Supplementary Online Content

Wang L, Paller CJ, Hong H, De Felice A, Alexander GC, Brawley O. Comparison of systemic treatments for metastatic castration-sensitive prostate cancer: a systematic review and network meta-analysis. *JAMA Oncol*. Published online January 14, 2021. doi:10.1001/jamaoncol.2020.6973

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods 1. Search Strategies

MEDLINE (PubMed interface)

#1	"Prostatic Neoplasms"[Mesh] OR (("Prostate"[Mesh] OR prostate*[tw] OR prostatic*[tw]) AND ("Neoplasms"[Mesh] OR neoplasm*[tiab] OR cancer[tw] OR cancers*[tw] OR cancerous*[tw] OR tumor*[tw] OR tumour*[tw]))
#2	"MDV 3100" [Supplementary Concept] OR MDV3100[tw] OR Enzalutamide[tw] OR "MDV-3100"[tw] OR xtandi[tw] OR "915087-33-1"[rn]
#3	"apalutamide" [Supplementary Concept] OR apalutamide[tw] OR "ARN-509"[tw] OR arn509[tw] OR erleada[tw] OR "956104-40-8"[rn]
#4	"abiraterone" [Supplementary Concept] OR abiraterone[tw] OR "CB-7598"[tw] OR CB7598[tw] OR "154229-19-3"[rn]
#5	"darolutamide" [Supplementary Concept] OR darolutamide[tw] OR "ORM-16497"[tw] OR "ORM-16555"[tw] OR "ODM-201"[tw] OR odm201[tw] OR "bay 1841788"[tw] OR "bay1841788"[tw] OR "1297538-32-9"[rn]
#6	"Docetaxel"[Mesh] OR Docetaxel[tw] OR Docetaxol[tw] OR "Taxoltere Metro"[tw] OR "RP 56976"[tw] OR RP56976[tw] OR Taxotere[tw] OR "NSC 628503"[tw] OR nsc628503[tw] OR Daxotel[rn] OR dexotel[tw] OR docefrez[tw] OR "lit 976"[tw] OR "lit976"[tw] OR oncodocel[tw] OR taxespira[tw] OR taxoter[tw] OR texot[tw] OR "114977-28-5"[rn]
#7	#2 OR #3 OR #4 OR #5 OR #6
#8	("Hormones"[Mesh] OR hormon*[tw] OR "Castration"[Mesh] OR castrat*[tw] OR androgen*[tw])
#9	#1 AND #7 AND #8
#10	((randomized controlled trial[pt]) OR (controlled clinical trial[pt]) OR (randomised[tiab] OR randomized[tiab]) OR (placebo[tiab]) OR (drug therapy[sh]) OR (randomly[tiab]) OR (trial[tiab]) OR (groups[tiab])) NOT (animals[mh] NOT humans[mh])
#11	#9 AND #10

EMBASE (OVID interface)

#1	'prostate tumor'/exp OR ('prostate'/exp AND 'neoplasm'/exp) OR ((prostate* OR prostatic*) NEAR/3 (neoplasm* OR cancer OR cancers* OR cancerous* OR tumor* OR tumour*)):ab,ti,kw,tn
#2	'enzalutamide'/exp OR (Enzalutamide OR "MDV-3100" OR xtandi OR "915087-33-1"):ab,ti,kw,tn
#3	'apalutamide'/exp OR (apalutamide OR "ARN-509" OR arn509 OR erleada OR "956104-40-8"):ab,ti,kw,tn
#4	'abiraterone'/exp OR (abiraterone OR "CB-7598" OR CB7598 OR "154229-19-3"):ab,ti,kw,tn
#5	'darolutamide'/exp OR (darolutamide OR "ORM-16497" OR "ORM-16555" OR "ODM-201" OR odm201 OR "bay 1841788" OR "bay1841788" OR "1297538-32-9"):ab,ti,kw,tn
#6	'docetaxel'/exp OR (Docetaxel OR Docetaxol OR "Taxoltere Metro" OR "RP 56976" OR RP56976 OR Taxotere OR "NSC 628503" OR nsc628503 OR Daxotel OR dexotel OR docefrez OR "lit 976" OR "lit976" OR oncodocel OR taxespira OR taxoter OR texot OR "114977-28-5"):ab,ti,kw,tn
#7	#2 OR #3 OR #4 OR #5 OR #6
#8	'hormone'/exp OR 'castration'/exp OR (hormon* OR castrat* OR androgen*):ab,ti,kw
#9	#1 AND #7 AND #8
#10	'crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blind procedure':de OR 'drug therapy'/lnk OR (random* OR factorial* OR crossover* OR cross NEXT/1 over* OR placebo* OR doubl* NEAR/1 blind* OR singl* NEAR/1 blind* OR assign* OR allocat* OR volunteer*):de,ab,ti
#11	#9 AND #10
#12	('animal'/exp OR 'animal experiment'/exp) NOT 'human'/exp
#13	#11 NOT #12

Cochrane Central Register of Controlled Trials (CENTRAL, Wiley interface)

#1	MeSH descriptor: [Prostatic Neoplasms] explode all trees
#2	((prostate* OR prostatic*) NEAR/3 (neoplasm* OR cancer OR cancers* OR cancerous* OR tumor* OR tumour*))
#3	#1 OR #2
#4	(Enzalutamide OR "MDV-3100" OR xtandi OR "915087-33-1")
#5	(apalutamide OR "ARN-509" OR arn509 OR erleada OR "956104-40-8")
#6	(abiraterone OR "CB-7598" OR CB7598 OR "154229-19-3")
#7	(darolutamide OR "ORM-16497" OR "ORM-16555" OR "ODM-201" OR odm201 OR "bay 1841788" OR "bay1841788" OR "1297538-32-9")
#8	MeSH descriptor: [Docetaxel] explode all trees

#9	(Docetaxel OR Docetaxol OR "Taxoltere Metro" OR "RP 56976" OR RP56976 OR Taxotere OR "NSC 628503" OR nsc628503 OR Daxotel OR dexotel OR docefrez OR "lit 976" OR "lit976" OR oncodocel OR taxespira OR taxoter OR texot OR "114977-28-5")
#10	#4 OR #5 OR #6 OR #7 OR #8 OR #9
#11	MeSH descriptor: [Hormones] explode all trees
#12	MeSH descriptor: [Castration] explode all trees
#13	(hormon* OR castrat* OR androgen*)
#14	{OR #11-#13}
#15	#3 AND #10 AND #14 in Trials

ClinicalTrials.gov

https://clinicaltrials.gov/ct2/results/refine?show_xprt=Y

(Prostatic Neoplasms) AND (Enzalutamide OR "MDV-3100" OR xtandi OR "915087-33-1" OR apalutamide OR "ARN-509" OR arn509 OR erleada OR "956104-40-8" OR abiraterone OR "CB-7598" OR CB7598 OR "154229-19-3" OR darolutamide OR "ORM-16497" OR "ORM-16555" OR "ODM-201" OR odm201 OR "bay 1841788" OR "bay1841788" OR "1297538-32-9" OR Docetaxel OR Docetaxol OR "Taxoltere Metro" OR "RP 56976" OR RP56976 OR Taxotere OR "NSC 628503" OR nsc628503 OR Daxotel OR dexotel OR docefrez OR "lit 976" OR "lit976" OR oncodocel OR taxespira OR taxoter OR texot OR "114977-28-5") AND (Hormone OR Castration OR androgen)

Filter with Study type “Interventional (Clinical Trial)” and Sex “Male”

EU Clinical Trials Register

https://www.clinicaltrialsregister.eu/ctr-search/search

(Prostatic Neoplasms) AND (Enzalutamide OR "MDV-3100" OR xtandi OR "915087-33-1" OR apalutamide OR "ARN-509" OR arn509 OR erleada OR "956104-40-8" OR abiraterone OR "CB-7598" OR CB7598 OR "154229-19-3" OR darolutamide OR "ORM-16497" OR "ORM-16555" OR "ODM-201" OR odm201 OR "bay 1841788" OR "bay1841788" OR "1297538-32-9" OR Docetaxel OR Docetaxol OR "Taxoltere Metro" OR "RP 56976" OR RP56976 OR Taxotere OR "NSC 628503" OR nsc628503 OR Daxotel OR dexotel OR docefrez OR "lit 976" OR "lit976" OR oncodocel OR taxespira OR taxoter OR texot OR "114977-28-5") AND (Hormone OR Castration OR androgen)

United States Food and Drug Administration (US FDA) and European Medicines Agency (EMA)

US FDA: https://www.accessdata.fda.gov/scripts/cder/daf/

EMA: https://www.ema.europa.eu/en/medicines

#1 Enzalutamide, #2 Apalutamide, #3 Abiraterone, #4 Darolutamide, #5 Docetaxel

eMethods 2. Models and WINBUGS code

The models and WINBUGS code used were adapted from Dias et al.[1]

Models

1. Network meta-analysis models for survivals with contrast-based likelihood and for adverse events with arm-based likelihood

1) For time-to-event outcomes, included trials reported contrast-based data: hazard ratio that is additive on log scale and assumed to be constant over time. Defining $y_{t_{i1}t_{ik}}$ as the log hazard ratio of the treatment in arm k of trial i, t_{i1}, relative to the treatment in arm 1 of trial i, t_{i1}, such that

$$y_{t_{i1}t_{ik}} \sim Normal\left(\delta_{t_{i1}t_{ik}}, V_{t_{i1}t_{ik}}\right)$$

where $\delta_{t_{i1}t_{ik}}$ is the mean and $V_{t_{i1}t_{ik}}$ is the variance. For the multi-arm trial STAMPEDE, we accounted for the correlation between $y_{t_{i1}t_{ik}}$ of different arms because they share the arm 1.

