# 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
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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.
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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
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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.
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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)
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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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