Supplementary Material

Wang L, Paller C, Hong H, De Felice A, Brawley O, Alexander GC. Comparison of treatments for nonmetastatic castration-resistant prostate cancer: A matching adjusted indirect comparison and network meta-analysis

Supplementary Methods

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
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#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	#11 OR #12 OR #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

Matching-Adjusted Direct Comparison Methods and Results

Methods

Matching-adjusted indirect comparison (MAIC) is a form of propensity score weighting, applicable where individual patient data (IPD) are available one trial and aggregate data (AD) in another.[1] Individuals in the IPD trial are weighted by the inverse of their propensity scores, to balance the baseline characteristics with that of the AD trial.[1]

1. If treatment t in the IPD trial were received by the AD trial population, the mean outcome $Y_{t_{IPD(AD)}}$ is estimated by taking the weighted average of the outcomes $Y_{t_{IPD(IPD)}}$ of the $N_{t_{IPD(IPD)}}$ individuals in treatment t arm of the IPD trial population

$$\hat{Y}_{t_{IPD(AD)}} = \frac{\sum_{i=1}^{N_{t_{IPD}}} Y_{t_{IPD(IPD)}} * w_{it_{IPD}}}{\sum_{i=1}^{N_{t_{IPD}}} w_{it_{IPD}}}$$

2. The weight $w_{it_{IPD}}$ assigned to the i-th individual receiving treatment t in the IPD trial is equal to the odds of being enrolled in the AD trial vs. the IPD trial. The weights are estimated using logistic regression

$$\log(w_{it_{IPD}}) = \alpha_0 + \alpha_1^T * X_{it_{IPD}}$$

Where $X_{it_{IPD}}$ is the covariate vector for the i-th individual receiving treatment t in the IPD trial. The regression parameters $\hat{\alpha}_1$were estimated using the method of moments proposed by Signorovitch et al.,[2] so that the weights exactly balance the mean covariates values between the weighted IPD trial population and AD trial population. When the mean covariate values of the AD trial $\bar{X}_{(AD)} = 0$, Signorovitch et al. show that it is equivalent to minimizing $\sum_t \sum_{i=1}^{N_{t_{IPD}}} \exp(\alpha_1^T * X_{it_{IPD}})$. Then

$$\hat{Y}_{t_{IPD(AD)}} = \frac{\sum_{i=1}^{N_{t_{IPD}}} Y_{t_{IPD(IPD)}} * \exp(\alpha_1^T * X_{it_{IPD}})}{\sum_{i=1}^{N_{t_{IPD}}} \exp(\alpha_1^T * X_{it_{IPD}})}$$

3. The indirect comparison between IPD trial treatment and AD trial treatment is estimated using

$$\hat{\Delta}_{t_{IPD}-t_{AD}} = g(\hat{Y}_{t_{IPD(AD)}}) - g(\hat{Y}_{t_{IPD(AD)}})$$

where $g(y)$is the appropriate link function for relative treatment effects: log link for the hazard of metastasis or death and logit link for the probability of serious adverse events. We weighted Cox regression and logistic regression to estimate the hazard ratio of metastasis or death and odds ratio of serious adverse events, respectively, from indirect comparison. The estimated hazard ratio/odds ratio were then fed into network meta-analysis models. For parametric survival network meta-analysis, the weighted Kaplan Meier estimates, i.e., the weighted events and risk sets at time intervals, of the IPD trial were fed into the models.

4. The standard error for MAIC estimates is calculated using the robust sandwich estimator[2] to account for uncertainties in estimated weights.

5. The effective sample size (ESS) of the pseudo-population is estimated by

$$ESS = \frac{\left(\sum_t \sum_{i=1}^{N_{t_{IPD}}} \hat{w}_{it_{IPD}}\right)^2}{\sum_t \sum_{i=1}^{N_{t_{IPD}}} \hat{w}_{it_{IPD}}^2}$$

As the relative treatment effects are estimated by weighting the IPD trial population, ESS is the number of independent, non-weighted individuals that would be required to provide an estimate with the same prediction as the weighted estimate.[1]

Results

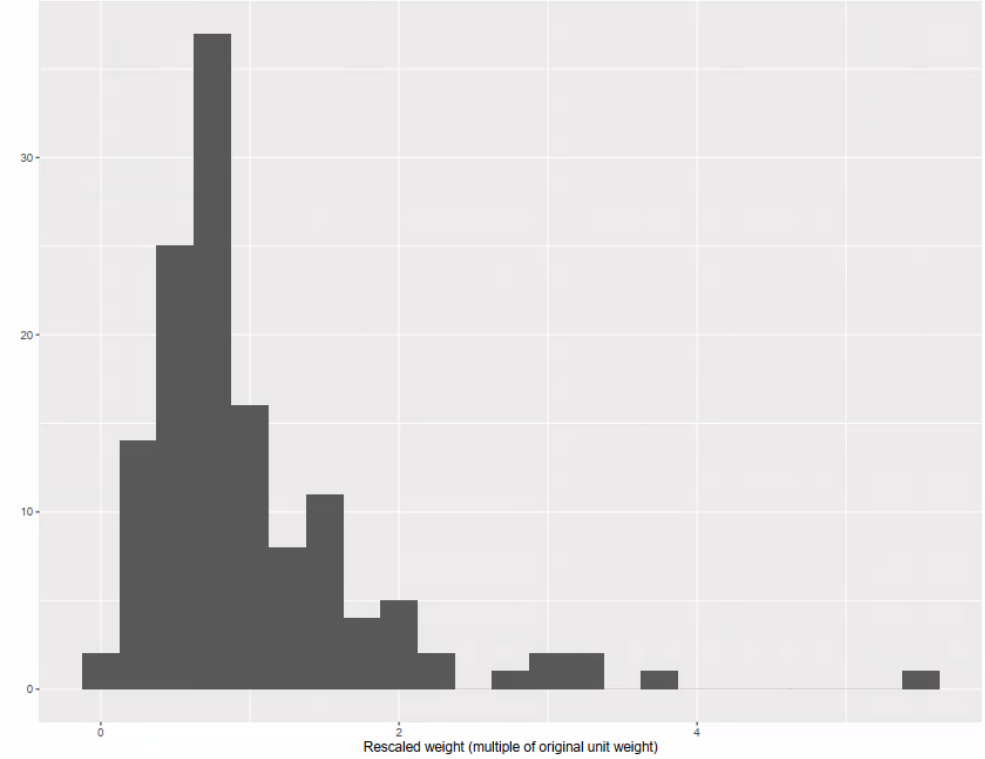
1. Distribution of rescaled weights.