$$\begin{pmatrix} y_{t_{i1}t_{i2}} \\ \cdots \\ y_{t_{i1}t_{ik}} \end{pmatrix} \sim Normal\left(\begin{pmatrix} \delta_{t_{i1}t_{i2}} \\ \cdots \\ \delta_{t_{i1}t_{ik}} \end{pmatrix}, \begin{bmatrix} V_{t_{i1}t_{i2}} & \cdots & se^2_{t_{i1}} \\ \vdots & \ddots & \vdots \\ se^2_{t_{i1}} & \cdots & V_{t_{i1}t_{ik}} \end{bmatrix} \right)$$

The variance-covariance matrix has off-diagonal elements $se^2_{t_{i1}}$ which is the variance in the arm 1 estimated according to methods proposed by Dias et al.[1] To model the outcome, an identity link function $g(\gamma)$ was used.

$$g(\gamma) = \delta_{t_{i1}t_{ik}}$$

2) For serious adverse event (SAE), included trials reported arm-based data: the number of patients in each arm and the number who experienced SAE. Defining $n_{t_{ik}}$ as the of number of patients receiving the treatment in arm k of trial i, t_{i1}, and $r_{t_{ik}}$ as the number of patients among $n_{t_{ik}}$who experienced SAE, such that

$$r_{t_{ik}} \sim Binomial\left(p_{t_{ik}}, n_{t_{ik}}\right)$$

where $p_{t_{ik}}$ is the probability that a patient experienced SAE.As arm-based likelihood was used, no correlation adjustment is needed at likelihood level for multi-arm trials.[1] To model the outcome, a logit link function $g(\gamma)$ will be used.

$$g(\gamma) = logit\left(p_{t_{ik}}\right) = \mu_i + \delta_{t_{i1}t_{ik}}$$

For trial i, μ_i is the log odds of SAE for the treatment in arm 1, and $\delta_{t_{i1}t_{ik}}$ is the log odds ratio of the treatment in arm k relative to the treatment in arm 1.

For either outcome, the trial specific relative effect $\delta_{t_{i1}t_{ik}}$ is drawn from a common random effects distribution

$$\delta_{t_{i1}t_{ik}} \sim Normal\left(d_{t_{i1}t_{ik}}, \sigma^2\right)$$

where $d_{t_{i1}t_{ik}}$ is the mean and σ^2 is the common between-study variance. We accounted for the correlation between $\delta_{t_{i1}t_{ik}}$ of different arms within the multi-arm trial.

$$\begin{pmatrix} \delta_{t_{i1}t_{i2}} \\ \cdots \\ \delta_{t_{i1}t_{i2}} \end{pmatrix} \sim Normal\left(\begin{pmatrix} d_{t_{i1}t_{i2}} \\ \cdots \\ d_{t_{i1}t_{ik}} \end{pmatrix}, \Sigma\left(\sigma^2, 0.5\right) \right)$$

$\Sigma(\sigma^2, 0.5)$ denotes a variance-covariance matrix with diagonal element σ^2 and off-diagonal elements $0.5\sigma^2$. It implies that the correlation between any two-treatment-contrast within a multi-arm trial is 0.5.[2] It follows that the fixed effects model is a special case, obtained by setting the σ^2 to zero, implying that $\delta_{t_{i1}t_{ik}} = d_{t_{i1}t_{ik}}$for all i.

In our study, we label placebo/no treatment as the overall reference, i.e., treatment No.1. According to consistency equation[3,4]

$$d_{t_{i1}t_{ik}} = d_{1t_{ik}} - d_{1t_{i1}}$$

where $d_{1t_{ik}}$ is the effect of the treatment in arm k of trial i relative to reference. And for any treatment s $(s > 1)$, the effect relative to reference, d_{1s}, is the basic parameter of interest in a network meta-analysis through which all treatments are to be compared and ranked.

2. Parametric survival meta-analysis models

We reconstructed time-to-event data from published Kaplan Meier curves using methods described in the statistical analysis section of the main paper. We fit a series of first-order fractional polynomial models with power parameter p={-2,-1,-0.5,0.5,1,2,3}, which include common parametric distributions for survival times such as Weibull (p=0) and Gompertz (p=1).[5] Deviance information criterion (DIC) was used to compare models and assess goodness of fit.[6]

Survival curves can be divided into J consecutive intervals over the follow-up period: $[t_1, t_2], (t_2, t_3], \ldots, [t_J, t_{J+1}]$, with t_1=0. For each time interval $j = 1, 2, 3, \ldots, J$,

$$r_{t_{ikj}} \sim Binomial\left(p_{t_{ikj}}, n_{t_{ikj}}\right)$$

where $r_{t_{ikj}}$ is the number of events derived from the reconstructed time-to-event data in the jth interval $[t_J, t_{J+1}]$ for treatment in arm k of trial i, $r_{t_{ikj}}$ is the number of participants at risk at the start of the jth interval, and $p_{t_{ikj}}$ is the event probability for the jth interval. When the time intervals are relatively short, the hazard $h_{t_{ikj}}$ is assumed to be constant within the time interval, such that

$$p_{t_{ikj}} = 1 - \exp\left(-h_{t_{ikj}} * du\right)$$

where du is the length of the interval. To model the outcome, a link function $g(\gamma)$ will be used.

$$g(\gamma) = log\left(h_{t_{ikj}}\right) = \alpha_{0,t_{ik}} + \alpha_{0,t_{ik}} * u_j{}^p$$

$$\begin{pmatrix}\alpha_{0,t_{ik}} \\ \alpha_{1,t_{ik}}\end{pmatrix} = \begin{pmatrix}\mu_{0,i} \\ \mu_{1,i}\end{pmatrix} + \begin{pmatrix}\delta_{0,t_{i1}t_{ik}} \\ d_{1,1t_{ik}} - d_{1,1t_{i1}}\end{pmatrix}$$

where $p = \{-2, -1, -0.5, 0, 0.5, 1, 2, 3\}$ and $u^0 = \ln(u)$. As mentioned in the main paper, this covers common parametric survival distributions such as Weibull ($p = 0$) and Gompertz ($p = 1$). And $\alpha_{0,t_{ik}}$ is the scale parameter and $\alpha_{1,t_{ik}}$ is the shape parameter.

$\delta_{0,t_{i1}t_{ik}}$ is the trial specific relative effect on scale parameter, drawn from a common random effects distribution

$$\delta_{0,t_{i1}t_{ik}} \sim Normal(, \sigma^2)$$

where σ^2 is the common between-study variance. We accounted for the correlation between $\delta_{0,t_{i1}t_{ik}}$of different arms within the multi-arm trial with the above mentioned method. It follows that the fixed effects model is a special case, obtained by setting the σ^2 to zero, implying that $\delta_{0,t_{i1}t_{ik}} = d_{0,1t_{ik}} - d_{0,1t_{i1}}$for all i.

$d_{1,1t_{ik}} - d_{1,1t_{i1}}$is the fixed treatment effect on shape parameter, which along with $u_j{}^p$ describes the change of log hazad ratio over time. In special cases where $d_{1,1t_{ik}} - d_{1,1t_{i1}}$ equals to zero, $\delta_{0,t_{i1}t_{ik}}$ is the trial specific hazard ratio.

For Bayesian inference, diffuse priors were ascribed to allow the observed trial data to be the main, overwhelming, influence on effect estimates.[7] Note that for network meta-analysis of randomized control trial data, pooling occurs at the relative effect level, i.e., we pool trial-specific relative effect $\delta_{t_{i1}t_{ik}}$ to estimate the d_{1s}, whereas μ_i is regarded as a nuisance parameter.

WINBUG code

1. Fixed effects model

```
model{              # *** PROGRAM STARTS

for (j in 1:N){               # LOOP THROUGH EVENTS
# time in months transformed according to power P
  timen[j]<-(time[j])
  timen1[j]<-(equals(P,0)*log(timen[j])+(1-equals(P,0))*pow(timen[j],P) )

  r[j]~dbin(p[j], z[j])              # likelihood
  p[j]<-1-exp(-h[j]*dt[j])              # hazard in each interval

# hazard over time
  log(h[j])<-Alpha[s[j],a[j],1]+Alpha[s[j],a[j],2]*timen1[j]
 }

for (i in 1:ns){              # LOOP THROUGH STUDIES
  for (k in 1:na[i]){              # LOOP THROUGH ARMS
```



```
   Alpha[i,k,1]<-mu[i,1]+d[t[i,k],1]-d[t[i,1],1]          # model for linear predictor of alpha_0
   Alpha[i,k,2]<-mu[i,2]+d[t[i,k],2]-d[t[i,1],2]          # model for linear predictor of alpha_1
  }
 }

# priors
for (i in 1:ns){              # LOOP THROUGH STUDIES
  mu[i,1:2] ~ dmnorm(mean[1:2],prec[,])          # vague priors for all trial baselines
 }
d[1,1]<-0              # alpha_0 treatment effect is zero for reference treatment
d[1,2]<-0              # alpha_1 treatment effect is zero for reference treatment

for (k in 2:nt){              # LOOP THROUGH TREATMENTS
  d[k,1:2] ~ dmnorm(mean[1:2],prec[,])          # vague priors for treatment effects
 }

# output
for (m in 1:maxt){              # create time points for output; maxt reflects maximum time point
  time1[m]<-(equals(P,0)*log(m) + (1-equals(P,0))*pow(m,P)   )
 }

# hazard ratios over time for all possible contrasts
for (c in 1:(nt-1)){
  for (k in (c+1):nt){
    for (m in 1:maxt){
      log(HR[c,k,m])<-(d[k,1]-d[c,1])+(d[k,2]-d[c,2])*time1[m]
     }
   }
 }

# provide estimates of survival probabilities over time by treatment
for (k in 1:nt){
  alpha0[k]<-mu[7,1]+d[k,1]          # alpha_0 by treatment using baseline from study 7 (STAMPEDE trial)
  alpha1[k]<-mu[7,2]+d[k,2]          # alpha_1 by treatment using baseline from study 7 (STAMPEDE trial)

  for (m in 1:maxt){
    log(HAZARD[k,m])<-alpha0[k]+alpha1[k]*time1[m]          # hazard over time by treatment
          CUM_H[k,m]<-sum(HAZARD[k,1:m])          # cumulative hazard over time by treatment
    T[k,m]<-1-exp(-CUM_H[k,m])          # mortality over time by treatment
          S[k,m]<-1-T[k,m]          # survival over time by treatment
          rk[k,m] <- rank(T[,m],k)          # rank over time by treatment
   }
 }
}          # *** PROGRAM ENDS


model{          # *** PROGRAM STARTS
for (j in 1:N){                                          # LOOP THROUGH EVENTS
```

