of OR and >50% decline in PSA were 64% (95% CI = 0.46-0.78, $I^2$ = 0%) and 88% (95% CI = 0.81-0.93, $I^2$ = 0%), respectively (Figure 5). Median OS and PFS were 24.6-28.2 months and 18.2-18.3 months, respectively (Table 2).

### Monoclonal antibodies with unfavorable results

Cixutumumab, figitumumab, carlumab, trastuzumab, LFA102, rilotumumab, and siltuximab did not show antitumor activity in early phase trials (Table 3) [12,14,45-50].

| Author | Trial phase | Drug combination | Target of MoAB | Problem | Outcomes |
|---|---|---|---|---|---|
| McHugh et al. (2020) [45] | Phase I | Cixutumumab + temsirolimus | IGF-1R | Metastatic CRPC | The combination therapy had limited anti-tumor activity and a greater than expected toxicity |
| De Bono et al. (2014) [46] | Phase II | Figitumumab + docetaxel | IGF-1R | Metastatic CRPC | No significant PSA response. The combination not recommended by authors in Bono et al. |
| Boudadi et al. (2018) [48] | Phase II | Ipilimumab + nivolumab | CTLA-4, PD-1 | Metastatic CRPC | Anti-tumor activity was only seen in patients with AR-V7 isoform of the androgen receptor. Tumor activity was not seen in other patients |
| Pienta et al. (2013) [47] | Phase II | Carlumab | MCP-1 | Metastatic CRPC | Well tolerated but did not show anti-tumor activity as a single agent |
| Fizazi et al. (2012) [12] | Phase II | Siltuximab + mitoxantrone/prednisone | IL-6 | Metastatic CRPC | The drug combination was well tolerated, improvement in outcomes was not demonstrated |
| Ziada et al. (2004) (NCT00003740) [14] | Phase II | Trastuzumab | HER2 | CRPC | Well tolerated with no anti-tumor activity |
| Minami et al. (2020) (NCT01610050) [49] | Phase I | LFA102 | Anti-prolactin receptor | Metastatic CRPC | Well tolerated with no anti-tumor activity |
| Ryan et al. (2013) (NCT00770848) [50] | Phase I/II | AMG 102 (rilotumumab) | Hepatocyte growth factor | Resistant CRPC | Well tolerated with no anti-tumor activity |

**TABLE 3: Early phase trials on monoclonal antibodies with no anti-tumor activity.**

MoAb = monoclonal antibody; IGF-1R = insulin-like growth factor-1 receptor; CRPC = castration-resistant prostate cancer; PSA = prostate-specific antigen; CTLA-4 = cytotoxic T-lymphocyte-associated antigen-4; PD-1 = programmed cell death protein 1; MCP-1 = monocyte chemotactic protein-1; IL-6 = interleukin 6; HER2 = human epidermal growth factor receptor 2.

### Ongoing clinical trials and interim results of ongoing trials

Interim results of ongoing clinical trials on pembrolizumab, avelumab, atezolizumab, pasotuxizumab, and tremelimumab have shown promising results alone or in combination with chemotherapy [51-58]. Combinations are given in Table 4.

| NCT/authors | No. of patients | Regimen | Target of antibody | Phase | Population | Outcome | Year of completion |
|---|---|---|---|---|---|---|---|
| Interim results of ongoing clinical trials | | | | | | | |

