# Appendix - clinical evaluation

## Appendix 1 Literature search

Databases: Ovid MEDLINE(R), Embase (Ovid), Cochrane Library: Central Register of Controlled Trials (Central), NHS Economic Evaluations Database (NHS EED). Centre for Reviews and Dissemination: NHS EED, Web of Science, PubMed, Epistemonikos, Google Scholar.
Date: 2015.03.03
Update: 2015.10.26
Study design: Randomized controlled trials (RCT), Economic evaluations (Ec. ev.), Health related quality of life.
Year: 2000-2015
Results RCT: 625 references (955 including duplicates)
Ec.Ev.: 267 references (407 including duplicates)
Searched by: Ingrid Harboe, research librarian
Search peer reviewed by Gyri Hval Straumann, research librarian

**Search strategies:**

**Databases**: **Embase and MEDLINE** (federated search)
Embase 1974 to 2015 March 05**,**
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) 1946 to Present

**Search filter**: Ovids Clinical Queries "therapy (maximizes specificity)" and RCT filter in Cochrane Handbook, chapter 6.4.11.1/2 (line 20-39).
Economic evaluations (Ec. ev.), Health related quality of life (line 47-78).
Subject heading codes:
Embase**:** oemezd (i.e. prostate cancer/ use oemezd)
MEDLINE**:** pmoz

| # | Searches | Results |
|---|---|---|
| 1 | prostate cancer/ use oemezd | 122243 |
| 2 | castration resistant prostate cancer/ use oemezd | 5435 |
| 3 | prostate adenocarcinoma/ use oemezd | 7524 |
| 4 | prostate carcinoma/ use oemezd | 20016 |

| | | |
|---|---|---|
| 5 | prostatic intraepithelial neoplasia/ use oemezd | 2276 |
| 6 | Prostatic Neoplasms/ or Castration-Resistant/ use pmoz | 127555 |
| 7 | (prostat* adj6 (advanc* or adenocarcinom* or carcinom* or cancer* or hormone refractory or malign* or metasta* or neoplas* or tumo*)).tw. | 266796 |
| 8 | or/1-7 | 324644 |
| 9 | cabazitaxel/ use oemezd | 1266 |
| 10 | enzalutamide/ use oemezd | 1516 |
| 11 | abiraterone/ use oemezd | 1520 |
| 12 | radium chloride ra 223/ use oemezd | 442 |
| 13 | (cabazitaxel or enzalutamide or abiraterone or "radium chloride ra 223" or alpharadin).tw. | 3633 |
| 14 | or/9-13 | 4933 |
| 15 | 8 and 14 | 4425 |
| 16 | exp animals/ | 39556423 |
| 17 | humans/ | 29904732 |
| 18 | 16 not (16 and 17) | 9654869 |
| 19 | 15 not 18 | 3672 |
| 20 | randomized controlled trial.pt. use pmoz | 414741 |
| 21 | controlled clinical trial.pt. use pmoz | 91958 |
| 22 | randomi*ed.ti,ab. use pmoz | 432363 |
| 23 | placebo.ab. use pmoz | 169071 |
| 24 | clinical trials as topic.sh. use pmoz | 179503 |
| 25 | randomly.ab. use pmoz | 242724 |
| 26 | trial.ti. use pmoz | 148354 |
| 27 | or/20-26 | 1033904 |
| 28 | 19 and 27 use pmoz | 277 |
| 29 | randomized controlled trial/ use oemezd | 389291 |
| 30 | crossover-procedure/ use oemezd | 44856 |
| 31 | double-blind procedure/ use oemezd | 126878 |
| 32 | single-blind procedure/ use oemezd | 21178 |

| | | |
|---|---|---|
| 33 | randomi*ed.ab. use oemezd | 542154 |
| 34 | placebo.ab. use oemezd | 219246 |
| 35 | randomly.ab. use oemezd | 306411 |
| 36 | trial.ti. use oemezd | 193227 |
| 37 | or/29-36 | 1084059 |
| 38 | 19 and 37 use oemezd | 514 |
| 39 | limit 19 to "therapy (maximizes specificity)" | 333 |
| 40 | 28 or 38 or 39 | 796 |
| 41 | limit 40 to yr="2000 -Current" | 796 |
| 42 | remove duplicates from 41 | 639 |
| 43 | limit 40 to yr="2015 -Current" | 49 |
| 44 | remove duplicates from 43 | 42 |
| 45 | 44 use pmoz | 32 |
| 46 | 44 use oemezd | 10 |
| 47 | "quality of life"/ or quality adjusted life year/ | 449564 |
| 48 | (EQ-5d or EQ5D or EQ 5D or euroqol 5d or euro qol).mp. | 12632 |
| 49 | (euroqol or euroqol-eq-5d or eq-5d-euroqol or eq-5d-3L or eq-5d-5L).mp. | 7397 |
| 50 | (((quality* or adjusted) adj3 life) or HRQL).mp. | 602167 |
| 51 | (qaly* or qald* or qale* or qtime* or qali*).mp. | 17592 |
| 52 | "Cost Benefit Analysis"/ use oemezd | 69857 |
| 53 | "Cost Effectiveness Analysis"/ use oemezd | 109347 |
| 54 | "Cost Utility Analysis"/ use oemezd | 6294 |
| 55 | (cost* adj2 (analys* or benefit* or effective* or minim* or utilit*)).tw. | 266497 |
| 56 | cba.tw. | 20159 |
| 57 | cea.tw. | 43654 |
| 58 | cua.tw. | 1915 |
| 59 | Economic Evaluation/ | 75732 |
| 60 | Health economics/ | 34885 |
| 61 | (health economic? or economic evaluation?).tw. | 26895 |

| | | |
|---|---|---|
| 62 | Pharmacoeconomics/ | 8803 |
| 63 | ((pharmacoeconomic? or pharmac*) adj economic?).tw. | 921 |
| 64 | or/47-63 | 1050982 |
| 65 | 19 and 64 | 475 |
| 66 | Cost-Benefit Analysis/ use pmoz | 134724 |
| 67 | (cost* adj2 (analys* or benefit* or effective* or minim* or utilit*)).tw. | 266497 |
| 68 | cba.tw. | 20159 |
| 69 | cea.tw. | 43654 |
| 70 | cua.tw. | 1915 |
| 71 | Economics, Medical/ use pmoz | 8921 |
| 72 | (health economic? or economic evaluation?).tw. | 26895 |
| 73 | Economics, Pharmaceutical/ use pmoz | 2649 |
| 74 | (pharmac* adj economic?).tw. | 921 |
| 75 | pharmacoeconomic?.tw. | 9216 |
| 76 | Technology Assessment, Biomedical/ use pmoz | 8462 |
| 77 | technology assessment?.tw. | 9579 |
| 78 | or/47-51,66-77 | 997710 |
| 79 | 19 and 78 | 463 |
| 80 | 65 or 79 | 479 |
| 81 | remove duplicates from 80 | 407 |
| 82 | 81 use pmoz | 27 |
| 83 | 81 use oemezd | 380 |

**Database: Cochrane Library**
Date: 2015.03.03 / 2015.10.26
Results: 89 trials / 15 trials/ 0 (zero) economic evaluations

| ID | Search | Hits |
|---|---|---|
| #1 | MeSH descriptor: [Prostatic Neoplasms] this term only | 3457 |
| #2 | MeSH descriptor: [Prostatic Neoplasms, Castration-Resistant] this term only | 17 |
| #3 | (prostat* near/6 (advanc* or adenocarcinom* or carcinom* or cancer* or hormone refractory or malign* or metasta* or neoplas* or tumo*)):ti,ab,kw | 5960 |
| #4 | #1 or #2 or #3 | 5960 |
| #5 | (Cabazitaxel* or Enzalutamid* or Abirateron* or "radium chloride ra 223" or alpharadin*):ti,ab,kw | 110 |
| #6 | #4 and #5 | 105 |
| #7 | #6 Publication Year from 2000 to 2015, in Trials | 89 |
| #8 | #6 Publication Year from 2015 to 2015 | 16 |
| #9 | eq-5d or euroqol 5d or HRQoL | 3850 |
| #10 | MeSH descriptor: [Quality of Life] this term only | 15367 |
| #11 | (((quality* or adjusted) near/3 life) or HRQL) | 49032 |
| #12 | (qaly* or qald* or qale* or qtime* or qali*) | 4267 |
| #13 | #9 or #10 or #11 or #12 | 49434 |
| #14 | #6 and #13 Publication Year from 2000 to 2015 | 23 |

**Database: CRD** (Economic evaluations)
Date: 2015.03.03
Results: 0

| | | |
|---|---|---|
| 1 | MeSH DESCRIPTOR Prostatic Neoplasms | 641 |
| 2 | MeSH DESCRIPTOR Prostatic Neoplasms, Castration-Resistant | 5 |
| 3 | (prostat* near6 (advanc* or adenocarcinom* or carcinom* or cancer* or hormone refractory or malign* or metasta* or neoplas* or tumo*)) | 704 |
| 4 | #1 OR #2 OR #3 | 793 |
| 5 | ((Cabazitaxel* or Enzalutamid* or Abirateron* or "radium chloride ra 223" or alpharadin*)) | 22 |
| 6 | #4 AND #5 | 19 |
| 7 | (#6) IN NHSEED | 0 |

**Database: Web of Science**
Date: 2015.03.03
Results: 62 trials + 21 trials

# 10 #7 AND #6
**Refined by: Databases:** ( WOS )
*Timespan=2015*
*Search language=Auto*

# 9 #7 AND #6
**Refined by: Databases:** ( WOS )
*Timespan=All years*
*Search language=Auto*

# 8 #7 AND #6
*Timespan=All years*
*Search language=Auto*

# 7 **YEAR PUBLISHED:** (2000-2015)
*Timespan=All years*
*Search language=Auto*

# 6 #4 AND #5
*Timespan=All years*
*Search language=Auto*

# 5 **TOPIC:** ("randomized controlled" or ranomiz* or randomly or "controlled clinical") *OR* **TITLE:** ("randomized controlled" or ranomiz* or randomly or "controlled clinical")
*Timespan=All years*
*Search language=Auto*

# 4 #1 AND #2
**Refined by: Databases:** ( WOS )
*Timespan=All years*
*Search language=Auto*

# 3 #1 AND #2
*Timespan=All years*
*Search language=Auto*

# 2 **TOPIC:** (cabazitaxel or enzalutamide or abiraterone or "radium chloride ra 223" or alpharadin) *OR* **TITLE:** (cabazitaxel or enzalutamide or abiraterone or "radium chloride ra 223" or alpharadin)
*Timespan=All years*
*Search language=Auto*

# 1 **TOPIC:** (prostat* cancer* or prostat* neoplas* or prostat* carcinoma* or prostat* tun
**TITLE:** (prostat* cancer* or prostat* neoplas* or prostat* carcinoma or prostat* tumo
*Timespan=All years*
*Search language=Auto*

**Database: PubMed**
Date: 2015.03.04 / 2015.10.26
Results: 64 trials / 21 trials
Search:
Search ((((((((((((((prostate cancer*[Title/Abstract] OR prostate neoplasm*[Title/Abstract] OR prostate carcinoma[Title/Abstract])) OR (prostatic cancer*[Title/Abstract] OR prostatic neoplasm[Title/Abstract] OR prostatic carcinoma[Title/Abstract] OR advanced prostate[Title/Abstract]) OR metastatic prostate[Title/Abstract]) OR malignant prostate[Title/Abstract])))))) OR (((prostate cancer[MeSH Terms]) OR prostate neolasms[MeSH Terms])) OR ((prostatic cancers[MeSH Terms]) OR prostatic neoplasms[MeSH Terms])))))))
AND
(((cabazitaxel[Title/Abstract] OR enzalutamide[Title/Abstract] OR abiraterone[Title/Abstract] OR radium chloride ra 223[Title/Abstract] OR alpharadin[Title/Abstract])))))
AND pubstatusaheadofprint))
AND ((trial[Title/Abstract] OR study[Title/Abstract]))
Filters: Clinical Trial

Date: 2015.10.26

Results: 3 (health economic evaluations ahead of print)
Search ((((((quality of life[Title/Abstract]) OR cost effectiveness analysis[Title/Abstract]) OR cost utility analysis[Title/Abstract]) OR cost benefit analysis[Title/Abstract]) OR economic evaluation[Title/Abstract])) AND ((((((((((((((((prostate cancer*[Title/Abstract] OR prostate neoplasm*[Title/Abstract] OR prostate carcinoma[Title/Abstract])) OR (prostatic cancer*[Title/Abstract] OR prostatic neoplasm[Title/Abstract] OR prostatic carcinoma[Title/Abstract] OR advanced prostate[Title/Abstract]) OR metastatic prostate[Title/Abstract]) OR malignant prostate[Title/Abstract])))))) OR (((prostate cancer[MeSH Terms]) OR prostate neolasms[MeSH Terms])) OR ((prostatic cancers[MeSH Terms]) OR prostatic neoplasms[MeSH Terms]))))))) AND (((cabazitaxel[Title/Abstract] OR enzalutamide[Title/Abstract] OR abiraterone[Title/Abstract] OR radium chloride ra 223[Title/Abstract] OR alpharadin[Title/Abstract])))))) AND pubstatusaheadofprint)

**Database: Epistemonikos**
Date: 2015.03.04.
Results: 13

((title:("prostate cancer" OR "prostate neoplasm*" OR "prostate carcinoma" OR "prostatic cancer*" OR "prostatic neoplasm*" OR "prostatic carcinoma” OR “prostate tumo*") OR abstract:("prostate cancer" OR "prostate neoplas*" OR "prostate carcinoma" OR "prostatic cancer*" OR "prostatic neoplasm*" OR "prostatic carcinoma" OR “prostate tumo*") OR title:(“advanced prostate” OR “malign prostate” OR “metastatic prostate”) OR abstract:("advanced prostate"OR "metastatic prostate"OR "malignant prostate")
AND
(title:(cabazitaxel OR enzalutamide OR abiraterone OR "radium chloride ra 223" OR alpharadin) OR abstract:(cabazitaxel OR enzalutamide OR abiraterone OR "radium chloride ra 223" OR alpharadin)))

**Source: Google Scholar**
Date: 2015.03.04
Results: 5 trials
Search:
Anywhere in the article:
prostate cancer AND cabazitaxel OR enzalutamide OR abiraterone OR "radium chloride ra 223" OR alpharadin AND "randomized controlled"
OR
prostate neoplasm AND cabazitaxel OR enzalutamide OR abiraterone OR "radium chloride ra 223" OR alpharadin AND "randomized controlled"
OR
"malignant prostate" AND cabazitaxel OR enzalutamide OR abiraterone OR "radium chloride ra 223" OR alpharadin AND "randomized controlled"
OR
"advanced prostate”  AND cabazitaxel OR enzalutamide OR abiraterone OR "radium chloride ra 223" OR alpharadin AND "randomized controlled"
“metastatic prostate” AND cabazitaxel OR enzalutamide OR abiraterone OR "radium chloride ra 223" OR alpharadin AND "randomized controlled"

**Sources: WHO International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.gov**
Date: 2016.01.12
Results: 307 ongoing trials
Search: prostate cancer (condition)
AND Abiraterone / Cabazitaxel/ Enzalutamide / Radium 223 dichloride (intervention)

## Appendix 2. List of excluded trials

### Excluded trial from our literature search, and the reason for exclusion

Correction to Abiraterone acetate for patients with metastatic castration-resistant prostate cancer progressing after chemotherapy: Final analysis of a multicentre, open-label, early-access protocol trial [Lancet Oncol 15, (2014), 1263-1268]. The Lancet Oncology 2014;15(12):e528.
*Correction*

Correction to Effect of enzalutamide on time to fi rst skeletal related event, pain, and quality of life in men with castration-resistant prostate cancer: Results from the randomised, phase 3 AFFIRM trial [Lancet Oncol (2014), 15, 1147-56]. The Lancet Oncology 2014;15(11):e475.
*Correction*

Armstrong AJ, Tombal B, Sternberg CN, Higano CS, Rathkopf DE, Loriot Y, et al. Primary, secondary, and quality-of-life endpoint results from PREVAIL, a phase 3 study of enzalutamide in men with metastatic castration resistant prostate cancer (mCRPC). J Clin Oncol 2014;1).
*Abstract, results available in full-text articles or ongoing trial*

