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Health technology assessment of four drugs for patients with metastatic castration resistant prostate cancer

Health technology assessment (HTA)
Metodevurdering

folkehelseinstituttet

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Norwegian Institute of Public Health
Oslo, August 2016

Key messages

Prostate cancer is the most common cancer among men in Norway with nearly 5000 new cases yearly. Advanced prostate cancer is not curable, but several new treatment alternatives have been developed in recent years.

In this Health Technology Assessment we have compared the relative effectiveness and cost-effectiveness of four drugs used for patients with metastatic castration resistant prostate cancer. The drugs are abiraterone, cabazitaxel, enzalutamide and radium-223.

Effectiveness:
For all patients, independent of previous treatment, all four intervention drugs compared with passive treatment (follow up time 12 to 49 months):

- probably increase median overall survival (reduce risk of death) by approximately four months
- probably increase the progression free survival period between one to five months
- may cause more serious adverse events (abiraterone, cabazitaxel, radium-223) or there may be little or no difference between the treatment groups (enzalutamide)
- probably improves the quality of life slightly

For all endpoints, we assessed the quality of evidence to be either moderate or low.

Cost-effectiveness:

- All four drug treatments, with the exception of radium-223 for docetaxel-naive patients, are more effective but also more costly than BSC.
- In the docetaxel-naive patients, the incremental cost-effectiveness ratios (ICERs) were NOK 984,163 for abiraterone and NOK 971,465 for enzalutamide.
- In the post-docetaxel patients ICERs were: NOK 789,128 for abiraterone, NOK 809,595 for enzalutamide NOK 993,004, for radium-223, and NOK 1,210,474 for cabazitaxel.
- Treatments are considered cost-effective if the willingness-to-pay per extra QALY gained is above the ICER. Substantial price discounts would be necessary for these four drug treatments to be cost-effective at a willingness-to-pay of NOK 500,000.

Title:
Health technology assessment of four drugs for patients with metastatic castration resistant prostate cancer

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Type of publication:

Health technology assessment

Health technology assessment (HTA) is a multidisciplinary process that summarizes information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner. Its aim is to inform the development of safe, effective health policies that are patient focused and that seek to achieve best value.

Doesn't answer everything:

- Excludes studies that fall outside of the inclusion criteria
- No recommendations

Publisher:

Norwegian Knowledge Centre for the Health Services

Updated:

Last search for trials:
October 2015
Last search for ongoing trials:
January 2016

Executive summary

Background

Prostate cancer is the most common cancer among Norwegian men and represents nearly 20 % of all new cancer cases. Most prostate cancers develop slowly, but metastatic prostate cancer is not currently curable. Several new drugs for treatment of metastatic prostate cancer have been developed during the last years. It is, however, unclear which of these new drugs are most effective and cost-effective. This health technology assessment aims at examining the relative effectiveness and cost–effectiveness of four drugs (abiraterone, cabazitaxel, enzalutamide and radium-223) for metastatic castration resistant prostate cancer.

Objective

To assess the clinical effectiveness, safety and cost-effectiveness of the new drugs used for patients with metastatic castration resistant prostate cancer relative to each other.

Method

We have performed this Health Technology Assessment in accordance with our Handbook.

We performed a systematic literature search for randomized controlled trials in October 2015 in relevant bibliographic databases. We contacted relevant pharmaceutical companies to obtain additional information. Full text publications of potentially eligible references were retrieved. Two authors reviewed eligible publications independently to identify publications that fulfilled our pre-specified inclusion criteria. We assessed all included studies for risk of bias. One author extracted data from the included clinical trials using a pre-designed data recording form and another author verified the data.

We conducted pairwise meta-analyses for each available endpoint for all possible combinations of interventions and controls with available evidence from included

trials. We performed network-meta-analyses where appropriate according to population, intervention, control and outcome. We ranked the different treatments in terms of their likelihood of leading to the best results for each endpoint by help of the surface under the cumulative ranking curve (SUCRA).

Two authors assessed the quality of the direct evidence, indirect evidence and the combined evidence from the network meta-analyses by using the GRADE methodology.

Our cost-effectiveness analysis was based on a probabilistic, discrete-time Markov cohort model with three health states: progression free survival, progressed disease and death. We ran separate models for the post-docetaxel and docetaxel-naive patient groups. The post-docetaxel model included all four medications, while the docetaxel-naive model examined only abiraterone and enzalutamide. We adjusted baseline transition probabilities using hazard ratios from the effect section of this report. Clinical experts provided advice about resource use during the course of treatment that we used in cost estimations for the model.

We relied on maximum pharmacy retail prices in the cost-effectiveness analyses because price discounts negotiated by the Drug Procurement Cooperation and the pharmaceutical companies are considered confidential.

Results

Our results for clinical effectiveness are based on eight randomized controlled trials, presented in 16 publications. The trials included a total of 7,314 patients, from more than 20 countries in Europe, North America and Asia, with histologically or cytologically confirmed diagnosis of progressive prostate cancer with soft tissue or bone metastases.

Our clinical evaluation based on the direct comparisons shows that for the all patients group (patients that had, or had not received chemotherapy), the four drugs probably increase median overall survival slightly compared with passive treatment. Median overall survival was increased by approximately four months for all treatment groups (HR 0.77 (95 % CI 0.70 to 0.93) for abiraterone, HR 0.70 (95 % CI 0.59 to 0.83) for cabazitaxel, HR 0.68 (0.59 to 0.79) for enzalutamide and HR 0.65 (95 % CI (0.48 to 0.87) for radium-223. We have low to moderate confidence in these estimates. All intervention drugs probably increases the progression free survival period slightly (between one to five months) compared with passive treatment (moderate quality evidence). Hazard ratio was 0.56 (95 % CI 0.44 to 0.70) for abiraterone, 0.75 (95 % CI 0.63 to 0.90) for cabazitaxel, 0.22 (95 % CI 0.16 to 0.30) for enzalutamide and 0.64 (0.54 to 0.77) for radium-223). The drugs probably improves the quality of life slightly (moderate quality evidence), but may cause more serious adverse events

(abiraterone, cabazitaxel, radium-223) or there may be little or no difference between the treatment groups (enzalutamide) (low or moderate quality evidence). The follow up time in the studies varied from 12 to 49 months.

In the docetaxel-naive model incremental cost-effectiveness ratios, which reflect the minimum willingness-to-pay at which a treatment could potentially be considered cost-effective, were NOK 984,163 for abiraterone and NOK 971,465 for enzalutamide.

In the post-docetaxel model the incremental cost-effectiveness ratios were NOK 993,004 for radium-223; NOK 789,128 for abiraterone; NOK 1,210,474 for cabazitaxel; and NOK 809,595 for enzalutamide.

At a willingness-to-pay of NOK 500,000, to be considered cost-effective for use among docetaxel-naive patients, the prices of abiraterone and enzalutamide would need to drop by approximately 54% and 55%, respectively. For use among post-docetaxel patients treatments could be considered cost-effective with price declines of 47% for abiraterone, 46% for enzalutamide, 67% for radium-223 and 37% for cabazitaxel.

Discussion

Scarcity of data is a limitation of this report. Only one or two head-to-head trials have been performed for each comparison versus placebo or “passive” treatment. We did not find any trials that have tested our interventions against each other directly. We therefore mainly present estimates of effect for head-to-head comparisons between the intervention and placebo or “passive” treatment. Our estimates for the comparisons between the interventions are therefore only based on indirect estimates and must be interpreted cautiously.

Our economic analysis has a number of limitations that should be considered when interpreting the cost-effectiveness results. One important caveat is that the analysis only examines the cost-effectiveness of included treatments, and does not address the best sequencing of these medications in prostate cancer treatment.

Because baseline survival information for the control arms was extrapolated beyond the end of trial follow-up periods, there is likely to be a good deal of uncertainty in our estimates of overall and progression-free survival in the model.

There is a large degree of uncertainty around the utility values used to capture health-related quality of life. Although, in the base case scenario, we applied the same utility values for all active treatments among patients with the same docetaxel status, the utility values reported in the literature varied widely among treatments.

Conclusion

We have assessed the clinical effectiveness, safety and cost-effectiveness of abiraterone, cabazitaxel, enzalutamide and radium-223 for patients with metastatic castration resistant prostate cancer relative to each other.

Our cost-effectiveness analysis indicates that at today's maximum pharmacy prices (AUP) none of the medications investigated can be considered cost-effective at what has typically been considered a reasonable willingness-to-pay.

For the docetaxel-naive patient group rebates on the AUP prices of approximately 54% for abiraterone and 55% for enzalutamide would be necessary for these medications to be cost-effective at a willingness-to-pay of NOK 500,000 per quality-adjusted life year. For post-docetaxel patients, the required rebates would be 47% for abiraterone, 46% for enzlutamide, 67% for radium-223 and 36% for cabazitaxel.

Hovedfunn (norsk)

Prostatakreft er den vanligste kreftformen blant menn i Norge med nesten 5000 nye tilfeller årlig. Avansert prostatakreft kan ikke kureres, men flere nye behandlingsalternativer har blitt utviklet de siste årene.

I denne metodevurderingen har vi sammenlignet klinisk effekt og kostnadseffektivitet av fire legemidler som brukes for pasienter med metastatisk kastrasjonsresistent prostatakreft. Legemidlene er abirateron, kabazitaxel, enzalutamid og radium-223.

Klinisk effekt:
For alle pasienter, uavhengig av tidligere behandling, vil behandling med alle de fire legemidlene sammenlignet med "passiv behandling" (oppfølgingstid 12 til 49 måneder):
• trolig øke median overlevelse (redusere risiko for død) med ca. fire måneder
• trolig forlenge progresjonsfri overlevelse periode med mellom en til fire måneder
• muligens føre til flere alvorlige bivirkninger eller det vil være liten eller ingen forskjell mellom behandlingsgruppene
• trolig forbedre livskvaliteten noe
Vi har lav til moderat tillit til resultatene.

Kostnadseffektivitet:

- Alle de fire medikamentelle behandlingene, med unntak av radium-223 for docetaksel-naive pasienter, var mer effektive, men også dyrere enn beste støttebehandling.
- For docetaksel-naive pasienter, var den inkrementelle kostnadseffektivitetsbrøken (ICER) NOK 984 163 for abirateron og kr 971 465 for enzalutamide
- For pasienter som har vært behandlet med docetaksel var den inkrementelle kostnadseffektivitetsbrøken NOK 789 128 for abirateron, NOK 809 595 for enzalutamid, NOK 993 004 for radium-223 og NOK 1.210.474 for kabazitaxel.
- Vi anser behandlinger som kostnadseffektive dersom betalingsvilligheten per ekstra vunnet kvalitetsjusterte leveår (QALY) er høyere enn ICER.
- Det vil være nødvendig med betydelige prisrabatter dersom disse fire legemidlene skal ansees som kostnadseffektive med en betalingsvillighet på NOK 500 000 per QALY.

Tittel:
Metodevurdering for fire legemidler for pasienter med metastaserende kastrasjonsresistent prostatakreft

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Publikasjonstype:
Metodevurdering

En metodevurdering er resultatet av å
- innhente
- kritisk vurdere og
- sammenfatte
relevante forskningsresultater ved hjelp av forhåndsdefinerte og eksplisitte metoder.

Minst ett av følgende tillegg er også med:
helseøkonomisk evaluering, vurdering av konsekvenser for etikk, jus, organisasjon eller sosiale forhold.

Svarer ikke på alt:

- Ingen studier utenfor de eksplisitte inklusjonskriteriene
- Ingen anbefalinger

Hvem står bak denne rapporten?

Kunnskapssenteret har skrevet rapporten på oppdrag fra Nye metoder, Helsedirektoratet

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Når ble litteratursøket utført?

Søk etter studier avsluttet : Oktober 2015

Søk etter pågående studier avsluttet:
Januar 2016

Sammendrag (norsk)

Metodevurdering for fire legemidler for pasienter med metastaserende kastrasjonsresistent prostatakreft

Bakgrunn

Prostatakreft er den vanligste kreftformen blant menn i Norge med nesten 5000 nye tilfeller hvert år. De fleste krefttilfeller utvikler seg sakte, men avansert prostatakreft kan foreløpig ikke kureres. Flere nye behandlingsalternativer for avansert prostatakreft har blitt utviklet de siste årene. Det er imidlertid uvisst hvilke av disse nye legemidlene som er mest effektive og kostnadseffektive.

I denne metodevurderingen har vi sammenlignet klinisk effekt og kostnadseffektivitet av fire legemidler som brukes for pasienter med metastatisk kastrasjonsresistent prostatakreft. Legemidlene er abirateron, kabazitaxel, enzalutamid og radium-223.

Problemstilling

Vi ville vurdere den kliniske effekten, sikkerhet og kostnadseffektiviteten av nye legemidler som brukes for pasienter med metastatisk kastrasjonsresistent relativt til hverandre.

Metode

Vi har utført denne metodevurderingen i samsvar med Kunnskapssenteret i Folkehelseinstituttet sin metodehåndbok «Slik oppsummerer vi forskning».

Vi utførte et systematisk litteratursøk etter randomiserte kontrollerte studier i oktober 2015 i relevante bibliografiske databaser. Vi kontaktet relevante farmasøytiske selskaper for å innhente ytterligere informasjon. To forfattere gjennomgikk fulltekst referanser som så ut til å oppfylle våre inklusjonskriterier uavhengig av hverandre. Vi vurderte alle inkluderte studiene for risiko for metodiske skjevheter. En forfatter ekstraherte data fra de inkluderte kliniske studiene ved hjelp av en pre-designet dataregistrering form og en annen forfatter verifiserte opplysningene.

Vi gjennomførte parvise metaanalyser for hvert endepunkt for alle mulige kombinasjoner av legemiddel og kontrollgruppe fra de inkluderte studiene. Vi utførte nettverksmetaanalyser der det var hensiktsmessig i forhold til populasjon, legemiddel, kontrollgruppe og endepunkt. Vi rangert de ulike behandlingene etter deres sannsynlighet for å føre til de beste resultatene for hvert endepunkt ved hjelp av overflaten under kumulative rangeringen kurven (SUCRA).

To forfattere vurderte vår tillitt til dokumentasjonen for de direkte sammenligningene, de indirekte sammenligningene og for nettverksmetaanalysene ved bruk av GRADE.

Vår kostnadseffektivitetsanalyse er basert på en probabilistisk, discrete-time Markov kohort modell med tre helsetilstander; progresjonsfri overlevelse, progrediert sykdom og død. Vi utførte separate modeller for docetaksel-naive pasienter og for pasienter som har blitt behandlet med docetaksel tidligere. Post-docetaxel modellen inkluderte alle de fire legemidlene, mens den docetaksel-naive modellen kun analyserte abirateron og enzalutamid. Vi justerte overgangssannsynligheter ved bruk av hasard ratio fra den kliniske effektdelen i denne rapporten. Kliniske eksperter gav oss råd om ressursbruk gjennom behandlingsforløpet som vi benyttet i kostnadsestimatene i modellen.

Vi har benyttet maksimal AUP (apotekenes utsalgspris) i våre kostnadseffektivitetsanalyser fordi prisrabattene som blir forhandlet frem av legemiddelinnkjøpssamarbeidet og de farmasøytiske selskapene ansees som konfidensielle.

Resultat

Våre resultater for klinisk effekt er basert på åtte randomiserte kontrollerte studier, presentert i 16 publikasjoner. 7314 pasienter med histologisk eller cytologisk bekreftet progressiv, metastatisk prostatakreft var inkludert i studiene. Studiene har blitt utført i mer enn 20 land i Europa, nord Amerika og Asia.

Våre analyser av effekt basert på de direkte sammenligningene viser at for alle pasientgrupper (pasienter som hadde, eller ikke hadde fått kjemoterapi tidligere), vil de fire undersøkte legemidlene trolig øke totaloverlevelse noe (redusere risiko for død) sammenlignet med passiv behandling. Median totaloverlevelse ble økt med ca. fire måneder i alle behandlingsgrupper (HR 0.77 (95 % CI 0.70 til 0.93) for abirateron, HR 0.70 (95 % CI 0.59 til 0.83) for kabazitaxel, HR 0.68 (0.59 til 0.79) for enzalutamid og HR 0.65 (95 % CI (0.48 til 0.87) for radium-223. Vi har lav til moderat tillitt til disse effektestimatene. Alle legemidlene vil trolig øke progresjonsfri overlevelse noe (mellom en til fem måneder) sammenlignet med passive behandling (moderat kvalitet). Hasard ratio var 0.56 (95 % CI 0.44 til 0.70) for abirateron, 0.75 (95 % CI

0.63 til 0.90) for kabazitaxel, 0.22 (95 % CI 0.16 til 0.30) for enzalutamid og 0.64 (0.54 til 0.77) for radium-223). Legemidlene øker sannsynligvis livskvaliteten litt (moderat kvalitet), men kan føre til flere alvorlige bivirkninger (abirateron, kabazitaxel, radium-223) eller det kan være liten eller ingen forskjell mellom behandlingsgruppene (enzalutamid) (lav eller moderat kvalitet). Oppfølgingstiden i studiene varierte fra 12 til 49 måneder.