2. Random effects model

```
model{          # *** PROGRAM STARTS

for (j in 1:N){          # LOOP THROUGH EVENTS
# time in months transformed according to power P
  timen[j]<-(time[j])
  timen1[j]<-(equals(P,0)*log(timen[j])+(1-equals(P,0))*pow(timen[j],P)   )

  r[j]~dbin(p[j], z[j])          # likelihood
  p[j]<-1-exp(-h[j]*dt[j])          # hazard in each interval
```



```
# hazard over time
 log(h[j])<-Alpha[s[j],a[j],1]+Alpha[s[j],a[j],2]*timen1[j]
 }

for (i in 1:ns){                  # LOOP THROUGH STUDIES
 w[i,1]<-0                 # adjustment for multi-arm trials is zero for control arm
 delta[i,1]<-0                  # treatment effect is zero for control arm

 for (k in 1:na[i]){                  # LOOP THROUGH ARMS
  Alpha[i,k,1]<-mu[i,1]+delta[i,k]                 # model for linear predictor of alpha_0
  Alpha[i,k,2]<-mu[i,2]+d[t[i,k],2]-d[t[i,1],2]                  # model for linear predictor of alpha_1
  }

 for (k in 2:na[i]){                  # LOOP THROUGH ARMS
  # trial-specific random effects distributions for alpha_0 treatment effects
  delta[i,k]~dnorm(md[i,k],taud[i,k])
  # mean of distributions (with multi-arm trial correction)
  md[i,k]<-d[t[i,k],1]-d[t[i,1],1] +sw[i,k]
  w[i,k] <- (delta[i,k] - d[t[i,k],1] + d[t[i,1],1])                  # adjustment for multi-arm trials
  sw[i,k] <- sum(w[i,1:k-1])/(k-1)                 # cumulative adjustment for multi-arm trials
  # precision of distributions (with multi-arm trial correction)
  taud[i,k] <- tau *2*(k-1)/k
  }
 }

# priors
for (i in 1:ns){                  # LOOP THROUGH STUDIES
 mu[i,1:2] ~ dmnorm(mean[1:2],prec[,])                  # vague priors for all trial baselines
 }
d[1,1]<-0                 # alpha_0 treatment effect is zero for reference treatment
d[1,2]<-0                 # alpha_1 treatment effect is zero for reference treatment

for (k in 2:nt){                  # LOOP THROUGH TREATMENTS
 d[k,1:2] ~ dmnorm(mean[1:2],prec[,])                  # vague priors for treatment effects
 }
sd~dunif(0,2)                  # vague prior for between-trial SD
tau<-1/(sd*sd)  # between-trial precision = (1/between-trial variance)

# output
for (m in 1:maxt){                  # create time points for output
 time1[m]<-(equals(P,0)*log(m) + (1-equals(P,0))*pow(m,P)  )
 }

# hazard ratios over time for all possible contrasts
for (c in 1:(nt-1)){
 for (k in (c+1):nt){
  for (m in 1:maxt){
   log(HR[c,k,m])<-(d[k,1]-d[c,1])+(d[k,2]-d[c,2])*time1[m]
   }
  }
 }
```



```
# provide estimates of survival probabilities over time by treatment
for (k in 1:nt){
  alpha0[k]<-mu[7,1]+d[k,1]                # alpha_0 by treatment using baseline from study 8
  alpha1[k]<-mu[7,2]+d[k,2]                # alpha_1 by treatment using baseline from study 8

  for (m in 1:maxt){
            log(HAZARD[k,m])<-alpha0[k]+alpha1[k]*time1[m]              # hazard over time by treatment
            CUM_H[k,m]<-sum(HAZARD[k,1:m])              # cumulative hazard over time by treatment
    T[k,m]<-1-exp(-CUM_H[k,m])              # mortality over time by treatment
            S[k,m]<-1-T[k,m]              # survival over time by treatment
            rk[k,m] <- rank(T[,m],k)              #rank over time by treatment
   }
 }
}               # *** PROGRAM ENDS
```


eTable 1. Data Items Extracted

Category	Data items
Trial design	Randomized controlled trials/single-arm trials, countries and centers, eligibility criteria, randomization (ratio and stratification), allocation concealment, masking, sponsor, median duration of follow-up
Trial arms	Drug name, dosage, frequency
Reported outcomes	Primary outcomes, secondary outcomes, safety outcomes
Baseline data	• Number of participants randomized. • Patient characteristics: age, Eastern Cooperative Oncology Group performance status score, serum prostate-specific antigen level, and other baseline characteristics reported
Efficacy outcomes	• Primary outcome of interest: radiographic progression-free survival • Secondary outcome of interest: overall survival Information extracted: the number of patients who had the event, the median follow-up time, median survival, and the hazard ratio will be extracted.
Safety outcomes	Proportion of patients who experienced serious adverse events by the end of study Information extracted: the number of patients included in the safety analysis, the median follow-up time, and the number of patients who had the event will be extracted.

Definitions of outcomes:

- Radiographic progression-free survival: time from randomization to radiographic progression based on Prostate Cancer Working Group 2 criteria for bone lesions and the Response Evaluation Criteria in Solid Tumors, version 1.1, for soft-tissue lesions, or death from any cause, whichever occurred first.
- Overall survival: time from randomization to death from any cause.
- Serious adverse event: an untoward medical occurrence associated with the use of a drug and results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.[8]

eTable 2. Outcomes Assessed in Included Trials

Trial ID	Outcome	Outcome definition
GETUG-AFU15	Overall survival	Time between randomization and death from any cause
	Radiographic progression-free survival	Radiographic progression or death. Radiographic progression was the occurrence of new bone lesions or RECIST progression, whichever happened first
	Biochemical progression-free survival	PSA progression per PSA Working Group definition or radiographic progression or death
	Time to subsequent treatment	Not reported
	QoL	European Organization for Research and Treatment of Cancer quality-of-life questionnaire C30
CHAARTED	Overall survival	Time from random assignment until death resulting from any cause
	Clinical progression free survival	Time until increasing symptomatic bone metastases; progression per RECIST criteria, version 1.0; or clinical deterioration due to cancer per investigator's opinion
	Time to development of CRPC	The time of random assignment until PSA progression, development of worsening symptoms, evidence of radiographic progression, or patient's deterioration as per investigator's opinion
	PSA level <0.2ng/ml at 6 months (%)	Not applicable
	PSA level <0.2ng/ml at 12 months (%)	Not applicable
	QoL	QoL by FACT-P
STAMPEDE	Overall survival	Time from randomization to death from any cause
	Progression-free survival	Time from randomisation to the first of: new disease or progression of: distant metastases, lymph nodes or local disease; or death from prostate cancer
	Failure-free survival	Time from randomisation to the first of: rising PSA; new disease or progression of: distant metastases, lymph nodes or local disease; or death from prostate cancer
	Metastatic progression-free survival	Time from randomisation to death from any cause, new metastases or progression of distant metastases
	Prostate cancer-specific survival	Time from randomisation to prostate cancer death
	Clinical Skeletal-related events	Pathologic fracture, spinal cord compression, requirement for radiation therapy to bone, requirement for surgery
	QoL	The EORTC QLQ-C30 with the prostate-specific module QLQ PR25
LATITUDE	Overall survival	Time from randomisation to death from any cause
	Radiographic progression-free survival	Time from randomization to the occurrence of radiographic progression or death from any cause. Radiographic progression of soft-tissue lesions was evaluated based on RECIST, version 1.1. Progression on bone scanning was assessed by adaptation of PCWG 2 criteria
	Time to PSA progression	Time to progression by PCWG3 criteria
	Time to initiation of chemotherapy	Time from randomisation to initiation of chemotherapy for prostate cancer
	Time to subsequent prostate cancer therapy	Time from randomisation to initiation of any subsequent therapy for prostate cancer, including hormonal therapy, chemotherapy, surgery, or radiotherapy
	Time to pain progression	Time from randomisation to first increase of at least 30% from baseline in the worst pain category on the BPI-SF as observed at two consecutive evaluations performed at least 4 weeks apart
	Time to next symptomatic skeletal event	Time from randomisation to any one of the following skeletal-related events: clinical or pathological fracture, spinal cord compression, palliative radiotherapy to bone, or surgery to bone
	Time to symptomatic local progression	Time to occurrence of urethral obstruction or bladder outlet obstruction
	Secondary progression-free survival	Time from randomisation to progression on subsequent treatment or death
	PSA response	A decrease of at least 50% from the baseline value
	Prostate cancer-specific survival	Not applicable
	Patient reported outcome	EuroQol five-dimensions, five-levels questionnaire, BPI-SF, Brief Fatigue Inventory, FACT-P version 4