Basch E, Ryan CJ, Kheoh T, Fizazi K, Logothetis CJ, Rathkopf DE, et al. The impact of abiraterone acetate (AA) therapy on patient-reported pain and functional status in chemotherapy-naive patients with progressive, metastatic castration-resistant prostate cancer (MCRPC). Ann Oncol 2012;23:ix295.
*Abstract, results available in full-text articles or ongoing trial*

Basch EM, De Bono JS, Scher HI, Molina A, Sternberg CN, Fizazi K, et al. Pain control and delay in time to skeletal-related events (SREs) in patients with metastatic castration-resistant prostate cancer (mCRPC) treated with abiraterone acetate (AA): Long-term follow-up. J Clin Oncol 2012;1).
*Not relevant outcomes*

Beer TM, Armstrong AJ, Sternberg CN, Higano CS, Iversen P, Loriot Y, et al. Enzalutamide in men with chemotherapy-naive metastatic prostate cancer (mCRPC): Results of phase III PREVAIL study. J Clin Oncol 2014;1).
*Review of trial*

Cella D, Ivanescu C, Holmstrom S, Bui CN, Spalding J, Fizazi K. Impact of enzalutamide on quality of life in men with metastatic castration-resistant prostate

cancer after chemotherapy: Additional analyses from the AFFIRM randomized clinical trial. Ann Oncol 2015;26(1):179-185.
*Post hos analysis, did nod extract data*

Climent MA, Sanchez A, Mellado B, Santander C, Cassinello J, Isabel Saez M, et al. Randomized phase II study of abiraterone acetate maintenance in combination with docetaxel after disease progression to abiraterone acetate in metastatic castration-resistant prostate cancer (mCRPC): ABIDO SOGUG trial. J Clin Oncol 2014;1).
*Ongoing investigator initiated trial*

Davis I, Kim CS, Kimura G, Lau W, Noonberg SB, Perabo F, et al. Enzalutamide in men with chemotherapy-naive metastatic castration resistant prostate cancer (mCRPC): Primary and Australian/Asian regional results of the phase 3 prevail study. Asia Pac J Clin Oncol 2014;10:259.
*Analysis of cohort of trial*

De Bono JS, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, et al. Primary, secondary, and quality-of-life endpoint results from the phase III AFFIRM study of MDV3100, an androgen receptor signaling inhibitor. J Clin Oncol 2012;1).
*Abstract, results available in full-text articles or ongoing trial*

De Bono JS, Logothetis CJ, Fizazi K, North S, Chu L, Chi KN, et al. Abiraterone acetate (AA) plus low dose prednisone (P) improves overall survival (OS) in patients (PTS) with metastatic castrationresistant prostate cancer (mcrpc) who have progressed after docetaxel-based chemotherapy (chemo): Results of cou-aa-301 a randomized double-blind placebo-controlled phase III study. Ann Oncol 2010;21:viii3.
*Abstract, results available in full-text articles or ongoing trial*

De Bono JS, Oudard S, Ozguroglu M, Hansen S, Machiels JH, Shen L, et al. Cabazitaxel or mitoxantrone with prednisone in patients with metastatic castration-resistant prostate cancer (mCRPC) previously treated with docetaxel: Final results of a multinational phase III trial (TROPIC). J Clin Oncol 2010;1).
*Abstract, results available in full-text articles or ongoing trial*

De Souza P, Rathkopf D, Smith M, Mulders P, Mainwaring P, North S, et al. Long-term safety and efficacy analysis of abiraterone acetate (AA) plus prednisone (P) in study COU-AA-302for metastatic castration-resistant prostate cancer. BJU Int 2013;112:13.
*Abstract, results available in full-text articles or ongoing trial*

Development JR. A phase 3, randomized, double-blind, placebo-controlled study of abiraterone acetate plus prednisone in asymptomatic or mildly symptomatic subjects with metastatic castration-resistant prostate cancer. 2012.
*Ongoing trial*

Development JR. Abiraterone Acetate in Asymptomatic or Mildly Symptomatic Patients With Metastatic Castration-Resistant Prostate Cancer. Clinical Trial 2013.
*Ongoing trial*

Donga P, Bilir P, Valderrama A, Li H, Munakata J. Health state utilities among metastatic castrate-resistant prostate cancer patients with and without symptomatic

skeletal events. International Journal of Radiation Oncology Biology Physics 2014;1):S706.
*Abstract, results available in full-text articles or ongoing trial*

Edwina SBB, Shore ND, Barber K, Ouatas T, Heidenreich A. TERRAIN: A randomized, double-blind, phase II study comparing MDV3100 with bicalutamide (Bic) in men with metastatic castrate-resistant prostate cancer (CRPC). J Clin Oncol 2012;1).
*Abstract, results available in full-text articles or ongoing trial*

Eisenberger MA, Hardy-Bessard AC, Ford D, Mourey L, Parente P, Mainwaring PN, et al. PROSELICA study update: Comparison of two doses of cabazitaxel (Cbz) plus prednisone (P) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) previously treated with a docetaxel (D)-containing regimen. J Clin Oncol 2013;1).
*Abstract, results available in full-text articles or ongoing trial*

Eisenberger MA, Hardy-Bessard AC, Mourey L, Mainwaring PN, Ford D, Shapiro JD, et al. Comparison of two doses of cabazitaxel plus prednisone in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) previously treated with a docetaxel (D)-containing regimen. J Clin Oncol 2012;1).
*Abstract, results available in full-text articles or ongoing trial*

Evans C, C SH, Keane T, Andriole G, Saad F, Iversen P, et al. Late-breaking Abstract, results available in full-text articles or ongoing trial: The prevail study: Primary and non-visceral / visceral disease subgroup results for enzalutamide-treated men with metastatic prostate cancer (MPC) that had progressed on adt. J Urol 2014;1):e223-e224.
*Not relevant population*

Fizazi K, De Bono J, Haqq C, Logothetis CC, Jones RJ, Chi K, et al. Abiraterone acetate plus low-dose prednisone has a favorable safety profile in metastatic castration-resistant prostate cancer progressing after docetaxel-based chemotherapy: Results from COU-AA-301, a randomized, double-blind, placebocontrolled, phase III study. European Urology, Supplements 2011;10 (2):338.
*Abstract, results available in full-text articles or ongoing trial*

Fizazi K, Larsen JS, Matheny S, Molina A, Li J, Todd MB, et al. Randomized double-blind, comparative study of abiraterone acetate (AA) plus low-dose prednisone (P) plus androgen deprivation therapy (ADT) versus ADT alone in newly diagnosed, high-risk, metastatic hormone-naive prostate cancer (mHNPC). J Clin Oncol 2013;1).
*Abstract, not relevant population*

Fizazi K, Scher HI, Molina A, Logothetis CJ, Jones RJ, Staffurth JN, et al. Final overall survival (OS) analysis of COU-AA-301, a phase 3 study of abiraterone acetate plus prednisone in patients with metastatic castration-resistant prostate cancer (mCRPC) pretreated with docetaxel. Eur J Cancer 2011;47:S483-S484.
*Abstract, results available in full-text articles or ongoing trial*

Harland S, De Bono JS, Haqq CM, Staffurth JN, Hao Y, Gagnon D, et al. Abiraterone acetate improves functional status in patients with metastatic castration-resistant

prostate cancer (mCRPC) post-docetaxel - Results from the COU-AA-301 phase 3 study. Eur J Cancer 2011;47:S484.
*Abstract, not relevant outcomes*

Konig F, Vogelzang NJ, Helle SI, Johannessen DC, O'Sullivan JM, Garcia-Vargas J, et al. Efficacy and safety of radium-223 dichloride (Ra-223) in castration-resistant prostate cancer (CRPC) patients with bone metastases who had prior or no-prior docetaxel in the phase 3 ALSYMPCA trial. Oncology Research and Treatment 2014;37:59.
*Abstract, results available in full-text articles or ongoing trial*

Loriot Y, Fizazi K, De Bono JS, Forer D, Hirmand M, Scher HI. Outcomes in patients with liver or lung metastatic castration-resistant prostate cancer (mCRPC) treated with the androgen receptor inhibitor enzalutamide: Results from the phase III AFFIRM trial. J Clin Oncol 2013;1).
*Not relevant population*

Mellado B, Sartor O, Vogelzang NJ, Hoskin P, Nilsson S, Coleman RE, et al. Further characterization of the effects on sequential treatment of docetaxel before or after radium-223 dichloride therapy in Castration-Resistant Prostate Cancer (CRPC) patients with symptomatic bone metastases included in the phase 3 ALSYMPCA trial. European Urology, Supplements 2014;13 (5):138.
*Not relevant population*

Miller K, Scher H, Fizazi K, Basch E, Sternberg C, Hirmand M, et al. Enzalutamide improves health-related quality of life in men with metastatic castration-resistant prostate cancer following docetaxel-based therapy: Results from the affirm study. Urology 2013;1):S52.
*Abstract, results available in full-text articles or ongoing trial*

Miller K, Scher HI, Fizazi K, Basch EM, Sternberg CN, Hirmand M, et al. Effect of enzalutamide on health-related quality of life (HRQoL) in men with metastatic castration-resistant prostate cancer (mCRPC) following docetaxel-based therapy: Results from the AFFIRM study. J Clin Oncol 2013;1).
*Abstract, results available in full-text articles or ongoing trial*

Mulders P, Fizazi K, Saad F, Sternberg CN, Taplin M, Miller K, et al. Enzalutamide, an androgen receptor signaling inhibitor, improves overall survival, time to first skeletal related event and pain. European Urology, Supplements 2012;11 (5):188-189.
*Abstract, results available in full-text articles or ongoing trial*

Mulders P, Scher H, Fizazi K, Saad F, Taplin M, Sternberg C, et al. MDV3100, an androgen receptor signaling inhibitor, improves overall survival in patients with prostate cancer post docetaxel: Results from the Phase 3 AFFIRM study. Urology 2012;1):S30.
*Abstract, duplicate*

Nilsson S, Franzen L, Parker C, Bolstad B, Ramdahl T, Thuresson M, et al. Alpha-emitting radium-223: Two years follow up from a randomized phase II study in patients with bone metastases from hormone refractory prostate cancer. European Journal of Cancer, Supplement 2009;7 (2-3):412.
*Poster, full text is included*

Nilsson S, Strang P, Aksnes AK, Franzn L, Olivier P, Pecking A, et al. A randomized, dose-response, multicenter phase II study of radium-223 chloride for the palliation of painful bone metastases in patients with castration-resistant prostate cancer. Eur J Cancer 2012;48(5):678-686.
*Dose-finding study*

Nilsson S, Strang P, Franzen L, Olivier P, Pecking A, Staffurth J, et al. A double-blind, randomised dose-response phase II, multicentre study of radium-223 for the palliation of painful bone metastases in castration refractory prostate cancer patients. European Journal of Cancer, Supplement 2009;7 (2-3):409.
*Poster, dose-finding study*

Ohlmann CH, Stockle M, Pfister D, De Bono JS, Molina A, Frohn C, et al. Improved Overall Survival (OS) in patients with metastatic Castration Resistant Prostate Cancer (mCRPC) progressing after docetaxel-based chemotherapy: Results from the phase III study COU-AA-301 with abiraterone acetate. Onkologie 2011;34:9-10.
*Abstract, results available in full-text articles or ongoing trial*

Oudard S. TROPIC: Phase III trial of cabazitaxel for the treatment of metastatic castration-resistant prostate cancer. Future Oncol 2011;7(4):497-506.
*Discussion*

Oudard S, Sengelov L, Mainwaring PN, Antoine TV, Theodore C, Kulikov E, et al. First-line use of cabazitaxel in chemotherapy-naive patients with metastatic castration-resistant prostate cancer (mCRPC): A three-arm study in comparison with docetaxel. J Clin Oncol 2012;1).
*Abstract, results available in full-text articles or ongoing trial*

Oudard SM, De Bono JS, Ozguroglu M, Hansen S, Machiels J, Shen L, et al. Cabazitaxel plus prednisone/prednisolone significantly increases overall survival compared to mitoxantrone plus prednisone/ prednisolone in patients with metastatic castration-resistant prostate cancer (mCRPC) previously treated with docetaxel: Final results with updated overall survival of a multinational phase III trial (tropic). Ann Oncol 2010;21:viii272.
*Abstract, results available in full-text articles or ongoing trial*

Parker C, Coleman RE, Nilsson S, Vogelzang N, Lloyd AJ, Staudacher K, et al. Updated survival, quality of life (QOL), and safety data of radium-223 chloride (RA-223) in patients with castration-resistant prostate cancer (CRPC) with bone metastases from the phase 3 double-blind, randomized, multinational study (ALSYMPCA). Ann Oncol 2012;23:ix296.
*Abstract, results available in full-text articles or ongoing trial*

Parker C, Heinrich D, Helle SI, O'Sullivan JM, Fossa S, Chodacki A, et al. Overall survival benefit and impact on skeletal-related events for radium- 223 chloride (Alpharadin) in the treatment of castration-resistant prostate cancer (CRPC) patients with bone metastases: A phase III randomized trial (ALSYMPCA). European Urology, Supplements 2012;11(1):e130-e130a.
*Abstract, results available in full-text articles or ongoing trial*

Parker C, Hoskin P, Pascoe S, Chodack A, O'Sullivan JM, Germa JR, et al. A double blind, randomised, dose finding, phase II, multicentre study of radium-223 for the treatment of patients with metastatic castration-refractory prostate cancer (CRPC):

EudraCT number: 2005-003680-22. European Journal of Cancer, Supplement 2009;7 (2-3):406.
*Abstract, results available in full-text articles or ongoing trial*

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1 June 2015 • Author: Victoria White

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EUCTR2009-013174-41-BE. A study of patients with prostate cancer who have previously been treated with docetaxel-based chemotherapy, where patients receive either study drug or placebo. 2009. https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2009-013174-41

## Appendix 4 Characteristics of included trials and Risk of Bias tables

### Study description

| |
|---|
| *Studies:* de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L, et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 2011;364(21):1995-2005.<br><br>Fizazi K, Scher HI, Molina A, Logothetis CJ, Chi KN, Jones RJ, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. The Lancet Oncology 2012;13(10):983-992.<br><br>Harland S, Staffurth J, Molina A, Hao Y, Gagnon DD, Sternberg CN, et al. Effect of abiraterone acetate treatment on the quality of life of patients with metastatic castration-resistant prostate cancer after failure of docetaxel chemotherapy. Eur J Cancer 2013;49(17):3648-3657.<br><br>**NCT00638690** |
| *Design:* Double blind, randomized, multinational (13 countries, 147 sites) study. No cross over between treatment groups before the analysis. |
| **Population:** 1195 patients with a histologically or cytologically confirmed prostate cancer, previously treatment with docetaxel, disease progression, serum testosterone level <50 ng/dl. ECOG performance status score of 2 or less. Median age 69. |
| *Intervention/comparators:* 1195 patients randomized in a 2:1 ratio to 1 g abiraterone (administered as four 250 mg tablets) (n=797) or four placebo tablets (n=398) orally once daily with prednisone at a dose of 5 mg orally twice daily. |
| **Endpoints:** PSA response rate (defined as the proportion of patients with a decrease of ≥50% in the PSA concentration from the pretreatment baseline PSA value), progression-free survival by prespecified radiographic criteria. Overall survival defined as the time from randomization to death from any cause and safety (de Bono 2011, Fizazi 2012). HRQoL measured using the FACT-P questionnaire (Harland 2013). |
| |
| *Follow-up:* A prespecified interim analysis was planned to be performed after 534 deaths had occurred. The median follow up in the overall study population was 12.8 months. Final analysis was performed after 775 deaths, before cross over from placebo to abiraterone acetate. Median follow up in final analysis was 20.2 months. |
| *Funding source:* Cougar Biotechnology/Janssen Research and Development |