For docetaksel-naive pasienter, var den inkrementelle kostnadseffektivitetsbrøken (ICER) NOK 984 163 for abirateron og kr 971 465 for enzalutamid. For pasienter som har vært behandlet med docetaksel var den inkrementelle kostnadseffektivitetsbrøken NOK 789 128 for abirateron, NOK 809 595 for enzalutamid NOK 993 004 for radium-223 og NOK 1.210.474 for kabazitaxel. Vi anser behandlinger som kostnadseffektive dersom betalingsvilligheten per ekstra vunnet kvalitetsjusterte leveår (QALY) er høyere enn ICER. Det vil være nødvendig med betydelige prisrabatter dersom disse fire legemidlene skal ansees som kostnadseffektive med en betalingsvillighet på NOK 500 000 per QUALY.

Med en betalingsvilje på kr 500 000, vil rabatter fra AUP prisene på ca 54 % for abirateron og 55 % for enzalutamid være nødvendig for at disse legemidlene skal være kostnadseffektiv for docetaksel-naive pasienter. For pasienter som tidligere har blitt behandlet med docetaksel, vil de nødvendige rabatter være 47 % for abirateron, 46 % for enzlutamid, 67 % for radium-223 og 36 % for kabazitaxel.

Diskusjon

Mangel på data er en begrensning i denne rapporten. Bare en eller to «head-to-head» studier er utført for hver sammenligning versus placebo eller "passiv" behandling. Vi fant ingen studier som har undersøkt legemidlene mot hverandre direkte. Vi har derfor i hovedsak presentert beregninger av effekten for head-to-head sammenligninger mellom intervensjon og placebo eller "passiv" behandling. Våre analyser for sammenligninger mellom legemidlene er derfor kun basert på indirekte estimater og må tolkes med forsiktighet.

Vår økonomiske analyse har en rekke begrensninger som bør vurderes ved tolkningen av kostnadseffektivitetsresultatene. En viktig faktor er at analysen undersøker kun kostnadseffektiviteten av de inkluderte behandlinger, og omhandler ikke den beste sekvensering av disse legemidlene i prostatakreftbehandling.

Siden data for baseline overlevelsesinformasjon for kontrollgruppene ble ekstrapolert ut over oppfølgingsperioden som var i studiene, er det sannsynlig at det er stor usikkerhet i våre estimater av generell og progresjonsfri overlevelse i modellen.

Det er en stor grad av usikkerhet rundt de livskvalitetsverdiene som brukes til å vurdere helserelatert livskvalitet. Selv om vi i basecase scenariet har anvendt de samme livskvalitetsverdier for alle de aktive behandlingene blant pasienter med samme docetaksel status, varierer litteraturen mye i sine anslag på livskvalitet for disse pasientene.

Konklusjon

Vi har vurdert den kliniske effekten, sikkerhet og kostnadseffektivitet av abirateron, kabazitaxel, enzalutamid og radium-223 for pasienter med metastatisk kastrasjonsresistent prostatakreft i forhold til hverandre.

Vår kostnadseffektivitetsanalyse indikerer at gitt dagens maksimale apotekenes utsalgspris (AUP) kan ingen av de undersøkte legemidlene betraktes som kostnadseffektive på bakgrunn av hva som til nå har blitt ansett som en rimelig betalingsvilje.

For docetaksel-naive pasienter vil rabatter fra AUP prisene på 54 % for abirateron og 55 % for enzalutamid være nødvendig for at disse legemidlene skal være kostnadseffektive ved en betalingsvilje på kr 500 000 per kvalitetsjusterte leveår. For pasienter som tidligere har blitt behandlet med docetaksel, vil de nødvendige rabatter være 47 % for abirateron, 46 % for enzlutamid, 67 % for radium-223 og 36 % for kabazitaxel.

Glossary and abbreviations	
AUP	The maximum pharmacy retail price (apotekenes utsalgspris)
CI	**Confidence interval.** A measure of uncertainty around the results of a statistical analysis that describes the range of values within which we can be reasonably sure that the true mean effect lies. Wider intervals indicate lower precision; narrower intervals, greater precision.
CrI	**Credible interval.** The credible interval is the Bayesian analogue to confidence intervals used in traditional frequentist statistical approaches.
CUA	**Cost-utility analysis.** An economic evaluation where health consequences are measured in **QALY**s.
EQ-5D	**European Quality of Life-5 Dimensions.** EQ-5D is a standardized instrument for use as a measure of health outcome.
FACT-P	**Functional Assessment of Cancer Therapy-Prostate**. A 39-item questionnaire for the assessment of Health Related Quality of Life in prostate cancer.
GDT	Guideline development tool
GRADE	Grading of Recommendations Assessments, Development, and Evaluation
HR	**Hazard Ratio.** Ratio of hazard rates. Ratio above 1 indicate increased instantaneous rate of an event. Ratios below 1 indicate a decrease in event rates.
HRQoL	Health related quality of life
HTA	Health Technology Assessments
ICER	**Incremental cost-effectiveness ratio**. The ratio of the difference in costs between two alternative health technologies to the difference in effectiveness between these two technologies. $ICER = \frac{Cost_{\text{intervention}} - Cost_{\text{comparator}}}{Effect_{\text{intervention}} - Effect_{\text{comparator}}} = \frac{\Delta C}{\Delta E}$
NHB	**Net Health Benefit.** In a decision-making process, a positive NHB suggests that the intervention represents good value for money $NHB = \Delta E - \frac{\Delta C}{\lambda}$
NMB	**Net Monetary Benefit.** In a decision-making process, a positive NMB suggests that the intervention represents good value for money. $NMB = \lambda \cdot \Delta E - \Delta C$
MD	Mean difference

Odds	The odds of an event happening is defined as the probability that an event will occur, expressed as a proportion of the probability that the event will not occur.
OR	**Odds ratio.** The ratio of the odds of an outcome in one treatment group divided by the odds of the same outcome in a different treatment group.
OS	Overall survival
PSA	Prostate specific antigen
PSA	**Probabilistic sensitivity analysis.** An analysis of the uncertainty related to all parameters in a decision analytic model. Typically performed by Monte Carlo simulation, hence by drawing values from probability distributions for all parameters simultaneously
QALY	**Quality-adjusted life-year.** A measure of health outcomes that combines quantity and quality of life by assigning to each year of life a weight from 1 (perfect health) to 0 (state judged equivalent to death) dependent on the individual's health related quality of life during that year
RCT	**Randomised controlled trial.** An experiment in which investigators use randomisation to allocate participants into the groups that are being compared. Usually allocation is made at the level of individuals, but sometimes it is done at group level e.g. by schools or clinics. This design allows assessment of the relative effects of interventions.
RR	**Relative risk / risk ratio.** The relative risk is the absolute risk (AR) in the intervention group divided by the AR in the control group. It is to be distinguished from odds ratio (OR), which is the ratio of events over non-events in the intervention group over the ratio of events over non-events in the control group.
SAE	Serious adverse events
SR	**Systematic review.** A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review. Statistical methods (meta-analysis) may or may not be used to analyse and summarise the results of the included studies.
Statistically significant	Means that the findings of a study are unlikely to have arisen because of chance. Significance at the commonly cited 5% level ($P < 0.05$) means that the observed difference or greater difference would occur by chance in only 1/20 similar cases. Where the word "significant" or "significance" is used without qualification in the text, it is being used in this statistical sense.
SUCRA	Surface under the cumulative ranking curve.

WTP (λ)	**Willingness to pay**. A pre-specified limit of what society is willing to pay for a given health unit (e.g. QALY or life year). In Norway it is common to use NOK 500 000 per QALY or life year in economic evaluations.

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Preface

This project was commissioned by The Regional Health Authorities Forum (Bestillerforum RHF). They wanted us to compare four new drugs which are under consideration for implementation in the national cancer guidelines in Norway. The new drugs will be compared to any drug treatment or placebo with regard to overall survival, progression free survival, health related quality of life and serious adverse events in patients with metastatic castrate-resistant prostate cancer (mCRPC). The results will be used to establish the effectiveness and cost-effectiveness of these drugs relative to each other.

Ingvil Sæterdal was lead reviewer for the clinical evaluation and Arna Desser led the health economic evaluation. Atle Fretheim and Brynjar Fure performed peer review of the report.

The project group consisted of:

- Ingvil Sæterdal and Eva Pike; clinical evaluation
- Arna Desser and Vida Hamida; health economic evaluation
- Jan Odgaard-Jensen; statistics
- Ingrid Harboe; information retrieval
- Marianne Klemp; responsible for the project

We would like to thank Sven Löffeler and Eline Aas for their expertise in this project. Norwegian Knowledge Centre for the Health Services assumes final responsibility for the content of this report.

The aim of this report is to support well-informed decisions in health care that lead to improved quality of services. The evidence should be considered together with other relevant issues, such as clinical experience and patient preference.

Signe Flottorp	Marianne Klemp	Ingvil Sæterdal	Arna Desser
Department director	*Research director*	*Lead reviewer, Clinical evaluation*	*Lead health economist*

Objective

To assess the clinical effectiveness, safety and cost-effectiveness of the new drugs used for patients with metastatic castration resistant prostate cancer relative to each other.

Background

Metastatic castration resistant prostate cancer

Prostate cancer is the most common cancer among Norwegian men and the most common cancer in Norway. It represents one out of six new cancer cases and 4,889 new cases were detected in 2014 (1).

Prostate cancer develops in the prostate, a gland in the male reproductive system. About 90 % of all prostate cancers are diagnosed in men aged 60 and older (2). Cancer that spreads from the prostate to another place in the body, either to bones or other organs, is called metastatic prostate cancer. Age, ethnicity, lifestyle, family history and genetic factors such as mutations in the breast cancer gene 2 (BRCA2 mutations) are the most important risk factors for developing prostate cancer.

In its early stages, prostate cancer usually causes no symptoms. More advanced disease may cause such symptoms as problems urinating, a slow and weak urinary stream, frequent urination, blood in the urine, and pain in the back and skeleton (1)

Stage of the cancer is usually classified using the Tumor Node Metastasis (TNM) classification system. The TNM system is based on the size and/or extent (reach) of the primary tumor (T), the amount of spread to nearby lymph nodes (N), and the presence of metastasis (M) or secondary tumors formed by the spread of cancer cells to other parts of the body. Prognosis is dependent on the stage at diagnosis. Metastatic castration resistant prostate cancer (TNM stage IV) had a five-year survival rate of 35.5 % in 2009-13 (1).

The patients in the included trials in this report had an ECOG (Eastern Cooperative Oncology Group) performance status score of 2 or less. The ECOG performance status was developed in order to describe a patient's level of functioning in terms of their ability to care for themselves, daily activity, and physical ability (walking, working, etc.) in a consistent manner between clinical trials.

ECOG Performance Status
Developed by the Eastern Cooperative Oncology Group, Robert L. Comis, MD, Group Chair.*

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self care; totally confined to bed or chair
5	Dead

*Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649-655.

Treatment alternatives

Current treatment strategy for prostate cancer is active surveillance, surgery, external radiation, brachytherapy, hormone therapy or combinations of these. For metastatic prostate cancer, androgen deprivation therapy is generally the initial treatment. If the cancer becomes “castrate resistant” or “hormone-refractory” (prostate specific antigen (PSA) level rises despite castrate levels of testosterone), docetaxel in combination with prednisone is standard treatment (3). Metastatic castration resistant prostate cancer is currently not curable, so treatment options are palliative or aim to prolong survival.

Several new treatment alternatives have been developed in recent years. In this Health Technology Assessment we will evaluate four relatively new drugs which are under consideration for implementation in the national cancer guidelines in Norway: abiraterone, cabazitaxel, enzalutamide, and radium-233 dichloride. The four drugs have different mechanisms of action. Abiraterone acts by blocking the enzyme cytochrome P450 c17 (CYP17), a critical enzyme in testosterone synthesis. Cabazitaxel is a taxane that inhibits cell division by inhibiting microtubules which are crucial for cell division. Enzalutamide is an androgen-receptor-signalling inhibitor that works by inhibiting the androgen from binding to its receptor, inhibiting the androgen receptor from entering the cell nucleus and inhibiting the androgen receptor from binding to DNA (4). Radium-223 is an alpha-emitting radiopharmaceutical

agent with a half-life of 11.4 days. Radium is preferentially absorbed by bone and alpha radiation has a short range in tissues. This reduces damage to surrounding healthy tissues. All four drugs have marketing authorisation in Norway.

The Norwegian Medicines Agency has previously performed Single Technology assessments for these drugs (5) however, the effectiveness and cost-effectiveness of these drugs relative to each other has not yet been established. Hence, there is a need to perform this HTA for patients with metastatic castration resistant prostate cancer in the Norwegian setting.

Introduction to systematic reviews of clinical effectiveness

Systematic reviews of clinical effectiveness are products of a comprehensive process, including: literature search, study selection, risk of bias evaluations, data extraction, combining findings and quality of evidence assessments.

Based on predefined research questions, an information specialist develops a search strategy to identify relevant publications in electronic databases for medical research. In addition, the literature search may include reviews of reference lists, contacting field experts and searching for unpublished studies. The aim is to identify all relevant literature and include studies based on predefined inclusion criteria, specifying relevant populations, interventions, comparisons, outcomes and study design. To reduce bias, two reviewers assess abstracts and potentially relevant full text publications independently for inclusion. The two reviewers also check that data from included studies are extracted correctly.

Further it is usual for systematic review to evaluate the included studies for risk of bias or quality. This information may be used in addition to similarity among participants, interventions, comparisons and outcomes in the decision as to whether effect estimates from several trials can be combined statistically in a meta-analysis. The risk of bias or quality should be used along the effect estimates when a conclusion is made in a systematic review.

Introduction to Economic Evaluations of Health Care Programmes

The basic task of any economic evaluation is to identify, measure and compare costs and consequences of the alternatives under consideration in an incremental analysis—one in which the differences in costs are compared with differences in consequences (6). Results of economic evaluations can be expressed as an incremental cost-effectiveness ratio (ICER), which is defined by the following equation:

$$ICER = \frac{Cost_{\text{intervention}} - Cost_{\text{comparator}}}{Effect_{\text{intervention}} - Effect_{\text{comparator}}} = \frac{\Delta C}{\Delta E}$$

Because the health care sector, like the society in general, is restricted by scarce resources and budget constraints, economic evaluations are important tools for decision makers facing questions of how to prioritize treatments and maximize health benefits using scarce resources. For an economic evaluation to be meaningful in a decision making process, the ICER must be judged with regard to a ceiling ratio that reflects the decision maker's maximum willingness to pay (WTP) for a health gain. The decision rule for an economic evaluation can therefore be expressed as

$$\frac{\Delta C}{\Delta E} < \lambda$$

where λ equals willingness to pay, and means that if the ICER of an intervention is below the ceiling ratio, introducing the intervention represents good value for money. Because the ICER has poor statistical properties, ICERs are often rearranged to express either incremental net monetary benefit (INMB) or incremental net health benefit (INHB), which yields the following decision rules related to INMB or INHB.

INMB: $\lambda \bullet \Delta E - \Delta C > 0$
INHB: $\Delta E - (\Delta C/\lambda) > 0$

An intervention can in other words be considered cost-effective if it yields a positive INHB or INMB.

Economic evaluations are often based on decision models (such as decision trees, Markov models, etc.) that calculate results based on various input parameters in the model. Because there are always uncertainties related to the values of these parameters, sensitivity analysis is an important feature of any economic evaluation based on a decision model framework. In short, sensitivity analysis illustrates how much the results vary when model parameters are changed.

Probabilistic sensitivity analysis (PSA) is a kind of sensitivity analysis. The advantage of probabilistic sensitivity analysis is that it makes it possible to take the uncertainties of all of the model-parameters into account simultaneously. The basic approach in probabilistic sensitivity analysis is to assign appropriate probability distributions to the model-parameters, which makes it possible to replace the "fixed" values of the parameters with values generated by random draws from the distributions. Doing this repeatedly, with a specified number of iterations, makes it possible to estimate the probabilities that alternative interventions are cost-effective, subject

to different ceiling values of willingness to pay. The calculation is based on the alternative that renders the highest values of NMB or NHB. Results from probabilistic sensitivity analysis are often presented as scatter plots, which show point estimates of the ICER for all iterations in the cost-effectiveness plane, and also as cost-effectiveness acceptability curves (CEACs), which show the probability of the alternatives being cost-effective subject to changing values of willingness to pay.