Trial ID	Outcome	Outcome definition
TITAN	Overall survival	Time from randomization to the date of death from any cause
	Radiographic progression-free survival	Time from randomization to first imaging-based documentation of progressive disease or death, whichever occurred first. Radiographic progressive disease: progression of soft-tissue lesions according to modified RECIST, version 1.1, or new bone lesions according to PCWG 2.
	Time to PSA progression	Time from randomization to date of PSA progression based on PCWG 2.
	Time to cytotoxic chemotherapy	Time from randomization to initiation of cytotoxic chemotherapy
	Time to pain progression	Time from randomization to pain progression (average increase in 2 points from baseline in BPI-SF worst pain intensity observed at two consecutive evaluations ≥3 weeks apart, with an average worst pain score of >4 in patients who have had no decrease in opioids or initiation of chronic opioids, whichever occurs first)
	Time to chronic opioid use	Time from randomization to chronic opioid use. Chronic opioid use was defined as administration of opioid analgesics for ≥3 weeks for oral or ≥7 days for nonoral formulations. For patients who were already receiving opioids at study entry, chronic opioid use was defined as a ≥30% increase in total daily dose of the opioid analgesics lasting for ≥3 weeks for oral or ≥7 days for nonoral formulations
	Time to skeletal-related event	Time from randomization to first observation of a skeletal-related event (symptomatic pathologic fracture, spinal cord compression, radiation to bone, or surgery to bone).
	Time to symptomatic local progression	Time from randomization to date of symptomatic local progression
	Second progression-free survival	Time from randomization to the first occurrence of investigator-determined disease progression (PSA progression, progression on imaging, or clinical progression) while the patient was receiving first subsequent therapy for prostate cancer or death due to any cause, whichever occurred first
	Patient-reported outcomes for health-related QoL	Pain, fatigue, prostate cancer symptoms, and overall health related QoL
ARCHES	Overall survival	Time from randomization to death from any cause
	Radiographic progression-free survival	"Time from randomization to the first objective evidence of radiographic disease progression, or death, whichever occurred first. Radiographic disease progression is defined by RECTST version 1.1 for soft tissue disease or the appearance of 2 or more new lesions on bone scan
	Time to PSA progression	Time from randomization to a >=25% increase and an absolute increase of >=2 ng/ml above the nadiar, which is confirmed by a second consecutive value at least 3 weeks later
	Time to initiation of new antineoplastic therapy	Time from randomization to the initiation of antineoplastic therapy (including cytotoxic and hormonal therapy) subsequent to the study treatments
	PSA undetectable rate	The percentage of subjects with detectable (>=0.2ng/ml) PSA at baseline, which becomes undetectable (<0.2ng/ml) during study treatment
	Objective response rate	The percentage of subjects with measurable disease at baseline who achieved a complete or partial response in their soft tissue disease using the RECIST version 1.1 criteria
	Time to deterioration in urinary symptoms	Time from randomization to the first deterioration in urinary symptoms defined as an increase in urinary symptoms scores, using a modified urinary symptoms scale derived from a selected subset of symptoms from the QLQ-PR-25 questionnaire module, by >=50% of the standard deviation observed in the modified urinary symptoms scale score at baseline
	Time to first symptomatic skeletal event	The time from randomization to the occurrence of the first symptomatic skeletal event, defined as radiation or surgery to bone, clinically apparent pathologic bone fracture, or spinal cord compression
Trial ID	**Outcome**	**Outcome definition**
	Time to castration resistance	Time from randomization to the first castration-resistant event (radiographic disease progression, PSA progression or symptomatic skeletal event with castration levels of testosterone, whichever occurs first.

	Patient-reported outcomes	FACT-P, QoL Prostate-Specific questionnaire, and BPI-SF
	Time to deterioration of quality of life	Time from randomization to a 10-point decrease in the FACT-P total score
	Time to pain progression	Time from randomization to an increase of >=30% in pain severity score from baseline using BPI-SF
	Time to progression of worst pain	Time from randomization to an increase of ≥ 2 points in worst pain from baseline using BPI-SF
	Time to progression of pain severity	Time from randomization to an increase of ≥ 2 points in pain severity score from baseline using BPI-SF
ENZAMET	Overall survival	The interval from randomization to death from any cause
	clinical progression-free survival	The earliest sign of radiographic progression according to the criteria of the PCWG 2 for bone lesions and RECIST, version 1.1, for soft-tissue lesions; the development of symptoms attributable to cancer progression; or the initiation of another anticancer treatment for prostate cancer.
	PSA progression-free survival	The interval from randomization to the earliest event of PSA progression according to the criteria of PCWG2, clinical progression, death from any cause

Abbreviation: BFI-SF, Brief Pain Inventory—Short Form; EORTC QLQ, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; FACT-P, Functional Assessment of Cancer Therapy-Prostate; PCWG, Prostate Cancer Working Group; PSA, prostate-specific antigen; QoL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumors;

eTable 3. Results of Included Trials for Overall Survival, Radiographic Progression Free Survival, and Serious Adverse Events

Trial ID	Experimental (added to ADT)	Comparator (added to ADT)	OS, HR (95%CI)	rPFS, HR (95% CI)	SAE, No./Total No. (%)	
			Experimental vs comparator	Experimental vs comparator	Experimental	Comparator
GETUG-AFU15	Docetaxel	No treatment	0.88 (0.68-1.14)	0.69 (0.55-0.87)	72/189 (38)	0/186 (0)
CHAARTED	Docetaxel	No treatment	0.72 (0.59-0.89)	0.62 (0.51-0.75)	116/390 (30)	12/392 (3)
STAMPEDE[a]	Docetaxel	No treatment	0.81 (0.69-0.95)	0.69 (0.59-0.81)	Not reported	Not reported
	Abiraterone	No treatment	0.61 (0.49-0.79)	0.45 (0.37-0.54)	Not reported	Not reported
LATITUDE[b]	Abiraterone	Placebo	0.616 (0.524-0.724)	0.47 (0.39-0.55)	192/597 (32)	151/602 (25)
TITAN	Apalutamide	Placebo	0.67 (0.51-0.89)	0.48 (0.39-0.60)	104/524 (20)	107/527 (20)
ARCHES	Enzalutamide	Placebo	0.81 (0.53-1.25)	0.39 (0.30-0.50)	104/572 (18)	112/574 (20)
ENZAMET	Enzalutamide	SNA	0.67 (0.52-0.86)	0.40 (0.33-0.47)	235/563 (42)	189/558 (34)

Abbreviation: ADT, androgen deprivation therapy; CI, confidence interval; HR, hazard ratio; OS, overall survival; rPFS, radiographic progression-free survival (including progression-free survival in STAMPEDE, time to clinical progression in CHAARTED, and clinical progression-free in ENZAMET); SAE, serious adverse events, SNA, Standard non-steroid antiandrogen (bicalutamide, nilutamide, or flutamide).

[a] STAMPEDE trial did not report SAE or AE that let to treatment discontinuation for metastatic castration-sensitive prostate cancer patients.

[b] LATITUDE trial allowed cross-over after the first interim analysis. Adjusted overall survival estimates for treatment switching was used.

[c] STAMPEDE trial is a multi-arm multi-stage platform design where different active treatments were tested at different time periods but shared the same control arm that enrolled patients continuously.

eTable 4. Relative Effect Estimates for All Possible Pairwise Treatment Comparisons

Overall survival, hazard ratio (95% CI)

Abiraterone acetate					
0.92 (0.67,1.25)	Apalutamide				
0.77 (0.65,0.92)	0.85 (0.63,1.14)	Docetaxel			
0.76 (0.48,1.19)	0.83 (0.50,1.38)	0.98 (0.63,1.53)	Enzalutamide		
0.61 (0.54,0.70)	0.67 (0.51,0.89)	0.79 (0.71,0.89)	0.81 (0.53,1.24)	Placebo/no treatment	
0.51 (0.30,0.85)	0.56 (0.31,0.98)	0.66 (0.39,1.09)	0.67 (0.52,0.86)	0.83 (0.50,1.36)	SNA

Radiographic progression-free survival, hazard ratio (95% CI)

Abiraterone acetate					
1.07 (0.83,1.37)	Apalutamide				
0.77 (0.65,0.91)	0.72 (0.57,0.92)	Docetaxel			
1.31 (0.99,1.75)	1.23 (0.88,1.72)	1.71 (1.30,2.27)	Enzalutamide		
0.51 (0.45,0.58)	0.48 (0.39,0.60)	0.67 (0.60,0.74)	0.39 (0.30,0.50)	Placebo/no treatment	
0.53 (0.37,0.74)	0.49 (0.34,0.72)	0.68 (0.49,0.95)	0.40 (0.34,0.48)	1.03 (0.75,1.41)	SNA

