# 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 |

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 index  Enzalutamide: 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 |

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)**]:**  Median  223radium : 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 |
| 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: 3/33  Placebo: 2/31  RR= 1.29 (95% CI 0.23-7.24)\*  **Serious AEs[**[**13**](#_ENREF_13)**]**  Radium-group: 8/33  Placebo: 14/31  RR= 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. |

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=96  Placebo: 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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