**Data extraction from de Bono 2011, Fizazi 2012 and Harland 2013**

| **Endpoints** | **Aberaterone + prednisone** (n=797) | **Placebo + predni-sone** (n=398) | **HR, p-values** |
|---|---|---|---|
| **Total no of deaths**<br>Median 12.8 months follow up<br><br>Median 20.2 months follow up | 333 (42%)<br><br>775 deaths in total (aberaterone and placebo groups) | 219 (55%) | |
| **Median overall survival** (months)<br>Median 12.8 months follow up<br><br>Median 20.2 months follow up | 14.8<br><br>15.8 (95% CI 14.8 – 17.0) | 10.9<br><br>11.2 (95% CI 10.4 – 13.1) | 0.66 (95% CI 0.55 to 0.78) p<0.001)<br><br>0.74 (95% CI 0.64 to 0.86) p<0.0001 |
| **PFS** (PSA progression)<br>Median time until PSA progression (months)<br><br>Median 12.8 months follow up<br><br>Median 20.2 months follow up | 10.2<br><br>8.5 (95% CI 8.3 – 11.1) | 6.6<br><br>6.6 (95% CI 5.6 – 8.3) | 0.58 (0.46 to 0.73) p<0.001<br><br>0.63 (0.52 to 0.78) p<0.0001 |
| **PFS response** (median radiographic progression-free survival)<br>(months)<br><br>Median 12.8 months follow up<br><br>Median 20.2 months follow up | 5.6<br><br>5.6 (5.6 – 6.5) | 3.6<br><br>3.6 (2.9 – 5.5) | 0.67 (0.59 to 0.78) p<0.001<br><br>0.66 (0.58 to 0.76) p<0.0001 |
| **PFS response (%)** (proportion of patients with PSA decline of 50% or higher according to PSAWG criteria) at month 20.2 | 235 (29.5%) | 22 (5.5%) | P<0.0001 |

| | | | |
|---|---|---|---|
| **Time to HRQoL detoriation**, FACT-P scale (days) | 419 | 253 | 0.607 (0.495 to 0.743) p<0.0001 |
| **HRQoL changes from baseline**, FACT-P | Not reported | Not reported | |
| **Any SAE** (Grade ≥3) number of patients (percent) | | | The results for adverse events are given as events per adverse event. It is not possible to provide an overall estimate for SAE without taking the risk of double counting. |

*Risk of Bias*: **NCT00638690**

| Entry/Domain | Judgement | Description |
|---|---|---|
| Random sequence generation? | Low risk | "..randomly assigned to treatment in a blinded manner by permuted block method via an interactive web response system using a randomisation schedule generated by an external vendor" |
| Allocation concealment? | Low risk | "The study sponsor, study personnell, patients and members of IDMC remained masked to treatment assignement until completion of study" |
| Blining of participants and personnel? | Low risk | See above |
| Blinding of outcome assessments? | Low risk | See above |
| Incomplete outcome data?<br><br>OS<br>PFS<br><br>HRQoL<br><br>SAE | <br><br>Low risk<br>Low risk<br><br>Low risk<br><br>Low risk | <br><br>Analysis on intention-to-treat population<br><br>Self reported, but blinded design<br><br>Safety analysis included all patients who received at least one dose of study drug |
| Selective reporting? | Low risk | Outcomes were pre-specified and reported on. |
| Other sources of bias? | Low risk | The study was funded by Janssen Research & Development |
| Conclusion | Low risk of bias for all endpoints | |

**Study description**

| |
|---|
| *Studies:*<br><br>Ryan CJ, Smith MR, De Bono JS, Molina A, Logothetis CJ, De Souza P, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med 2013;368(2):138-148.<br><br>Rathkopf DE, Smith MR, De Bono JS, Logothetis CJ, Shore ND, De Souza P, et al. Updated interim efficacy analysis and long-term safety of abiraterone acetate in metastatic castration-resistant prostate cancer patients without prior chemotherapy (COU-AA-302). Eur Urol 2014;66(5):815-825.<br><br>Ryan CJ, Smith MR, Fizazi K, Saad F, Mulders PFA, Sternberg CN, et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): Final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. The Lancet Oncology 2015;16(2):152-160.<br><br>**NCT00887198** |
| *Design:* Double blind, randomized, multinational study. Crossover between treatment groups after second interim analysis |
| **Population:** 1088 patients with a metastatic, histologically or cytologically confirmed adenocarcinoma of the prostate; PSA progression according to PCWG2 criteria or radiographic progression in soft tissue or bone with or without PSA progression, ongoing androgen deprivation with a serum testosterone level <50 ng/dl. ECOG performance status score of 0 or 1. Patients who had received previous therapy with ketoconazole for more than 7 days were excluded. Median age 71.0 (abiraterone + prednisone) and 70.0 (prednisone alone). |
| *Intervention/comparators:* 1088 patients randomized in a 1:1 ratio to 1 g abiraterone (administered as four 250 mg tablets) (n=546) or four placebo tablets (n=542) orally once daily with prednisone at a dose of 5 mg orally twice daily. |
| **Endpoints:** Radiographic progression-free surviv, overall survival defined as the time from randomization to death from any cause and functional status measured with FACT-P questionnaire (forfatter 201x). |
| |
| *Follow-up:* A planned interim analysis of overall survival was performed after 333 deaths were observed (second interim analysis). The median follow up duration for all patients was 22.2 months. Final analysis was planned after 773 death events had occurred. At a median follow up of 49.2 months, 741 of the pre-specified 773 death events had occurred. Patients were allowed to cross over after 2nd interim analysis. |
| *Funding source:* Janssen Research and Development, formerly Cougar Biotechnology |

**Data extraction from** *NCT00887198*

| **Endpoints** | **Abiraterone + prednisone** (n=546) | **Placebo + prednisone** (n=542) | **HR, p-values** |
|---|---|---|---|
| **Total no of deaths**<br>Median 22.2 months follow up | 147 (27%)<br><br>354 (65%) | 186 (34%)<br><br>387 (67%) | HR 0.75 (95% CI 0.61 to 0.93), p=0.01<br><br>HR 0.81 (95% CI 0.70 to 0.93) |

| | | | |
|---|---|---|---|
| Median 49.2 months follow up | | | HR 0.74 (95% CI 0.60 to 0.88), adjusted for cross over effect using the IPE method |
| **Median overall survival (months)**<br>Median 22.2 months follow up | Not reached | 27.2 (95% CI 26.0 to not reached) | HR 0.75 (95% CI 0.61 to 0.93), p=0.01 |
| Median 27.1 months follow up | 35.3 | 30.1 | HR 0.79 (0.66 to 0.95), p=0.0151 |
| Median 49.2 months follow up | 34.7 (95% CI 32.7-36.8) | 30.3 (95% CI 28.7-33.3) | HR 0.74, 95% CI 0.60-0.88, adjusted for cross over effect using the IPE method |
| **PFS**<br>(PSA progression)<br><br>Patients with decline of ≥50% in PSA level (based on modified PCWG2 criteria),<br><br>Median 22.2 months follow up | 62% | 24% | RR 2.59 (2.19 to 3.05), p<0.001 |
| **PFS**<br>Median time to PSA progression (months)<br><br>Median 22.2 months follow up | 11.1 | 5.6 | HR 0.49 (0.42 to 0.57), p<0.001 |
| Median 27.1 months follow up | 11.1 | 5.6 | HR 0.5 (0.43 to 0.58), p<0.0001 |
| **PFS**<br>(radiographic progression)<br>Median time to progression (months)<br><br>First interim analysis | Median not reached | 8.3 | HR 0.43 (95% CI 0.35 to 0.52), p<0.001<br><br>HR 0.53 (95% CI 0.45 to 0.62), p<0.001 |

| | | | |
|---|---|---|---|
| Median 22.2 months follow up<br><br>Median 27.1 months follow up | 16.5<br><br>16.5 | 8.3<br><br>8.2 | HR 0.52 (95% CI 0.45 to 0.61) |
| **Time to HRQoL detoriation**, FACT-P scale<br>(months)<br>Median 22.2 months follow up<br><br>Median 27.1 months follow up | 12.7<br><br>12.7 | 8.3<br><br>8.3 | HR 0.78 (0.66 to 0.92)<br><br>HR 0.79 (0.67 to 0.93) |
| **Grade 3 or 4 AE** number of patients (percent)<br><br>Median 22.2 months follow up<br><br>Median 49.2 months follow up | 258 (48%), n=542<br><br>290 (54%), n=542 | 225 (42%), n=540<br><br>236 (44%), n=540 | |

**Comments:**

*Risk of Bias*: **NCT00887198**

| Entry/Domain | Judgement | Description |
|---|---|---|
| Random sequence generation? | Low risk | "… were randomly assigned with a permuted block allocation scheme via a web response systemin a 1:1 ratio to receive…" |
| Allocation concealment? | Low risk | See above |
| Blining of participants and personnel? | Low risk | Double-blind study |
| Blinding of outcome assessments? | Low risk | Double-blind study |
| Incomplete outcome data?<br><br>OS | Low risk | Intention-to-treat population |

| | | |
|---|---|---|
| PFS<br><br>HRQoL<br><br><br><br>SAE | Low risk<br><br>Low risk<br><br><br><br>Low risk | <br><br>Patient reported, but blinded design<br><br><br><br>Safety analysis included all patients who received study drug. Safety data were analyzed before cross-over |
| Selective reporting? | Low risk | Study protocol available, all outcomes were pre-specified and reported on. |
| Other sources of bias? | Low risk for OS (adjusted for crossover) and SAE (analysis before crossover)<br><br>High risk for HRQoL and PFS at 27.1 months follow up | Patients were allowed to cross over after review of the second interim analysis.<br><br>The study was funded by Janssen research & Development |
| Conclusion | Low risk of bias for all endpoints | |

**Study description**

| |
|---|
| *Study:* de Bono JS, Oudard S, Ozguroglu M, Hansen S, Machiels J-P, Kocak I, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet 2010;376(9747):1147-1154.<br><br>**NCT00417079** |
| *Design:* Open-label, randomized, multinational (146 centres in 26 countries) study. No cross over between treatment groups. |
| **Population:** 755 patients with pathologically proven prostate cancer with documented disease progression during or after completion of docetaxel treatment. ECOG performance status grade of 0-2. Previous or ongoing castration by orchiectomy or LHRH agonists. Patients who had previous mitoxantrone therapy, radiotherapy to 40% or more of the bone marrow, or cancer therapy other than LHRH within 4 weeks before enrollement were excluded. Median age 67 (mitoxantrone) and 68 (cabazitaxel). |
| *Intervention/comparators:* 755, randomly assigned to cabizataxel (n=378) 25 mg/m$^2$ intravenously over 1 h or mitoxantrone (n=377) 12 mg/m$^2$ intravenously over 15-30 min on day 1 of each 21-day cycle. All patients received oral prednisone 10 mg daily (or similar doses of prednisolone where prednisone was unavailable) |
| **Endpoints:** Overall survival, calculated from date of randomization to death. Progression-free survival, defined as the time between randomization and the first date of pregression as measured by PSA progression, tumour progression, pain progression, or death. Safety (adverse events) |
| *Follow-up:* The median follow-up for both treatment groups combined was 12.8 months. An interim analysis of overall survival was planned after 307 events, but was actually done after 365 events (with adjustments). |
| *Funding source:* Sanofi-Aventis |

**Data extraction: de Bono 2010**

| Endpoints | Cabazitaxel+prednisone (n=378) | Mitoxantrone+prednisone (n=377) | HR, p-values |
|---|---|---|---|
| **Total no of deaths** Median 12.8 months follow up | 234 | 279 | |
| **Median overall survival (months)** Median 12.8 months follow up | 15.1 (95% CI 14.1 to 16.3) | 12.7 (95% CI 11.6 to 13.7) | HR 0.70 (95% CI 0.59 to 0.83), p<0.0001 |
| **PFS** (PSA progression) Median time until PSA progression (months) | 6.4 (95% CI 2.2 to 10.1) | 3.1 (95% CI 0.9 to 9.1) | HR 0.75 (95% CI 0.63 to 0.90) |
| **Median PFS** (composite endpoint of progression – free survival, defined as the time between randomization and the first date of progression as measured by PSA progression, tumour progression, pain progression, or death) | 2.8 (95% CI 2.4 to 3.0) | 1.4 (95% CI 1.4 to 1.7) | HR 0.74 (95% CI 0.64 to 0.86), p<0.0001 |
| **Any SAE** number of patients (percent) | | | The results for adverse events are given as events per adverse event. It is not possible to provide an overall esti- |

| | | | |
|---|---|---|---|
| | | | mate for SAE without taking the risk of double counting. |

**Comments:**

*Risk of Bias*: de Bono 2010/NCT00417079

| Entry/Domain | Judgement | Description |
|---|---|---|
| Random sequence generation? | Low risk | "Patients were centrally randomly assigned..." "A contact research organisation was responsible for randomising patients using an interactive voice response system and for the computer-generated random allocation schedule, but had no other involvement in trial" |
| Allocation concealment? | Low risk | «A dynamic allocation method was used to avoid treatment assignement imbalances within a centre" |
| Blining of participants and personnel? | Low risk | "Patients and treating physicians were not masked to treatment allocation". We assume that this will have no impact on the endpoints. |
| Blinding of outcome assessments? | Low risk | The study team was masked to the data analysis |
| Incomplete outcome data?<br><br>OS<br>PFS<br><br>SAE | <br><br>Low risk<br>Low risk<br><br>Low risk | <br><br>Analyses of intention to treat population<br><br>Safety analysis included all patients who received at least one dose of study drug |
| Selective reporting? | Low risk | Outcomes mentioned in procedures were reported on |
| Other sources of bias? | Low risk | The study was funded by Sanofi-Aventis |
| Conclusion | Low risk of bias for all outcomes | |

**Study description**

| |
|---|
| *Studies:* Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med 2014;371(5):424-433<br>Loriot Y. et al. Effect of enzalutamide on health-related quality of life, pain, and skeletal-related events in asymptomatic and minimally symptomatic, chemotherapy-naive patients with metastatic castration-resistant prostate cancer (PREVAIL): results from a randomised, phase 3 trial. Lancet Oncol 2015;16(5):509-21.<br>**NCT01212991** |
| *Design:* Double blind, randomized, multinational in North America, Asia and Europe. No cross over between treatment groups. |
| **Population:** 1717 patients with histologically or cytologically confirmed adenocarcinoma of the prostate with documented metastases and PSA progression, radiographic progression or both. ECOG performance status grade of 0 or 1. Median age 72.0 (enzlutamide) and 72.0 (placebo). No prior cytotoxic chemotherapy, ketoconazole or abiraterone acetate. |
| *Intervention/comparators:* 1717, randomized 1:1 to 160 mg oral enzalutamide (n=872) or placebo (n=845) once daily. Treatment continued until occurrence of unacceptable adverse events, confirmed radiographic progression, or skeletal-related event warranting the initiation of cytotoxic chemotherapy for treatment of prostate cancer. |
| **Endpoints:** Beer 2014: Radiographic progression-free survival defined as the time from randomization to the first objective evidence of radiographic disease progression assessed by the blinded independent central review facility or death due to any cause within 168 days after treatment discontinuation. Time to PSA progression defined as the time from randomisation to first confirmed PSA progression for all patients (PSA progression date: for patients with PSA declines at week 13, the date that a ≥25% increase and an absolute increase of ≥ 2 ng/ml above nadir was documented. For patients without PSA decline at week 13, the PSA progression date was defined as the date that a ≥25% increase and an absolute increase of ≥2 ng/ml above baseline was documented. Overall survival defined as the time from randomization to death from any cause. Quality of life measured using FACT-P. Safety (adverse events)<br>Loriot 2015: HRQoL (FACT-P, EQ-5D) |
| |
| *Follow-up:* The interim analysis of overall survival was to be conducted after the occurrence of approximately 516 deaths. Median duration of follow up for survival was 26 months.<br>The study was stopped after a planned interim survival analysis done at 540 reported deaths showed a benefit in favour of enzalutamide (data cutoff Sept 16, 2013) |
| *Funding source:* Medivation and Astellas Pharma |