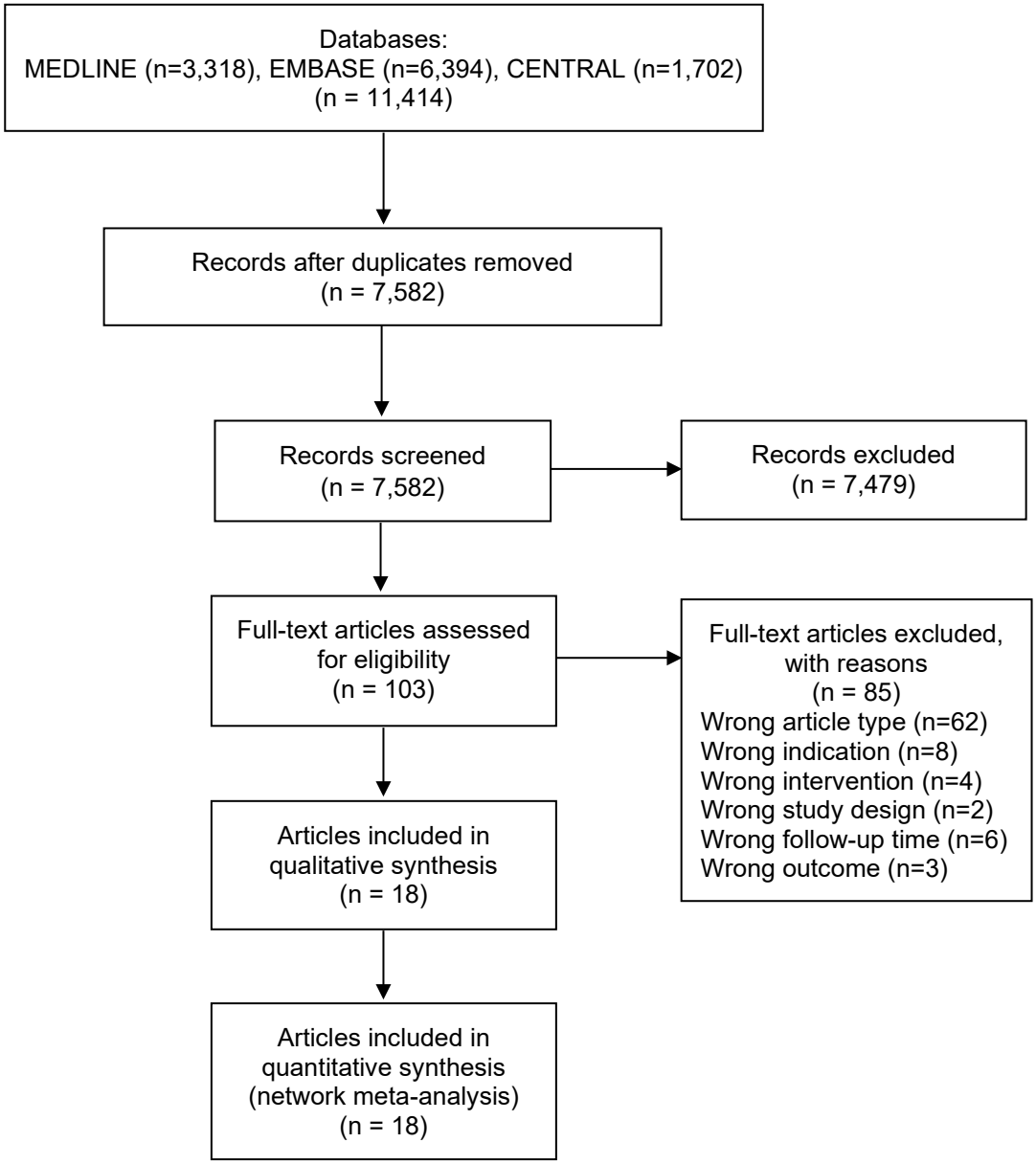
Serious adverse events, odds ratio (95% CI)

Abiraterone acetate					
1.46 (0.99,2.16)	Apalutamide				
0.06 (0.03,0.11)	0.04 (0.02,0.08)	Docetaxel			
1.54 (1.05,2.28)	1.06 (0.70,1.62)	25.62 (13.59,52.42)	Enzalutamide		
1.42 (1.10,1.83)	0.97 (0.72,1.31)	23.45 (13.37,45.15)	0.92 (0.68,1.23)	Placebo/no treatment	
2.16 (1.37,3.43)	1.48 (0.91,2.41)	35.89 (18.15,76.32)	1.40 (1.09,1.79)	1.53 (1.04,2.25)	SNA

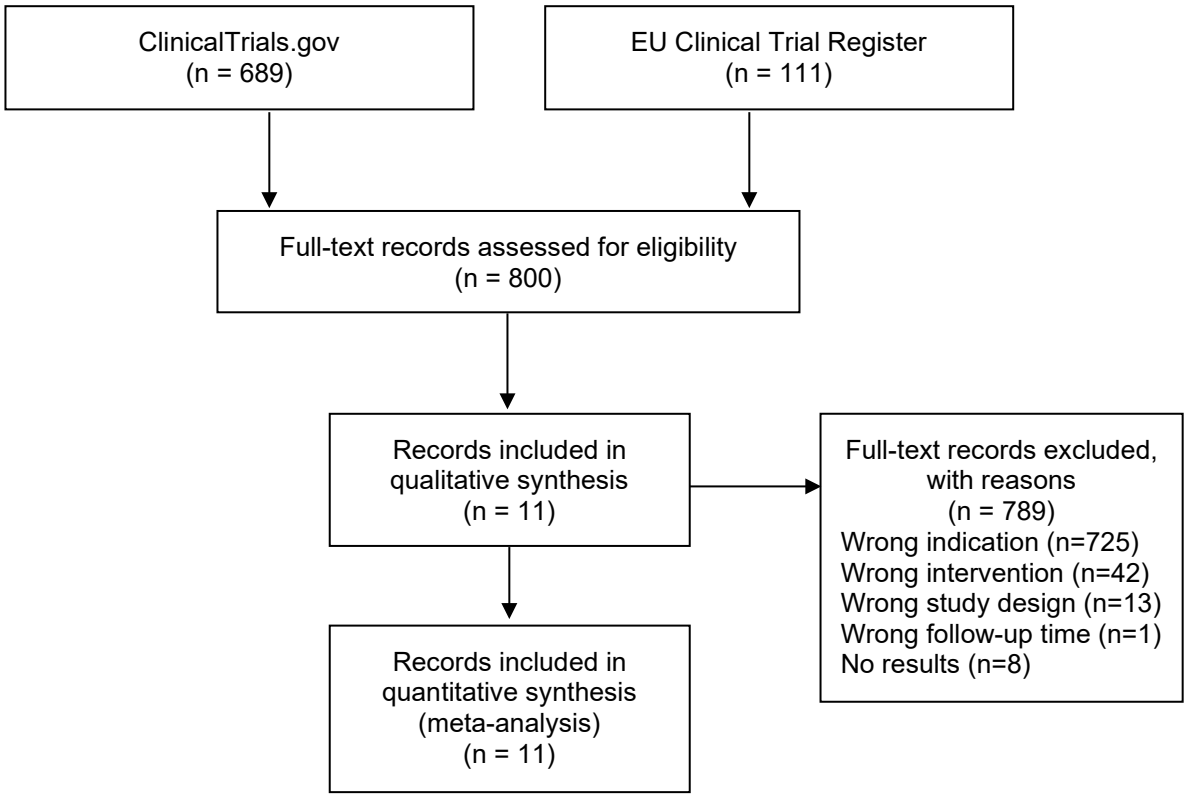
Abbreviation: CI, credible interval; Standard non-steroid antiandrogen (bicalutamide, nilutamide, or flutamide).