| Study | N | Treatment | Target | Phase | Population | Outcome | Year |
|---|---|---|---|---|---|---|---|
| Gurney et al. (2019) (NCT02861573) [51] | 41 | Pembrolizumab + olaparib | PD-1 | Ib/II | Metastatic CRPC | PSA response 12%, well-tolerated | 2025 |
| Gurney et al. (2019) [51] | 72 | Pembrolizumab + docetaxel + prednisone | PD-1 | Ib/II | Metastatic CRPC | PSA response 31%, well-tolerated | 2025 |
| Gurney et al. (2019) [51] | 69 | Pembrolizumab + enzalutamide | PD-1 | Ib/II | Metastatic CRPC | PSA response 27%, well-tolerated | 2025 |
| Bryce et al. (2020) (NCT03409458) [52] | 14 | Avelumab + PT-112 | PD-L1 | I/II | Metastatic CRPC | Well tolerated with evidence of efficacy, PSA response 21% | 2021 |
| Aggarwal et al. (2020) (NCT03910660) [53] | 6 | BXCL701 (DPP4 inhibitor) + pembrolizumab | PD-1 | Ib | Metastatic CRPC | Well tolerated | 2022 |
| Patel et al. (2020) (NCT03406858) [54] | 33 | Pembrolizumab + HER2 bi-armed activated T cells | PD-1 | II | Metastatic CRPC | PSA response 2/6 patients, well-tolerated | 2021 |
| Dorff et al. (2020) (NCT03024216) [55] | 37 | Atezolizumab + sipuleucel-T | PD-L1 | I | Metastatic CRPC | Well tolerated with clinical activity | 2025 |
| Agarwal et al. (2020) (NCT03170960) [56] | 44 | Cabozantinib + atezolizumab | PD-L1 | Ib | Metastatic CRPC | Well tolerated with clinical activity | 2021 |
| Hummel et al. (2021) (NCT01723475) [57] | 47 | Pasotuxizumab, PSMA bispecific T-cell engager monotherapy | PSMA | I | Metastatic CRPC | Well tolerated with clinical activity | 2018 |
| Hotte et al. (2019) (NCT02788773) [58] | 52 | Durvalumab with or without tremelimumab | CTLA-4 + PD-L1 | II | Metastatic CRPC | No activity with durvalumab only, clinical activity reported with combination therapy | 2020 |
| Ongoing clinical trials | | | | | | | |
| NCT03815942 | 23 | Nivolumab + ChAdOx1-MVA 5T4 vaccine | Anti-PD-1 | I/II | CRPC | Efficacy and safety (active, not recruiting) | 2021 |
| NCT04458311 | 55 | Tildrakizumab + abiraterone acetate | Anti-IL-23 | I/II | Metastatic CRPC | Efficacy and safety (recruiting) | 2024 |
| NCT03204812 | 27 | Durvalumab plus tremelimumab | Anti-PD-L1 and anti-CTLA-4 | II | Metastatic CRPC | Efficacy and safety (active, not recruiting) | 2021 |
| NCT04336943 | 30 | Durvalumab + olaparib | Anti-PD-L1 | II | Biochemically recurrent prostate cancer | Efficacy and safety (recruiting) | 2024 |
| NCT03910660 | 40 | Talabostat mesylate + pembrolizumab | Anti-PD-1 | I/II | Metastatic CRPC | Efficacy and safety (active, not recruiting) | 2022 |
| NCT04071236 | 24 | Radium Ra 223 + peposertib + avelumab | Anti-PD-L1 | I/II | Advanced metastatic CRPC | Efficacy and safety (recruiting) | 2023 |
| NCT04104893 | 30 | Pembrolizumab | Anti-PD-1 | II | Metastatic CRPC characterized by a mismatch repair deficiency or biallelic CDK12 inactivation | Efficacy and safety (recruiting) | 2023 |
| | | Abiraterone acetate, | | | | | |