**Data extraction:** Beer 2014 and Loriot 2015

| **Endpoints** | **Enzalutamide** (n=872) | **Placebo** (n=845) | **HR, p-values** |
|---|---|---|---|
| **Total no of deaths** Median 26 months follow up | 299 | 357 | |
| **Median overall survival** (months) | Not reached | 31.0 | |

| | | | |
|---|---|---|---|
| Median 26 months follow up | | | 27% decrease in the risk of death: HR (95% CI) 0.73 (0.63 to 0.85), p<0.001 |
| **PFS** (PSA progression) Median time until PSA progression (months) | 11.2 | 2.8 | HR 0.17 (0.15 to 0.20), p<0.001 |
| **PFS** (radiographic progression) | | | 81% reduction in the risk of radiographic progression or death: HR 0.19 (95% CI 0.15 to 0.23), p<0.001 |
| **Rates of PFS** (radiographic PFS) at month 12 | 65% | 14% | |
| **Time to HRQoL detoriation**, FACT-P scale (months) | 11.3 (95% CI 11.1 to 13.9) | 5.6 (95% CI 5.5 to 5.6) | HR 0.63 (95% CI 0.54 to 0.72); P<0.001 |
| **HRQoL changes from baseline**, FACT-P | -5.08 (-6.87 to -3.28) | -10.87 (-13.49 to -8.25) | Treatment difference (enzalutamide minus placebo) 5.80 (3.18 to 8.41) |
| **Time to HRQoL detoriation**, EQ-5D (months)<br><br>Utility index<br><br>Visual analogue scale | <br><br>19.2 (95% CI 16.4 to 21.9)<br>22.1 (95% CI 19.4 to 27.7) | <br><br>11.1 (95% CI 8.3 to 13.7)<br>13.8 (95% CI 11.1 to 16.6) | <br><br>Censored<br>HR 0.62 (95% CI 0.52 to 0.73); p<0.0001<br>HR 0.67 (95% CI 0.56 to 0.80); p<0.0001 |
| **HRQoL changes from baseline**, EQ-5D<br><br>Utility index<br>VAS score<br><br><br>Baseline | <br><br>-0.07 (-0.09 to -0.05)<br>-5.19 (-7.14 to -3.23)<br><br><br>0.85, SD 0.15 | <br><br>-0.10 (-0.14 to -0.06)<br>-9.76 (-12.61 to -6.92)<br><br>0.84, SD 0.17 | Treatment difference (enzalutamide minus placebo)<br><br>0.03 (-0.00 to 0.07); p=0.080<br>4.58 (1.85 to 7.31); p=0.0010 |
| **Any SAE** number of patients (percent) | 279/871 (32) | 226/844 (27) | |

**Comments:**

*Risk of Bias*: Beer 2014 and Loriot 2015

| Entry/Domain | Judgement | Description |
|---|---|---|
| Random sequence generation? | Low risk | "Patients were randomly assigned (1:1) to receive either enzalutamide or placebo capsules by centrally administered, permuted-block method and stratified by study site." |
| Allocation concealment? | Low risk | «All patients, investigators, site personnel, and funder personnel were masked to treatment assignment» |
| Blining of participants and personnel? | Low risk | See above |
| Blinding of outcome assessments? | Low risk | See above |
| Incomplete outcome data?<br><br>OS<br>PFS<br><br>HRQoL<br><br><br><br>SAE | <br><br>Low risk<br>Low risk<br><br>Low risk<br><br><br><br>Low risk | <br><br>"Efficacy data were analysed for inent-to-treat population"<br><br>Self reported: "HRQoL and pain data were prospectively collected with validated patient self-reported questionnaires". Blinded design<br><br>Safety analysis included all patients who received at least one dose of study drug (p 6 in Loriot 2015) |
| Selective reporting? | Low risk | Study protocol available, all outcomes were pre-specified and reported on. |
| Other sources of bias? | Low risk | The study was funded by Astellas Pharma and Medivation |
| Conclusion | Low risk of bias for all endpoints | |

**Study description**

*Studies:* Fizazi K, Scher HI, Miller K, Basch E, Sternberg CN, Cella D, et al. Effect of enzalutamide on time to first skeletal-related event, pain, and quality of life in men with castration-resistant prostate cancer: Results from the randomised, phase 3 AFFIRM trial. The Lancet Oncology 2014;15(10):1147-1156.

| |
|---|
| Scher HI, Fizazi K, Saad F, Taplin M-E, Sternberg CN, Miller K, et al. Increased Survival with Enzalutamide in Prostate Cancer after Chemotherapy. N Engl J Med 2012;367(13):1187-1197.<br><br>**NCT00974311** |
| *Design:* Double blind, randomized, multinational (156 sites in 15 countries). No cross over between treatment groups. |
| **Population:** 1199 patients with a histologically or cytologically confirmed diagnosis of prostate caner, castrate levels of testesterone (<50 ng/dl), previous treatment with docetaxel and progressive disease defined according to PCWG2 criteria, including three increasing values of PSA or radiographically confirmed progression with or without a rise in the PSA level. ECOG performance status score of 2 or less. Median age 69. |
| *Intervention/comparators:* 1199 patients randomized in a 2:1 ratio to 160 mg oral enzalutamide (n=800) or placebo (n=399) once daily |
| **Endpoints:** Overall survival defined as the time from randomization to death from any cause. Time to PSA progression. For patients with PSA declines at week13, the PSA progression date was defined as the date that a ≥25% increase and an absolute increase of ≥2 ng/ml above the nadir was documented. For patients with no PSA declines at week 13, PSA progression date was defined as the date that a ≥25% increase and an absolute increase of ≥2 ng/ml above the baseline was documented. Radiographic progression-free survival defined as the time from randomization to the earliest objective evidence of radiographic disease progression. Quality of life measured using FACT-P. Safety (adverse events) |
| *Follow-up:* A single interim analysis was planned to be performed after 520 deaths had occurred. Median duration of follow up for survival was 14.4 months. |
| *Funding source:* Medivation and Astellas Pharma |

**Data extraction from Scher 2012 and Fizazi 2014**

| **Endpoints** | **Enzalutamide** (n=800) | **Placebo** (n=399) | **HR, p-values** |
|---|---|---|---|
| **Total no of deaths** (%) | 308 (39) | 212 (53) | |
| **Median overall survival** (months)<br><br>14.4 months median duration of follow up | 18.4 (95% CI 17.3 to not yet reached) | 13.6 (95% CI 11.3 to 15.8) | 37% reduction in the risk of death<br>HR 0.63 (95% CI 0.53 to 0.75); p<0.001 |
| **PFS** (PSA progression) Median time to PSA progression (months) | 8.3 (95% CI 5.8 to 8.3) | 3.0 (95% CI 2.9 to 3.7) | HR 0.25 (95% CI 0.20 to 0.30) p<0.001 |
| **PFS** (median radiographic progression-free survival) (months) | 8.3 (95% CI 8.2 to 9.4) | 2.9 (95% CI 2.8 to 3.4) | HR 0.40 (95% CI 0.35 to 0.47); p<0.001 |

| | | | |
|---|---|---|---|
| **Time to HRQoL detoriation**, FACT-P total score | 9.0 (95% CI 8.3 to 11.1) | 3.7 (95% CI 3.0 to 4.2) | HR 0.45 (95% CI 0.37 to 0.55); p<0.0001 |
| **Any AES Grade ≥3** number of patients (percent)) | 362 (45) | 212 (53) | |

*Risk of Bias*: NCT00974311

| Entry/Domain | Judgement | Description |
|---|---|---|
| Random sequence generation? | Low risk | "Patients..were randomly assigned to a study treatment centrally by means of an interactive voice-response system" |
| Allocation concealment? | Low risk | "All patients, investigators, site personnel, and the sponsor's staff were masked to treatment assignment" |
| Blining of participants and personnel? | Low risk | See above |
| Blinding of outcome assessments? | Low risk | See above |
| Incomplete outcome data?<br><br>OS<br>PFS<br><br>HRQoL<br><br>SAE | <br><br>Low risk<br>Low risk<br><br>Low risk<br><br>Unclear risk | <br><br>Analysis on intention to treat population<br><br>Self reported, blinded design<br><br>Safety population not described |
| Selective reporting? | Low risk | Study protocol available, all outcomes were pre-specified and reported on. |
| Other sources of bias? | Low risk | The study was funded by Astellas Pharma and Medivation |
| Conclusion | Low risk of bias for all endpoints | |

**Study description**

*Studies:* Shore N. et al. TERRAIN trial: Prostate-Specific antigen kinetics and quality of life results of enzalutamide versus bicalutamide in metastatic castration-resistant prostate cancer. J Urol 2015;193 (4,Suppl.):e411, Abstract. PIL-LBA4.

Shore ND et al. Efficacy and safety of enzalutamide versus bicalutamide for patients with metastatic prostate cancer (TERRAIN): a randomised, double-blind , phase 2 study.

| |
|---|
| **NCT01288911** |
| *Design:* Randomized trial. North American and European study sites. No cross over between treatment groups. |
| **Population:** 375 patients with asymptomatic or minimally symptomatic mCRPC were randomized 1:1 to enzalutamide (160 mg/day) or bicalutamide (50 mg/day). At base line, median PSA was 21 ng/ml, 74% of patients had ECOG score of 0 and median FACT-P total score was 121. Patients with prior chemotherapy were excluded. |
| *Intervention/comparators:* 375, randomized 1:1 to 160 mg oral enzalutamide (n=184) or bicalutamide (50 mg) (n=191) per day. |
| **Endpoints**: Median time to PSA progression, patients achieving ≥50% and 90% PSA response, time to ≥50% and 90% PSA decrease from baseline, time to FACT-P total score detoriation, FACT-P total score, SAE |
| *Follow-up:* Unclear follow-up time |
| *Funding source:* Astellas Pharma and Medivation |

**Data extraction: NCT01288911**

| **Endpoints** | **Enzalutamide** (n=184) | **Bicalutamide** (n=191) | **HR, p-values** |
|---|---|---|---|
| **Total no of deaths** Median x months follow up | 9 | 3 | |
| **Median overall survival** (months) | No data | | |
| **PFS** (PSA progression) Median time until PSA progression (months) | 19.4 (95% CI 16.6 to not reached) | 5.8 (95% CI 5.6 to 8.3) | HR 0.28 (95% CI 0.20 to 0.39), p<0.0001 |
| **PFS** (median radiographic progression-free survival) (months) | Not reached (95% CI 25.6 to not reached) | 16.4 (95% CI 11.1 to 18.1) | HR 0.51 (95% CI 0.36 to 0.74), p<0.0002 |
| **PFS** (PSA progression)<br><br>Time to ≥50% PSA decrease from baseline (months)<br><br>Time to ≥90% PSA decrease from baseline | 2.8 (95% CI 2.8 to 2.8)<br><br>5.4 (3.0 to 5.7) | Median and 95% CI are not observed because a low number of patients achieved these events | HR 7.0 (95% CI 4.8, 10.2), p<0.0001<br><br>13.9 (7.2, 26.8) |

| | | | |
|---|---|---|---|
| | | | |
| **Time to HRQoL detoriation**<br>Time to FACT-P total score detoriation (defined as a 10-point decrease from base line (scale 0 to 156) (months) | 13.8 (11.1 to 22.0) | 8.5 (5.8 to 11.3) | 0.63 (95% CI 0.46 to 0.88) |
| **HRQoL total score**<br>patients with FACT-P total score response, % | 33.0 | 22.0 | |
| **Any SAE**<br>(percent) | 57 (31%) | 44 (23%) | |

**Comments:**

*Risk of Bias*: **NCT01288911**

| Entry/Domain | Judgement | Description |
|---|---|---|
| Random sequence generation? | Low risk | "Eligible patients were randomly assigned (1:1) vi an interactive voice response system" |
| Allocation concealment? | Low risk | "Participants, investigators and those assessing outcomes were masked to group assignement" |
| Blining of participants and personnel? | Low risk | See above |
| Blinding of outcome assessments? | Low risk | See above |
| Incomplete outcome data?<br>PFS<br><br>HRQoL<br><br>SAE | <br>Low risk<br><br>Low risk<br><br>Low risk | <br>Analysis on intention to treat population<br>Self reported<br><br>Analysed in all patients who received at least one dose of study drug |
| Selective reporting? | Low risk | Study protocol available, all outcomes were pre-specified and reported on |

| | | |
|---|---|---|
| Other sources of bias? | Low risk | The study was funded by Astellas Pharma and Medivation |
| Conclusion | Low risk of bias for all outcomes | |

**Study description**

| |
|---|
| *Study:*<br>Parker C, Nilsson S, Heinrich D, Helle SI, O'Sullivan JM, Fossa SD, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med 2013;369(3):213-223.<br>Hoskin P, Sartor O, O'Sullivan JM, Johannessen DC, Helle SI, Logue J, et al. Efficacy and safety of radium-223 dichloride in patients with castration-resistant prostate cancer and symptomatic bone metastases, with or without previous docetaxel use: a prespecified subgroup analysis from the randomised, double-blind, phase 3 ALSYMPCA trial. Lancet Oncol 2014;15(12):1397-1406.<br>**NCT00699751** |
| *Design:* Double-blind, randomized, multinational (136 centres in 19 countries) study. Analyses performed before crossover between treatment groups. |
| **Population:** 921 patients with histologically confirmed, progressive castration-resistant prostate cancer with two or more bone metastases detected on skeletal scintigraphy and no known visceral metastases, receiving best standard of care, and had received docetaxel, were not healthy enough or declined to receive it, or it was not available. ECOG performance status grade of 0-2. Median age 71 (radium-223) and 71 (placebo). |
| *Intervention/comparators:* 921, randomly assigned to receive six intravenous injections of radium-223 (n=614) (50 kBq per kilogram of body weight) or placebo (n=307) every 4 weeks. |
| **Endpoints:** Overall survival, defined as the time from randomization to death. QoL (FACT-P) and Safety (adverse events) |
| *Follow-up:* Prespecified interim analysis of overall survival was conducted when 314 deaths had occurred (approximetely 50% of the deaths). An updated analysis was performed when 528 deaths had occurred, before any crossover treatment with radium-223 was administered. |
| *Funding source:* Algeta and Bayer healthCare Pharmaceuticals |

**Data extraction from: NCT 00699751**

| **Endpoints** | **Radium-223** (n=614) | **Placebo** (n=307) | **HR, p-values** |
|---|---|---|---|
| **Total no of deaths** After updated analysis | 333 (54%) | 195 (64%) | |
| **Median overall survival** (months) | | | |
| First interim analysis | 14.0 | 11.2 | HR 0.70 (95% CI 0.55 to 0.88), p=0.002 |
| Updated analysis | 14.9 | 11.3 | |

| | | | |
|---|---|---|---|
| | | | HR 0.70 (95% CI 0.58 to 0.83), p<0.001 |
| **PFS** (PSA progression) Median time until increase in PSA level (months) | 3.6 | 3.4 | HR 0.64 (95% CI 0.54 to 0.77) |
| ~~**PFS** (radiographic progression)~~ | | | |
| ~~**Rates of PFS** (radiographic PFS) at month 12~~ | | | |
| **HRQoL changes from baseline**, FACT-P **(**mean change from baseline at week 16**)** | -2.7 | -6.8 | p=0.006 |
| **Time to HRQoL detoriation**, EQ-5D<br><br>**HRQoL changes from baseline**, EQ-5D | | | |
| **GRADE 3 or 4 AE** number of patients (percent) | 339 (56%) | 188 (62%) | |

*Risk of Bias*: **NCT00699751**

| Entry/Domain | Judgement | Description |
|---|---|---|
| Random sequence generation? | Low risk | " The randomisation was done with an interactive voice response system, taking into account trial stratification factors" |
| Allocation concealment? | Low risk | "The system assigned patients a randomisation number and a treatment. The randomisation number was provided to the site investigators, but the assigned treatment was not" |

| | | |
|---|---|---|
| Blining of participants and personnel? | Low risk | "Because radium-223 is radioactive, an individual not masked to treatment at each centre calculated study drug treatment and filled the syringe for masked distribution. All others (including patients, investigators, and study funders) were masked to the allocated treatment group" |
| Blinding of outcome assessments? | Low risk | "The blinded database was held by a third-party contract clinical research organization that provided data to the independent data and safety monitoring committee, assembled by sponsors. After the independent data and safety monitoring committee recommended unblinding of the data, analyses were performed as defined…" |
| Incomplete outcome data?<br><br>OS<br>PFS<br><br>HRQoL<br><br>SAE | <br><br>Low risk<br>Low risk<br><br>Low risk<br><br>Low risk | <br><br>Efficacy data were analysed for inent-to-treat population<br><br>Self reported<br><br>Safety analysis included all patients who received at least one injection of study drug |
| Selective reporting? | Low risk | Study protocol available. Pre-specified outcomes are reported on. |
| Other sources of bias? | Low risk | The study was funded by Algeta ASA and Bayer HealthCare Pharmaceuticals |
| Conclusion | Low risk of bias for all endpoints | |

