# Evidence tabel

Uitgangsvraag:

Wat is de aanbevolen 2e lijns behandeling bij progressie tijdens/na docetaxel bij patiënten met een mCRPC?

P: Patiënten met gemetastaseerd castratie-resistent prostaatcarcinoom (mCRPC) tijdens of na behandeling met chemotherapie (docetaxel)

I: Cabazitaxel, Abiraterone, Enzalutamide, Radium-223, Sipuleucel-T, anti-androgenen

C: Placebo of prednison

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

1. **Cabazitaxel and predinison vs prednisone and mtioxantrone**

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| **I Study ID** | **II Method** | **III Patient characteristics** | **IV Intervention(s)** | **V Results** | **VII Critical appraisal of study quality** |
| **TROPIC**   * De Bono et al, 2010[[1](#_ENREF_1)] * Bahl et al, 2013[[2](#_ENREF_2)] | * Design: RCT * Conflicts of interest reported and several authors have conflicts with the pharmaceutical industry * Setting: 146 centres in 26 countries * Sample size: 755 patients * Median follow-up: 12.8 months * Protocol: NCT00417079 | * Eligibility criteria: Pathologically proven prostate cancer with documented disease progression during or after completion of docetaxel treatment. At least 18 years, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2. * Patient characteristics: * Median age: Mitoxantrone 67 years (61-72), Cabazitaxel 68 (62-73). * ECOG performance status 0 or 1: Mitoxantrone 91%, Cabazitaxel 93%. | * Cabazitaxel (25mg/m2 ) +Prednisone 10mg (N = 378)   versus   * Prednisone 10mg oral + mitoxantrone 12mg/m2 (N = 377) | **Progression-free survival[1]**  Median (months)   * Cabazitaxel: 2.8 (95%-CI: 2.4 – 3.0) * Mitroxantrone: 1.4 (95%-CI: 1.4 – 1.7) * HR: 0·74 (95% CI 0·64–0·86)   **Overall survival[1]**  Median (months)   * Cabazitaxel: 15.1 (95%-CI: 14.1 – 16.3) * Mitroxantrone: 12.7 (95%-CI: 11.6 – 13.7) * HR:0·70 (95% CI 0·59–0·83**)**   **2 year survival [3]**   * Cabazitaxel: 60/378 * Mitroxantrone: 31/377 * OR 2.11 ((95% CI 1.33-3.33)   **Quality of life:**  Not reported  **Toxicity**  Overall toxicity not reported | * High risk of bias due to no blinding participants |

ECOG: Eastern Cooperative Oncology Group , RCT randomized controlled trial,

1. **Abiraterone and prednison versus placebo and 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-301**   * Fizazi et al, 2012[[3](#_ENREF_3)] * Goodman et al, 2014[[4](#_ENREF_4)] * Harland et al, 2013[[5](#_ENREF_5)] * Logothetis et al, 2012[[6](#_ENREF_6)] * Mulders et al, 2014[[7](#_ENREF_7)] * De Bono 2011[[8](#_ENREF_8)] | * RCT * Conflicts of interest reported and some authors have some conflicts. * 147 sites in 13 countries. * Sample size: 1195 patients. * Median follow-up: 12.8 months. * Protocol: NCT00638690. | * Eligibility criteria: mCRPC patients after docetaxel treatment and a maximum of two previous chemotherapies. * Patient characteristics: * Median age: group abiraterone: 69 (range: 42-92), group placebo: 69 (range: 39-90). * ECOG score: 0 or 1 group abiraterone: 715/797, group placebo: 353/398. 2 group abiraterone: 82/797, group placebo: 45/398. | * Abiraterone acetate plus prednisone (n=797)   versus   * Placebo pus prednisone (n=398) | **Radiographic progression-free survival** (months)[[3](#_ENREF_3)]  Median   * Abiraterone: 8.5 (95%-CI: 8.3-11.1) * Placebo:6.6 (95%-CI: 5.6 – 8.3) * HR: 0.66 (0.58−0.76)   **Overall survival** (months)[[3](#_ENREF_3)]  Median   * Abiraterone:15.8 (95%-CI: 14.8-17.0) * Placebo:11.2 (95%-CI: 10.4 – 13.1) * HR: 0.74 (95%-CI: 0.64–0.86)   **Quality of Life according to the FACT-P instrument** [[5](#_ENREF_5)]  **Symptomatic improvement during follow-up in the FACT-P total scale**   * Abiraterone: 271/563 (48.1%) * Placebo:87/273 (31.9%) * RR: 1.51 (95%-CI: 1.24 – 1.83)\*   **Toxicitiy**  **Treatment-related AE (Grade III or IV)** [[3](#_ENREF_3)]   * Abiraterone: 182/791 (24.0%) * Placebo:76/394 (20.0%) * RR: 1.19 (95%-CI: 0.94 – 1.51)\* | * Low risk of bias. |

AE adverse event, ECOG: Eastern Cooperative Oncology Group , HR hazard ratio, RCT randomised controlled trial, \*: self-calculated, not reported in article.