| NCT02703623 | 198 | apalutamide, prednisone +/- ipilimumab | Anti-CTLA-4 | II | Metastatic CRPC | Efficacy and safety (active, not recruiting) | 2022 |
|---|---|---|---|---|---|---|---|
| NCT04159896 | 49 | ESK981 + nivolumab | Anti-PD-1 | II | Metastatic CRPC | Efficacy and safety (recruiting) | 2022 |
| NCT03367819 | 134 | Isatuximab + cemiplimab | Anti-CD-38 and Anti-PD-1 | I/II | Metastatic CRPC | Efficacy and safety (active, not recruiting) | 2021 |
| NCT03805594 | 43 | Lutetium Lu 177-PSMA-617 + pembrolizumab | Anti-PSMA + anti-PD-1 | I | Metastatic CRPC | Efficacy and safety (recruiting) | 2022 |
| NCT02499835 | 66 | Vaccine therapy + pembrolizumab | Anti-PD-1 | I/II | Metastatic CRPC | Efficacy and safety (active, not recruiting) | 2021 |
| NCT04471974 | 54 | Pembrolizumab + ZEN-3694 + enzalutamide | Anti-PD-1 | II | Metastatic CRPC | Efficacy and safety (recruiting) | 2025 |
| NCT04592237 | 120 | Cetrelimab + cabazitaxel + carboplatin + niraparib | Anti-PD-1 | II | Aggressive prostate cancer | Efficacy and safety (recruiting) | 2025 |
| NCT02312557 | 58 | Pembrolizumab + enzalutamide | Anti-PD-1 | II | Metastatic CRPC | Efficacy and safety (active, not recruiting) | 2022 |
| NCT03217747 | 184 | PF-04518600 + avelumab + utomilumab | Anti-OX40, anti-PDL1, and anti-CD137 | I/II | Patients with advanced malignancies | Efficacy and safety (recruiting) | 2023 |
| NCT02601014 | 15 | Ipilimumab + nivolumab | Anti-CTLA-4 and anti-PD-1 | II | AR-V7-expressing metastatic CRPC | Efficacy and safety (active, not recruiting) | 2022 |
| NCT04068896 | 90 | NGM120 | GFRAL antagonist blocking GDF15 | I | Metastatic CRPC | Efficacy and safety (recruiting) | 2021 |
| NCT03849469 | 242 | Pembrolizumab + XmAb22841 | Anti-PD-1 + anti-CTLA-4 | I | Selected advanced solid tumors (DUET-4) | Efficacy and safety (recruiting) | 2027 |
| NCT03517488 | 154 | XmAb20717 | Anti-PD-1/anti-CTLA-4 | I | Advanced solid tumors | Efficacy and safety (recruiting) | 2021 |
| NCT03454451 | 378 | CPI-006 + pembrolizumab | Anti CD73 + anti-PD-1 | I | Metastatic CRPC | Efficacy and safety (recruiting) | 2023 |
| NCT03330405 | 216 | Avelumab + talazoparib | Anti-PD-L1 | II | CRPC | Efficacy and safety (active, not recruiting) | 2021 |
| NCT04423029 | 260 | Nivolumab + DF6002 | Anti-PD-1 | I/II | Metastatic solid tumors | Efficacy and safety (recruiting) | 2024 |
| NCT03207867 | 376 | PDR001 + NIR178 | Anti-PD-1 | II | CRPC, solid tumors, and lymphoma | Efficacy and safety (recruiting) | 2021 |
| NCT03983954 | 45 | Naptumomab + durvalumab | Anti-5T4 and anti-PD-L1 | I | Solid tumor that is metastatic/advanced | Efficacy and safety (recruiting) | 2022 |
| NCT03970382 | 148 | Nivolumab | Anti-PD-1 | I | Locally advanced or metastatic solid tumors | Efficacy and safety (recruiting) | 2024 |

**TABLE 4: Ongoing clinical trials and interim results of ongoing trials presented in conferences.**

NCT = National Clinical Trial; DPP4 = dipeptidyl peptidase 4; HER2 = human epidermal growth factor receptor 2; PD-1 = programmed cell death protein 1; PD-L1 = programmed death-ligand 1; CTLA-4 = cytotoxic T-lymphocyte-associated antigen-4; IL-23 = interleukin 23; CRPC = castration-resistant prostate cancer; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen.

## Discussion

Docetaxel is the most used chemotherapy-based treatment for metastatic CRPC as docetaxel improved OS, PFS, and PSA levels in RCT [59]. Among non-chemotherapy drugs, alpharadin, abiraterone, radium-223 dichloride, etc., showed improvement in survival rates with anti-tumor activity [60]. Among immunotherapies, sipuleucel-T extended OS without improving PFS [61]. However, these therapies are not curative, responses are rarely durable, and are poorly tolerated by some patients. Additional treatment options are needed for better outcomes. In RCTs, majorly monoclonal antibodies were used in combination with docetaxel or in patients refractory to docetaxel therapy. According to the pooled results, monoclonal antibodies improved PFS and PSA response as compared to placebo.