**Study description**

| |
|---|
| *Studies:*<br>Nilsson S, Franzen L, Parker C, Tyrrell C, Blom R, Tennvall J, et al. Bone-targeted radium-223 in symptomatic, hormone-refractory prostate cancer: a randomised, multicentre, placebo-controlled phase II study. Lancet Oncol 2007;8(7):587-594. |
| *Design:* Double-blind, randomised study conducted in 11 centres in Sweden, Norway and the UK. No cross over between treatment groups. |
| **Population:** 64 patients with histologically or cytologically confirmed adenocarcinoma of the prostate; multiple bone metastases or one painful lesion with two consecutive rising amounts of serum PSA.. ECOG performance status score 0-2. All patients had either bilateral otchidectomy or |

| |
|---|
| continued treatment on a LHRH agonist. No chemotherapy, immunotherapy or external beam radiotherapy within the past 6 weeks. Median age 73 (radium-223) and 72 (placebo). |
| *Intervention/comparators:* 64 patients randomized to four repeated monthly injections of 50 kBq/kg $^{223}$Ra (n=33) or repeated injections of saline (n=31) |
| **Endpoints:** Overall survival, PSA progression (defined as an increase of 25% from nadir in patients without confirmed PSA response and 50% in those with a confirmed PSA response, bone-specific ALP concentration, time to occurrence of skeletal-related events, safety (adverse events) |
| |
| *Follow-up:* Patients were followed for survival and long-term toxic effects at 18 and 24 months. |
| *Funding source:* Algeta ASA |

**Data extraction from Nilsson 2007**

| **Endpoints** | **Radium-223** (n=33) | **Placebo** (n=31) | **HR, p-values** |
|---|---|---|---|
| **Total no of deaths** | | | |
| Median overall survival (weeks) | 65.3 (95% CI 48.7 to ∞) | 46.4 (95% CI 32.1 to 77.4) | P=0.066, log rank<br>HR for survival adjusted for baseline covariates was 2.12 (95% CI 1.13 to 3.98, p=0.020, Cox regression). Placebo vs Radium-223 (placebo used as intervention in analysis).<br><br>Radium-223 vs placebo: HR 0.47 (95% CI 0.25 to 0.89) |
| **Overall survival at** 18 months | 15 patients survived at 18 months | 8 patients survied at 18 months | |
| **Median time to PFS** (PSA progression) (weeks) | 26 | 8 | P=0.040, log rank |
| | | | |
| **Any SAE** (number of patients) | 8<br>12 SAE in 8 patients | 14<br>19 SAE in 14 patients | |

## Appendix 5 Tables of results from network meta analyses

**Note:** First column denotes intervention and first row denotes comparator. When reading from left to right, a ration of less than 1 indicates a favour towards intervention, and a ratio of greater than 1 indicates a favour towards comparator.

*Table 5.1 Overall survival from network meta-analyses (HR (95% CI))*

| | Placebo / prednisone | Enzalutamide | Radium-223 | Abiraterone | Cabazitaxel |
|---|---|---|---|---|---|
| Placebo / prednisone | 1 | | | | |
| Enzalutamide | 0.73 (0.45-1.75) | 1 | | | |
| Radium-223 | 0.65 (0.26-1.36) | 0.89 (0.24-2.03) | 1 | | |
| Abiraterone | 0.77 (0.39-1.67) | 1.07 (0.33-2.51) | 1.19 (0.44-4.24) | 1 | |
| Cabazitaxel | 0.70 (0.24-1.98) | 0.97 (0.22-2.83) | 1.08 (0.31-4.41) | 0.91 (0.23-3.06) | 1 |

*Table 5.2 Progression free survival from network meta-analyses (HR (95% CI))*

| | Placebo / prednisone | Enzalutamide | Radium-223 | Abiraterone | Cabazitaxel |
|---|---|---|---|---|---|
| Placebo / prednisone | 1 | | | | |
| Enzalutamide | 0.22 (0.10-0.52) | 1 | | | |
| Radium-223 | 0.65 (0.22-4.47) | 2.95 (0.79-36.32) | 1 | | |
| Abiraterone | 0.56 (0.24-1.63) | 2.54 (0.82-8.29) | 0.86 (0.14-3.83) | 1 | |
| Cabazitaxel | 0.74 (0.17-2.34) | 3.38 (0.69-12.04) | 1.14 (0.03-4.99) | 1.32 (0.20-6.18) | 1 |

*Table 5.3 Serious adverse events from network meta-analyses (RR (95% CI))*

| | Placebo / prednisone | Enzalutamide | Radium-223 | Abiraterone |
|---|---|---|---|---|
| Placebo / prednisone | 1 | | | |
| Enzalutamide | 1.08 (0.55-2.22) | 1 | | |
| Radium-223 | 0.77 (0.28-1.71) | 0.71 (0.20-1.99) | 1 | |
| Abiraterone | 1.22 (0.36-4.09) | 1.13 (0.27-4.50) | 1.57 (0.39-7.91) | 1 |

*Table 5.4 Health related quality of life (free from HRQoL detrioioration) from network meta-analyses (MD (95% CI))*

| | Placebo / prednisone | Enzalutamide | Abiraterone |
|---|---|---|---|
| Placebo / prednisone | 1 | | |
| Enzalutamide | 0.56 (0.11-1.24) | 1 | |

| | | | |
|---|---|---|---|
| Abiraterone | 0.69 (0.09-1.47) | 1.24 (0.22-3.48) | 1 |

*Table 5.5 Health related quality of life (FACT-P total score) from network meta-analyses (MD (95% CI))*

| | Placebo / predni-sone | Enzalutamide | Radium-223 |
|---|---|---|---|
| Placebo / prednisone | 1 | | |
| Enzalutamide | 5.78 (-0.94,12.51) | 1 | |
| Radium-223 | 4.09 (-2.67,10.91) | -1.71 (-11.17,7.86) | 1 |

# Appendix 6 Summary of Findings tables for the direct evidence from the network meta-analyses

**Interventions compared to placebo/"passive treatment" for metastatic prostate cancer**

**Patient or population**: metastatic castration resistant prostate cancer
**Intervention**: Abiraterone, cabazitaxel, enzalutamide or Radium-223
**Comparison**: Placebo or other "passive" treatment

| **Outcome** Overall survival | **Anticipated absolute effects*** (95% CI) | | Relative effect (95% CI) | № of participants (studies) | Quality of the evidence (GRADE) |
|---|---|---|---|---|---|
| | **Risk with Placebo/»passive treatment»** | **Risk with intervention** | | | |
| **Abiraterone** follow up: range 20 months to 49 months | | | **HR 0.77** (0.39 to 1.67) | (2 RCTs) [1] | ⨁⨁◯◯ Low [5] |
| **Cabazitaxel** follow up: median 13 months | | | **HR 0.70** (0.24 to 1.98) | (1 RCT) [2] | ⨁⨁◯◯ Low [5] |
| **Enzalutamide** follow up: range 14 months to 26 months | | | **HR 0.73** (0.45 to 1.75) | (2 RCTs)[3] | ⨁⨁◯◯ Low [5] |
| **Radium-223** | | | **HR 0.65** (0.26 to 1.36) | (2 RCTs) [4] | ⨁⨁◯◯ Low [5] |

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CrI:** Credibility interval; **HR:** Hazard Ratio; **RR:** Risk ratio

**GRADE Working Group grades of evidence**
**High quality:** We are very confident that the true effect lies close to that of the estimate of the effect
**Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
**Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
**Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1. COU-AA-301, COU-AA-302
2. TROPIC
3. AFFIRM and PREVAIL
4. ALSYMPCA, Nilsson 2007
5. The 95% CrI overlaps no effect, very wide CI

## Appendix 7. Choice of baseline survival data

For the docetaxel-naive model, we were able to use data that detailed time-to-event and censoring to determine which parametric distribution best characterized overall survival (OS) and radiographic progression-free survival (rPFS) for the model's control arm. Figure 7.1 shows OS for best supportive care (BSC) arm of the abiraterone trial (COU-AA-302) among docetaxel-naive patients. The yellow points represent survival based on the Kaplan-Meier plot data, with 57 months of follow-up. The colored curves show alternate choices for the parametric distribution that best characterizes the data. Sections of the curves beyond 57 months represent extrapolated data based on the relevant parametric distribution. The gamma distribution provided the best fist according to the Akaike information criterion (AIC). All of the distributions overestimated early survival, but the gamma distribution was least problematic in terms of a thick tail, which would lead to overestimation of future survival. We used the gamma distribution in our calculations of transition probabilities (see Appendix 8).

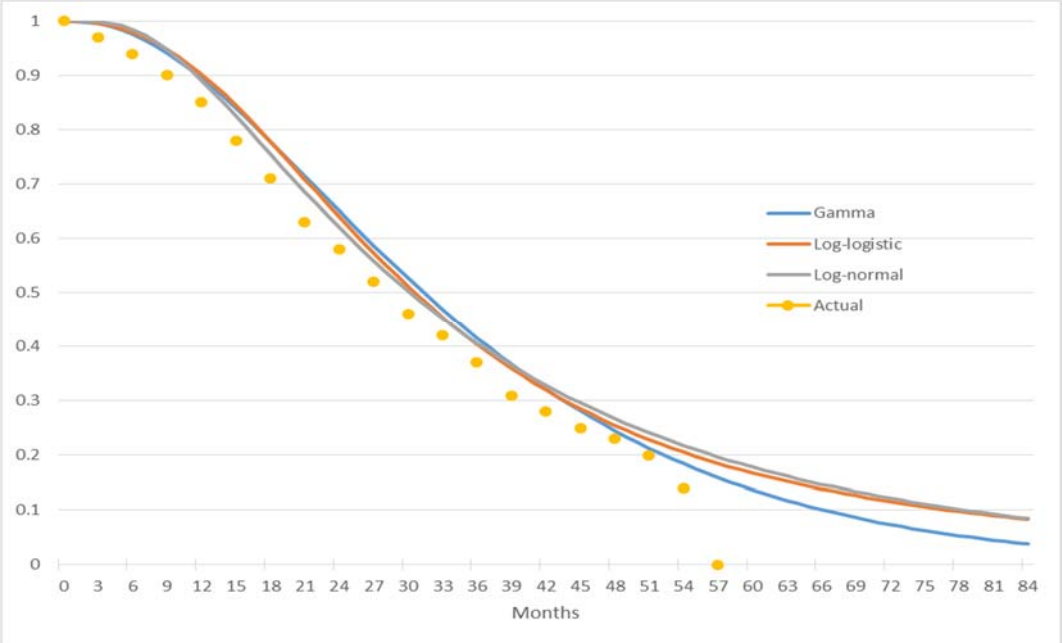


Figure 7.1. Kaplan-Meier data and parametric distributions for OS in BSC arm of COU-AA-302 study (abiraterone, docetaxel-naive)

Figure 7.2 shows PFS for the BSC arm of the abiraterone trial (COU-AA-302) among docetaxel-naive patients. The yellow points represent survival based on the Kaplan-Meier data, with 57 months of follow-up. The colored curves show alternate choices for the parametric distribution that best characterizes the data. Sections of the curves beyond 57 months represent extrapolated data based on the relevant parametric distribution. Although the generalized gamma actually had the best fit based

on AIC criteria, beyond 36 months we felt that it was influenced too much by the very small number of remaining non-progressed patients (18 of 542), and would therefore result in a large overestimation of progression-free survival in the extrapolation period. Therefore, we chose the log-normal distribution to use in our calculations of transition probabilities.

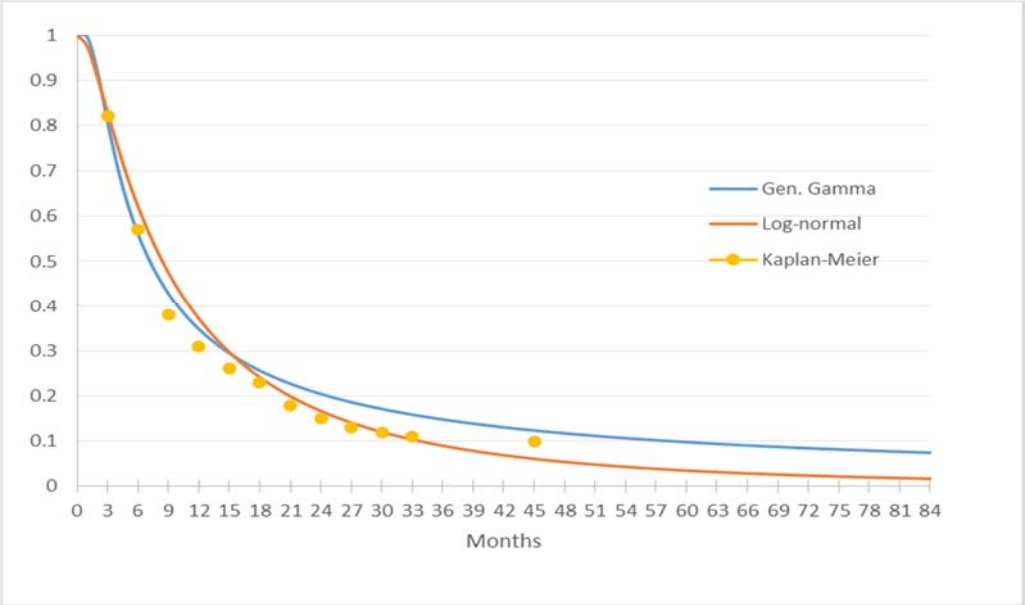


Figure 7.2. Kaplan-Meier data and parametric distributions for PFS in BSC arm of COU-AA-302 study (abiraterone, docetaxel-naive)

For the post-docetaxel model, we relied on data extracted from Kaplan-Meier plots for OS and PFS from the enzalutamide AFFIRM trial to fit exponential trend lines in Excel. The equations for the trend lines formed the basis for calculating transition probabilities. We constrained the trend lines to have a y-intercept equal to one. For progression-free survival, we had Kaplan-Meier plots for PSA progression and radiographic progression. Figures 7.3 shows the Kaplan-Meier points and the trend line for OS with extrapolation of OS to 5 years (blue dotted line).

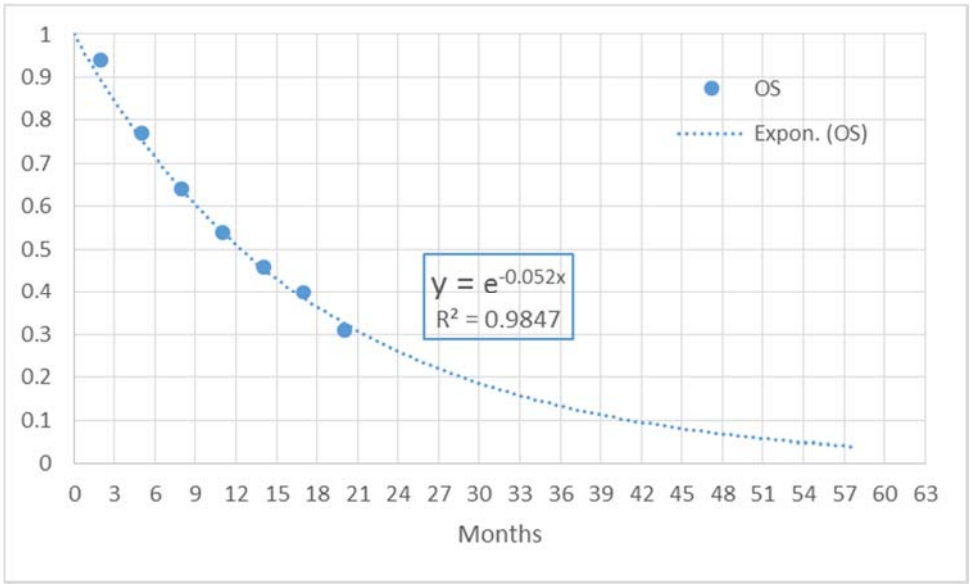


Figure 7.3. OS Kaplan-Meier points and trend line for BSC post-docetaxel

In Figure 7.4 we show Kaplan-Meier points and PFS data based on both radiographic (blue) and PSA (orange) definitions of progression. We show extrapolation only to 30 months since by then progression-free survival approaches zero along both curves. Given the better fit of the rPFS trend line to the underlying data ($R^2$ =0.9752 vs. $R^2$ = 0.7367 for the PSA trend line), we chose to use rPFS in the model. Doing so also made computations of transition probabilities for the post-docetaxel model more comparable to those of the docetaxel-naive model.