Another result from probabilistic sensitivity analysis is the expected value of perfect information (EVPI). This number indicates the value to society to have more accurate information about the decision, given a willingness to pay. If EVPI for a given population seems large, it might be of interest to determine for which parameters it would be most useful to obtain additional data. Expected value of perfect information for parameters is a more time-consuming analysis that can help determine for which single parameters or groups of parameters it is most cost-effective to conduct new research.

In short, making a model probabilistic means that it is possible to estimate the uncertainty associated with a decision to implement alternative interventions, and it provides a possibility of estimating the value of collecting additional information from new research.

Priority setting criteria

According to Norwegian policy documents (7), a treatment should be prioritized if the following criteria are met:

The disease is severe: A disease is considered severe to the degree that it causes pain and discomfort, loss of physical, psychological and social function and if it limits the individual in his or her daily activities. Severity is also evaluated according to the risk increase the disease entails in terms of death, disability and discomfort, if treatment is postponed.
The treatment is effective: The patient should be expected to benefit from treatment in terms of longevity or improved quality of life of certain duration. The treatment effectiveness should also be well documented.

The treatment is cost-effective: The additional costs of the treatment should be reasonable compared to the additional benefits.

There is no academic or political consensus regarding what constitutes a reasonable relationship between incremental costs and effects in Norway. For this reason, we use a range of potential willingness-to-pay (WTP) values throughout our report. When necessary for price scenarios, we use a value of NOK 500,000 per quality adjusted life year in our analyses.

Clinical evaluation – Methods

We have performed a Health Technology Assessment (HTA) consisting of a systematic review of clinical effectiveness and a health economic evaluation. We have performed the HTA in accordance with the handbook from the Norwegian Knowledge Centre (8).

Literature search

Research librarian Ingrid Harboe planned and executed all systematic searches in collaboration with the project group, and Gyri Hval Straumann peer reviewed the search strategy.

We systematically searched for literature in the following databases:

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and ovid MEDLINE(R) 1946 to Present
- Embase (Ovid) 1946 to Present
- Cochrane Library: Central Register of Controlled Trials (Central)
- NHS Economic Evaluations Database (NHS EED)
- Centre for Reviews and Dissemination: NHS EED
- ISI Web of Science
- PubMed (epub ahead of print citations)
- Epistemonikos
- Google Scholar

To limit retrieval to randomized controlled trials, we used a methodology search filter. The search filter consisted of a combination of Randomized Controlled Trial.pt (publication type), Randomized Controlled Trial (MeSH) and random* as a text word (*=truncation). Trials about animals or animal experiments were removed. We limited year of publication to 2000 to current since the interventional drugs have entered market recently and we did not expect to find relevant trials with publication date before this. Our search strategy combined selected index and free text terms. The complete search strategy is listed in appendix 1. Last search for trials was carried out in end of October 2015.

We searched for ongoing trials in Clinical Trials.gov and WHO International Clinical Trials Registry Platform (ICTRP) in January 2016.

Furthermore, we contacted the pharmaceutical companies with marketing authorization for the relevant drugs in Norway (Astellas Pharma, Bayer, Janssen and Sanofi) to obtain additional information and, if any, unpublished results that could be relevant to the reviewed topic and fulfilled the inclusion criteria. Supplemental information was considered.

Inclusion criteria

The inclusion criteria for the clinical evaluation were defined as follows:

Population:	Patients with metastatic castrate-resistant prostate cancer (mCRPC) aged 18 or older
Intervention:	Abiraterone Cabazitaxel Enzalutamide Radium-223 dichloride The above interventions given as monotherapy (including add-on) or in combination with each other.
Control:	Any drug treatment or placebo
Endpoints:	Overall survival (or time to death) Progression free survival (different definitions exists. Our order of preference is: 1) Prostate Specific Antigen (PSA) progression 2) radiographic progression 3) Alkaline Phosphatase Level (ALP) progression Health related quality of life (measured with EQ-5D, SF-6D or disease specific instrument such as FACT-P) Serious adverse events
Study design:	Randomised controlled trials
Languages:	No language restrictions was applied during the literature search, but we only included trials written in English or any of the Scandinavian languages.

Selection of articles

Two of the authors worked independently and in pairs and reviewed all citations generated by the search to identify potentially relevant publications based on title and/or abstract. We retrieved full text articles of all potentially relevant publications and worked independently and in pairs to assess whether these publications should be included according to the inclusion criteria. We resolved disagreements by discussion.

Assessment of methodological quality

We assessed the included publications for possible risk of bias according to our Handbook (8). Two of the authors performed and agreed upon the assessments working independently. We resolved disagreements by discussion.

Data extraction

One of the authors extracted data from the included publications and another author verified the data.

We extracted the following data: Information about the study (authors, year of publication, setting, study design, name of clinical trial, identification number and funding); participant characteristics (number of participants in the trial, age, disease stage, previous drug treatment); intervention and control characteristics (which drugs, doses, length of use); endpoints (which endpoints were examined, methods used to analyse outcome data, length of follow up and loss to follow up).

Statistical analyses and presentation of results

Measures of treatment effect

We expressed the comparative effectiveness of the treatments as the relative risk (RR) of dichotomous endpoints, hazard ratio (HR) for time-to-event endpoints and mean difference (MD) for continuous endpoints. If a continuous outcome had been measured/reported using different instruments/scales in the included randomized controlled trials, we would have calculated the standardised mean difference (SMD). For all endpoints 95% confidence intervals (CI, results from pairwise meta-analyses) or credible intervals (CrI, results from network meta-analyses) were calculated for the RR, HR, MD or SMD. The credible interval is the Bayesian analogue to the confidence intervals used in traditional frequentist statistical approaches. We considered a result "significant" if the CrI did not include RR/HR = 1 or MD/SMD=0.

Meta-analyses

If appropriate according to population, intervention, control and endpoint, we performed meta-analyses. First, we conducted pairwise meta-analyses for each available endpoint for all possible combinations of interventions and controls with available evidence from included trials. Random effect models were assumed. Estimates of RR, HR, MD, or SMD with corresponding 95% CI were provided. These analyses were performed using the software RevMan 5.3.

Second, we performed a network meta-analysis (NMA) for each endpoint individually. We did this by combining both direct and indirect effects of the interventions of interest for each endpoint. The analysis was based on Multiple Treatments Meta-analysis (MTM) as described by Salanti (9). We used the arm-based network meta-analysis method (a Bayesian method based on Markov Chain Monte Carlo simulation). All NMAs were performed using Winbugs version 1.4.3 (Imperial College and MRC, UK). The statistical analysis was based on binomial likelihoods (dichotomous endpoints) and normal likelihood (continuous endpoints), with vague priors for the trial baselines, basic parameters (normal distribution with mean 0 and standard deviation 0.0001) and the random effects standard deviation (uniformly distributed in the interval 0 to 2), and takes the correlation structure induced by multi-arm trials into account. For time-to-event endpoints (overall survival and progression free survival), with HR as the measure of effect, we used the method described by Woods et al. (10) to combine hazard ratios, cumulative number of events, and median survival statistics. We used a random effects model. We intended to check for incoherence between direct and indirect evidence by "node-splitting" (11) if the same comparison had both direct and indirect evidence. We calculated the direct and indirect estimates of effect and the corresponding Bayesian "P-values" for incoherence.

We ranked the different drug treatments in terms of their likelihood of leading to the best results for each endpoint. We based the rankings on the surface under the cumulative ranking curve (SUCRA) (12). We interpreted the rankings cautiously taking into account the quality of the evidence.

The estimated treatment effect based on the direct evidence from the network meta-analysis may differ somewhat from the results from the pairwise comparisons obtained from RevMan. The differences are due to the use of different methods (RevMan and network meta-analysis), but both are based upon the same pairwise dataset from the included trials.

Where data were available, we intended to carry out subgroup analyses for different categories of the population (for example previously untreated/treated patients) and different uses of the drugs (for example as mono-or combination therapy). However, we decided not to carry out these analyses due to scarcity in data.

Dealing with missing data

For the endpoint progression free survival, we assumed that participants who dropped out experienced disease progression if a hazard ratio between intervention and control was not reported. For all other endpoints, we did not perform imputations for missing data. We based the statistical analyses on the intention-to-treat principle (all participants analysed in the group to which they were allocated, and all available data included in the analyses).

Grading the quality of evidence

Two of the authors assessed the overall quality of the evidence for each endpoint using GRADE (Grading of Recommendations, Assessment, Development and Evaluation). We followed the guidelines provided by the GRADE working group (13) and categorized our confidence in the effect estimates into four levels: high, moderate, low or very low, table 1.

Table 1: Significance of the four levels of evidence

Grade	Definition
High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low	Any estimate of effect is very uncertain.

The quality of the direct evidence, indirect evidence, and the combined evidence from the network meta-analyses was evaluated using the GRADE approach for network meta-analyses (14). We assessed the quality of the evidence (the confidence we have to the estimates) using GRADE for all endpoints for all comparisons with direct evidence (head-to-head trials). This also allowed us to assess the quality of evidence for each loop of indirect evidence defined in the network meta-analysis. The quality of the indirect evidence was equal to the lowest quality of the comparisons in that loop. The quality of the combined evidence from the network meta-analysis is based upon the highest quality obtained from the respective direct and indirect assessments.

We used the Guideline Development Tool (GDT) (15), to enter results for and evaluating the quality of the direct evidence both from the RevMan analysis and the network meta-analysis. We also used the Guideline Development Tool to prepare "Summary of Findings tables".

Clinical evaluation - Results

Result of literature search

The literature search for randomized controlled trials was conducted in March 2015 and updated in October 2015. After removal of duplicates, we identified 625 references in the first search and an additional 267 references in the update search. We received 48 references from the pharmaceutical companies with marketing authorization for the relevant drugs in Norway. After reading titles and abstracts, we considered 126 references to be potentially eligible and read these publications in full text. We excluded 111 publications listed in appendix 2, and examined 16 publications for the present report. While preparing the draft of this report, we became aware of one additional article, published in January 2016 that met our inclusion criteria. In order to be as current as possible, we decided to include this publication (16). A flow diagram for the selection process is shown in figure 1.

Possibly relevant ongoing trials are listed in appendix 3.

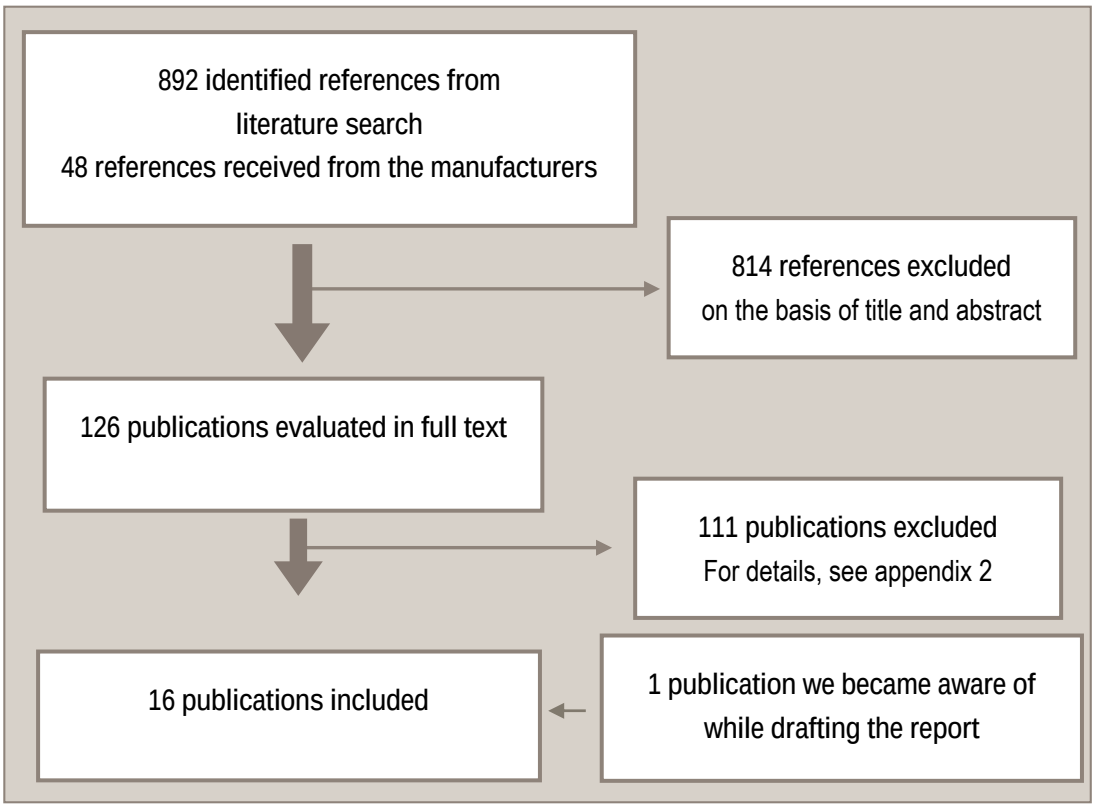

Figure 1 *Flow diagram of selection of literature*

Description of included trials

We included eight randomized controlled trials published from 2007 to 2016 in a total of 16 publications. An overview of the included publications is given in tables 2 to 5 and characteristics of the included trials are shown in appendix 4.

Table 2. Overview of included randomized controlled trials with abiraterone

Study	Intervention (number of patients)	Comparator (number of patients)	Population	Endpoints used in report	Follow-up (median duration of follow up for OS)
De Bono 2011 NCT00638690 (17)	Abiraterone acetate plus prednisone (n=797)	Placebo plus prednisone (n=398)	Previous treatment with docetaxel	Total no of deaths, OS, PFS	12.8 months
Fizazi 2012/ COU-AA-301 NCT00638690 (18)	As above	As above	As above	Total no of deaths, OS, PFS	20.2 months
Harland 2013 NCT00638690 (19)	As above	As above	As above	HRQoL	20.2 months
Ryan 2013/ COU-AA-302 NCT00887198 (20)	Abiraterone acetate plus prednisone (n=546)	Placebo plus prednisone (n=542)	No previous treatment with ketocanozole lasting more than 7 days	Total no of deaths, OS, PFS, SAE, HRQoL	22.2 months
Rathkopf 2014 NCT00887198 (21)	As above	As above	As above	OS, PFS, HRQoL	27.1 months*
Ryan 2015* NCT00887198 (22)	As above	As above	As above	Total no of deaths, OS, PFS, SAE	49.2 months

*Patients were allowed to cross over from the placebo/prednisone group to receive abiraterone after the 2nd interim analysis (22.1 months)

Table 3. Overview of included randomized controlled trials with cabazitaxel

Study	Intervention (number of patients)	Comparator (number of patients)	Population	Endpoints used in report	Follow-up (median duration of follow up for OS)
de Bono 2010/ TROPIC NCT00417079	Cabazitaxel plus prednisone	Mitoxantrone plus prednisone	Previous treatment with docetaxel	Total no of deaths, OS, PFS	12.8 months

(23)	(n=378)	(n=377)			

Table 4. Overview of included randomized controlled trials with enzalutamide

Study	Intervention (number of patients)	Comparator (number of patients)	Population	Endpoints used in report	Follow-up (median duration of follow up for OS)
Scher 2012/AFFIRM NCT00974311 (24)	Enzalutamide (n=800)	Placebo (399)	Previous treatment with docetaxel	Total no of deaths, OS, PFS, SAE	14.4 months
Fizazi 2014 NCT00974311 (25)	As above	As above	As above	HRQoL	
Beer 2014/ PREVAIL NCT01212991/ (26)	Enzalutamide (n=872)	Placebo (n=845)	No previous treatment with cytotoxic chemotherapy, ketocanozole, or abiraterone acetate	Total no of deaths, OS, PFS, SAE	26 months
Loriot 2015 NCT01212991 (27)	As above	As above	As above	HRQoL	
Shore 2015, Shore 2016/ TERRAIN NCT01288911 (16, 28)	Enzalutamide (n=184)	Bicalutamide (n=191)	No information available on prior chemotherapy	PFS, SAE, HRQoL	20.0 months

Table 5. Overview of included randomized controlled trials with radium-223

Study	Intervention (number of patients)	Comparator (number of patients)	Population	Endpoints used in report	Follow-up (median duration of follow up for OS)
Parker 2013, Hoskin 2014/ ALSYMPCA NCT00699751 (29, 30)	Radium-223 (n=614)	Placebo (n=307)	Both previous and no treatment with docetaxel	Total no of deaths, OS, PFS, SAE, HRQoL	
Nilsson 2007 (31)	Radium-223 (n=33)	Placebo (n=31)	No previously treatment with chemotherapy	OS, SAE	18 months

Population and setting

In total, 7,314 patients with histologically or cytologically confirmed diagnosis of progressive prostate cancer with soft tissue or bone metastases were included in the eight trials. The ECOG (Eastern Cooperative Oncology Group) performance status score was 2 or less for all participants. The patients had been previously treated with chemotherapy (mainly docetaxel) in three of the trials (AFFIRM, COU-AA-301 and TROPIC); two trials (ALSYMPCA and Nilsson 20017) included patients that had or had not received chemotherapy; and three trials included patients that had not received prior chemotherapy (PREVAIL, COU-AA-302 and TERRAIN). For the two trials with Radium-223, one of the inclusion criteria was detection of bone metastasis. The median age ranged from 67 to 73 years. The multinational trials were conducted in more than 20 countries in Europe, North America and Asia.

