# Evidence tabel PICO 2

**Uitgangsvraag:** Wat is de aanbevolen 1e lijns behandeling bij patiënten met een mCRPC?

P Chemotherapie-naïeve patiënten met gemetastaseerd castratie-resistent prostaatcarcinoom (mCRPC)

 I Pre-chemotherapie (abiraterone of enzalutamide, radium 223, anti-androgeen)

C Placebo of prednison

O Progressie-vrije overleving, Algehele overleving, Kwaliteit van leven, Toxiciteit

1. **Abiraterone en prednison versus prednison**

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| **I Study ID** |  **II Method** | **III Patient characteristics** | **IV Intervention(s)** | **V Results**  | **VII Critical appraisal of study quality** |
| **COU-AA-302 study*** Ryan et al, 2013[[1](#_ENREF_1)]]
* Basch et al, 2013[[2](#_ENREF_2)]
* Rathkopf et al, 2014[[3](#_ENREF_3)]
* Ryan et al, 2015[[4](#_ENREF_4)]
* Morris et al, 2015[[5](#_ENREF_5)]
 | * RCT
* Conflicts of interest reported
* 151 sites in 12 countries. 2009-2010
* Sample size: 1088
* Duration of follow-up: median 49.2 months
* Clinicaltrials.gov: NCT00887198
 | * **Eligibility criteria:**

Male patients aged >18 yr with chemotherapy-naive mCRPC* **Patient characteristics**:

Median age 71.0 (44-95) vs 70.0 (44-90);  | * Abiraterone plus prednisone (n=546)

versus* Prednisone alone (n=542)
 | **Radiographic progression-free survival [5]**Abiraterone: 271/546 (65%)Placebo: 336/542 (71%)HR 0.53 (0.45-0.62). **Overall survival [4]:**End of follow up, deaths:Abiraterone: 354/546 (65%)Placebo: 387/542 (71%)HR 0.81 (0.70-0.93) p=0.0033. **Toxictiy/ AEs (grade 3-4)[4]**Abiraterone: 290/542 (54%)Prednisone: 236/540 (44%)**Quality of Life[2]**FACT-P total score deterioration (%) \* at 1 year:Abiraterone: 354/546 (64.8%)Prednisone: 431/542 (79.5%)RR 0.82 (95% CI 0.76-0.88) P<0.001  | * Low risk of bias
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AE adverse event, FACT-P functional Assessment of Cancer Therapy- Prostate, HR hazard ratio, RCT randomised controlled trial, RR risk ratio, \* self calculated

1. **Enzalutamide versus placebo**

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| **I Study ID** |  **II Method** | **III Patient characteristics** | **IV Intervention(s)** | **V Results**  | **VII Critical appraisal of study quality** |
| **PREVAIL trial*** Beer et al, 2014[[6](#_ENREF_6)]
* Loriot et al, 2015[[7](#_ENREF_7)]
 | * RCT
* Conflicts of interest are reported online
* 207 sites globally, 2010-2012
* Sample size: 1717 patients
* Duration of follow-up: median approximately 22 months.
* Clinicaltrials.gov: NCT01212991
 | * **Eligibility criteria:**

Adenocarcinoma of the prostate with metastases Continued androgen-deprivation therapy, chemotherapy-naïve.**Patient characteristics:.** Median age 72 (range 43-93) vs 71 (42-93). | * Enzalutamide (160mg) 1dd (n=872)

versus * Placebo 1dd (n=845)
 | **Radiographic progression-free survival at 12 months[6]:**Enzalutamide: 65%Placebo:14%HR 0.19 (0.15-0.23).**Overall survival at 12 months[6]:** Enzalutamide 797/872 (91%) Placebo: 701/845 (83%)HR 0.71 (0.60-0.84).**Quality of Life[7]:**Improvement at any time during the trial FACT-P Enzalutamide: 327/826 (40%)Placebo: 181/790 (23%)RR= 1.73(95%CI 1.48-2.01)\* p<0.001**Quality of Life[7]:**Improvement at any time during the trial EQ-5D utility indexEnzalutamide: 224/812 (28%)Placebo: 99/623 (16%)RR= 1.74 (95% CI 1.40-2.15)\* p<0.001**Toxicity: any ≥ Grade 3 [6]**Enzalutamide:374/871 (43%)Placebo: 313/844 (37%)RR= 1.16 (95% CI 1.03-1.30)\*  | * Low risk of bias
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AE adverse event, HR hazard ratio, RCT randomised controlled trial, RR risk ratio, \* self calculated