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** |
| **AFFIRM-trial**   * Scher et al, 2012[[9](#_ENREF_9)] * Fizazi et al, 2014[[10](#_ENREF_10)] * Cella et al, 2015[[11](#_ENREF_11)] * Merseburger et al, 2015[[12](#_ENREF_12)] * Sternberg et al, 2014[[13](#_ENREF_13)] | * RCT * Conflicts of interest reported and some authors have some conflicts. * 156 sites in 15 countries. * Sample size: 1199 patients * Median follow-up: 14.4 months. * Protocol: NCT00974311. | * Eligibility criteria: Histologically or cytologically confirmed mCRPC that had previous treatment with docetaxel, and progressive disease defined according to PCWG2 criteria. * Patient characteristics: * Median age: enzalutamide 69.0 (41-92), placebo: 69.0 (49-89). * ECOG score: 0: group enzalutamide: 298 (37%), placebo: 156 (39%). 1: group enzalutamide: 432 (54%). Placebo: 211 (53%). 2: group enzalutamide 70 (9%), placebo: 32 (8%). | * Enzalutamide oral 160mg per day (N = 800)   versus   * Placebo (N = 399) | **Radiographic progression-free survival** (months) [[9](#_ENREF_9)]:  Median   * Enzalutamide:8.3 (95%-CI: 8.2–9.4) * Placebo:2.9 (95%-CI: 2.8–3.4) * HR: 0.40 (95%-CI: 0.35–0.47)   **Overall survival** (months) [[9](#_ENREF_9)]:  Median   * Enzalutamide:18.4 (95%-CI: 17.3-not yet reached) * Placebo:13.6 (95%-CI: 11.3 – 15.8) * HR: 0.63 (95%-CI: 0.53 – 0.75)   **Quality of Life according to the FACT-P instrument** [[10](#_ENREF_10)]  **Symptomatic improvement during follow-up in the FACT-P total scale**   * Enzalutamide:275/652 (42%) * Placebo: 36/248 (15%) * RR: 2.91 (95%-CI: 2.12 – 3.98)\*   **Toxicity**  **Incidence of ≥1 AE (Grade III, IV, or V)** [[9](#_ENREF_9)]:   * Enzalutamide:362/800 (45.3%) * Placebo:212/399 (53.1%) * RR: 0.85 (95%-CI: 0.76 – 0.96)\* | * Low risk of bias |

AE adverse event, ECOG: Eastern Cooperative Oncology Group , HR hazard ratio, RCT randomised controlled trial, \*: self-calculated, not reported in article.

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**   * Parker et al, 2013[[14](#_ENREF_14)] * Hoskin et al, 2014[[15](#_ENREF_15)] * Sartor et al, 2014[[16](#_ENREF_16)] * Nome et al. 2014[[17](#_ENREF_17)] | * RCT * Conflicts of interest reported and some authors have some conflicts. * 136 study centres in 19 countries * Sample size: 921 patients, 526 received docetaxel previously. * Follow-up: 3 years * Protocol: NCT00699751 | * Eligibility criteria: Histologically confirmed mCRPC and had received docetaxel, were not healthy enough or declined to receive it, or it was not available. * Patient characteristics: * Not stratified between the patients that received docetaxel and those that did not. | * Six intravenous injections of radium-223 (at a dose of kBq per kilogram of body weight) (n=352, that received docetaxel)   versus   * Matching –placebo (n=174, that received docetaxel) | **Progression-free survival:**   * Not reported.   **Overall survival stratified for the patients that DID receive docetaxel** (months)[[14](#_ENREF_14)]  Median   * Radium-223: 14.4 (95%-CI: 12.5 – 15.5) * Placebo:11.3 (95%-CI: 10.0 – 12.9) * HR: 0.71 (95%-CI: 0.56-0.89).   **Quality of life:**   * Not reported.   **Toxicity**  At least one AE for subgroup that DID receive docetaxel (GRADE III or IV)[[14](#_ENREF_14)]   * Radium-223: 213/347 (61.4%) * Placebo: 128/171 (74.9%) * RR: 0.82 (95%-CI: 0.73 – 0.93)\* | * Low risk of bias. |

AE adverse event, HR hazard ratio, RCT randomized controlled trial, \*: self-calculated, not reported in article.

1. **Orteronel plus prednisone versus placebo plus prednisone**

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| **I Study ID** | **II Method** | **III Patient characteristics** | **IV Intervention(s)** | **V Results** | **VII Critical appraisal of study quality** |
| * **Fizazi** et al, 2015[[18](#_ENREF_18)] | * RCT * Conflicts of interest reported and some authors have some conflicts. * 260 study centers in 42 countries. * Sample size: 1099 patients * Median follow-up: placebo: 10.7 months (0.4-27.1), orteronel: 10.6 months (0.2 – 29.5). * Protocol: NCT01193257 | * Eligibility criteria: histologically or cytologically confirmed mCRPC with evidence of disease progression after receiving docetaxel. * Patient characteristics: * Median age: orteronel 69.5 (range: 43-89), placebo: 70 (48-87). * ECOG score: 0: group orteronel: 42%, placebo: 40%. 1: group orteronel: 50%. Placebo: 53%. 2: group orteronel: 9%, placebo: 7%.. | * Oral orteronel 400 mg plus predinosone 5 mg (n=734)   versus   * Placebo plus prednisone twice daily (n=365) | **Progression-free survival** (months):  Median   * Orteronel: 8.3 months (95%-CI: 7.8 – 8.5) * Placebo: 5.7 months (95%-CI: 5.5 – 7.0) * HR: 0.760 (95%-CI: 0.653 – 0.885)   **overall survival** (months):  Median   * Orteronel: 17.0 months (95%-CI: 15.2 – 19.9) * Placebo: 15.2 months (95%-CI: 13.5 – 16.9) * HR: 0.886 (95%-CI: 0.739-1.062)   **Quality of life:**   * Not reported.   **Toxicity: Any adverse event (Grade 3 or more).**   * Orteronel: 506/732 (69.1%) * Placebo: 199/362 (54.9%) * RR: 1.26 (95%-CI: 1.13 – 1.40)\* | * Unclear risk of bias (no description of blinding) |

AE adverse event, ECOG: Eastern Cooperative Oncology Group , HR hazard ratio, RCT randomised controlled trial, \*: self-calculated, not reported in article.

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