Interventions and comparators

The four interventions defined in our inclusion criteria (abiraterone, cabazitaxel, enzalutamide, and radium-223 dichloride [radium-223]) are represented in the included trials. Abiraterone was administered as four 250 mg tablets once daily in combination with 5 mg oral prednisone. Each cycle of treatment was 28 days. The control group received placebo tablets in combination with prednisone. Cabazitaxel was administered as 25 mg/m² intravenously at day one of each 21-day cycle. The comparator was 12 mg/m² mitoxantrone. The participants also received 10 mg oral prednisone daily in both arms. Enzalutamide was administered orally at a dose of 160 mg daily. The control group received placebo in two trials, and bicalutamide as 50 mg/day in one trial. Radium-223 was provided as four (Nilsson 2007) or six (ALSYMPCA) intravenous injections at a dose of 50 kBq per kilogram of body weight. The control arm received placebo. One injection was administered every 4 weeks.

Endpoints

Of the eight included trials, five reported on all our predefined endpoints: overall survival, progression free survival, health related quality of life and serious adverse events (Affirm, Prevail, COU-AA-301/302 and ALSYMPCA). The endpoints were well defined and harmonized in their definitions across the included trials. The Terrain trial reported on progression free survival, serious adverse events and health related quality of life. Nilsson 2007 reported on overall survival and serious adverse events, and the Tropic trial reported on overall survival and progression free survival.

Overall survival was defined as the time from randomization to death from any cause.

Progression free survival was defined as either a decrease in PSA of 50% or higher from the pretreatment baseline, time to PSA progression (defined as a 25% increase

over the nadir PSA value), radiographic progression-free survival defined as soft-tissue disease progression by modified Response Evaluation Criteria In Solid Tumors (RECIST) criteria or time to an increase in the total alkaline phosphatase level. We have used time to PSA progression in our analysis.

Health related quality of life was measured as change in FACT-P total score or as time to HRQoL deterioration (time from date of randomization to ≥10-point decrease in the global FACT-P score at a post baseline assessment compared with baseline).

Serious adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events. We defined serious adverse events as GRADE 3 and higher in our analysis.

Risk of Bias

We assessed the risk of bias for the endpoints in the included trials to be of either low, high or unclear risk of bias. We assessed most of the endpoints to be of low risk of bias, except for health related quality of life which we assessed as high risk since the endpoint was reported by the participant. We also assessed progression free survival at 27.1 month follow up in the trial with abiraterone that allowed cross over after the 2nd interim report (22.1 months) (21) to be of high risk of bias. The risk of bias assessments are shown in appendix 4.

Presentation of results

For each endpoint and each comparison, we performed pairwise comparison meta-analysis using RevMan and present the results in the text and Summary of Findings tables below. These analyses are based on the head-to-head comparisons in the included trials. We performed the analysis for patients that had or had not received chemotherapy (all patients), that were naive to chemotherapy (chemotherapy naive) and that had received chemotherapy (post chemotherapy).

In the network meta-analysis, we combined both direct and indirect effects of the interventions of interest for each endpoint and present the results as a figure (evidence network) and in tables. We have chosen to see all the comparators used in the trials. These comparators were either “placebo” or another treatment. We refer to these treatment comparators as “passive” treatments in our report.

We ranked the different drug treatments in terms of their likelihood of leading to the best results for each endpoint based on the surface under the cumulative ranking

curve (SUCRA). We present the results for the network meta-analysis for the endpoint overall survival. We have not presented the results for the other endpoint due to scarce data.

Abiraterone

Two trials (COU-AA-301, COU-AA-302) reported results for the direct comparison between abiraterone and placebo for both chemotherapy naive and previously treated participants. For all patient groups, abiraterone probably increases median overall survival, i.e. reduces risk of death, and decreases the total number of deaths during the follow-up period (moderate and low quality evidence), and probably increases the progression free survival period (moderate quality evidence) compared with passive treatment. Abiraterone probably improves the quality of life slightly (moderate quality evidence), but probably causes more serious adverse events (moderate quality evidence). All results and quality ratings are shown in the Summary of Findings table, table 6.

Table 6 Summary of findings table for abiraterone versus placebo

Outcomes** Population	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of evidence
	Assumed risk Placebo	Corresponding risk Abiraterone			
Total no of deaths					
All patients	645 per 1 000	535 per 1 000 (451 to 645)	RR 0.83 (0.70 to 1.00)	2283 (2 studies)	⊕⊕◯◯ Low [3,4]
Median overall survival (months)					
All patients			HR 0.77 (0.70 to 0.86) [1]	2283 (2 RCTs) [2]	⊕⊕⊕◯ MODERATE [3]
Chemotherapy naive	30.3 (28.7 to 33.3)	34.7 (32.7 to 36.8)	HR 0.81 (0.70 to 0.93) [1b]	1088 (1 RCT) [2b]	⊕⊕⊕◯ MODERATE [3b]
Post chemotherapy	11.2 (10.4 to 13.19	15.8 (8.3 to 11.1)	HR 0.74 (0.64 to 0.86)	1195 (1 RCT) [1c]	⊕⊕⊕◯ MODERATE [4b]
Progression free survival (median time until PSA progression)					
All patients			HR 0.56 (0.44 to 0.70)	(2 RCTs) [2]	⊕⊕◯◯ LOW [4,5]
Chemotherapy naive			HR 0.50 (0.43 to 0.58)	(1 RCT) [2b]	⊕⊕⊕◯ MODERATE [4b]
Post chemotherapy			HR 0.63 (0.52 to 0.78)	1195 (1 RCT) [1c]	⊕⊕⊕◯ MODERATE [4b]
Free from HRQoL deterioration - FACT-P					

All patients			HR 0.70 (0.54 to 0.90)	(2 RCTs) [2]	⊕⊕◯◯ LOW [4,5]
Chemotherapy naive			HR 0.79 (0.67 to 0.93)	(1 RCT) [2b]	⊕⊕⊕◯ MODERATE [4b]
Post chemotherapy			HR 0.61 (0.50 to 0.74)	(1 RCT) [1c]	⊕⊕⊕◯ MODERATE [4b]
Serious adverse events					
All patients	437 per 1 000	533 per 1 000 (472 to 607)	RR 1.22 (1.08 to 1.39)	1082 (1 RCT) [6]	⊕⊕⊕◯ MODERATE [5]
Chemotherapy naive	437 per 1 000	533 per 1 000 (472 to 607)	RR 1.22 (1.08 to 1.39)	1082 (1 RCT) [2b]	⊕⊕⊕◯ MODERATE [4b]
Post chemotherapy	The results for adverse events are given as events per adverse event. It is not possible to provide an overall estimate for SAE without a risk of double counting				

*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).

**Follow up 12.8 to 49.2 months

CI: Confidence 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. Follow-up relative effect is 20,2 months
2. COU-AA 301 and COU-AA 302
3. Wide range in number of deaths
4. I-square>70%
5. Wide CI
6. COU-AA 302
7. Follow-up for absolute estimates is 12.8 months in one trial and 49.2 months in the other trial

1b. Follow-up relative effect is 20,2 months
2b. COU-AA-302
3b. Wide range in number of deaths
4b. Wide CI
5b. Follow-up for absolute estimates is 12.8 months

1c. COU-AA-301

Cabazitaxel

One trial (TROPIC) reported results for the direct comparison between cabazitaxel and mitoxantrone for patients previously treated with chemotherapy. Cabazitaxel probably slightly increase median overall survival, i.e. reduces risk of death, and decreases the total number of deaths during the follow up period (moderate quality evidence), and probably slightly increases the progression free survival period (moderate quality evidence) compared with passive treatment. We did not find any results for health related quality of life. We did not perform any analysis for serious adverse events, but the TROPIC trial concluded that the most common significant grade 3 or

higher adverse events were neutropenia (82 % in the cabazitaxel group vs 58 % in the mitoxantrone group) and diarrhea (6 % vs <1 %). All results and quality ratings are shown in the Summary of Findings table, table 7.

Table 7 Summary of findings table for cabazitaxel versus mitoxantrone

Outcomes** Population	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of partici-pants (studies)	Quality of evidence
	Assumed risk mitoxantrone	Corresponding risk cabazitaxel			
Total no of deaths					
Post che-motherapy	740 per 1 000	622 per 1 000 (562 to 681)	RR 0.84 (0.76 to 0.92)	755 (1 study)	⊕⊕⊕◯ MODERATE [2]
Median overall survival (months)					
Post che-motherapy	12.7 (11.6 to 13.7)	15.1 (14.1 to 16.3)	HR 0.70 (0.59 to 0.83)	755 (1 RCT) [1]	⊕⊕⊕◯ MODERATE [2]
Progression free survival (median time until PSA progression)					
Post che-motherapy			HR 0.75 (0.63 to 0.90)	(1 RCT) [1]	⊕⊕⊕◯ MODERATE [2]
Serious adverse events					
Post che-motherapy	TROPIC trial concluded that the most common significant grade 3 or higher adverse events were neutropenia (82 % in the cabazitaxel group vs 58 % in the mitoxantrone group) and diarrhea (6 % vs <1 %).				

*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).

** Follow up 12.8 months

CI: Confidence 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. TROPIC
2. Wide CI

Enzalutamide

Three trials (AFFIRM, PREVAIL and TERRAIN) reported results for the direct comparison between enzalutamide and placebo or bicalutamide for patients naive to chemotherapy and previously treated.

For the all patients group, enzalutamide probably increase median overall survival, i.e. reduces risk of death, and decreases the total number of deaths during the follow-up period (moderate quality evidence) and probably increases the progression free survival period (moderate quality evidence) compared with placebo or passive treatment. Enzalutamide probably improves the quality of life slightly (moderate quality evidence) and there may be little or no difference between the treatment groups when it comes to serious adverse event (low quality evidence). All results and quality ratings are shown in the Summary of Findings table, table 8.

Table 8 Summary of findings table for enzalutamide versus placebo or bicalutamide

Outcomes** Population	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of evidence
	Assumed risk Placebo or bicalutamide	Corresponding risk Enzalutamide			
Total no of deaths					
All patients	457 per 1 000	352 per 1 000 (316 to 393)	RR 0.77 (0.69 to 0.86)	2916 (2 RCTs) [1]	⊕⊕⊕◯ MODERATE [2]
Median overall survival (months)					
All patients			HR 0.68 (0.59 to 0.79)	2916 (2 RCTs) [1]	⊕⊕⊕◯ MODERATE [2]
Chemotherapy naive	31.0	Not reached (estimated at 32.4)	HR 0.73 (0.63 to 0.85)	1717 (1 RCT) [1b]	⊕⊕⊕◯ MODERATE [2b]
Post chemotherapy	13.6 (11.3 to 15.8)	18.4 (17.3 to not yet reached)	HR 0.63 (0.53 to 0.75)	1199 (1 RCT) [1c]	⊕⊕⊕◯ MODERATE [2c]
Progression free survival (median time until PSA progression)					
All patients			HR 0.22 (0.16 to 0.30)	(3 RCTs) [3]	⊕⊕⊕◯ MODERATE [4]
Chemotherapy naive			HR 0.21 (0.13 to 0.34)	(2 RCTs) [3b]	⊕⊕◯◯ LOW [4b,5b]
Post chemotherapy			HR 0.25 (0.20 to 0.30)	(1 RCT) [1c]	⊕⊕⊕◯ MODERATE [3c]
Progression free survival (radigraphic) Chemotherapy naive (used in economic evaluation)			HR 0.31 [0.11, 0.83]		⊕⊕◯◯ LOW [4b,5b]
Free from HRQoL deterioration - FACT-P					
All patients			HR 0.56 (0.44 to 0.71)	(3 RCTs) [3b]	⊕⊕⊕◯ MODERATE [4b]
Chemotherapy naive			HR 0.63 (0.55 to 0.72)	(2 RCTs) [3b]	⊕⊕⊕⊕ HIGH

Post che-motherapy			HR 0.45 (0.37 to 0.55)	(1 RCT) [1c]	⊕⊕⊕◯ MODERATE [3c]
HRQoL FACT-P (negated)					
All patients	The mean hRQoL FACT-P (negated) was 0	The mean hRQoL FACT-P (negated) in the intervention group was 5,8 more (3,18 more to 8,41 more)	-	1717 (1 RCT)	⊕⊕⊕◯ MODERATE [5]
Chemotherapy naive	-	-		-	-
Post che-motherapy	-	-		-	-
Serious adverse events					
All patients	336 per 1 000	366 per 1 000 (272 to 487)	RR 1.09 (0.81 to 1.45)	3289 (3 RCTs) [3]	⊕⊕◯◯ LOW [4,6]
Chemotherapy naive	261 per 1 000	318 per 1 000 (277 to 365)	RR 1.22 (1.06 to 1.40)	2090 (2 RCTs) [3b]	⊕⊕⊕◯ MODERATE [5b]
Post che-motherapy	531 per 1 000	452 per 1 000 (404 to 510)	RR 0.85 (0.76 to 0.96)	1199 (1 RCT) [1c]	⊕⊕⊕◯ MODERATE [3c]

*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).

**Follow up 14 to 26 months

CI: Confidence 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. AFFIRM, PREVAIL
2. Wide range in number of deaths
3. AFFIRM, PREVAIL, TERRAIN
4. I-square > 65%
5. Wide CI
6. The 95% CI overlaps no effect

1b. PREVAIL
2b. Wide range in number of deaths
3b. PREVAIL and TERRAIN
4b. I-square>70%
5b. Wide CI

1c. AFFIRM
2c. Wide range in number of deaths
3c. Wide CI

Radium-223

Two trials (ALSYMPCA and Nilsson 2007) reported results for the direct comparison between radium-223 and placebo. Participants included patients that had received docetaxel, were not healthy enough or declined to receive it, or it was not available. For the all patient group, radium-223 probably increases median overall survival, i.e. reduces risk of death, and decreases the total number of deaths during the follow-up period (moderate quality evidence), and probably increases the progression free survival period (moderate quality evidence) compared with passive treatment. Radium-223 probably improves the quality of life slightly (moderate quality evidence) and there may be little or no difference between the treatment groups when it comes to serious adverse events. All results and quality ratings are shown in the Summary of Findings table, table 9.