Checkpoint inhibitors, including PD-1, programmed death-ligand 1 (PD-L1), and CTLA-4 inhibitors, have shown efficacy in urothelial and other solid tumors [62-65]. However, the microenvironment of prostate cancer is more immunosuppressive as compared to other tumors [66,67]. Ipilimumab (CTLA-4 inhibitor) improved PFS and PSA levels in both trials, including docetaxel pre-treated and treatment naïve patients. It was well tolerated in both trials. OS was not prolonged on normal follow-up. However, long-term follow-up of five years showed better OS in the ipilimumab group as compared to placebo [68]. More trials are now conducted on combination therapy of ipilimumab. In the trial conducted by Boudadi et al. (2018) [48], 1 mg/kg of ipilimumab was used with nivolumab and anti-tumor activity was only reported in a small group of patients. However, according to the preliminary results of a trial by Sharma et al. (2020), 3 mg of ipilimumab with nivolumab showed anti-tumor activity in all subsets of patients and a large-scale phase II trial is in progress on ipilimumab + nivolumab in metastatic CRPC patients [16]. Another RCT is in progress to assess the efficacy and safety of ipilimumab in combination with abiraterone acetate, apalutamide, and prednisone. Ongoing clinical trials are also testing nivolumab in combination with ChAdOx1-MVA 5T4 vaccine, ESK981 (Pan-VEGFR/Tie2 tyrosine kinase inhibitor), and DF6002 (binds interleukin 12 (IL-12) receptor).

In a multicohort phase II trial by Antonarakis et al. (2020), pembrolizumab showed anti-tumor activity in docetaxel pretreated patients and the observed survival estimates are promising [17]. Although 5% of the patients showed OR, the response was durable. Pembrolizumab monotherapy was well tolerated, and no unexpected toxicities were reported. A combination of pembrolizumab with olaparib, enzalutamide, and docetaxel is tested in KEYNOTE-365, and the early results have shown anti-tumor activity of these combinations and are well tolerated [51]. According to the results of a phase II trial by Graff et al. (2020), pembrolizumab addition to enzalutamide showed anti-tumor activity in patients refractory to enzalutamide alone, and the response was durable [42]. Another trial was conducted on the addition of pembrolizumab to the anti-tumor DNA vaccine. The addition of pembrolizumab showed better results in terms of PSA decline, OR, and CD-8+ T cell infiltration into tumor lesions as compared to vaccination alone. More trials are in progress to assess the efficacy and safety of pembrolizumab in combination with dipeptidyl peptidase 4 (DPP4) inhibitor BXCL701, HER2 bi-armed activated T cells, talabostat mesylate, lutetium lu 177-PSMA-617, vaccine therapy, ZEN-3694 + enzalutamide, enzalutamide, XmAb22841, and CPI-006 (Table 4). Avelumab, atezolizumab, tremelimumab, cemiplimab, cetrelimab, XmAb20717, PDR001, and durvalumab are other checkpoint inhibitors that are getting tested alone and in combination therapy for the treatment of CRPC.

The anti-angiogenic drug, bevacizumab, also improved PFS and PSA levels without any improvement in OS. Bevacizumab was also tested in combination regimens. Among the combination regimens, the four-drug regimen of bevacizumab with docetaxel + thalidomide + prednisone and lenalidomide + docetaxel + prednisone showed the best efficacy outcomes, and toxicities were manageable (Figure 5 and Table 2). Early anti-tumor activity was reported with the addition of thalidomide and bevacizumab to docetaxel as compared to docetaxel alone. Bevacizumab in combination with satraplatin has shown promising results in early phase trials in docetaxel refractory patients. The addition of everolimus (mammalian target of rapamycin (mTOR) inhibitor) to docetaxel + bevacizumab did not show better outcomes as compared to docetaxel + bevacizumab in the early-phase trial.