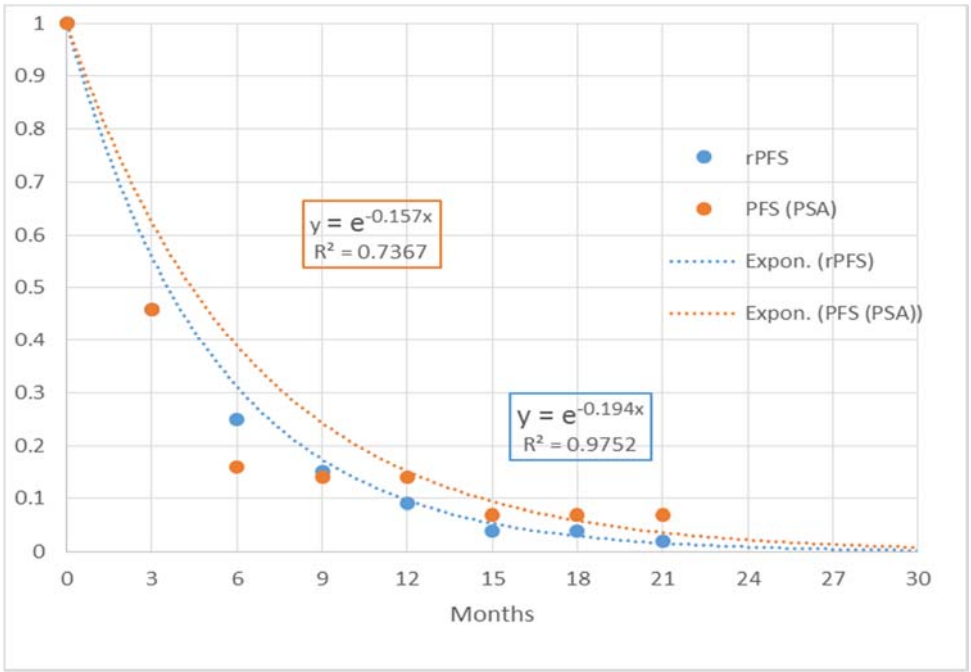


Figure 7.4. Kaplan-Meier points and trend lines for rPFS and PSA-PFS for BSC post-docetaxel

## Appendix 8 Estimation of the transition probabilities

The decision model we use corresponds to the generic case of a three-state illness to death model with no recovery, for instance illustrated by Jackson[1] and Welton[2] in the form of a transition probability matrix. The transition probability matrix has a solution for each transition probability, but its estimation requires individual-level event history data on transitions.

Lacking such detailed data, we estimated the transition probabilities from aggregate data, using the cumulative density functions for overall survival and progressive-free-survival as a starting point for approximating the transition probabilities.

Transition probabilities can be estimated using the formulas suggested in Briggs[3] pp.53 for a simple discrete-time Markov-model with two states, alive and dead, for the transition from alive to dead:

$$tp(t_u) = 1 - \frac{\mathrm{S(t)}}{\mathrm{S(t-u)}}\ ,where$$

$t_u$ denotes time measured in integers for the cycle-length u.
$tp(t_u)$ is the discrete transition probability between time-points t-u

S(t) is equivalent to the complement of the survivor function, which is one minus the cumulative density function, S(t)= 1- F(t), yielding:

$$tp(t_u) = 1 - \frac{1-\mathrm{F(t)}}{1-\mathrm{F(t-u)}}$$

The above formulae can be used to calculate the baseline transition from alive to dead in the model, both from progression free survival (PFS) and progressed disease (PD), if we assume the same mortality regardless of progression status. The formula is summarized below, where the subscript for F denotes the cumulative density function for overall survival (OS).

[1] Christopher H. Jackson (2011). Multi-State Models for Panel Data: The msm Package for R. Journal of Statistical Software, 38(8), 1-29. URL http://www.jstatsoft.org/v38/i08/.
[2] Welton et al. 2012. Evidence Synthesis for Decision Making in Healthcare. John Wiley & Sons. Chapter 10.
[3] Briggs 2006. Decision modelling for health economic evaluation. Oxford University Press. Page 53.

$$p(PFS/PD \rightarrow dead) = 1 - \frac{1 - \mathrm{F}_{OS}(\mathrm{t})}{1 - \mathrm{F}_{OS}(\mathrm{t} - \mathrm{u})}$$

The theoretically best approach to estimate the transition probability from PFS to PD (1 to 2) is one minus the probability of death minus the probability of staying in PFS. However, we could not estimate the transition probability this way because the OS and PFS functions sometimes return values such that the sum of the probabilities exceed one. This discrepancy with the basic properties of probabilities is related to the separate estimation of survival functions for two partially overlapping events, where the transitions from PFS to dead are included as events in both survival functions.

We instead calculated the transitions to death (PFS→death and PD →death) and to progressed disease (PFS→PD) in two steps, so that the probability of transition from PFS to PD is the conditional probability:

$$p(PFS \rightarrow PD|Survival) = \frac{p(\{PFS \rightarrow \mathrm{PD}\} \cap \{PFS \rightarrow \text{ not dead}\})}{\mathrm{p}(\{PFS/PD \rightarrow \text{ not dead}\})} = \frac{p(\{PFS \rightarrow \mathrm{PD}\})}{\mathrm{p}(\{PFS/PD \rightarrow \text{ not dead}\})}$$

$$= \frac{1 - p(PFS/PD \rightarrow \text{dead}) - p(PFS \rightarrow \mathrm{PFS})}{\mathrm{p}(\{PFS/PD \rightarrow \text{ not dead}\})}$$

$$= \frac{p(PFS/PD \rightarrow \text{not dead}) - p(PFS \rightarrow \mathrm{PFS})}{\mathrm{p}(\{PFS/PD \rightarrow \text{ not dead}\})}$$

$$= 1 - \frac{p(PFS \rightarrow \mathrm{PFS})}{\mathrm{p}(\{PFS/PD \rightarrow \text{ not dead}\})}$$

$$= 1 - \frac{\frac{\mathrm{S}_{PFS}(\mathrm{t})}{\mathrm{S}_{PFS}(\mathrm{t-u})}}{\frac{\mathrm{S}_{OS}(\mathrm{t})}{\mathrm{S}_{OS}(\mathrm{t-u})}} = 1 - \left(\frac{\mathrm{S}_{PFS}(\mathrm{t}) * \mathrm{S}_{OS}(\mathrm{t-u})}{\mathrm{S}_{PFS}(\mathrm{t-u}) * \mathrm{S}_{OS}(\mathrm{t})}\right)$$

The transition probability $p(PFS \rightarrow PD|Survival)$, is one minus the ratio of the probability of staying in the PFS state to the probability of not dying.

The probability of death calculated based on the available data (Kaplan-Meier curves) represents the overall probability of death from the states progression-free (PFS) and progressed (PD) combined. As mentioned above, by using this as the transition probability from PFS to Dead and from PD to Dead one assumes that the risk of dying is the same for PFS and PD. This assumption may not always hold.

If one assumes instead that the risk of dying from PD is (constantly) $X$ times as high as the risk of dying from PFS, then the total risk of dying (where the number of patients in the PFS state and PD state equal #PFS and #PD, respectively) can be written as:

$$P(death) = \frac{P(death \mid PFS) * \#PFS + X * P(death \mid PFS) * \#PD}{\#PFS + \#PD}$$

$$= \frac{P(death \mid PFS) * (\#PFS + X * \#PD)}{\#PFS + \#PD}$$

Consequently,

$$P(death|PFS) = \frac{P(death) * (\#PFS + \#PD)}{(\#PFS + X * \#PD)}$$

Calculations of the survivor function for the PFS and Survival directly provide the expected number of patients in the states PFS and dead for each time point. The number of patients in the state PD can be calculated as (#Total - #PFS - #Dead). Based on this it is possible to calculate

$$P(PFS\ to\ PD|survival)(t) = \frac{\#PD(t+1) - \#PD(t) * (1 - X * P(death|PFS)(t))}{\#PFS(t) * (1 - P(death|PFS)(t))}$$

For both the docetaxel-naive and post-docetaxel models, we assumed that X, the ratio of the risk of dying from PD to the risk of dying from PFS, was equal to 3. This provided numbers of patients in the PFS, PD and Dead states that were most consistent with information from the Kaplan-Meier plots for the relevant survival probabilities. We calculated transition probabilities (PFStoDead, PDtoDead and PFStoPD) for the longest possible time horizon for which the all probabilities remained positive: 7 years for the docetaxel-naive model and 5 years for the post-docetaxel model.

**Table 8.1 Transition probabilities used in models**

| | Docetaxel-naive model (7-year time horizon) | | | Post-docetaxel model (5-year time horizon) | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Best supportive care | | | Best supportive care | | | Radium-223 | | |
| Cycle | PFStoDead | PDtoDead | PFStoPD | PFStoDead | PDtoDead | PFStoPD | PFStoDead | PDtoDead | PFStoPD |
| 0 | 0.00033 | 0.00099 | 0.02458 | 0.05067 | 0.15201 | 0.00046 | 0.00046 | 0.01409 | 0.00455 |
| 1 | 0.00142 | 0.00425 | 0.06845 | 0.04006 | 0.12019 | 0.00619 | 0.00619 | 0.04302 | 0.01388 |
| 2 | 0.00255 | 0.00766 | 0.08399 | 0.03391 | 0.10172 | 0.14431 | 0.14431 | 0.07036 | 0.02270 |
| 3 | 0.00354 | 0.01063 | 0.08810 | 0.02992 | 0.08975 | 0.37494 | 0.37494 | 0.07445 | 0.02402 |
| 4 | 0.00440 | 0.01320 | 0.08787 | 0.02714 | 0.08143 | 0.50880 | 0.50880 | 0.06173 | 0.01991 |
| 5 | 0.00516 | 0.01549 | 0.08586 | 0.02513 | 0.07538 | 0.57444 | 0.57444 | 0.05644 | 0.01821 |
| 6 | 0.00585 | 0.01756 | 0.08311 | 0.02360 | 0.07081 | 0.60597 | 0.60597 | 0.05654 | 0.01824 |
| 7 | 0.00649 | 0.01946 | 0.08008 | 0.02242 | 0.06727 | 0.62032 | 0.62032 | 0.05882 | 0.01897 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 8 | 0.00707 | 0.02122 | 0.07700 | 0.02149 | 0.06447 | 0.62542 | 0.62542 | 0.06162 | 0.01988 |
| 9 | 0.00762 | 0.02286 | 0.07398 | 0.02074 | 0.06223 | 0.62524 | 0.62524 | 0.06422 | 0.02071 |
| 10 | 0.00814 | 0.02441 | 0.07106 | 0.02013 | 0.06040 | 0.62191 | 0.62191 | 0.06631 | 0.02139 |
| 11 | 0.00862 | 0.02586 | 0.06827 | 0.01964 | 0.05891 | 0.61667 | 0.61667 | 0.06783 | 0.02188 |
| 12 | 0.00908 | 0.02723 | 0.06563 | 0.01922 | 0.05767 | 0.61024 | 0.61024 | 0.06883 | 0.02220 |
| 13 | 0.00951 | 0.02853 | 0.06312 | 0.01888 | 0.05663 | 0.60308 | 0.60308 | 0.06935 | 0.02237 |
| 14 | 0.00992 | 0.02977 | 0.06075 | 0.01859 | 0.05576 | 0.59550 | 0.59550 | 0.06948 | 0.02241 |
| 15 | 0.01032 | 0.03095 | 0.05850 | 0.01834 | 0.05503 | 0.58770 | 0.58770 | 0.06929 | 0.02235 |
| 16 | 0.01069 | 0.03207 | 0.05637 | 0.01814 | 0.05441 | 0.57980 | 0.57980 | 0.06883 | 0.02220 |
| 17 | 0.01105 | 0.03314 | 0.05435 | 0.01796 | 0.05388 | 0.57190 | 0.57190 | 0.06816 | 0.02199 |
| 18 | 0.01139 | 0.03416 | 0.05244 | 0.01781 | 0.05344 | 0.56406 | 0.56406 | 0.06734 | 0.02172 |
| 19 | 0.01171 | 0.03514 | 0.05062 | 0.01768 | 0.05305 | 0.55632 | 0.55632 | 0.06639 | 0.02142 |
| 20 | 0.01202 | 0.03607 | 0.04889 | 0.01757 | 0.05272 | 0.54871 | 0.54871 | 0.06535 | 0.02108 |
| 21 | 0.01232 | 0.03697 | 0.04725 | 0.01748 | 0.05244 | 0.54125 | 0.54125 | 0.06424 | 0.02072 |
| 22 | 0.01261 | 0.03784 | 0.04568 | 0.01740 | 0.05220 | 0.53395 | 0.53395 | 0.06308 | 0.02035 |
| 23 | 0.01289 | 0.03867 | 0.04419 | 0.01733 | 0.05199 | 0.52681 | 0.52681 | 0.06190 | 0.01997 |
| 24 | 0.01316 | 0.03947 | 0.04276 | 0.01727 | 0.05181 | 0.51985 | 0.51985 | 0.06071 | 0.01958 |
| 25 | 0.01342 | 0.04025 | 0.04139 | 0.01722 | 0.05166 | 0.51306 | 0.51306 | 0.05951 | 0.01920 |
| 26 | 0.01366 | 0.04099 | 0.04008 | 0.01718 | 0.05153 | 0.50645 | 0.50645 | 0.05831 | 0.01881 |
| 27 | 0.01391 | 0.04172 | 0.03883 | 0.01714 | 0.05141 | 0.50000 | 0.50000 | 0.05713 | 0.01843 |
| 28 | 0.01414 | 0.04241 | 0.03762 | 0.01710 | 0.05131 | 0.49371 | 0.49371 | 0.05596 | 0.01805 |
| 29 | 0.01436 | 0.04309 | 0.03647 | 0.01708 | 0.05123 | 0.48759 | 0.48759 | 0.05482 | 0.01768 |
| 30 | 0.01458 | 0.04375 | 0.03535 | 0.01705 | 0.05115 | 0.48163 | 0.48163 | 0.05370 | 0.01732 |
| 31 | 0.01480 | 0.04439 | 0.03428 | 0.01703 | 0.05109 | 0.47582 | 0.47582 | 0.05260 | 0.01697 |
| 32 | 0.01500 | 0.04501 | 0.03325 | 0.01701 | 0.05103 | 0.47016 | 0.47016 | 0.05153 | 0.01662 |
| 33 | 0.01521 | 0.04562 | 0.03225 | 0.01699 | 0.05098 | 0.46465 | 0.46465 | 0.05049 | 0.01629 |
| 34 | 0.01540 | 0.04621 | 0.03129 | 0.01698 | 0.05094 | 0.45926 | 0.45926 | 0.04947 | 0.01596 |
| 35 | 0.01560 | 0.04679 | 0.03036 | 0.01697 | 0.05091 | 0.45407 | 0.45407 | 0.04849 | 0.01564 |
| 36 | 0.01578 | 0.04735 | 0.02947 | 0.01696 | 0.05088 | 0.44891 | 0.44891 | 0.04753 | 0.01533 |
| 37 | 0.01597 | 0.04791 | 0.02860 | 0.01695 | 0.05085 | 0.44388 | 0.44388 | 0.04660 | 0.01503 |
| 38 | 0.01615 | 0.04845 | 0.02775 | 0.01694 | 0.05082 | 0.43916 | 0.43916 | 0.04570 | 0.01474 |
| 39 | 0.01633 | 0.04898 | 0.02694 | 0.01693 | 0.05080 | 0.43417 | 0.43417 | 0.04482 | 0.01446 |
| 40 | 0.01650 | 0.04950 | 0.02614 | 0.01693 | 0.05079 | 0.42937 | 0.42937 | 0.04398 | 0.01419 |
| 41 | 0.01667 | 0.05002 | 0.02537 | 0.01692 | 0.05077 | 0.42658 | 0.42658 | 0.04315 | 0.01392 |
| 42 | 0.01684 | 0.05052 | 0.02462 | 0.01692 | 0.05076 | 0.41800 | 0.41800 | 0.04236 | 0.01366 |
| 43 | 0.01701 | 0.05102 | 0.02390 | 0.01692 | 0.05075 | 0.42050 | 0.42050 | 0.04158 | 0.01341 |
| 44 | 0.01717 | 0.05152 | 0.02319 | 0.01691 | 0.05074 | 0.41360 | 0.41360 | 0.04084 | 0.01317 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 45 | 0.01733 | 0.05200 | 0.02249 | 0.01691 | 0.05073 | 0.40121 | 0.40121 | 0.04011 | 0.01294 |
| 46 | 0.01750 | 0.05249 | 0.02182 | 0.01691 | 0.05072 | 0.40605 | 0.40605 | 0.03941 | 0.01271 |
| 47 | 0.01766 | 0.05297 | 0.02116 | 0.01690 | 0.05071 | 0.39519 | 0.39519 | 0.03872 | 0.01249 |
| 48 | 0.01782 | 0.05345 | 0.02052 | 0.01690 | 0.05071 | 0.42880 | 0.42880 | 0.03806 | 0.01228 |
| 49 | 0.01797 | 0.05392 | 0.01989 | 0.01690 | 0.05070 | 0.31067 | 0.31067 | 0.03742 | 0.01207 |
| 50 | 0.01813 | 0.05439 | 0.01927 | 0.01690 | 0.05070 | 0.39927 | 0.39927 | 0.03680 | 0.01187 |
| 51 | 0.01829 | 0.05486 | 0.01867 | 0.01690 | 0.05070 | 0.46517 | 0.46517 | 0.03619 | 0.01167 |
| 52 | 0.01845 | 0.05534 | 0.01808 | 0.01690 | 0.05069 | 0.52375 | 0.52375 | 0.03560 | 0.01149 |
| 53 | 0.01860 | 0.05581 | 0.01750 | 0.01690 | 0.05069 | 0.26363 | 0.26363 | 0.03503 | 0.01130 |
| 54 | 0.01876 | 0.05628 | 0.01693 | 0.01690 | 0.05069 | 0.26799 | 0.26799 | 0.03448 | 0.01112 |
| 55 | 0.01892 | 0.05675 | 0.01637 | 0.01689 | 0.05068 | 0.26007 | 0.26007 | 0.03394 | 0.01095 |
| 56 | 0.01908 | 0.05723 | 0.01582 | 0.01689 | 0.05068 | 0.69722 | 0.69722 | 0.03342 | 0.01078 |
| 57 | 0.01924 | 0.05771 | 0.01528 | 0.01689 | 0.05068 | 0.00000 | 0.00000 | 0.03291 | 0.01062 |
| 58 | 0.01940 | 0.05820 | 0.01475 | 0.01689 | 0.05068 | 0.00000 | 0.00000 | 0.03242 | 0.01046 |
| 59 | 0.01956 | 0.05869 | 0.01422 | 0.01689 | 0.05068 | 0.00000 | 0.00000 | 0.03194 | 0.01030 |
| 60 | 0.01973 | 0.05918 | 0.01370 | | | | | | |
| 61 | 0.01989 | 0.05968 | 0.01319 | | | | | | |
| 62 | 0.02006 | 0.06019 | 0.01268 | | | | | | |
| 63 | 0.02024 | 0.06071 | 0.01218 | | | | | | |
| 64 | 0.02041 | 0.06123 | 0.01168 | | | | | | |
| 65 | 0.02059 | 0.06177 | 0.01118 | | | | | | |
| 66 | 0.02077 | 0.06232 | 0.01069 | | | | | | |
| 67 | 0.02096 | 0.06288 | 0.01020 | | | | | | |
| 68 | 0.02115 | 0.06345 | 0.00971 | | | | | | |
| 69 | 0.02135 | 0.06404 | 0.00922 | | | | | | |
| 70 | 0.02155 | 0.06464 | 0.00874 | | | | | | |
| 71 | 0.02176 | 0.06527 | 0.00825 | | | | | | |
| 72 | 0.02197 | 0.06591 | 0.00776 | | | | | | |
| 73 | 0.02219 | 0.06657 | 0.00727 | | | | | | |
| 74 | 0.02242 | 0.06725 | 0.00678 | | | | | | |
| 75 | 0.02265 | 0.06796 | 0.00628 | | | | | | |
| 76 | 0.02290 | 0.06870 | 0.00578 | | | | | | |
| 77 | 0.02316 | 0.06947 | 0.00527 | | | | | | |
| 78 | 0.02342 | 0.07026 | 0.00476 | | | | | | |
| 79 | 0.02370 | 0.07110 | 0.00424 | | | | | | |
| 80 | 0.02399 | 0.07196 | 0.00371 | | | | | | |
| 81 | 0.02429 | 0.07287 | 0.00318 | | | | | | |