Table 9 Summary of findings table for radium-223 versus placebo

Outcomes Population	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of evidence
	Assumed risk Placebo	Corresponding risk Radium-223			
Total no of deaths					
All patients	562 per 1 000	472 per 1 000 (427 to 528)	RR 0.84 (0.76 to 0.94)	1035 (2 RCTs	⊕⊕⊕◯ MODERATE [2]
Median overall survival (months)					
All patients	11.3[1b] 46.4[1c] (32.1 to 77.4) weeks	14.9[1b] 65.3[1c] (48.7 to ∞) weeks	HR 0.65 (0.48 to 0.87)	985 (2 RCTs) [1]	⊕⊕⊕◯ MODERATE [2]
Chemotherapy naive			HR 0.69 (0.52 to 0.92)	(1 RCT) [1b]	⊕⊕⊕◯ MODERATE [2b]
Post chemotherapy			HR 0.70 (0.56 to 0.88)	(1 RCT) [1c]	⊕⊕⊕◯ MODERATE [2c]
Progression free survival (median time until PSA progression)					
All patients			HR 0.64 (0.54 to 0.77)	(1 RCT) [3]	⊕⊕⊕⊕ HIGH
Chemotherapy naive			HR 0.52 (0.39 to 0.68)	(1 RCT) [1b]	⊕⊕⊕◯ MODERATE [2b]
Post chemotherapy			HR 0.74 (0.59 to 0.93)	(1 RCT) [1c]	⊕⊕⊕◯ MODERATE [3c]
Free from HRQoL deterioration - FACT-P					
All patients	-	-	-	-	-

Chemotherapy naive	-	-	-	-	-
Post chemotherapy	-	-	-	-	-
HRQoL FACT-P (negated)					
All patients	The mean hRQoL (negated) was 0	The mean hRQoL (negated) in the intervention group was 4,1 fewer (7,02 fewer to 1,18 fewer)	-	(1 RCT)	⊕⊕⊕◯ MODERATE [4]
Chemotherapy naive					
Post chemotherapy					
Serious adverse events					
All patients	598 per 1 000	472 per 1 000 (299 to 735)	RR 0.79 (0.50 to 1.23)	985 (2 RCTs) [1]	⊕⊕◯◯ LOW [5,6]
Chemotherapy naive	592 per 1 000	575 per 1 000 (480 to 687)	RR 0.97 (0.81 to 1.16)	383 (1 RCT) [1b]	⊕⊕◯◯ LOW [3b]
Post chemotherapy	749 per 1 000	614 per 1 000 (546 to 696)	RR 0.82 (0.73 to 0.93)	518 (1 RCT) [1c]	⊕⊕⊕◯ MODERATE [4c]

*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).

CI: Confidence 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. ALSYMPCA, Nilsson 2007
2. Wide range in number of deaths
3. ALSYMPCA
4. Wide CI
5. I-square = 50%
6. CI includes both benefit and harm

1b. ALSYMPCA
2b. Wide CI
3b. Wide CI including both benefit and harm

1c. ALSYMPCA
2c. Wide range in death ratio
3c. Wide CI
4c. Wide range in harm

Network meta-analysis for overall survival

The evidence network for overall survival is shown in figure 2.

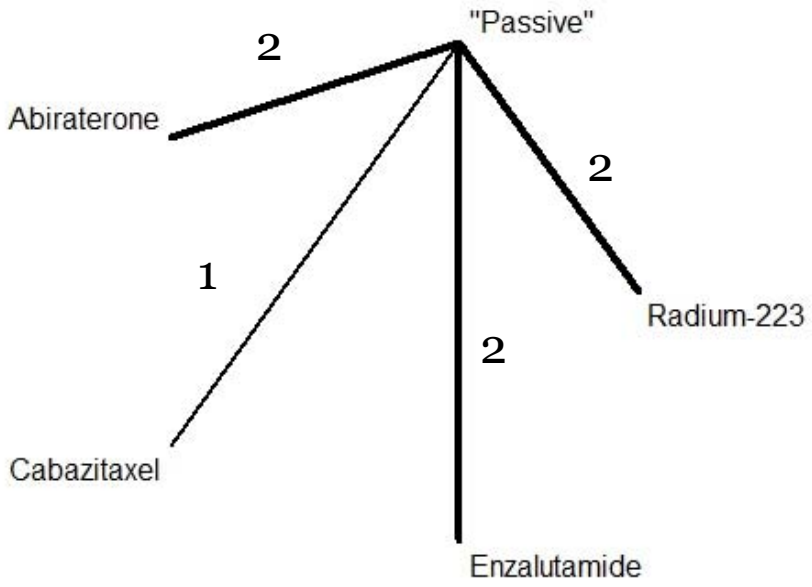

Figure 2. *Evidence network for overall survival*

A summary of results for the random effects network meta-analyses for the comparisons between the interventions and the common comparator placebo or passive treatment are presented in table 10. In addition, a ranking of the included interventions is presented using surface under the cumulative ranking curve (SUCRA).

Table 10 Hazard ratios for overall survival from network meta-analyses

Intervention	Hazard Ratio relative to placebo or passive treatment (network meta-analysis)	SUCRA	Quality of evidence for the network meta-analysis
Radium-223	0.65 (0.26-1.36)	0.76	Low
Cabazitaxel	0.70 (0.24-1.98)	0.62	Low
Enzalutamide	0.73 (0.45-1.75)	0.56	Low

Abiraterone	0.77 (0.39-1.67)	0.46	Low
Placebo or passive treatment / prednisone	1	0.11	-

Based on results of the network meta-analysis we found that all the drugs showed a benefit compared to placebo/passive treatment, but the credible intervals included both benefit and harm. Our confidence in these estimates are low due to this imprecision. The ranking measured by SUCRA suggests that radium-223 have the highest probability of good performance.

Hazard ratios and quality assessments for direct and indirect comparisons for median overall survival from the network-meta analysis are shown in table 11.

Table 11 Estimates of overall survival and quality assessments for direct and indirect comparisons from network meta-analysis

Comparison (study)	Direct evidence		Indirect evidence		Network meta-analysis	
	HR (95% CI)	Quality of evidence	HR (95% CI)	Quality of evidence	HR (95% CI)	Quality of evidence
Abiraterone vs placebo	0.77 (0.39-1.67)	Low	-	-	0.77 (0.39-1.67)	Low
Cabazitaxel vs placebo	0.70 (0.24-1.98)	Low	-	-	0.70 (0.24-1.98)	Low
Enzalutamide vs placebo (xxx)	0.73 (0.45-1.75)	Low	-	-	0.73 (0.45-1.75)	Low
Radium-223 vs placebo	0.65 (0.26-1.36)	Low	-	-	0.65 (0.26-1.36)	Low
Abiraterone vs Enzalutamide	-	-	1.07 (0.33-2.51)	Low	1.07 (0.33-2.51)	Low
Abiraterone vs Radium-223	-	-	1.19 (0.44-4.24)	Low	1.19 (0.44-4.24)	Low
Cabazitaxel vs Enzalutamide	-	-	0.97 (0.22-2.83)	Low	0.97 (0.22-2.83)	Low
Cabazitaxel vs Radium-223	-	-	1.08 (0.31-4.41)	Low	1.08 (0.31-4.41)	Low
Cabazitaxel vs Abiraterone	-	-	0.91 (0.23-3.06)	Low	0.91 (0.23-3.06)	Low
Radium-223 vs Enzalutamide	-	-	0.89 (0.24-2.03)	Low	0.89 (0.24-2.03)	Low

The full network meta-analysis results comparing all available treatments are presented in appendix 5. The quality rating assessments (GRADE evaluations) are shown in detail in appendix 6.

For overall survival, the results of the pairwise estimates from the RevMan analyses and the corresponding comparisons in the network meta-analyses, are consistent. That means, the results from network meta-analyses and pairwise comparisons are similar in magnitude and direction. However, the degree of uncertainty is higher for the estimates from the network meta-analysis due to lower precision (i.e. wide CrIs).

Economic evaluation - Methods

General

We conducted a cost-utility analysis in order to assess the cost-effectiveness of new medications for patients with castration-resistant metastatic prostate cancer (mCRCP). All costs are in 2016 Norwegian kroner (NOK). Effects are measured as quality-adjusted life-years (QALYs). Both costs and effects were discounted at an annual discount rate of 4% as recommended by the Norwegian Ministry of Finance and guidelines for health economic evaluation in the health sector (32).

The analysis employed a health care perspective, which includes direct costs and effects related to the health care sector. This is the most appropriate perspective for prioritizing interventions when the decision maker's objective is to maximize health within a fixed health care budget. An alternative perspective, recommended by methodological guidelines for economic evaluation in the health sector, is a societal perspective that includes consequences for all part of the economy, including time costs, the deadweight loss of taxation and any productivity changes, but excluding transfers such as value added tax. This perspective is more appropriate if an increase in the health budget is assumed or in settings where prioritization of interventions across sectors of the economy is relevant, as for public health interventions.

We expressed results as mean incremental cost-effectiveness ratios (ICERs) from 10,000 runs of the base-case model. To examine uncertainty in model parameters, we performed probabilistic sensitivity analysis, designed as a Monte Carlo simulation with 10,000 iterations.

Interventions and Model Structure

Interventions

We evaluated four medications (Table 12), which we refer to by their active ingredients, for treatment of patients with mCRPC: abiraterone, enzlutamide, radium-223 and cabazitaxel.

Table Econ1. *Interventions included in the health economic analyses*

Interventions
Abiraterone acetate, 250 mg (Zytiga)
Cabazitaxel, 60 mg (Jevtana)
Enzalutamide, 40 mg (Xtandi)
Radium-223 dichloride*, 100 kBq (Xofigo)

*maximum of 6 treatments

Model structure

To assess the cost-effectiveness of the relevant medications for patients with castration-resistant, metastatic prostate cancer we developed a probabilistic Markov model using TreaAge Pro ® 2015. Markov models follow a cohort of patients over a specified time horizon as they progress through disease-related health states, making them an appropriate choice for modeling chronic illnesses (6).

Our model (Figure 3) includes three mutually exclusive disease-related states: Progression-free disease (PFS) (1), Progressed disease (PD) (2), and Death (3). All patients enter the model in the progression-free disease state. At the end of each model cycle patients can either remain in their current state or progress to another state as shown by the arrows. Transition probabilities, derived from overall survival (OS) and progression-free survival (PFS) data, determine the movement of patients through the model at each cycle. Patients cannot return to an earlier state, that is, treatments are not curative and death is an absorbing state. Costs and utilities (effects) are assessed at each cycle.

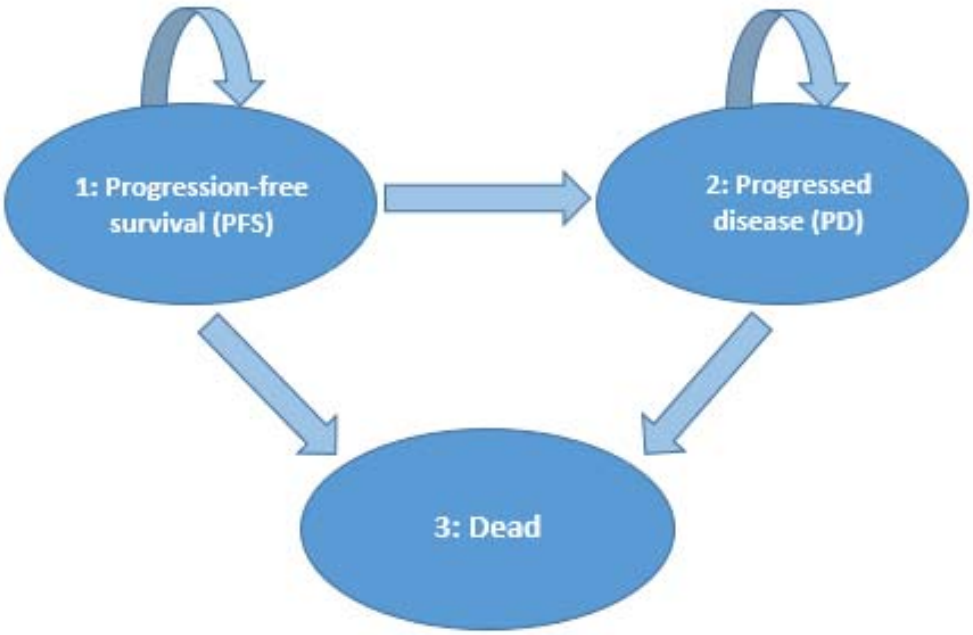

Figure 3. *Diagram of the health states and possible transitions in the Markov model.*

Based on advice from clinical experts we created two versions of the model: one for the population of mCRPC patients who had progressed on or after chemotherapy treatment with docetaxel (*post-docetaxel*) and a second for mCRPC patients for whom docetaxel was not yet considered an appropriate treatment (*docetaxel-naive*). The model time horizon for the post-docetaxel and docetaxel-naive models are five and seven years, respectively. Both models have a cycle length of one month. The small number of patients in the included trials who were still alive and under follow-up after indicated time horizons made it impossible to reliably extrapolate survial results beyond that time frame. This issue is discussed in detail in Appendix 7. The post-docetaxel model included all four interventions; the docetaxel-naive model excluded cabazitaxel and radium-223.[1] In both models, we used Best Supportive Care (BSC) as the comparator.

Model Parameters

The methods used to derive model parameters and the information sources are described below. Detailed information can be found in Appendices 7 – 10.

[1] Cabazitaxel was excluded from the docetaxel-naive model because its marketing authorization is only for patients who have had prior treatment with docetaxel. Radium-223 was excluded after careful analysis indicated that it was not cost-effective at any price relative to BSC.

Transition probabilites

Choice of survival data for comparator (Best Supportive Care)
When possible, the efficacy measures (hazard ratios) from the clinical trials should be applied to Norwegian epidemiological data for the relevant patient group in order to capture the effect of treatment on clinical outcomes; however, no appropriate Norwegian data was available. Although a prostate cancer registry exists in Norway, it does not track survival for the mCRPC population. A study (33) of survival and prognostic factors among Norwegian mCRPC patients without life-prolonging treatment estimated overall survival, but provided no information about progression-free survival. In addition, because patients in the study were those who could not have had treatment with docetaxel, the overall survival results might not have been comparable to results in the included trials. We therefore decided to draw data for the comparator arm in each model from the comparator arm of an included trial for which patient-level data, detailing time-to-event and censoring information, was available from the pharmaceutical company.

Initially, we planned to use patient-level data provided for the comparator arms from the radium-223 ALSYMPCA trial, a single trial designed to assess the clinical effect of radium-223 among mCRPC patients who were docetaxel-naive and those who had prior docetaxel treatment. However, we determined that transitions to progressed disease and to death occurred more quickly in the radium-223 trial than among the other interventions and decided that this could significantly bias the results for the other interventions in the model. As a result, we decided to choose the appropriate comparator arm for the model from one of the other trials. Appendix 7 provides details about our decisions.

Patient-level data were provided for abiraterone, but only for docetaxel-naive patients so we used it as the comparator in the docetaxel-naive model. The patient-level data measured radiographic progression-free survival (rPFS), so that is the measure of progression used in the model. For the post-docetaxel model, we relied on the BSC arm from the enzalutamide (AFFIRM) trial (24) because there was longer follow-up than was available for the other interventions. We also used rPSF as the measure of progression in the post-docetaxel model.

In order to avoid bias in the analysis of radium-223 we decided to use patient-level data from the intervention arm of the radium-223 ALSYMPCA trial to estimate transition probabilities for the radium treatment arm in our model, rather than applying the hazard ratio from the radium trial to the model comparator. After careful analysis, we determined that radium-223 was not a relevant treatment choice among docetaxel-naive patients.

Calculating transition probabilities
To estimate transition probabilities for the models we first needed to determine the cumulative density functions for overall survival and progression-free survival for

control arm and radium-223 treatment arm for each model. Doing so requires patient-level time-to-event data used to construct Kaplan-Meier curves. We received this data for radium-223 (post-docetaxel and docetaxel-naive) and for abiraterone (docetaxel-naive) and were able to fit parametric survival functions using R version 3.2.2, with best fit assessed using the Akaike information criterion (AIC) (Table 13). Because there is no formal test for goodness-of-fit based on AIC, we checked that survival probabilities estimated using the parametric functions were consistent with reported Kaplan-Meier results. The fitted parametric functions allowed us to extrapolate survival beyond the study follow-up period and estimate transition probabilities for the model time horizon.

For the post-docetaxel model, we did not receive any patient-level data so we extracted survival probabilities, measured in 3-month intervals, from Kaplan-Meier plots for the control arm in the enzalutamide AFFIRM study (24). We then used Excel 2013 to fit an exponential trend line relationship to the Kaplan-Meier survival data and used it to extrapolate survival probabilities for the model time horizon.

Table 13. *Fitted distributions or trend lines for overall survival and progression free survival in BSC and radium-223 arms*

	Data source	Overall survival	Progression free survival
		Post-docetaxel model	
BSC	K-M plots from BSC arm AFFIRM study Scher (2012)	OS = exp(-0.052*cycle) R^2=0.9847	PFS = exp(-0.194*cycle) R^2=0.9752
Radium-223	Patient level data ALSYMPCA	*Log-logistic* shape = 2.0349 scale = 14.1281	*Generalized gamma* mu = 1.1952 sigma = 0.2452 Q = - 1.4162
		Docetaxel-naive model	
BSC	Patient level data COU-AA-302	*Gamma* shape = 2.5376 rate = 0.0706	*Log-normal* meanlog=2.1287 sdlog=1.0852

We used the transition probability formula detailed in Briggs (34) as the basis for calculating transition probabilities from alive to dead (transitions from health state 1 to 3 and 2 to 3) and from progression free survival to progressed disease (1 to 2). From the fundamental relationships for probabilities of mutually exclusive events, it follows that in theory the transition probability from PFS to PD is one minus the probability of death minus the probability of remaining in the PFS state.