Abituzumab improved the progression of the disease, but the results were not statistically significant. In our analysis, the trial with intetumumab was the outlier and intetumumab caused worsening in PFS or PSA levels. However, intetumumab did not increase adverse events as compared to placebo. Intetumumab might have interacted with docetaxel, resulting in lower efficacy.

Lack of improvement in OS despite changes in PFS and PSA levels might be due to the unique response of CRPC to these drugs. Also, the patients with metastatic CRPC are generally older than patients with other types of cancer, e.g., breast cancer and lung cancer, and comparatively more patients have bone metastasis [69-71]. Other possible explanations can be the unique mechanism of action of these drugs or flaws in trial designs. These drugs might show some improvement in OS if followed for longer durations. Further studies should be conducted on how to utilize the anti-tumor activity of these monoclonal antibodies.

Denosumab targets receptor activator of nuclear factor kappa-B ligand (RANKL) and is an anti-bone resorptive agent. It delayed skeletal-related adverse events as compared to zoledronic acid in patients with CRPC with bone metastasis in RCT. Zoledronic acid was proved better than a placebo in an RCT [72]. However, increased incidence of osteonecrosis of the jaw was associated with denosumab as compared to

zoledronic acid. A meta-analysis showed similar results for denosumab in the prevention of skeletal-related adverse events as compared to zoledronic acid [73]. Moreover, an RCT by Smith et al. (2012) tested denosumab for the prevention of bone metastasis [25]. Denosumab significantly improved bone metastasis-free survival and time to first bone metastasis as compared to placebo. The major adverse event observed in the denosumab group was the osteonecrosis of the jawbone.

In a non-comparative randomized study, cixutumumab (IGF-1R inhibitor) and ramucirumab (VEGFR inhibitor) were used with mitoxantrone-prednisone. PFS in the cixutumumab group was similar to the projected value, while ramucirumab showed better PFS as compared to the projected value (6.7 months vs. 3.9 months). The incidence of adverse events was similar to expectations. Ramucirumab has shown improvement in OS in RCTs on other solid tumors [74]. Another trial by McHugh et al. (2020) has also shown no activity of cixutumumab with temsirolimus [45].

Among monoclonal antibodies, PD-1 inhibitors, PD-L1 inhibitors, and CTLA-4 inhibitors have the potential to become the drugs of the future for patients with prostate cancer. More multicenter randomized clinical trials should focus on finding the efficacy and appropriate combination of these medications. However, the role of monoclonal antibodies in prostate cancer is still debated.

## Conclusions

Monoclonal antibodies were well tolerated and showed better outcomes in terms of PFS and >50% decline in PSA levels compared to placebo. However, OS was only improved with ipilimumab as compared to placebo on long-term follow-up of five years. Denosumab delayed skeletal-related adverse events as compared to zoledronic acid in CRPC with bone metastasis. Denosumab also delayed bone metastasis as compared to placebo in patients with metastatic CRPC. Pembrolizumab, avelumab, atezolizumab, pasotuxizumab, and tremelimumab have shown promising results in the early phase trials. More multicenter, double-blind clinical trials may be needed to confirm these results.