eFigure 1. Flowchart of Study Selection Process

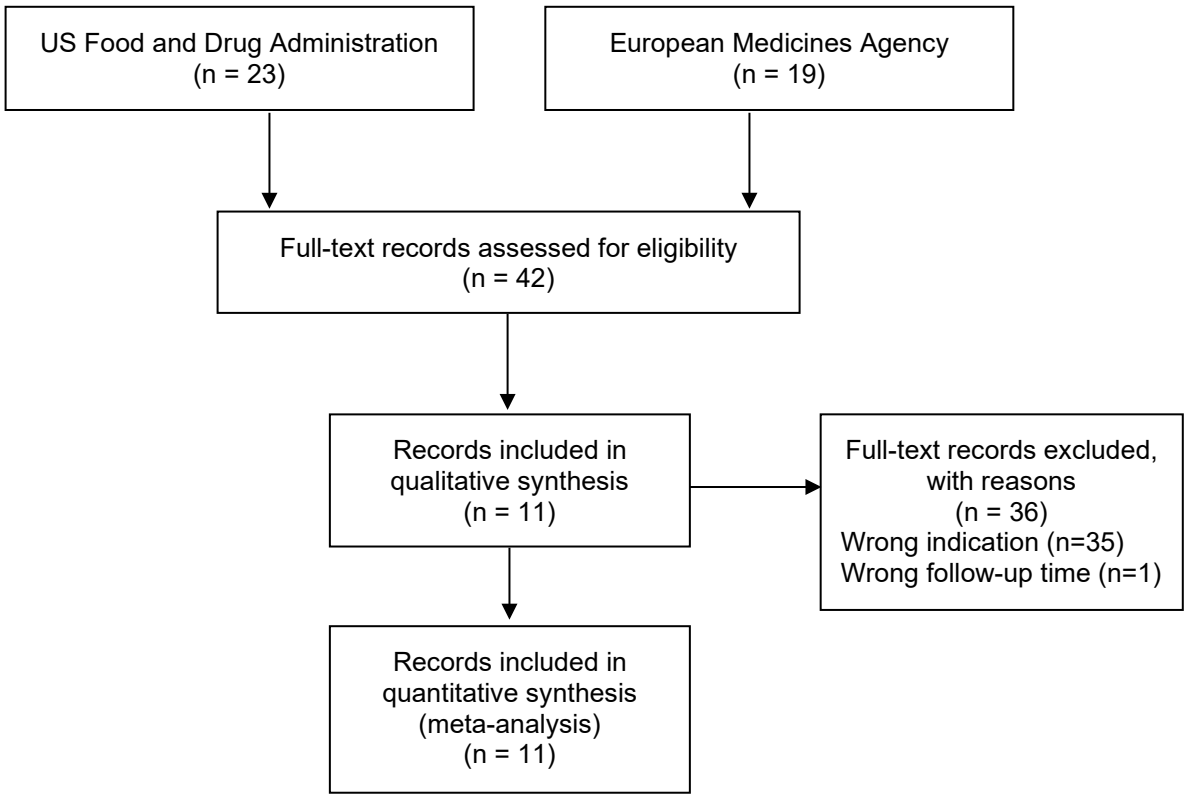
Bibliographic databases



Trial registries

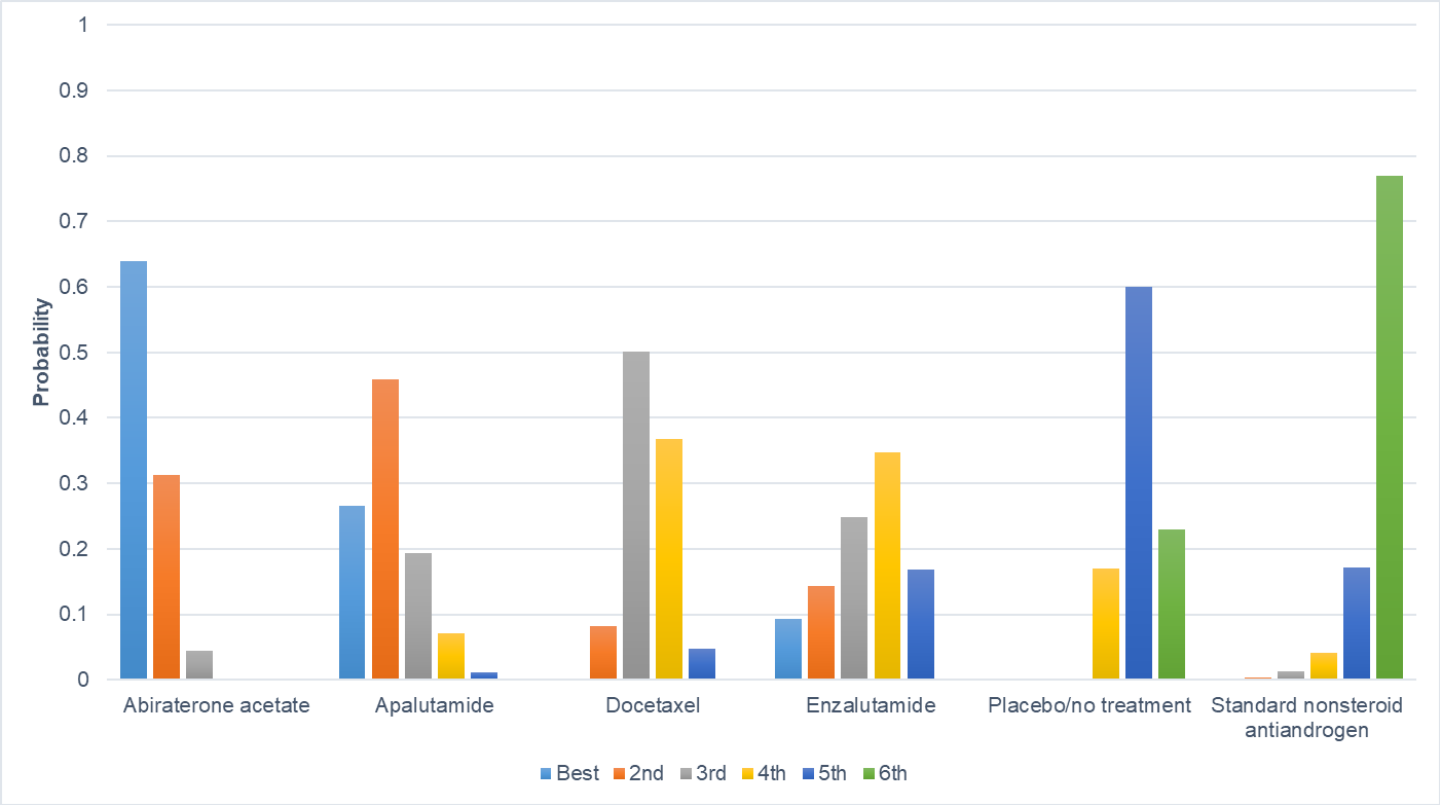


Regulatory documents

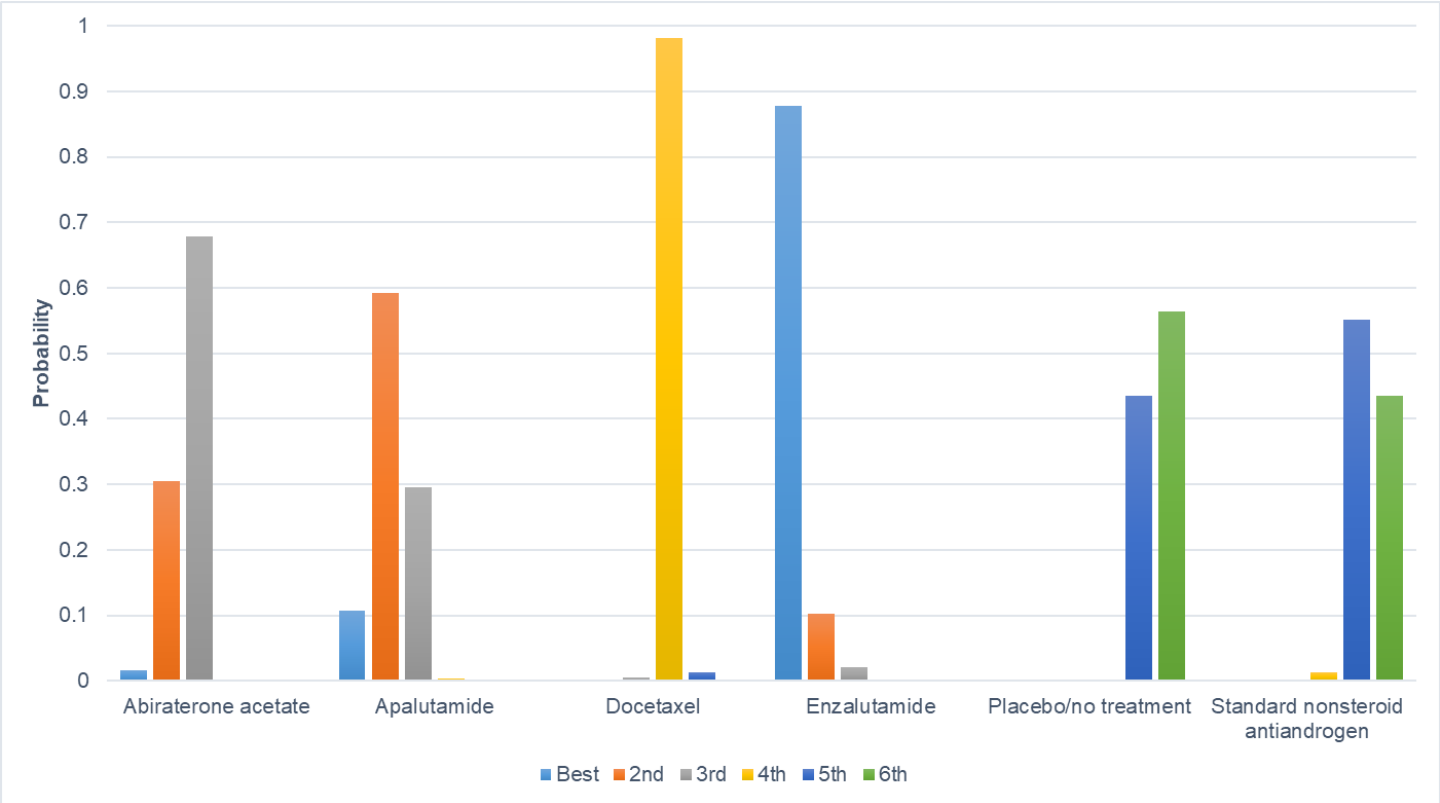


eFigure 2. Treatment Ranking Probabilities for Overall Survival, Radiographic Progression-Free Survival, and Serious Adverse Events