In practice, however, trial results report only the overall survival rate, which includes survival from both the progression free and progressed disease states. Using the fundamental relationship described above can lead to double counting. To avoid

this possibility, we calculate the transition probability from PFS to PD in two steps, as shown in the decision tree (Figure 4), first with regard to death (overall survival) and then for progression, conditional on having survived.

It is still necessary to assume something about the relationship between survival in the progress-free state versus the progressed disease state. One possibility would be to assume that the two are equal, in other words, that the probability of death is independent of progression status. Because this seemed unreasonable for mCRPC patients, we permitted unequal probabilities of death from the PFS and PD states, but assumed a constant value of 3 for the ratio of the probability of death from PD to the probability of death from PFS. Appendix 8 provides a more detailed explanation of estimating transition probabilities for the models.

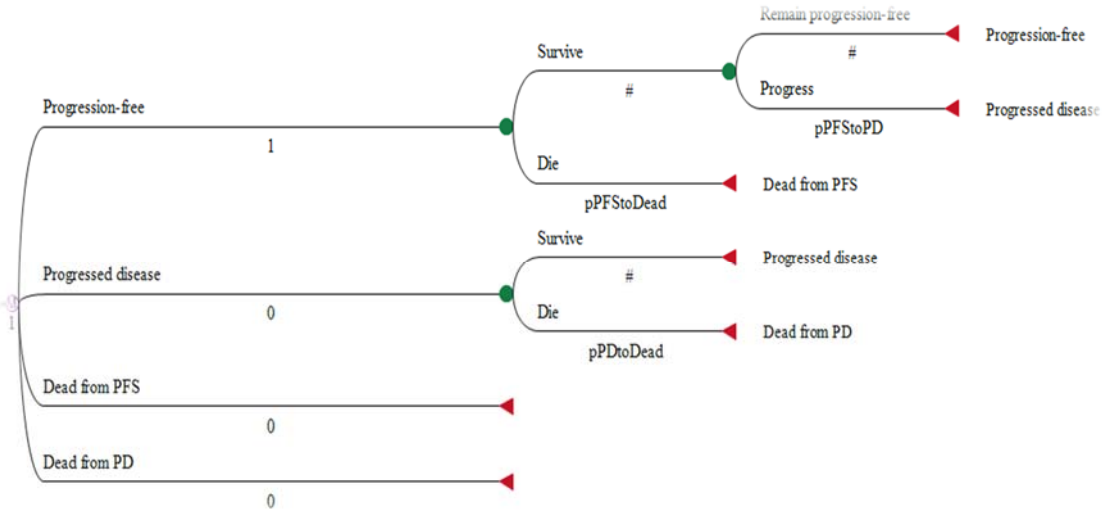

Figure 4. Decision tree strutcture for the Markov model

Treatment Effects

We compared the interventions in each model by applying hazard ratios taken from the effect section of this report (Tables 6-9)[2] to the BSC arm chosen for each model.[3] The hazard ratio for OS among docetaxel-naive abiraterone patients reflects the ITT population and is unadjusted for crossover that was allowed after the trial's second interim analysis. We conducted a scenario analysis that substituted a hazard ratio that was adjusted crossover. Because our comparator transition probabilities relied on radiographic progression-free survival (rPFS) we also used the rPFS hazard ratios in the models, except for cabazitaxel and radium-223 in the post-docetaxel model

[2] Hazard ratios for radiographic PFS, which reflect a single study, are taken from Appendix 4.
[3] As discussed above, we incorporate the treatment effects for radium-223 by using transition probabilities derived from patient-level data rather than applying a hazard ratio relative to the model comparator arm.

because only PSA progression was reported. Table 14 reports all hazard ratios used in the models.

We made several assumptions in constructing the economic model:

- BSC patients in the individual studies are assumed to be drawn from the same population so that it is possible to apply hazard ratios from one intervention to the transition probabilities of the BSC group from a different intervention
- The relationship between the time-to-events (survival and disease progression) of BSC and each of the treatments is constant over time.
- The hazard ratio for overall survival applies equally to individuals in the PFS and PD states.

We captured uncertainty around the hazard ratios using log-normal distributions.

Table 14. *Hazard ratios* used to modify the basecase probability of death and radiographic progression, by model version*

A. *Post-docetaxel model* [a]

Active ingredient	Overall Survival (95% CI)	Radiographic PFS (95% CI)
Abiraterone	0.74 (0.64, 0.86)	0.66 (0.58, 0.76)
Enzalutamide	0.63 (0.53, 0.75)	0.40 (0.35, 0.47)
Cabazitaxel	0.70 (0.59, 0.83)	0.75 (0.63, 0.90)[b]

[a] For Radium-223, we base transition probabilities on patient data rather than hazard ratios.
[b] based on PSA PFS

B. *Docetaxel-naive model*

Active ingredient	Overall Survival (95% CI)	Radiographic PFS (95% CI)
Abiraterone	0.81 (0.70, 0.93)[a]	0.52 (0.45, 0.61)
Enzalutamide	0.73 (0.63, 0.85)	0.31 (0.11, 0.83)

[a] OS hazard ratio for abiraterone is based on the ITT population and is unadjusted for crossover that was permitted in the COU-AA-301 trial after 27.1 months. The OS hazard ratio, adjusted for crossover was 0.74 (0.60, 0.88).

* OS hazard ratios are taken from Tables 6-9. Radiographic PFS hazard ratios reflecting a single study are from Appendix 4

Costs

For each treatment alternative, we calculated the average monthly cost per patient in the PFS and PD health states. Included costs were drug costs (with drug administration costs, where applicable), patient monitoring costs, hospital costs associated with serious adverse events or palliative care during treatment, and costs of end-of-life care. For the docetaxel-naive version of the model, we also included the cost of further treatment with an alternative intervention after disease progression occurs under the initial intervention.

We relied on DRG codes (35) for unit costs associated with hospital care; tariffs from the Regulations on ambulatory services for unit costs of a range of outpatient test and consultations; and information from county health services and private providers for costs associated with services not provided by the secondary health system. We assumed that most mCRPC patients would quickly reach their maximum annual copay contribution, so we included relevant copayment amounts in our calculations as they represent costs that must be covered by the health care system. All costs were measured in 2016 Norwegian kroner (NOK). Appendix 9 provides detailed information on all cost calculations. A summary of unit costs used in the calculations is included in the appendix as Table 9.1.

We used gamma distributions to capture uncertainty around estimated costs.

Drug costs

Drug costs included in the model reflect the maximum pharmacy retail (AUP) price, including VAT. This will most likely provide an unrealistic assessment of a treatment's cost-effectiveness. We planned to conduct sensitivity analyses to determine the price at which each drug can be considered cost-effective.

Table 15 presents monthly drug costs, estimated based on recommended doses. For tablets, monthly drug cost is the price of a daily dose multiplied by 365/12. We assumed that patients receive treatment with their initial intervention only while they remain progression free.

Table 15. *Drug costs per patient, including VAT (NOK)*

Drug	Dosage and recommended treatment regimen [a]	Dosage form [a]	AUP price (NOK) [a]	Units per package [a]	Monthly drug cost (NOK)
Abiraterone (Zytiga)	1,000 mg taken as single daily dose [b]	Tablet 250 mg	33,875.25	120	34,346
Enzalutamide (Xtandi)	160 mg taken as single daily	Tablet 40 mg	33,015.30	112	35,865
Radium-223 (Xofigo)	50 kBq per kg, at 4 week intervals for 6 injections	Vial	45,010.40	1 [c]	45,010
Cabazitaxel (Jevtana)	25 mg/m^2 every 3 weeks (IV) [b]	Vial	43,624.70	1 [c]	62,994
Prednisolone (Nycomed)	10 mg. daily	Tablet 5mg	82.00	100	50

IV: intravenous; mg: milligram; kg: kilogram; kBq: kilobecquerel
[a] Source: Norwegian Medicines Agency (SLV) 2016.
[b] Taken with 10 mg prednisolone, daily.
[c] Assumes that excess amounts of preparation cannot be used for another patient.

Radium-223 and cabazitaxel are administered intravenously at a hospital or clinic. Each involves material and time costs associated with preparation and administration of the treatment and, in the case of cabazitaxel, of required pre-treatment medications. Estimated per-cycle drug administration costs were NOK 400 for radium-223 and NOK 1565 for cabazitaxel. Appendix 9, Table 9.2 provides details.

Monitoring costs

A Norwegian Medicines Agency report on abiraterone (36) provided detailed information on resources used in Norway to monitor patients in the intervention and prednisolone (BSC) arms of the COU-AA-301 trial. We relied on expert advice from Arne Stensrud Berg (attending physician, Cancer division, Drammen Hospital) and Andreas Stensvold (leader, Cancer division, Østfold Hospital) to verify that the information is still current. Based on their advice we applied the same resource use to enzalutamide, radium-223 and cabazitaxel, with two exceptions. The additional monitoring required for abiraterone patients during the first three months of treatment is not necessary for the other medications. Cabazitaxel has slightly higher resource use in the progression-free state because medical examinations occur every third week (during the treatment visit), rather than on a monthly basis. We calculated monitoring costs separately for the PFS and PD health states, but assumed that these costs did not vary between the post-docetaxel and docetaxel-naive model versions. Table 16 provides total monitoring costs by health state. Appendix 9, Table 9.3 provides detailed information about the components of monitoring costs.

Table 16. *Monthly monitoring costs (NOK) by health state* [a]

Treatment	Progression free	Progressed disease
BSC	3158	4389
Abiraterone (during 1st 3 months)	6229	NA
Abiraterone (beyond 1st 3 months) Enzalutamide Radium-223	3158	4389
Cabazitaxel	4564	4389

NA: not applicable

[a] Sources for resource use: SLV (2012); Expert advice.

Treatment-related serious adverse events (SAEs)

All serious adverse events related to treatment are assumed to occur in the progression free health state. The monthly probability of experiencing an SAE varies according to treatment received and whether the patient has had prior docetaxel treatment or is docetaxel-naive. Because SAEs reported in the clinical effects portion of this report were based on combined results across docetaxel status, and definitions of SAEs varied somewhat across studies, we collected the data used to calculate

monthly probabilities of SAEs from ClinicalTrials.gov, which requires reporting of SAEs based on a consistent definition (37). Table 17 reports the expected monthly hospital costs associated with SAEs and monthly rates of SAE occurrence. Appendix 9, Table 9.4 provides detailed the information behind the calculations.

Table 17. *Monthly hospital costs (NOK) of treatment-related serious adverse events, by docetaxel status*

Treatment	Post-docetaxel model		Docetaxel-naive model	
	Rate per monthly cycle	Cost	Rate per monthly cycle	Cost
BSC	0.0434	908	0.0180	300
Abiraterone	0.0301	636	0.0178	376
Enzlutamide	0.0410	866	0.0252	532
Radium-223	0.0621	1312	0.0465	982
Cabazitaxel	0.0380	803	NA	NA

NA: Not applicable

Radiotherapy

Radiotherapy can be an important component of pain management for mCRPC patients. The frequency of therapy and the percent of patients who receive it can vary according to health state (PFS vs. PD), and treatment intervention. Our experts advised that patients receiving treatment with radium-223 generally have less need for radiotherapy. Table 18 presents the cost of radiotherapy for these groups. Appendix 9, Table 9.5 provides detailed information behind the calculations.

Table 18. *Monthly cost of radiotherapy (NOK) by health state* [a]

Treatment	Progression free	Progressed disease
Radium-223	3013	1506
BSC Abiraterone Enzalutamide Cabazitaxel	7532	4519

[a] Source for resource use: Expert advice.

Additional treatment after progression (docetaxel-naive patients only)

Current treatment practice often includes subsequent treatment with a different medication once a patient progresses on the first-line medication. For the abiraterone and enzalutamide arms in the docetaxel-naive model, we included the costs of receiving a second-line treatment as a one-time cost incurred at the transition from the progression-free to the progressed health state (Table 19). We calculated the costs based on expert advice that in Norway approximately 80% of abiraterone

and enzalutamide patients receive subsequent treatment. Of these, approximately 70% receive docetaxel, 10% radium-223, and 20% change to either enzalutamide or abiraterone (based on which they received initially). We allowed for only one additional treatment and did not change the clinical effect already experienced from the first treatment. Appendix 9, Table 9.6 provides detail of the calculations.

Table 19. *Medication costs of a second-line treatment after progression*

Initial treatment	Cost of second-line treatment (NOK)
Abiraterone	90,581
Enzalutamide	86,980

End-of-Life costs

We calculated costs incurred during the final three months of life based on earlier estimates of resource use (36) that were confirmed by our clinical experts. We included end-of-life costs in the model as a one-time transition cost from either PFS to Dead or PD to dead. Costs included home visits by either a nurse or doctor, nursing home stays, palliative outpatient treatment and palliative inpatient care at a hospital or palliative center during the final two weeks of life. Total end-of-life costs were NOK 119,362. Appendix 9 Table 9.7 provides details of the calculations.

Health-related Quality of Life

We conducted a systematic search for published utility weights that were relevant for our model population and treatment options. We searched primarily for values from multi-attribute utility (MAU) instruments, but were willing to consider utility weights based on mapping from a disease-specific instrument to a MAU system. For consistency, and noting that different utility instruments can yield different utility weights for the same health state, we focused on values based on EQ-5D, the most commonly used instrument.

We drew utility values from several sources. For the BSC treatment group in both the post-docetaxel and docetaxel-naive versions of the model, we obtained utility values for the progression free health state from Diels, et al. (38), which presented a new model for mapping values from the FACT-D prostate cancer quality-of-life instrument to EQ-5D utilities. The model was based on a large cross-sectional study of HRQoL among 602 mCRPC patients, from six European countries, at various stages of treatment. Sullivan, et al. (39), examined changes over time in HRQoL, as measured by EQ-5D and several disease-specific instruments, among a cross-sectional sample of 280 European mCRPC patients. The article provides the frequently cited EQ-5D utility decrement associated with disease progression in the BSC patient group.

We selected EQ-5D utility values collected as part of the enzalutamide clinical trials (AFFIRM: post-docetaxel group; PREVAIL: docetaxel-naive group) to use in the

base-case model as the utility weights for all interventions. These were easiest to incorporate in our models because they included the effects of serious adverse events in the calculations. Ghatnekar et al. (40) calculated theEQ-5D utility value for stable disease and the disutility of progressive disease using data collected during the AF-FIRM trial. For the docetaxel-naive group we use EQ-5D utility data from Loriot, et al. (27).

Although published EQ-5D utility values were available for radium-223 (41) they were based on the total patient population (combined docetaxel-naive and post-docetaxel groups) and reflected average utility over the total treatment period, which could not easily be used to determine quality of life in the progression-free versus progressed health states. In general, they were lower than the other utility values we encountered.

Table 20 presents the utility values used for the base case model. We used Beta distributions to capture uncertainty in utility values for progression-free state and the decrement subtracted to obtain utilities for progressed disease.

Table 20. *Quality of Life utilities and decrements [a] (s.e. or CI)*

Treatment	Post-docetaxel		Docetaxel-naive	
	Progression Free	Progressed	Progression Free	Progressed
BSC	0.60 (0.03)	- 0.07 (0.02)	0.70 (0.02)	- 0.07 (0.02)
Active interventions	0.688 (0.0184)	- 0.088 (0.0177)	0.85 (0.038)	- 0.07 (-0.09,-0.05)

se: standard error; CI: confidence interval
[a] Decrements are shown as negative values and indicate the reduction in utility occurring at progression

Economic evaluation – Results

General

We calculated costs and effectiveness (measured in QALYs) for all treatments in each model using a Monte Carlo analysis with 10,000 iterations. We present the results as the incremental cost-effectiveness ratio (ICER) for each intervention relative to the common comparator. The ICER represents the lowest willingness-to-pay at which a treatment could be considered cost-effective, given current drug prices. Because there is no official Norwegian threshold value for willingness-to-pay (WTP) for an additional QALY, we will assess cost-effectiveness by examining a range of potential WTP values per QALY gained.

Docetaxel-naive model

Incremental cost-effectiveness results

The results of the base-case analysis for the docetaxel-naive model are presented in Table 21. Both treatments are more effective, but also more expensive than BSC. ICERs for abiraterone and enzalutamide are, respectively, NOK 984,163 and 971,465. Abiraterone is extended dominated by enzalutamide and BSC. Figure 5 presents the same information as a cost-effectiveness frontier. Figure 6 illustrates the effect of uncertainty in the model parameters affect the costs and effects of treatment for each intervention.