## Appendices

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| P | I | C | O | S |
|---|---|---|---|---|
| "Prostatic Neoplasms, Castration-Resistant"[Mesh] | "Antibodies, Monoclonal" [Mesh] | | | |
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| PubMed search string: (((((((((((((((((((((((((((((((((("Prostatic Neoplasms, Castration-Resistant"[Mesh]) OR (Prostatic Neoplasms, Castration-Resistant)) OR (Castration-Resistant Prostatic Neoplasm)) OR (Prostatic Neoplasms, Castration Resistant)) OR (Androgen-Insensitive Prostatic Neoplasms)) OR (Androgen Insensitive Prostatic Neoplasms)) OR (Androgen-Resistant Prostatic Neoplasms)) OR (Androgen Resistant Prostatic Neoplasms)) OR (Prostatic Neoplasms, Hormone Refractory)) OR (Hormone Refractory Prostatic Neoplasms)) OR (Prostatic Neoplasms, Androgen-Independent)) OR (Neoplasm, Androgen-Independent Prostatic)) OR (Prostatic Neoplasm, Androgen-Independent)) OR (Prostatic Neoplasms, Androgen Independent)) OR (Prostatic Neoplasms, Androgen-Insensitive)) OR (Androgen-Insensitive Prostatic Neoplasm)) OR (Prostatic Neoplasms, Androgen Insensitive)) OR (Prostatic Neoplasms, Androgen-Resistant)) OR (Androgen-Resistant Prostatic Neoplasm)) OR (Prostatic Neoplasm, Androgen-Resistant)) OR (Prostatic Neoplasms, Androgen Resistant)) OR (Androgen-Independent Prostatic Neoplasms)) OR (Androgen Independent Prostatic Neoplasms)) OR (Castration-Resistant Prostatic Neoplasms)) OR (Castration Resistant Prostatic Neoplasms)) OR (Cancers, Castration-Resistant Prostatic)) OR (Androgen-Insensitive Prostatic Cancer)) OR (Androgen Insensitive Prostatic Cancer)) OR (Androgen-Resistant Prostatic Cancer)) OR (Androgen Resistant Prostatic Cancer)) OR (Prostatic Cancer, Hormone Refractory)) OR (Prostatic Cancer, Androgen-Independent)) OR (Androgen-Independent Prostatic Cancers)) OR (Prostatic Cancer, Androgen Independent)) OR (Prostatic Cancers, Androgen-Independent)) OR (Prostatic Cancer, Androgen-Insensitive)) OR (Androgen-Insensitive Prostatic Cancers)) OR (Cancer, Androgen-Insensitive Prostatic)) OR (Cancers, Androgen-Insensitive Prostatic)) OR (Prostatic Cancer, Androgen Insensitive)) OR (Prostatic Cancers, Androgen-Insensitive)) OR (Prostatic Cancer, Androgen-Resistant)) OR (Androgen-Resistant Prostatic Cancers)) OR (Cancer, Androgen-Resistant Prostatic)) OR (Cancers, Androgen-Resistant Prostatic)) OR (Prostatic Cancer, Androgen Resistant)) AND ((((("Antibodies, Monoclonal"[Mesh]) OR (Monoclonal Antibodies)) OR (Monoclonal Antibody)) OR (Antibody, Monoclonal)) AND ((((((((((((("Prostatic Neoplasms"[Mesh]) OR (Prostatic Neoplasms)) OR (Neoplasms, Prostate)) OR (Prostate Neoplasm)) OR (Neoplasms, Prostatic)) OR (Prostatic Neoplasm)) OR (Prostate Cancer)) OR (Prostate Cancers)) OR (Cancer of the Prostate)) OR (Prostatic Cancer)) OR (Prostatic Cancers)) OR (Cancer of Prostate))) = 424 | | | | |
| Embase search string: ('castration resistant prostate cancer'/exp OR 'crpc (castration resistant prostate cancer)' OR 'castrate resistant prostate cancer' OR 'castration resistant prostate cancer' OR 'castration-resistant pc' OR 'castration-resistant pca' OR 'castration-resistant prostatic neoplasms' OR 'hormone refractory prostate cancer' OR 'prostatic neoplasms, castration-resistant') AND ('monoclonal antibody'/exp OR 'antibodies, monoclonal' OR 'antibodies, monoclonal, humanized' OR 'antibodies, monoclonal, murine derived' OR 'antibodies, monoclonal, murine-derived' OR 'antibody, monoclonal' OR 'clonal antibody' OR 'hybridoma antibody' OR 'monoclonal antibodies' OR 'monoclonal antibody') = 2,427 | | | | |
| Web of Science: with keywords mentioned above = 49 | | | | |
| Cochrane: with keywords mentioned above = 60 | | | | |
| ClinicalTrials.gov: prostate cancer + monoclonal antibodies = 109 | | | | |
| Total = 2,960 | | | | |

**TABLE 5: Keywords and search strings.**

## Additional Information

### Disclosures

**Human subjects:** All authors have confirmed that this study did not involve human participants or tissue. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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