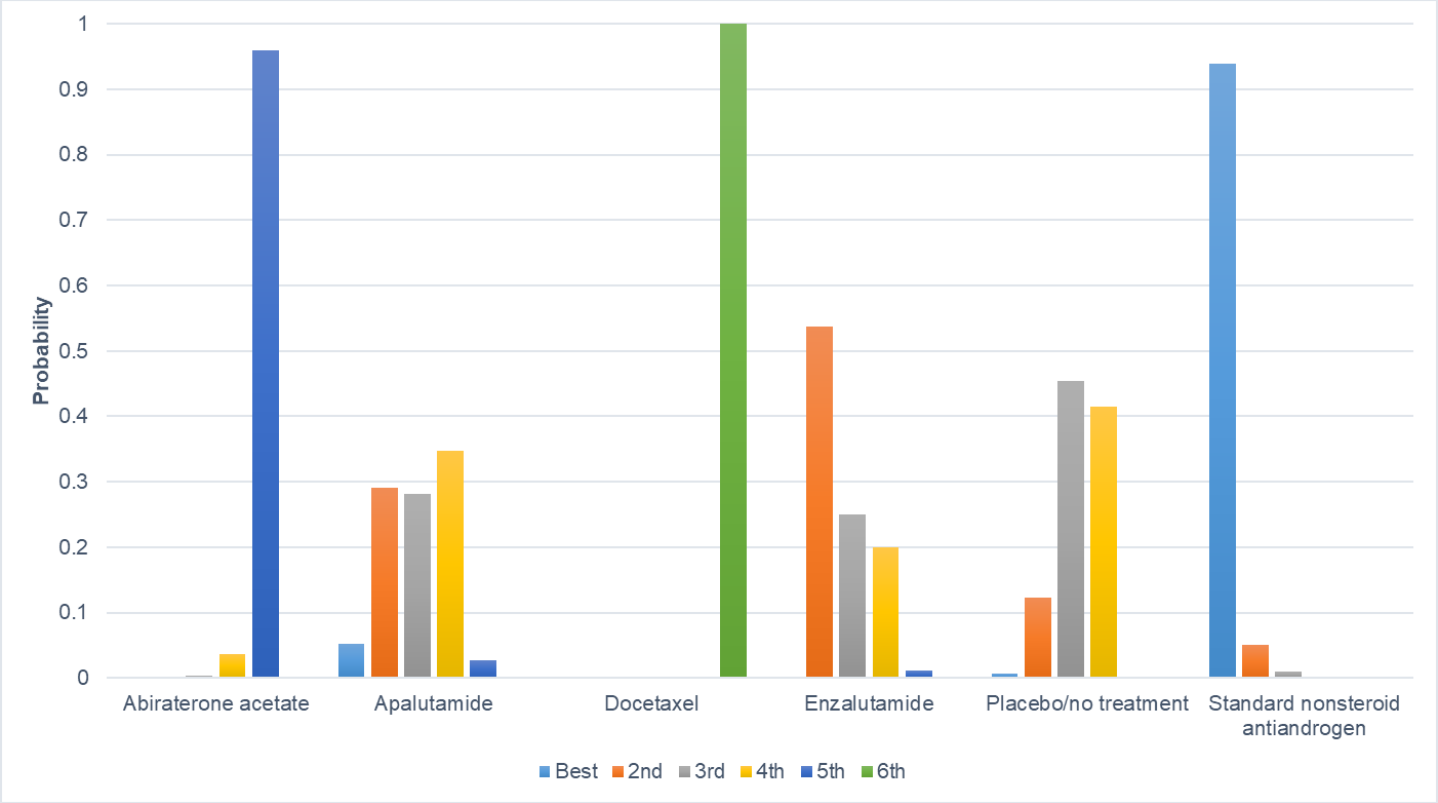
Overall survival



Radiographic progression free survival



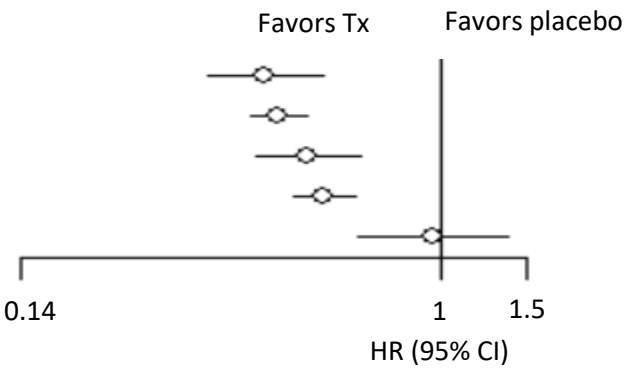
Serious Adverse events



eFigure 3. Network Meta-analysis Results for Subgroups Based on Disease Volume

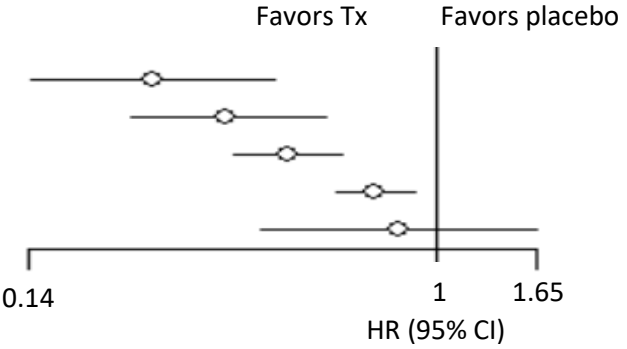
Radiographic progression-free survival, high disease volume

Treatment	Median rank	HR (95%CI)
Enzalutamide	1	0.43 (0.33-0.56)
Abiraterone acetate	2	0.46 (0.40-0.53)
Apalutamide	3	0.53 (0.41-0.68)
Docetaxel	4	0.57 (0.49-0.66)
SNA	5	0.96 (0.67-1.36)
vs Placebo/no treatment		Reference



Radiographic progression-free survival, low disease volume

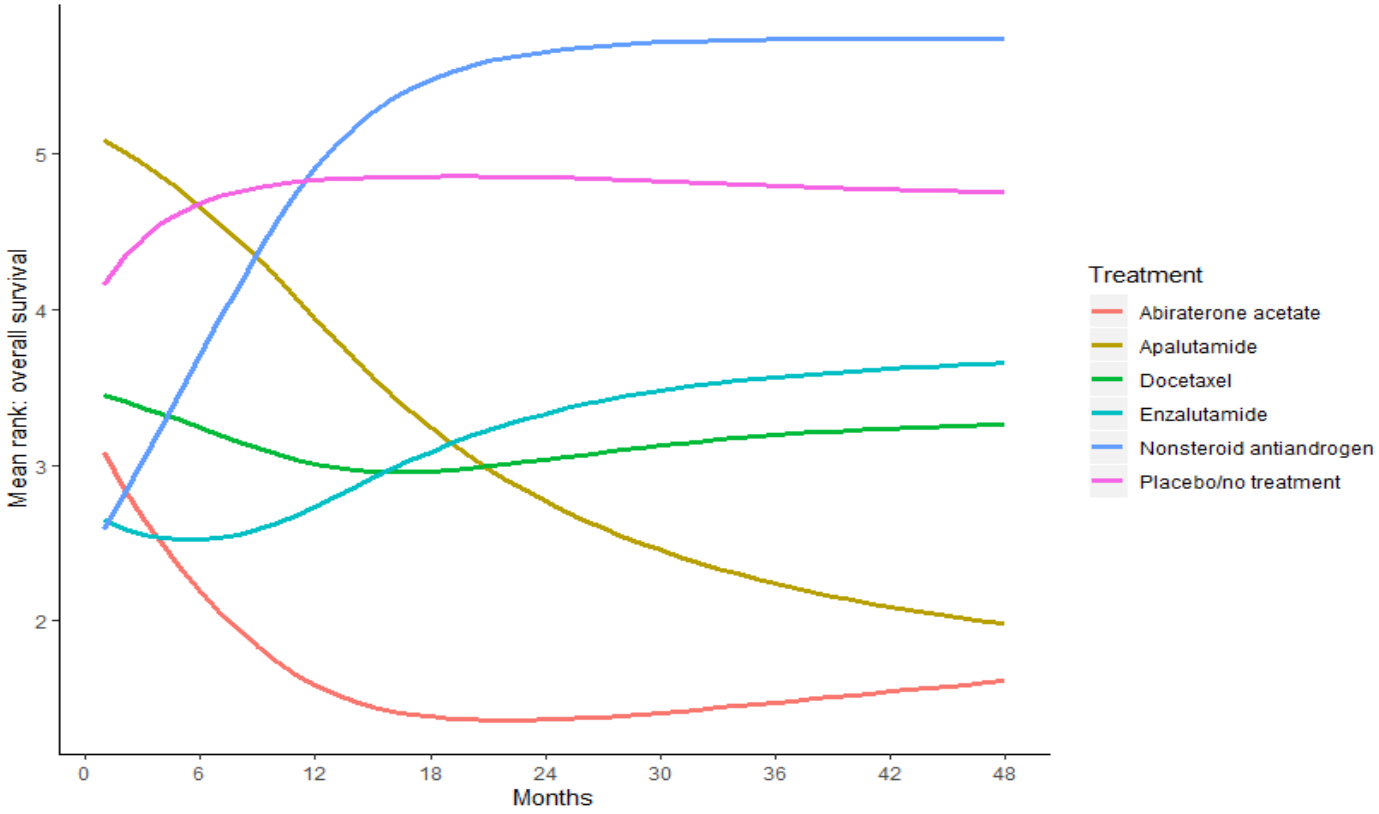
Treatment	Median rank	HR (95%CI)
Enzalutamide	1	0.25 (0.14-0.45)
Apalutamide	2	0.36 (0.22-0.58)
Abiraterone acetate	3	0.48 (0.37-0.63)
Docetaxel	4	0.74 (0.61-0.91)
SNA	5	0.83 (0.42-1.64)
vs Placebo/no treatment		Reference