Table 21: *Results of the incremental analysis* for docetaxel-naive model*

Intervention	Costs (NOK)	Incremental Cost	Effects (QALY)	Incremental Effect	ICER
BSC	426,270		1.81		
Abiraterone [a]	1,602,653	1,176,383	3.00	1.20	984,163
Enzalutamide	2,085,232	1,658,961	3.51	1.71	971,465

* ICERs are relative to BSC

[a] Abiraterone is extended dominated.

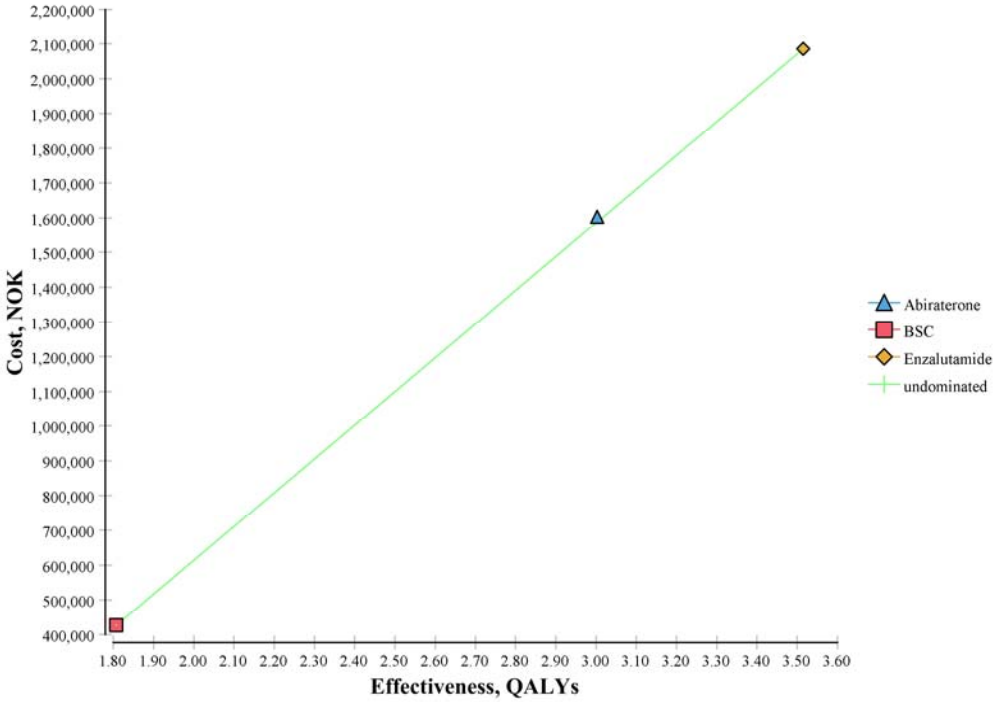

***Figure 5**. Cost-effectiveness graph, docetaxel-naive model*

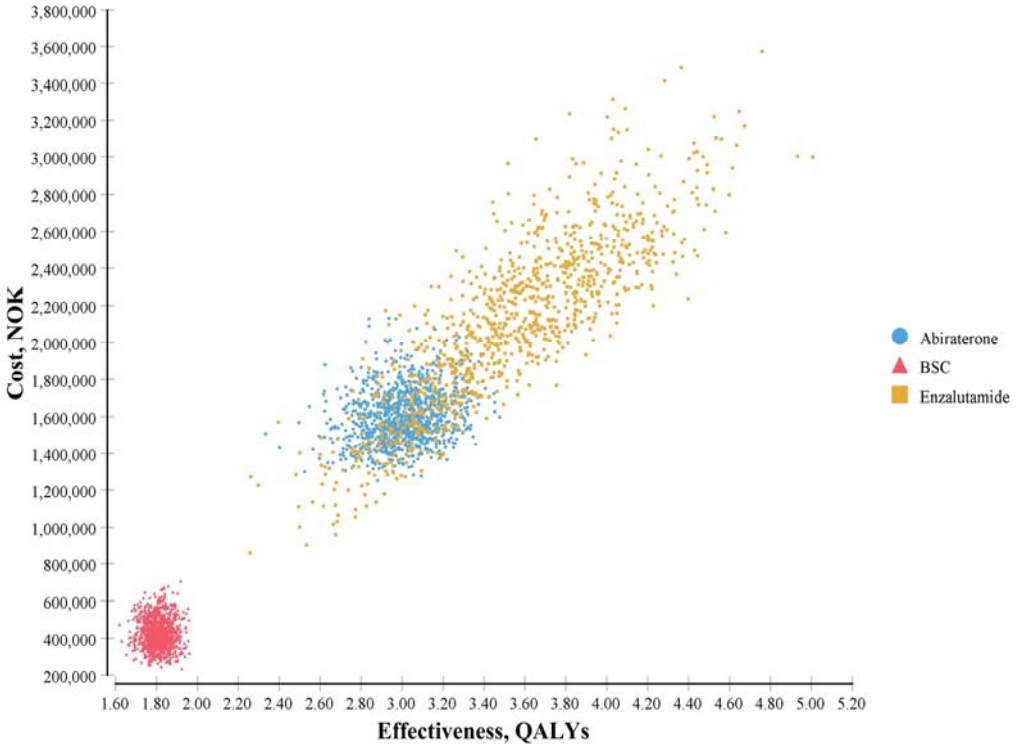

***Figure 6**. Cost-effectiveness scatterplot, docetaxel-naive model*

The cost-effectiveness acceptability curve is presented in Figure 7. The curves show the probability (read along the vertical axis) that a given treatment will be the most cost-effective option at a given WTP (read along the horizontal axis). BSC is most likely to be the most cost-effective choice unless the WTP is above approximately NOK 1,000,000 per QALY. Enzalutamide is most likely to be the cost-effective alternative when WTP exceeds NOK 1,000,000. Abiraterone is extended dominated by enzalutamide and BSC.

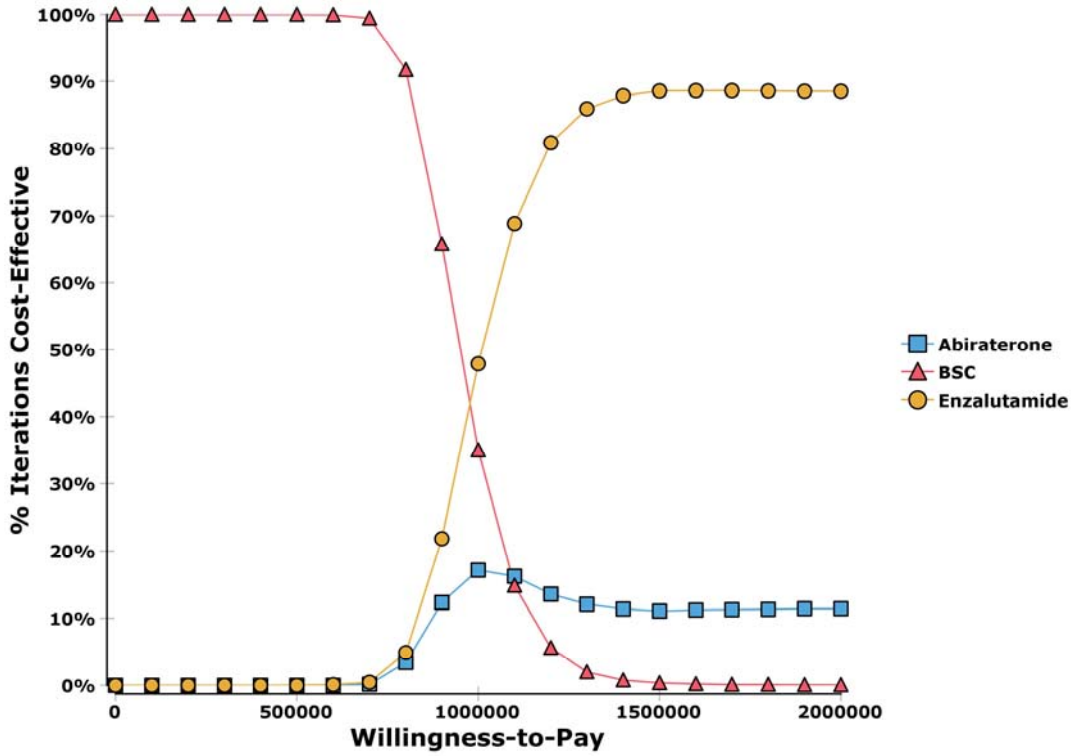

Figure 7. Cost-effectiveness acceptability curve, docetaxel-naive model

The results presented above do not, in fact, provide a clear answer to the question about which treatment is most cost-effective because the drug prices on which the results are based are maximum pharmacy retail (AUP) prices rather than the actual negotiated prices that hospital pharmacies pay for the drugs. We examine this issues in a scenario analysis of drug prices.

Sensitivity and scenario analyses

We conducted one-way sensitivity analyses of drug prices to determine at what price each treatment would be considered cost effective. We also conducted a scenario analysis to determine the impact of using the adjusted (for crossover) OS hazard ratio versus the unadjusted hazard ratio as the measure of effect for abiraterone.

Price analyses

To gain a clearer idea of cost-effectiveness, we conducted one-way sensitivity analyses to determine at what price each treatment would be considered cost-effective for a WTP of NOK 500,000. Table 22 presents the results of the analysis. It indicates that AUP prices (including VAT) would have to decline to approximately NOK 15,600 (54% decline) for abiraterone and to NOK 14,900 (55% decline) for enzalutamide for them to be cost-effective at a WTP of NOK 500,000.

Table 22. *Approximate drug price (including VAT) at which treatment is cost-effective for a willingness-to-pay of 500,000 NOK/QALY gained*

Intervention	Current maximum pharmacy retail price (AUP)	Price at which treatment is cost-effective at WTP = 500,000 NOK	Required rebate for cost-effectiveness at WTP = 500,000 NOK
Abiraterone	33,875	15,600	54%
Enzalutamide	33,015	14,900	55%

* See Table 15 for relationship between AUP price and price per monthly cycle used in model.

Abiraterone overall survival (OS) hazard ratio adjusted for crossover

In the docetaxel-naive abiraterone study, crossover from the BSC group to the treatment group was permitted after the second interim analysis (22). In our main analysis we used the unadjusted OS hazard ratio (HR=0.81), based on the ITT group, as the effect estimate. Here we examine the impact of using the adjusted OS hazard rate (HR=0.74) instead. The iterative parameter estimated (IPE) method was used to adjust the hazard ration (22). Table 23 provides results of the scenario analysis. The ICERs for abiraterone and enzalutamide were, respectively, 937,165 and NOK 970,255.

Table 23: *Results of the incremental analysis* for docetaxel-naive model*

Intervention	Costs (NOK)	Incremental Cost	Effects (QALY)	Incremental Effect	ICER
BSC	426,247		1.81		
Abiraterone	1,612,809	1,186,562	3.07	1.27	937,165
Enzalutamide	2,089,895	1,663,649	3.52	1.71	970,255

* ICERs are relative to BSC

Figure 8 provides the cost-acceptability curves, which indicate that the treatment most likely to be the most cost-effective choice is BSC, for WTP per QALY under NOK 1,000,000; abiraterone, for WTP between NOK 1,000,000 and 1,100,000; and enzalutamide for WTP above 1,100,000.

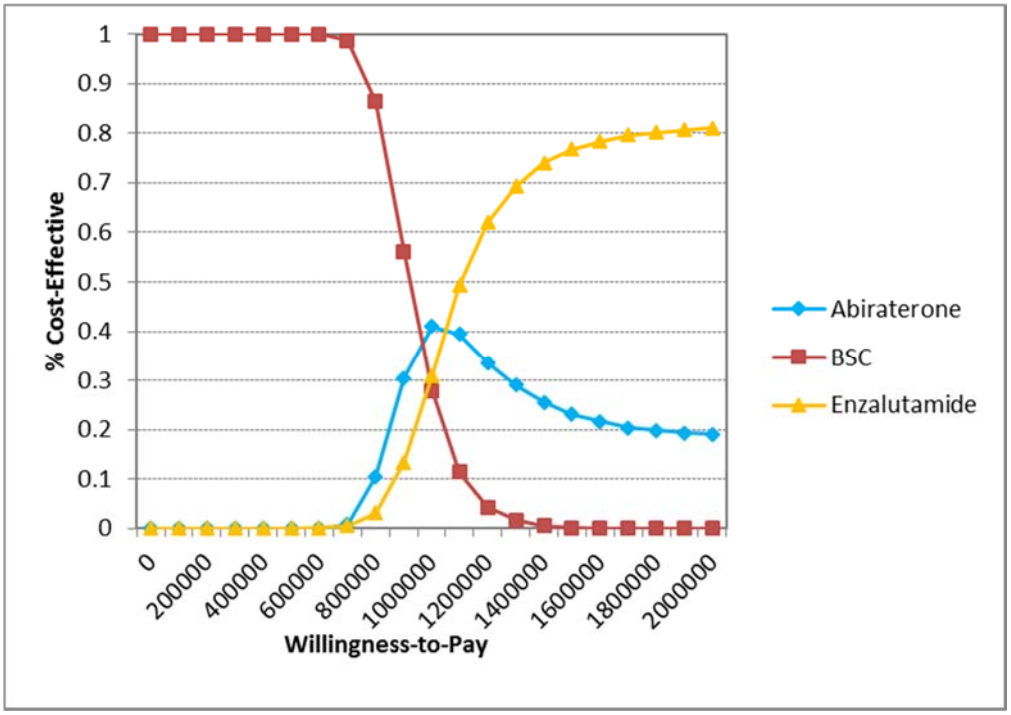

Figure 8. *Cost-effectiveness acceptability curve, scenario analysis with adjusted OS hazard ratio for abiraterone in docetaxel-naive model.*

Post-docetaxel model

Incremental cost-effectiveness results

The results of the base-case analysis for the post-docetaxel model are presented in Table 24. All treatments are more effective than BSC, but are also more expensive. Enzalutamide has the largest effect, but is also the most expensive treatment. Abiraterone and enzalutamide have the lowest ICERs, at NOK 789,128 and 809,595, respectively. Radium-223 and cabazitaxel are extended dominated by other treatments.

Table 24: *Results of the incremental analysis* for mCRPC patients with prior docetaxel treatment*

Intervention	Costs (NOK)	Incremental Cost	Effects (QALY)	Incremental Effect	ICER
BSC	256,400		0.8		
Radium-223 [a]	382,770	126,370	0.93	0.13	993,004
Abiraterone	629,551	373,151	1.28	0.47	789,128
Cabazitaxel [a]	834,465	578,065	1.28	0.48	1,210,474
Enzalutamide	863,192	606,792	1.55	0.75	809,595

* ICERs are relative to BSC

[a] Treatments are extended dominated.

The cost-effectiveness acceptability curve is presented in Figure 9. The curves show the probability (read along the vertical axis) that a given treatment will be the most cost-effective option based on a given WTP (read along the horizontal axis). For a WTP under approximately NOK 800,000, BSC is the most likely to be the cost-effective option. Enzalutamide is most likely to be the cost-effective alternative when WTP exceeds NOK 800,000. Although there is a range of WTP values for which abiraterone would be considered cost-effective (see Table 24), uncertainty in the model makes it unlikely that it would ever be the treatment with the highest probability of being most cost-effective given current maximum pharmacy retail prices.