| | | | |
|---|---|---|---|
| 82 | 0.02461 | 0.07382 | 0.00263 |
| 83 | 0.02494 | 0.07482 | 0.00207 |

## Appendix 9. Costs

*Unit costs*

We used the unit costs detailed in Table 9.1 to calculate all costs used in the economic model. We retrieved information from several sources, as shown in the table. We used 2016 price data in the report.

Unit costs for outpatient patient treatment are based on tariffs (Normaltariffen – Fastleger 2015-2016). Tariffs are multiplied by 2, in accordance with Directorate of Health guidelines, to account for the fact that, on average, the tariff covers approximately 50% of the costs of the providers.

The 2016 value of a DRG point, used for hospital and ambulatory clinic costs, was NOK 42,081. For radiology services (X-ray, CT, MR, etc.), total cost is calculated by adding the copayment (Takst 202, NOK 227) and the reimbursement from the State, and dividing the result by 40%, in order to take into account that the grant finances 60% of the cost.

Patient copayment is included because we expected that the great majority of patients would pay the amount in user fees that entitle them to a health care exemption card (frikort) in the course of few months every calender year.

For other tests (EKG, PSA, Hematological analysis, etc.) reimbursement is calculated by dividing the reimbursement by 40% (as above). These tests are already covered by the patient copayment for the visit (201b, NOK 320).

**Table 9.1.a. Outpatient unit costs**

| Resource | Code | Renumeration (pub. reimbursement + copay) | Total cost (2 x renumeration) | Source |
|---|---|---|---|---|
| **GP visit** | 2ad+2cd+2dd | 412 | 824 | Normaltariffen - fastleger 2015-2016 |
| **GP home visit** | 11ak | 267 | 534 | |
| **EKG and interpretation** | 707 | 120 | 240 | |

**Table 9.1.b. Unit costs at hospital or ambulatory clinic**

| Resource | DRG /reimbursement category | DRG-weight / reimbursement | 100% refund | Source |
|---|---|---|---|---|
| **Oncologist/Urologist visit** | 912A | 0.05 | 2,104 | ISF re-gelverk 2016, IS-2417 |
| **External radiation therapy** | 850A+851N | 0.068 & (3*0.044) | 60,260 | |
| **In-patient treatment of AE caused by medical treament** | 453B | 0.502 | 21,125 | |
| **Palliative end-of-life care (day patient)** | 959W | 0.140 | 5,891 | |
| **Patient copayment - Visit with specialist** | 201b | 320 | | Forskrift om utgifter til polikli-nisk helse-hjelp, siste endret 2016-02.05-101 |
| **Patient copayment - Radiology** | 202 | 227 | | |
| **CT-scan** | CT3 | 501 | 1,820 | |
| **MRI** | MR3 | 1030 | 3,143 | |
| **Bone scintigraphy** | NM2 | 521 | 1,870 | |
| **Chest x-ray** | RG2 | 52 | 698 | |
| **PSA** | 707c | 27 | 67.5 | |
| **Hematological anal-ysis** | 707b | 12 | 30 | |
| **Lipid test (Total cho-lesterol)** | 707a | 4 | 10 | |
| **Liver function test (Analysis of ALAT & GT)** | 707a | 4 | 10 | |
| **Kidney function test (Analysis of kreatin** | 707a | 4 | 10 | |
| **EKG and interpreta-tion** | 707 | 120 | 240 | |

**Table 9.1.c. Unit costs for municipality or private services**

| Service | Price (NOK) | Source |
|---|---|---|
| **Home visit, nurse** | 730 per hour | Finance department, Oslo municipality |
| **Nursing home stay** | 2,500 per day | Finance department, Oslo municipality |

| | | |
|---|---|---|
| **Hospice stay** | 8,000 per day | Hospice Lovisenberg |

*Drug administration costs*

Cabazitaxel and radium-223 are administered by intravenously at a hospital. Docetaxel can be given as a subsequent treatment for docetaxel-naive patients who progress on or after first-line treatment with abiraterone or enzalutamide. Table 9.2 details the cost of administering these drugs. Financial advisors in the cancer section at OUS provided the information for cabazitaxel and docetaxel.

**Table 9.2. Administration costs (NOK) for cabazitaxel, radium-223 and docetaxel**

| Resource | Cabazitaxel | Docetaxel | Radium-223 |
|---|---|---|---|
| **Infusion specialist *** | 896.25 | 896.25 | Administration costs for radium-223 are taken from an SLV report from 2014. They did not provide a detailed accounting of costs |
| **Infusion preparation** | 533 | 533 | |
| **Materials, including pre-treatment drugs** | 136 | 139 | |
| **Total** | **1565.25** | **1569.25** | **400** |

***** Average hourly cost for an infusion specialist at OUS is NOK 597.5 (=wage rate NOK 239 divided by 0.4 to capture the portion of costs not reimbursed by the State). Total infusion time is 1.5 hours.

*Monitoring costs*

We based monitoring frequencies on information included in a report by the Norwegian Medicines Agency (SLV, 2012) and confirmed by our experts. Monitoring costs during treatment (pre-progression) were assumed similar across treatments with two exceptions: abiraterone requires special monitoring during the first three months of treatment; cabazitaxel monitoring occurs at three-week intervals to coincide with treatments, which results in additional specialist visits. Monitoring after disease progression is the same across all treatment groups. Table 9.3 summarizes calculations of monthly cost and provides the monthly frequency multiplied by share of patients monitored. Frequencies for abiraterone during the first three treatment months are for the three-month period. Total costs in tables 3 b, c, and d include costs of infrequent tests (lipid, liver function, kidney function), which are not listed individually.

**Table 9.3. Monthly monitoring costs in NOK**

**9.3.a. Monthly monitoring costs for abiraterone, first three treatment months**

| Resource | 3-month frequency *x* share of patients | Unit cost | Monthly cost |
|---|---|---|---|
| **Clinic specialist visit (Oncologist/urologist)** | 6 | 2,904 | 5,808 |
| **CT-scan** | 0.5 | 1,820 | 303 |
| **MRI** | 1 | 3,143 | 1,048 |
| **Bone scintigraphy** | 1 * 75% | 1,870 | 468 |
| **Chest x-ray** | 1 * 50% | 698 | 116 |
| **EKG scan/interpretation** | One at start, 50% | 240 | 40 |
| **Hematolgical analysis** | 6 | 30 | 60 |
| **PSA test** | 1 | 68 | 23 |
| **Lipid test (Total cholesterol)** | 1 | 10 | 3 |
| **Liver function test (ALAT & GT analysis)** | 6 | 10 | 20 |
| **Kidney function test (kreatin analysis)** | 3 | 10 | 10 |
| *Total monthly cost during first 3 months* | | | **7899** |

### 9.3.b. Monthly monitoring costs during treatment. BSC, enzalutamide, radium-223, and abiraterone (after first 3 months of treatment)

| Resource | Monthly frequency *x* share of patients | Unit cost | Monthly cost |
|---|---|---|---|
| **Clinic specialist visit (oncologist/urologist)** | 1 | 2,904 | 2,904 |
| **GP visit** | 0.42 | 824 | 343 |
| **CT-scan** | 0.167 * 50% | 1,820 | 152 |
| **MRI** | 0.083 | 3,143 | 262 |
| **Bone scintigraphy** | 0.083 | 1,870 | 156 |
| **Chest x-ray** | 0.083 * 50% | 1,870 | 78 |
| **Hematological analysis** | 1 | 30 | 30 |
| **PSA test** | 0.5 | 68 | 34 |
| *Total monthly cost* | | | **3,958** |

### 9.3.c. Monthly monitoring costs during treatment. Cabazitaxel

| Resource | Monthly frequency *x* share of patients | Unit cost | Monthly cost |
|---|---|---|---|
| **Clinic specialist visit (oncologist/urologist)** | 1.42 | 2,904 | 4,114 |
| **GP visit** | 0.83 | 824 | 714 |
| **CT-scan** | 0.167 * 50% | 1,820 | 152 |
| **MRI** | 0.083 | 3,143 | 262 |
| **Bone scintigraphy** | 0.083 | 1,870 | 156 |
| **Chest x-ray** | 0.083 * 50% | 1,870 | 78 |
| **Hematological analysis** | 1.42 | 30 | 43 |
| **PSA test** | 0. 72 | 68 | 49 |
| *Total monthly cost* | | | **5,698** |

### 9.3.d. Monthly monitoring costs after progression. All treatments

| Resource | Monthly frequency *x* share of patients | Unit cost | Monthly cost |
|---|---|---|---|
| **Clinic specialist visit (oncologist/urologist)** | 1 | 2,904 | 2,904 |
| **GP visit** | 0.83 | 824 | 714 |
| **CT-scan** | 0.083 | 1,820 | 152 |
| **MRI** | 0.125 | 3,143 | 262 |
| **Bone scintigraphy** | 0.083 | 1,870 | 156 |
| **Chest x-ray** | 0.083 * 50% | 1,870 | 78 |
| **PSA test** | 0.5 | 68 | 34 |
| *Total monthly cost* | | | **4,389** |

*Serious adverse events*

Table 9.4 provides calculations of monthly costs of serious adverse events (SAEs) for each treatment arm. We used event frequency data and length of follow-up reported on ClinicalTrials.gov to calculate the one-month probability of experiencing an SAE based on the standard formula for converting annual to monthly probabilities. Monthly cost is then the monthly rate of SAE multiplied by the unit treatment cost. In order to avoid a downward bias in the monthly rates, we relied on interim rather than final data if the frequency of SAEs during the interim period was much higher

than during the addition follow-up time. SAE rates for the BSC arm reflect the weighted averages of control arms of the included studies, with the exception of the cabazitaxel study, for which mitoxantrone, an active treatment without life-extending effects, was the considered comparable to a placebo for survival related effects. The unit cost for treating a serious adverse event is NOK 21,125. (Appendix 9, Table 9.1)

### Table 9.4. Serious adverse events, cost per one-month cycle

#### 9.4.a. Monthly cost of serious adverse events, post-docetaxel model

| Treatment | % Patients with SAE | Follow-up (months) | Monthly rate | Monthly cost |
|---|---|---|---|---|
| **BSC** | 46.6% | (see individual studies) | 0.0434 | 908 |
| **Abirateron** | 46.1% | 20.2 | 0.0301 | 636 |
| **Enzalutamide** | 45.3% | 14.4 | 0.0409 | 866 |
| **Radium-223** | 51.9% | 11.4 | 0.0621 | 1,312 |
| **Cabazitaxel** | 39.1% | 12.8 | 0.0379 | 803 |

#### 9.4.b. Monthly cost of serious adverse events, docetaxel-naive model

| Treatment | % Patients with SAE | Follow-up (months) | Monthly rate | Monthly cost |
|---|---|---|---|---|
| **BSC** | 27.0% | (see individual studies) | 0.0142 | |
| **Abiraterone** | 32.8% | 22.2 | 0.0178 | 376 |
| **Enzalutamide** | 42.9% | 22.0 | 0.0252 | 532 |

*Radiotherapy*

We calculated total monthly costs of radiotherapy by taking the product of the unit cost of radiotherapy (NOK 60,260), the share of patients who receive treatment and the average number of treatment courses per year, and then dividing by 12. According to experts, patients treated with radium-223 have less frequent radiotherapy than others.

### Table 9.5. Monthly cost of radiotherapy

| Health state | Treatment | Frequency and % patients | Unit cost | Monthly cost |
|---|---|---|---|---|
| **Pre-progression** | BSC<br>Abiraterone<br>Enzalutamide | 50% of patients, 3 courses per year | 60,260 | **7532** |

| | | | | |
|---|---|---|---|---|
| | Cabazitaxel | | | |
| | Radium-223 | 30% of patients,<br>2 courses per year | 60,260 | **3013** |
| **Post-progression** | BSC<br>Abiraterone<br>Enzalutamide<br>Cabazitaxel | 30% of patients,<br>3 courses per year | 60,260 | **4519** |
| | Radium-223 | 20% of patients<br>1.5 course per year | 60,260 | **1506** |

*Additional treatment after progression (docetaxel-naive patients only)*

Based on expert advice, we assumed that approximately 80% of docetaxel-naive patients in Norway receive a second active treatment after progression on the first-line treatment with either abiraterone or enzalutamide. The extra cost associated with each second-line medication is the product of its monthly price, average treatment duration (as a second-line treatment) and the medication's share among those receiving an additional treatment. We calculated the expected total cost of extra treatment following first-line treatment by summing these costs and multiplying by the share of patients who receive additional treatment. We assumed fixed values for shares and duration, and introduced uncertainty around the estimated percent of patients receiving an additional treatment as a gamma distribution in the model. The maximum pharmacy retail price (AUP) of docetaxel, based on the recommended dosage is NOK 15,078. We did not use this price in our calculations below because there was no easily feasible way to adjust for the fact that the actual negotiated price is lower, and we did not want an artificially high price for docetaxel to influence our results.