1. **Radium-223 versus placebo**

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| **I Study ID** |  **II Method** | **III Patient characteristics** | **IV Intervention(s)** | **V Results**  | **VII Critical appraisal of study quality** |
| **ALSYMPCA**Hoskin et al, 2014[[8](#_ENREF_8)]Parker et al, 2013[[9](#_ENREF_9)]Sartor et al, 2014[[10](#_ENREF_10)]Nome et al 2015 [[11](#_ENREF_11)] | * RCT
* Conflicts of interest reported and several authors have conflicts with the pharmaceutical industry.
* Sample size: 921 patients (395 chemotherapy naive)
* Setting: 136 study centers in 19 countries
* Follow-up: 3 years
* Protocol: NCT00699751
 | * **Eligibility criteria**:

Castration-resistant prostate cancer with metastases who had received docetaxel or declined or were not healthy enough to receive docetaxel* **Patient characteristics**:

Median age: 74 (range: 49-90) vs 74 (52-94), ECOG score:  0: 29%,vs 25%. 1: 54% vs 65%. ≥2 16% vs 11%. | * 223radium (n=262)

versus* placebo (n=133)
 | **Progression-free survival:** not reported.**Overall survival [**[**8**](#_ENREF_8)**]:**Median223radium : 16.1 months(95%-CI: 13.9 – 17.8)Placebo:11.5 months (95%-CI: 9.5 – 14.1)HR 0.69 (95%-CI: 0.52-0.92).**Quality of life:** not reported.**Toxicity AEs: grade >=3[**[**8**](#_ENREF_8)**]**223radium : 145/253 (57.3%)Placebo: 77/130 (59.2%)RR=0.97 (95% CI 0.81-1.16 )\* | * Low risk of bias
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| Nilsson et al, 2007[[12](#_ENREF_12)]Nilsson et al, 2013[[13](#_ENREF_13)] | * RCT
* Conflicts of interest are reported
* 11 centers in Sweden, Norway and the UK
* Sample size: 64 patients
* Study years: 2004-2005
* Duration of follow-up: at least 18 months (range 18–24).
* Protocol not found
 | * **Eligibility criteria**:

Adenocarcinoma of the prostate with metastases and had not received chemotherapy the last 6 weeks.* **Patient characteristics:**

Median age: 73 (57-88) vs 72 (60-84) | * 223radium (n = 33)

versus* Placebo (n = 31)
 | **Progression-free survival:** not reported.**Overall survival at 24 months[12]:** 223radium : 10/33 (30%)Placebo: 4/31 (13%)HR 0.48 (95% CI 0.26-0.88) **Quality of life:** not reported.**Toxicity****Haematological AEs: grade 3-4[**[**13**](#_ENREF_13)**]**Radium-group: 3/33Placebo: 2/31RR= 1.29 (95% CI 0.23-7.24)\* **Serious AEs[**[**13**](#_ENREF_13)**]** Radium-group: 8/33Placebo: 14/31RR= 0.52 (95%CI 0.25-1.06)\*  | * High risk of bias because of no blinding of patients and personnel after 12 months with 24 months follow-up.
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AE adverse event, HR hazard ratio , RCT ransomized controlled trial, RR Risk ratio \* self calculated

1. **Bicalutamide versus placebo**

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| **I Study ID** |  **II Method** | **III Patient characteristics** | **IV Intervention(s)** | **V Results**  | **VII Critical appraisal of study quality** |
| * Akaza et al, 2009[[14](#_ENREF_14)]
* Arai et al, 2008[[15](#_ENREF_15)]
 | * RCT
* Conflicts of interest are reported
* 49 centers, Japan, 2000-2001
* Sample size: 205 patients
* Median follow-up: 5.2 years
* No protocol found
 | * Eligibility criteria: age ≥20 years; previously untreated, advanced (stage C or D) prostate cancer
* Patient characteristics:

Age <75y: 53 (52%) vs 50 (49.5%) Clinical stage: C,D1: 59 (57.8%) vs 57 (56.4%); D2: 43 (42.2%) vs.44 (43.6%).  | * Bicalutamide (80 mg) n=102

versus* Placebo n=101
 | **Progression-free survival**not reported.**Overall survival[**[**14**](#_ENREF_14)**]**5 year:Bicalutamide: 75.3%Placebo: 63.4%HR: 0.78 (95% CI 0.60-0.99)**Quality of Life[**[**15**](#_ENREF_15)**]**FACT-P total score difference between baseline and 24 weeks.Bicalutamide: 4.86 ( SD18.44) n=96Placebo: 1.67 ( SD17.97)P=0.228 **Toxicity**Not reported. | Unclear risk of bias because of details lacking regarding randomisation, allocation concealment, blinding, and a protocol. |

FACT-P functional Assessment of Cancer Therapy- Prostate, HR hazard ratio, RCT randomized controlled trial, SD standard deviation,

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