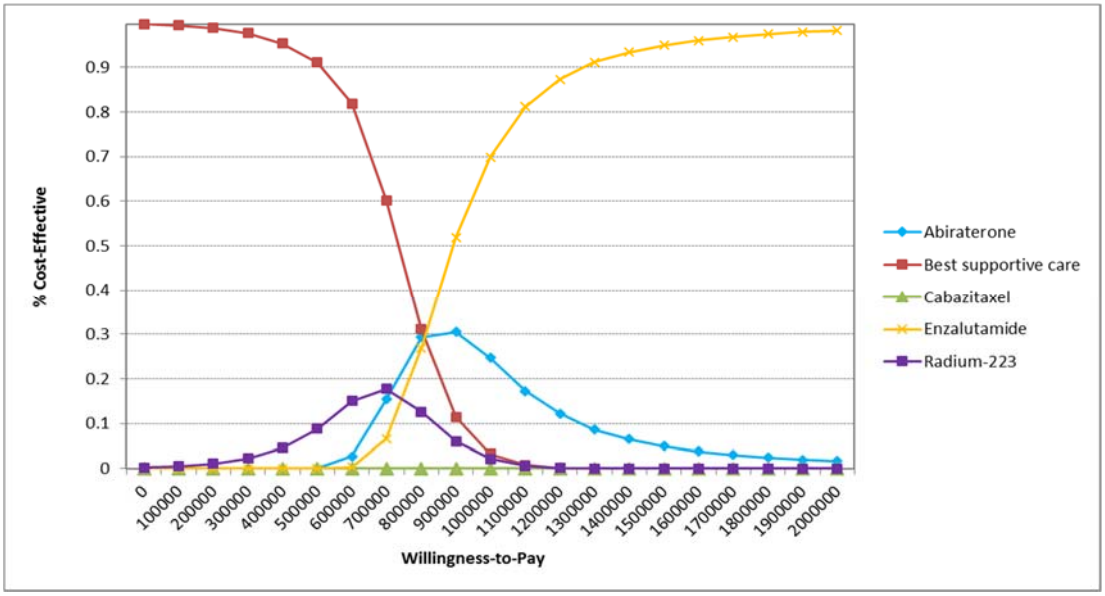

***Figure 9**. Cost-effectiveness acceptability curve, post-docetaxel*

Sensitivity analysis

As discussed for the docetaxel-naive model, the results presented here do not provide a clear answer to the question about which treatment is most cost-effective because the drug prices on which the results are based are maximum pharmacy retail (AUP) prices rather than the actual negotiated price that the hospital procurer pays for the drugs. To gain a clearer idea of cost-effectiveness, we conducted a sensitivity analysis to determine at what price each treatment would be considered cost-effective for a WTP of NOK 500,000.

Table 25 presents the results of the analysis. It indicates that the AUP price of abiraterone would have to drop to NOK 17,900 (47%); enzalutamide to NOK 17,900 (46%), cabazitaxel to NOK 14,400 (67%) and Radium-223 to NOK 28,200 (36%) for

each to be cost-effective at a WTP of NOK 500,000. These prices include value added tax paid by the hospital sector; the actual acquisition price would need to be lower.

Table 25. *Approximate drug price (including VAT) at which treatment is cost-effective at a willingness-to-pay of 500,000 NOK/QALY gained*

Intervention	Current maximum pharmacy retail price (AUP)	Price at which treatment is cost-effective at WTP = NOK 500,000	AUP rebate required for cost-effectiveness at WTP= NOK 500,000
Abiraterone	33,875	17,900	47%
Enzalutamide	33,015	17,900	46%
Cabazitaxel	43,625	14,400	67%
Radium-223	45,010	28,200	37%

* See Table 15 for relationship between AUP price and price per monthly cycle used in the-model.

Discussion

In this Health Technology Assessment we have systematically reviewed and assessed the effectiveness of four drugs for castrate resistant, metastatic prostate cancer (abiraterone, cabazitaxel, enzalutamide and radium-223). We have included eight randomized controlled trials in the analysis. We have focused on the clinically important endpoints overall survival, progression free survival, serious adverse events and health related quality of life.

We used two versions of a three-state Markov model to analyze the cost-effectiveness of abiraterone, cabazitaxel, enzalutamide and radium-223 relative to a common comparator, with costs measured in NOK and effects measured in quality-adjusted life-years (QALYs). The first version of the model focused on docetaxel-naive patients (only abiraterone and enzalutamide were included in the model). In the second version we examined the cost-effectiveness of all four drugs among patients who had experienced treatment with docetaxel.

To the best of our knowledge, ours is the first attempt to model the cost-effectiveness of different treatments available for patients with metastatic castration-resistant prostate cancer. To date, cost-effectiveness evaluations of the interventions examined in this report have been single technology assessments, that is, they have focused on one medication compared to placebo or another active treatment as comparator. While cost-effectiveness results based on single technology assessments are an important part of the process for evaluating the cost-effectiveness of new treatments, they do not provide the necessary comparisons for determining cost-effectiveness among a group of treatments that target the same condition. As such, our results fill an important gap in the literature about these medications.

Summary of key findings

Our clinical evaluation based on the direct comparisons shows that for the all patients group (patients that had, or had not received chemotherapy), the four drugs probably increase median overall survival slightly compared with passive treatment.

We have low to moderate confidence in the estimates. All intervention drugs probably increases the progression free survival period slightly (between one to five months) compared with passive treatment (moderate quality evidence). The drugs probably improves the quality of life slightly (moderate quality evidence), but may cause more serious adverse events (abiraterone, cabazitaxel, radium-223) or there may be little or no difference between the treatment groups (enzalutamide) (low or moderate quality evidence). The follow up time in the studies varied from 12 to 49 months.

When compared in a network meta-analysis, radium-223 seems to have a higher probability of improved chance of median overall survival than the other therapies. Our confidence in this estimate is low.

For all endpoints, we assessed the quality of evidence to be either moderate of low. The main reasons for downgrading were imprecise results (wide confidence intervals that included both benefit and harm) or inconsistency between trials.

All four drug treatments, with the exception of radium-223 for docetaxel-naive patients, are more effective but also more costly than BSC. In the docetaxel-naive model, the incremental cost-effectiveness ratios (ICERs) were NOK 996,500 for abiraterone and NOK 983,305 for enzalutamide. In the post-docetaxel model ICERs were: NOK 992,621 for radium-223, NOK 808,625 for abiraterone, NOK 1,227,012 for cabazitaxel, and NOK 824,762 for enzalutamide. Treatments are considered cost-effective if the willingness-to-pay per extra QALY gained is above the ICER. Substantial price discounts would be necessary for the treatments to be cost-effective at a willingness-to-pay of NOK 500,000.

Strengths and limitations of this report

The results for the clinical effectiveness are based on clinical trials of a randomized controlled design. We expect that randomized controlled trials are more robust against bias than observational studies, and are therefore the preferred design when studying the effect of an intervention. However, for endpoints related to harm, observational and registry studies might have been more appropriate.

Scarcity of data is a limitation of this report. Only one or two head-to-head trials have been performed for each comparison versus placebo or “passive” treatment. We did not find any trials that tested our interventions against each other directly.

Our estimates for the comparisons between the interventions are therefore only based on indirect estimates and must be interpreted cautiously.

The comparators used in the trials were placebo (in trials with abiraterone, enzalutamide and radium-223), bicalutamide (one trial with enzalutamide) or mitoxantrone (one trial with cabazitaxel). Although bicalutamide is an anti-androgen drug and mitoxantrone is a chemotherapy drug we have chosen to see all the comparators used as "placebo" or "passive" treatments for the network meta-analyses.

For the network meta-analysis, we chose to combine the results for each endpoint for patients previously treated with and not treated with docetaxel or another chemotherapy. We did this due to lack of data. By not combining the populations, we would have had only one or two trials trial for each comparison. Although these trials were methodologically well performed, we were not confident that this study or these studies represented the true estimate of effect and decided to combine the studies representing each comparison.

Since the time that the trials included in this report were initiated, the treatment schedule for metastatic castrate resistant prostate cancer might have changed. We have been told (personal communication) that clinicians sometimes decide to initiate treatment with docetaxel along with androgen deprivation therapy. This treatment schedule has been tested for metastatic hormone-sensitive prostate cancer (42). This change in practice guidelines might affect the population that is available for the newer drugs included in this report if in the future only patients previously treated with docetaxel will be available for further treatment.

Our economic analysis has a number of limitations that should be considered when interpreting the cost-effectiveness results. One important caveat is that the analysis only examines the cost-effectiveness of included treatments, and does not address the best sequencing of these medications in prostate cancer treatment as no studies have examined this issue. Limitations that we discuss in turn include issues related to choice of comparator, modeling of effect, measurement of costs, choice of utility values and problems related to radium-223.

We would have preferred to use Norwegian data as the basis for the comparator in our model, but appropriate data were not available. Because there were no trials making direct comparisons among the interventions included in this report, we used best supportive care as the common comparator in both versions of the model (post-docetaxel and docetaxel-naive). A more appropriate choice might have been to use docetaxel as comparator for the docetaxel-naive model version as docetaxel had been the standard treatment before abiraterone, enzalutamide and radium-223

gained market authorization. Doing so would have provided a more realistic assessment of the incremental costs and effects of the newer medications since research (43) already indicated that docetaxel provides cost-effective survival benefits relative to BSC. Another option could have been to include docetaxel as an additional treatment arm in the docetaxel-naive model.

For a model to be useful, it must accurately capture the effect of treatment on the target population. Certain assumptions that we imposed, could cause our model to fall short. Using the BSC arms from the AFFIRM (enzalutamide) and COU-AA-302 (abiraterone) trials as comparators in, respectively, the post-docetaxel and docetaxel-naive versions of the model, requires the assumption that the BSC patients in each of the individual studies are randomly drawn from the same population. If this is not the case, the hazard ratios observed between the intervention and comparator in one study might not accurately reflect treatment with a different medication.

Using hazard ratios to model the effect of treatment on overall and progression-free survival implies that the relationship between the time-to-events (survival and disease progression) of BSC and the time-to-events of each of the treatments is constant over time. If this is not the case, the model may not provide an accurate picture of transitions over time from one model state to another, resulting in unreliable estimates of total costs and benefits of treatment. We also assume that the hazard ratio for overall survival applies equally to individuals in the PFS and PD states. If this is not the case, the model may overestimate survival benefits of treatment.

Because baseline survival information for the control arms was extrapolated beyond the end of trial follow-up periods, there is likely to be a good deal of uncertainty in our estimates of overall and progression-free survival in the model. Some of the best-fitting parametric distributions for overall survival in the comparator arm exhibited “fat tails”, that is, the distribution overestimated the percentage of people who were long-term survivors. This was an issue in the docetaxel-naive model and resulted in a large cohort of patients who were still alive far beyond the 60-month point at which there were no patients still alive in the study. This would tend to bias ICERs downwards, potentially causing treatments to seem cost-effective when they many not be. Time horizons that extend well beyond robust follow-up data will exacerbate the problem, something we tried to limit by restricting time horizons to five years for the post-docetaxel group and seven years for the docetaxel-naive.

In the absence of detailed studies that track Norwegian resource use in a cohort of mCRPC patients during different phases of treatment, an accurate assessment of resource use is quite difficult. In addition, our simplifying assumptions that many costs were identical across medications, might be incorrect. Because we based prices mainly on DRGs and tariffs for examinations and tests performed at ambulatory

clinics, our price information is also inexact. Also problematic is the fact that prices negotiated for medications used in Norwegian hospitals are now considered confidential. This, coupled with the lack of a defined threshold reflecting the opportunity cost of resources used in the health sector, makes it quite difficult to assess the cost-effectiveness of new treatments, a problem we addressed by performing scenario analyses.

There is a large degree of uncertainty around the utility values used to capture health-related quality of life. Although, in the base-case scenario, we applied the same utility values for all active treatments among patients with the same docetaxel status, the utility values reported in the literature varied widely among treatments. The utility values that we used in the post-docetaxel, based on EQ-5D AFFIRM (enzalutamide) trial, 0.688 for the progression-free state and 0.60 for progressed disease, seemed consistent with other values in the literature (38). Values associated with other treatments in the post-docetaxel group ranged from 0.78 for abiraterone in the progression-free state, to values from 0.60 before progression to 0.54 after progression for radium-223, depending on the progression definition used. In the docetaxel-naive model, the best available utility data, indicated baseline utilities of 0.85 for the enzalutamide treatment group and 0.84 for the BSC group in among patients with an average age of 72, a level that is equal to utilities typically reported by healthy individuals of the same age. To the extent that these values are high, our results would make treatments appear more cost-effective than they are.

Radium-223 presented challenges for our economic analysis because its marketing authorization is limited to mCRPC patients with only bone metastases. Because intervention and control patients in the clinical trial progressed more rapidly with respect to overall survival and progression-free survival than their counterparts in the other trials, we could not use hazard ratios to compare radium-223 to the other medications in our model. For the post-docetaxel model, we used available patient level data to estimate transition probabilities directly. We intended to do the same for the docetaxel-naive model, but decided to exclude radium-223 from that analysis after initial results indicated that it had a lower incremental cost-effectiveness than the BSC arm of the model. Model results seem comparable to findings in a single technology from the National Institute for Health and Care Excellence (NICE) in England (44), which approved radium-223 for use among patients with only bone metastases provided they had already had been treated with docetaxel and the drug price was discounted substantially.

A common concern about cost-effectiveness analyses of radium-223 is that defining disease progression based on PSA-progression, as is often done, disadvantages radium-233 compared to other treatments; ALP-progression is offered as a more appropriate alternative. This concern is less important in our analysis because we used

common quality of life utility values (from enzalutamide), which were higher than the utility values from the radium-223 study, in the post-docetaxel model. The boost from these higher utility values is likely to outweigh the disadvantage of not capturing ALP-progression.

Our cost-effectiveness calculations were complicated by the fact that we only had access to maximum pharmacy prices (AUP) for the drugs under consideration. This would have posed less of a problem if Norway had an official threshold value for willingness-to-pay for an additional quality-adjusted life year. Lacking that information, we used a threshold value of NOK 500,000 in scenario analyses to determine the maximum price at which each drug would be cost effective. A threshold value of NOK 300,000 – 800,000 has been mentioned as the *de facto* value that has been applied in Norwegian drug pricing decision in recent years (45). Because malignant prostate cancer ranks relatively low in a list of serious illnesses with a significant health loss, as measured by good life-years lost, (46) we felt that it was most appropriate to use an average threshold value. A relatively high threshold value is sometimes considered appropriate for end-of-life treatments, but mean life expectancy, particularly for docetaxel-naive patients is above what is generally considered "end-of-life".

Our results compared to other findings/other reviews or results

Both the Norwegian Medicines Agency and the National Institute for Health and Care Excellence (NICE) in England have performed single technology assessments on the four drugs we have included in this report.

NICE (47) provides evidence based recommendations for using abiraterone in combination with prednisone and enzalutamide as an option for treating metastatic hormone-relapsed prostate cancer in patients who have no or mild symptoms after androgen deprivation therapy has failed, and before chemotherapy is indicated. Enzalutamide is only recommended when the company provides it with a discount, and abiraterone is only recommended when the company rebates the drug cost from the 11th month until the end of treatment for people who remain on treatment for more than 10 months. Cabazitaxel is only recommended for people with hormone-refractory metastatic prostate cancer who have had treatment with docetaxel. For adults with hormone-relapsed prostate cancer with symptomatic bone metastases and no known visceral metastases, radium-223 is recommended only if they have had treatment with docetaxel and the company provides an agreed upon discount.

In Norway, the “Beslutningsforum for Nye Metoder” has decided that abiraterone and enzalutamide are clinically equal for second line treatment of metastatic castration resistant prostate cancer. Enzalutamide should be the first choice due to today’s price setting. They decided not to introduce cabazitaxel in the Norwegian specialist health care. Radium-223 can be introduced for this patient group when the patients have symptomatic bone metastasis.

In our health technology assessment, we included all relevant trials found through our systematic search for literature or received from the manufacturers. To our knowledge, no other relative comparison of either effectiveness or cost-effectiveness, based on all available evidence, has been conducted for the four drugs included in our report. We have therefore conducted this health technology assessment to be able to identify which intervention is most cost-effective in Norway.

We have chosen not to explicitly compare our incremental cost-effectiveness results with the results of other published single technology assessments. Any such comparison of results would be highly dependent on differences among analyses in how data on clinical effectiveness were used in the model, which structural assumptions were made, and which cost and quality of life data were included.

Conclusion

We have assessed the clinical effectiveness, safety and cost-effectiveness of abiraterone, cabazitaxel, enzalutamide and radium-223, relative to each other, for patients with metastatic castration resistant prostate cancer.

Our cost-effectiveness analysis indicates that at today's maximum pharmacy prices (AUP) none of the medications investigated can be considered cost-effective at what has typically been considered a reasonable willingness-to-pay.

For the docetaxel-naive patient group rebates on the AUP prices of approximately 58% for abiraterone and 59% for enzalutamide would be necessary for these medications to be cost-effective at a willingness-to-pay of NOK 500,000 per quality-adjusted life year. For post-docetaxel patients, the required rebates would be 48% for abiraterone, 49% for enzlutamide, 69% for radium-223 and 35% for cabazitaxel.

Need for further research

This analysis only examines the cost-effectiveness of included treatments relative to each other, and does not address the best sequencing of these medications in prostate cancer treatment. Future research is needed to address sequencing issues.

Head-to head trials of two or more active medications will also be needed.
We also lack register data following mCRPC patients in Norway and more comprehensive costing data.

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