**Table 9.6. Cost of additional active treatment (docetaxel-naive model)**

| | **Following first-line abiraterone** | | | **Following first-line enzalutamide** | | |
|---|---|---|---|---|---|---|
| *Additional treatment* | *Share* [a] | *Duration (months)* | *Cost* | *Treatment distribution* | *Duration (months)* | *Cost* |
| Docetaxel | 70% | 6.6 | (confidential) | 70% | 6.6 | (confidential) |
| Abiraterone | NA | NA | NA | 20% | 8.3 | 55,033 |
| Enzalutamide | 20% | 8 | 59,536 | NA | NA | NA |
| Radium-223 | 10% | 6 | 27,246 | 10% | 6 | 27,246 |
| **Total cost** [b] | | | **90,583** | | | **86,981** |

[a] Share is the percent of patients with additional treatment who receive the indicate drug.

[b] Total cost assumes that only 80% of patients receive a second-line treatment.

*End-of-life costs*

Table 9.7 reports costs end-of-life costs, those occurring within the last three months of life, based on resource use described by experts. We included end-of-life costs in the model as a one-time transition cost that occurs at transition to death. Although a DRG-weight exists for inpatient hospice treatment at a hospital or palliative center, we received information from the Norwegian Directorate of Health that it does not reflect actual costs of hospice care. Instead, we contacted Hospice Lovisenberg (Oslo), a private provider and the Center for Palliative Care at Helse Bergen and received similar estimates of approximately NOK 8,000 per day. We included uncertainty in the estimates using beta distributions for probabilities of using resources, gamma distributions for costs, and normal distributions for number of days.

**Table 9.7. End-of-life costs**

| Resource | % Patients and resource use | Total usage | Unit cost (NOK) | Total cost (NOK) (3-month period) |
|---|---|---|---|---|
| **Home visit (nurse)** | 40%, 20 hours | 8 hours | 730 | 5,840 |
| **Home visit (doctor)** | 30%, 5 hours | 1.5 hours | 534 | 801 |
| **Nursing home stay** | 50%, 5 weeks | 17.5 days | 2,500 | 39,375 |
| **Hospice care (inpatient)** | 80%, 1-2 weeks | 8.8 days | 8,000 | 70,400 |
| **Palliative care (outpatient)** | 30%, 2 days | 0.6 days | 5,891 | 2,946 |
| **Total for 3 months** | | | | **119,362** |

## Appendix 10. Distributions in the model

Tables 10.1 and 10.2 provide the information used to characterize uncertainy around parameters in the post-docetaxel and docetaxel-naive model.

## Table 10.1. Distributions in the post-docetaxel model

| Type | Name | Param 1 | Param 2 |
|---|---|---|---|
| Beta | dist_monthly_prob_AE_abir | ((((((0.0301))))^2)*(1-((((0.0301))))))/(((0.0301/(2*1.96))^2)-((((0.0301)))))) | ((1-((((0.0301)))))*(((1-((((0.0301)))))*((((0.030 |
| Beta | dist_monthly_prob_AE_BSC | (((0.043)^2)*(1-(0.043))/((((0.043*.1)/(2*1.96))^2)-(0.043)) | ((1-(0.043))*(((1-(0.043 |
| Beta | dist_monthly_prob_AE_caba | ((((0.038))^2)*(1-((0.038)))/((((0.038*1)/(2*1.96))^2)-((0.038))) | ((1-((0.038)))*(((1-((0.0 |
| Beta | dist_monthly_prob_AE_enza | ((((((0.0410))))^2)*(1-((((0.0410)))))/((((0.0410*0.1)/(1.96*2))^2)-((((0.0410)))))) | ((1-((((0.0410)))))*(((1-((((0.0410)))))*((((0.041 |
| Beta | dist_monthly_prob_AE_radium223 | ((((0.0621))^2)*(1-((0.0621)))/(((0.0621*0.1)/(2*1.96))^2)-((0.0621))) | ((1-((0.0621)))*(((1-((0.0621)))*((0.0621)))/ |
| Beta | dist_prob_GP_visit | ((((.3))^2)*(1-((.3)))/(((.2*.3)/(2*1.96))^2)-((.3))) | ((1-((.3)))*(((1-((.3)))*(( |
| Beta | dist_prob_Hospice_stay | ((((.8))^2)*(1-((.8)))/(((.1/(2*1.96)))^2)-((.8))) | ((1-((.8)))*(((1-((.8)))*(( |
| Beta | dist_prob_nurse_visit | ((((.4))^2)*(1-((.4)))/(((.20*.4)/(2*1.96))^2)-((.4))) | ((1-((.4)))*(((1-((.4)))*(( |
| Beta | dist_prob_nursing_home_stay | (((.5)^2)*(1-(.5))/((.2/(2*1.96))^2)-(.5)) | ((1-(.5))*(((1-(.5))*(.5))/ |
| Beta | dist_prob_Palliative_daycare | (((.25)^2)*(1-(.25))/((.1/(2*1.96))^2)-(.25)) | ((1-(.25))*(((1-(.25))*(.2 |
| Beta | dist_QALY_decrement_BSC | ((((0.07))^2)*(1-((0.07)))/(((0.02))^2)-((0.07))) | ((1-((0.07)))*(((1-((0.07 |
| Beta | dist_QALY_decrement_enza* | ((((0.088))^2)*(1-((0.088)))/((((0.0177))^2)-((0.088))) | ((1-((0.088)))*(((1-((0.0 |
| Beta | dist_uPFS_BSC | (((0.6)^2)*(1-(0.6))/((.03)^2)-(0.6)) | ((1-(0.6))*(((1-(0.6))*(0. |
| Beta | dist_uPFS_enza* | ((((0.688))^2)*(1-((0.688)))/((((0.0184))^2)-((0.688))) | ((1-((0.688)))*(((1-((0.6 |
| Gamma | dist_admin_cost_caba | (((1565))^2)/(((1565/(2*1.96)))^2) | ((1565))/(((1565/(2*1.9 |
| Gamma | dist_admin_cost_radium223 | ((400)^2)/((400/2)^2) | (400)/((400/2)^2) |
| Gamma | dist_cost_AE_treatment | (((21125))^2)/(((21125/2))^2) | ((21125))/(((21125/2))^ |
| Gamma | dist_cost_monitor_PFS | ((3158)^2)/((3158/2)^2) | (3158)/((3158/2)^2) |
| Gamma | dist_cost_monitor_PFS_abir_3_months | ((6299)^2)/((6299/2)^2) | (6299)/((6299/2)^2) |
| Gamma | dist_cost_monitor_PFS_caba | ((4564)^2)/((4564/2)^2) | (4564)/((4564/2)^2) |
| Gamma | dist_cost_monitor_Progressed | ((4389)^2)/((4389/2)^2) | (4389)/((4389/2)^2) |
| Gamma | dist_cost_nurse_hourly | (((730))^2)/(((.25*730)/(2*1.96))^2) | ((730))/(((.25*730)/(2*1 |
| Gamma | dist_cost_Radiotherapy_PD | ((4519)^2)/((4519/2)^2) | (4519)/((4519/2)^2) |
| Gamma | dist_cost_Radiotherapy_PFS | ((7532)^2)/((7532/2)^2) | (7532)/((7532/2)^2) |
| Gamma | dist_cost_Radiotherapy_Radium_PD | ((1506)^2)/((1506/2)^2) | (1506)/((1506/2)^2) |
| Gamma | dist_cost_Radiotherapy_radium_PFS | ((3013)^2)/((3013/2)^2) | (3013)/((3013/2)^2) |
| Gamma | dist_daily_cost_Hospice_stay | ((8000)^2)/((2000/(2*1.96))^2) | (8000)/((2000/(2*1.96) |
| Gamma | dist_daily_cost_Nursing_home | ((2250)^2)/((500/(2*1.96))^2) | (2250)/((500/(2*1.96))^ |
| LogNormal | dist_HR_OS_Abir_vs_BSC | ln(0.74) | (ln(0.86)-ln(0.64))/(2*1. |
| LogNormal | dist_HR_OS_Caba_vs_BSC | ln(0.70) | (ln(0.83)-ln(0.59))/(2*1. |
| LogNormal | dist_HR_OS_Enza_vs_BSC | ln(0.63) | (ln(0.75)-ln(0.53))/(2*1. |
| LogNormal | dist_HR_PFS_Abir_vs_BSC | ln(0.66) | (ln(0.76)-ln(0.58))/(2*1. |
| LogNormal | dist_HR_PFS_Caba_vs_BSC | ln(0.75) | (ln(0.90)-ln(0.63))/(2*1. |
| LogNormal | dist_HR_PFS_Enza_vs_BSC | ln(0.40) | (ln(0.47)-ln(0.35))/(2*1. |
| Normal | dist_number_days_Hospice_stay | 11 | 7/(2*1.96) |

* QALY values used for both enzalutamide and abiraterone

## Table 10.2. Distributions in the docetaxel-naive model

| Type | Name | Param 1 | Param 2 |
|---|---|---|---|
| Beta | dist_monthly_prob_AE_abir | ((((((0.0178)))))^2)*(1-((((0.0178)))))/(((((0.0178*0.1)))/(2*1.96))^2)-((((0.0178)))) | ((1-((((0.0178)))))*(((1-((((0.0178)))))*((((0.0178)))))/(((((0.0178*0.1)))/(2*1.96))^2)-1)) |

| | | | |
|---|---|---|---|
| Beta | dist_monthly_prob_AE_BSC | ((((0.0142))^2)*(1-((0.0142)))/((((0.0142*.1)/(2*1.96))^2)-((0.0142))) | ((1-((0.0142)))*(((1-((0.0142)))*((0.0142)))/(((((0.0142*.1)/(2*1.96)))^2)-1)) |
| Beta | dist_monthly_prob_AE_enza | (((((0.0252)))^2)*(1-(((0.0252))))/((((0.0252*0.1))/(2*1.96))^2)-(((0.0252)))) | ((1-(((0.0252))))*(((1-(((0.0252))))*(((0.0252))))/(((((0.0252*0.1))/(2*1.96))^2)-1)) |
| Beta | dist_prob_further_treatment | ((((((.8))))^2)*(1-((((.8)))))/(((((.1/(2*1.96)))))^2)-((((.8))))) | ((1-((((.8)))))*(((1-((((.8)))))*((((.8)))))/(((((.1/(2*1.96)))))^2)-1)) |
| Beta | dist_prob_GP_visit | ((((.3))^2)*(1-((.3)))/(((.2*.3)/(2*1.96))^2)-((.3))) | ((1-((.3)))*(((1-((.3)))*((.3)))/(((.2*.3)/(2*1.96))^2)-1)) |
| Beta | dist_prob_Hospice_stay | (((.8)^2)*(1-(.8))/((.1/(2*1.96))^2)-(.8)) | ((1-(.8))*(((1-(.8))*(.8))/((.1/(2*1.96))^2)-1)) |
| Beta | dist_prob_nurse_visit | ((((.4))^2)*(1-((.4)))/(((.20*.4)/(2*1.96))^2)-((.4))) | ((1-((.4)))*(((1-((.4)))*((.4)))/(((.20*.4)/(2*1.96))^2)-1)) |
| Beta | dist_prob_nursing_home_stay | (((.5)^2)*(1-(.5))/((.2/(2*1.96))^2)-(.5)) | ((1-(.5))*(((1-(.5))*(.5))/((.2/(2*1.96))^2)-1)) |
| Beta | dist_prob_Palliative_daycare | (((.25)^2)*(1-(.25))/((.1/(2*1.96))^2)-(.25)) | ((1-(.25))*(((1-(.25))*(.25))/((.1/(2*1.96))^2)-1)) |
| Beta | dist_QALY_decrement_BSC | (((0.07)^2)*(1-(0.07))/((0.02/(2*1.96))^2)-(0.07)) | ((1-(0.07))*(((1-(0.07))*(0.07))/((0.02/(2*1.96))^2)-1)) |
| Beta | dist_QALY_decrement_enza* | ((((((0.07))))^2)*(1-(((((0.07)))))/(((0.0077))^2)-(((((0.07))))) | ((1-((((0.07)))))*(((1-((((0.07)))))*((((0.07)))))/(((0.0077))^2)-1)) |
| Beta | dist_uPFS_BSC | (((0.7)^2)*(1-(0.7))/((0.02/(2*1.96))^2)-(0.7)) | ((1-(0.7))*(((1-(0.7))*(0.7))/((0.02/(2*1.96))^2)-1)) |
| Beta | dist_uPFS_enza* | (((((0.85)))^2)*(1-(((0.85))))/((0.0051)^2)-(((0.85)))) | ((1-(((0.85))))*(((1-(((0.85))))*(((0.85))))/((0.0051)^2)-1)) |
| Gamma | dist_admin_cost_doce | ((1569)^2)/((314/(2*1.96))^2) | (1569)/((314/(2*1.96))^2) |
| Gamma | dist_cost_AE_treatment | (((21125))^2)/(((21125/2))^2) | ((21125))/(((21125/2))^2) |
| Gamma | dist_cost_monitor_PFS | (((3158))^2)/(((3158/2))^2) | ((3158))/(((3158/2))^2) |
| Gamma | dist_cost_monitor_PFS_abir_3_months | (((6299))^2)/(((6299/2))^2) | ((6299))/(((6299/2))^2) |
| Gamma | dist_cost_monitor_Progressed | ((4389)^2)/((4389/2)^2) | (4389)/((4389/2)^2) |
| Gamma | dist_cost_nurse_hourly | (((730))^2)/(((.25*730)/(2*1.96))^2) | ((730))/(((.25*730)/(2*1.96))^2) |
| Gamma | dist_cost_Radiotherapy_PD | ((4519)^2)/((4519/2)^2) | (4519)/((4519/2)^2) |
| Gamma | dist_cost_Radiotherapy_PFS | ((7532)^2)/((7532/2)^2) | (7532)/((7532/2)^2) |
| Gamma | dist_cost_treat_after_enza | (((108726))^2)/((((108726*.1)/(2*1.96)))^2) | ((108726))/(((((108726*.1)/(2*1.96)))^2) |
| Gamma | dist_cost_treat_post_abir | (((113229))^2)/((((113229*.1)/(2*1.96)))^2) | ((113229))/(((((113229*.1)/(2*1.96)))^2) |
| Gamma | dist_cost_treat_post_BSC | ((21157)^2)/((21157*2/(2*1.96))^2) | (21157)/((21157*2/(2*1.96))^2) |
| Gamma | dist_daily_cost_Hospice_stay | ((8000)^2)/((2000/(2*1.96))^2) | (8000)/((2000/(2*1.96))^2) |
| Gamma | dist_daily_cost_Nursing_home | ((2250)^2)/((500/(2*1.96))^2) | (2250)/((500/(2*1.96))^2) |
| LogNormal | dist_HR_OS_Abir_vs_BSC_unadjusted | ln(0.81) | (ln(0.93)-ln(0.70))/(2*1.96) |
| LogNormal | dist_HR_OS_Abir_vs_BSC_adjusted | ln(0.74) | (ln(0.88)-ln(0.60))/(2*1.96) |

| | | | |
|---|---|---|---|
| LogNormal | dist_HR_OS_Enza_vs_BSC | ln(0.73) | (ln(0.85)-ln(0.63))/(2*1.96) |
| LogNormal | dist_HR_PFS_Abir_vs_BSC | ln(0.52) | (ln(0.61)-ln(0.45))/(2*1.96) |
| LogNormal | dist_HR_PFS_Enza_vs_BSC | ln(0.31) | (ln(0.83)-ln(0.11))/(2*1.96) |
| Normal | dist_number_days_Hospice_stay | 11 | 7/(2*1.96) |

* QALY values used for all active treatments