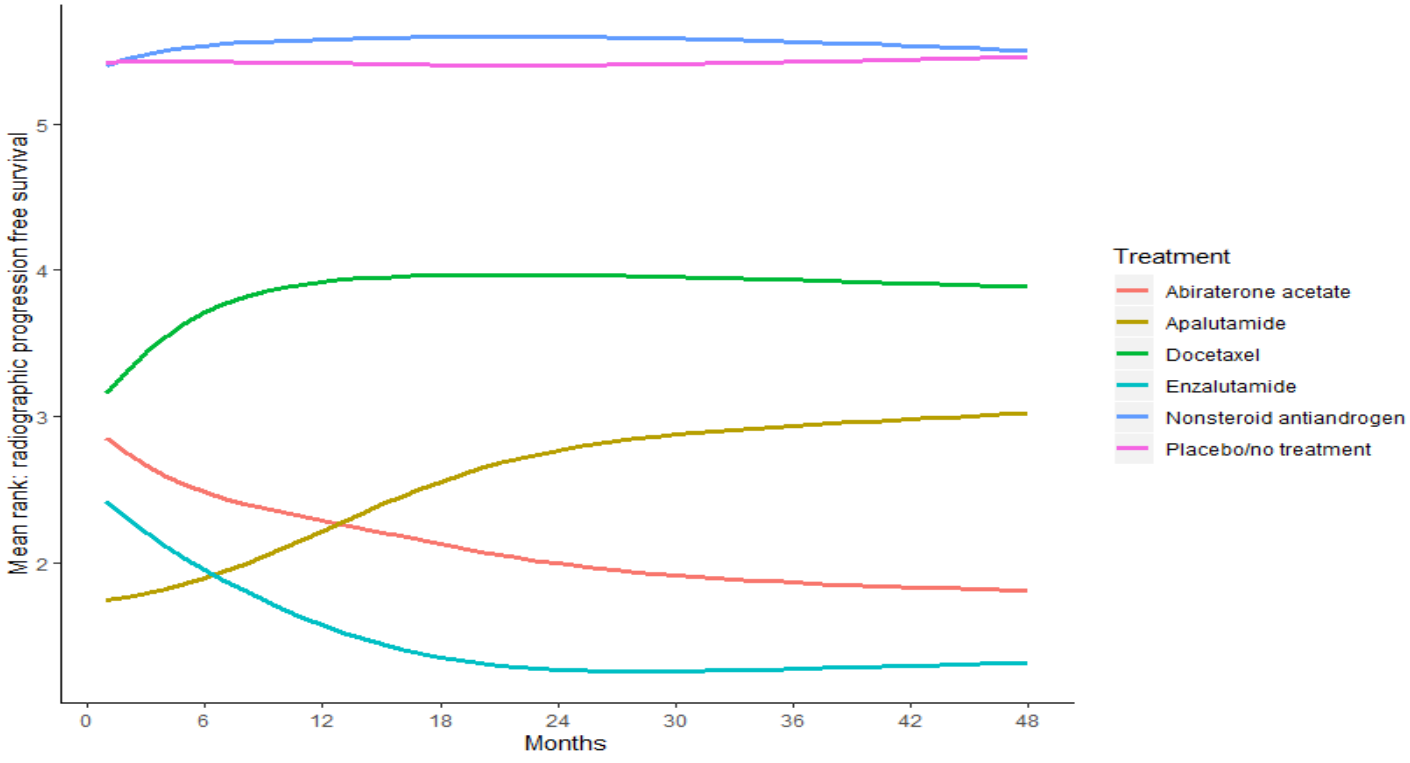
High volume disease was defined as presence of visceral metastases or four or more bone metastases, with at least one outside the vertebral column or pelvis the CHAARTED trial criteria.[9]

eFigure 4. Treatment ranking over time derived from parametric survival network meta-analysis

Overall survival

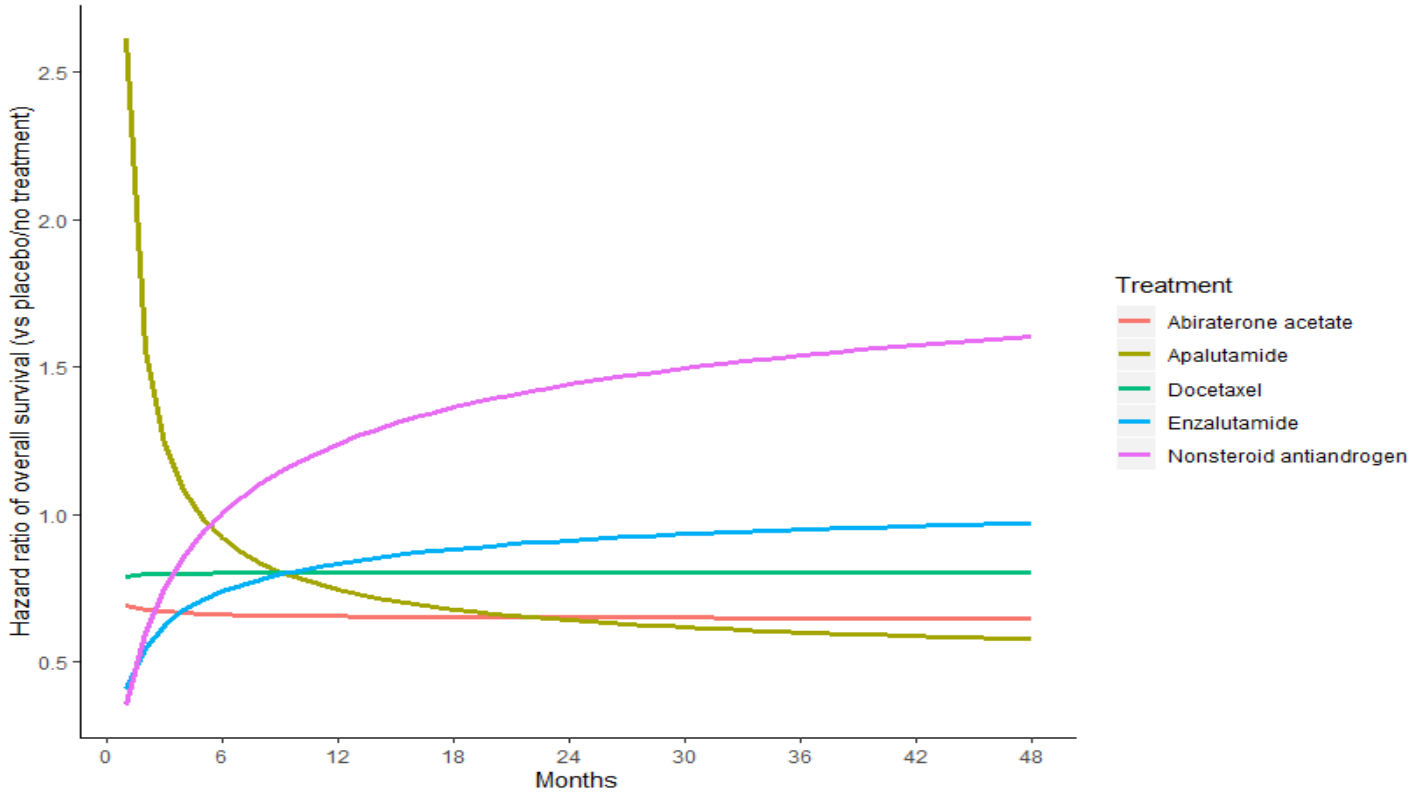


Radiographic progression free survival

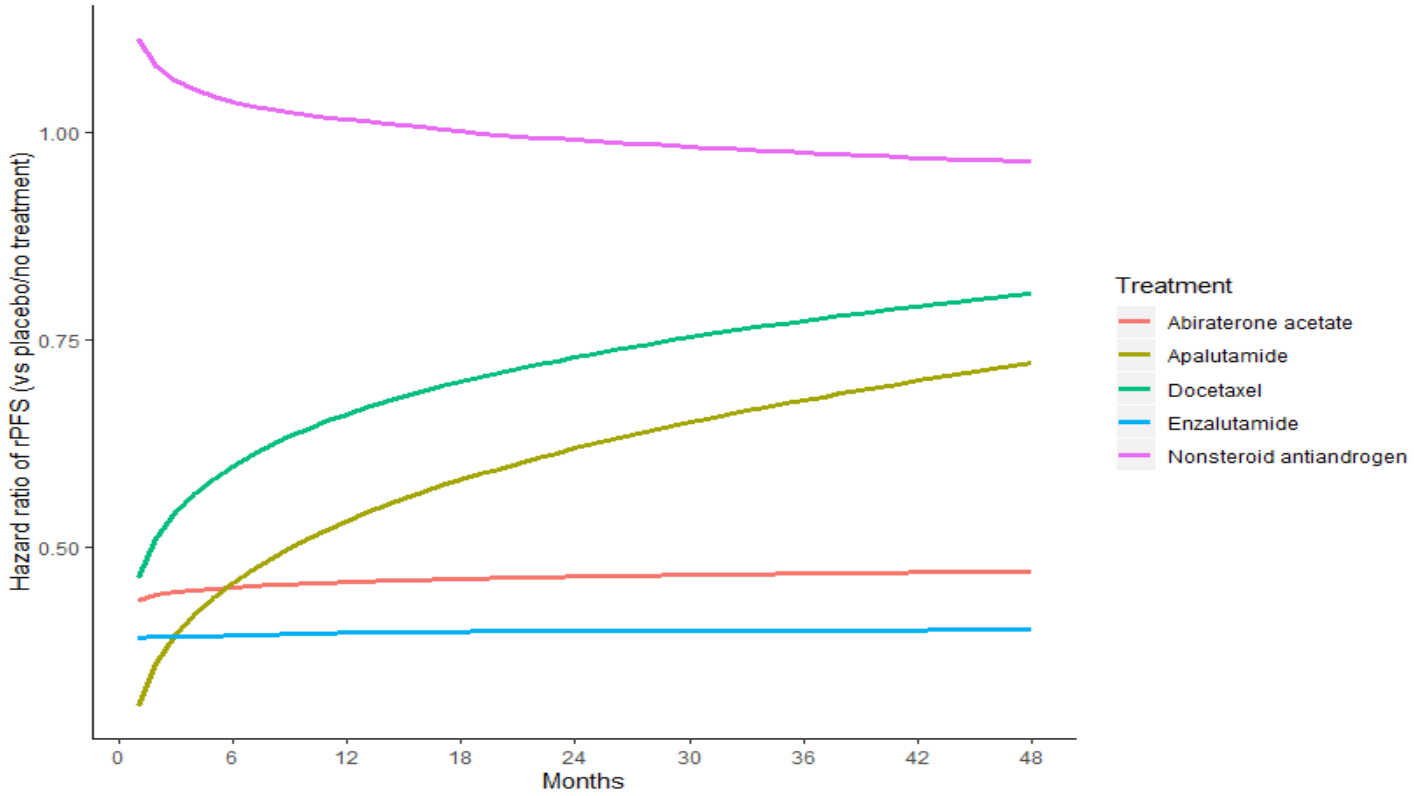


eFigure 5. Hazard Ratios over time derived from parametric survival network meta-analysis

Overall survival



Radiographic progression free survival



Abbreviation: rPFS, radiographic progression free survival.

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