	Min	1st quartile	Median	Mean	3rd quartile	Max
Value	0.01	0.57	0.77	1.00	1.21	5.54

The rescaled weight is calculated as

$$\widetilde{w} = \frac{\widehat{w}_{it_{IPD}}}{\sum_{i=1}^{N_{t_{IPD}}} \widehat{w}_{it_{IPD}}} * N_{t_{IPD}}$$

Rescaled weights are relative to the original unit weights of each individual; a rescaled weight>1 indicates that an individual carries more weight in the pseudo population than in IPD trial population, and a rescaled weight<1 indicates that an individual carries less weight.



2. The estimated ESS is 81.
3. The mean covariate values before and after weighting

		Age group (%)					**ECOG performance status (%)**		**PSA (mean)**	**Prior prostatectomy or radiation therapy (%)**	
		<65	65-69	70-74	75-84	>=85	0	1		Yes	No
IMAAGEN before weighting		16.8	22.9	30.5	22.1	7.6	85.5	14.5	21.1	89.3	10.7
IMAAGEN after weighting		12.3	17.8	21.6	39.8	8.5	77.4	22.6	15.2	76.6	23.4
SPARTAN		12.3	17.8	21.6	39.8	8.5	77.4	22.6	15.2	76.6	23.4

Supplementary Table 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[a]	Primary outcomes, secondary outcomes, safety outcomes
Baseline data	Patient characteristics: age, Eastern Cooperative Oncology Group performance status score, serum prostate-specific antigen level, and other baseline characteristics reported Information extracted: number of participants randomized, mean (standard deviation) and (or) median (range/interquartile range) for continuous variables and number (%) for categorical variables
Efficacy outcomes	Primary outcome of interest: Metastasis-free survival Secondary outcome of interest: overall survival Information extracted: number of patients who had the event, median follow-up time, median survival, hazard ratio (95% confidence interval), and Kaplan-Meier curves
Safety outcomes	Proportions of patients who experienced any serious adverse event Proportions of patients who experienced any grade 3 or 4 adverse event Information extracted: number of patients included in the safety analysis, median follow-up time, and number of patients who had the event

[a]Definitions of outcomes: 1) Metastasis-free survival: time from randomization to radiographic evidence of metastasis or death from any cause, whichever occurs first. 2) Overall survival: time from randomization to death from any cause. 3) 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.[3] 4) Grade 3 or 4 adverse event: any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that has a severity of: grade 3, severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living; or grade 4, life-threatening consequences; urgent intervention indicated.[4]

Supplementary Table 2. Efficacy Outcomes Assessed in Included Trials[a]

Trial ID	Outcome	Outcome definition
ARN-509-001	MFS	Time from randomization to new metastatic lesions on CT/MRI by modified RECIST or on bone scan, or death from any cause
	12-week PSA response	Percent change in PSA at 12 weeks and maximal change at any time by PCWG2
	Time to PSA progression	Time from randomization to PSA progression by PCWG2
SPARTAN	MFS	Time from randomization to first evidence of radiographically detectable bone or soft tissue distant metastasis or death from any cause
	OS	Time from randomization to death from any cause
	Time to metastasis	Time from randomization to first evidence of radiographically detectable bone or soft tissue distant metastasis
	PFS	Time from randomization to first documentation of radiographic progressive disease based on RECIST 1.1, or death from any cause
	Time to symptomatic progression	Time from randomization to a skeletal-related event, pain progression, or worsening of disease-related symptoms leading to the initiation of a new systemic anticancer therapy or the time to the development of clinically significant symptoms due to local or regional tumor progression leading to surgery or radiation therapy
	Time to initiation of cytotoxic chemotherapy	Time from randomization to the initiation of cytotoxic chemotherapy
	Time to PSA progression	Time from randomization to PSA progression by PCWG2 criteria
	PSA response rate	Percent of patients who achieved a 50% or greater reduction in PSA
	Secondary PFS	Time from randomization to investigator-assessed disease progression (by PSA, metastatic disease on imaging, or symptomatic, or any combination thereof) during the first subsequent treatment of mCRPC, or death
	QoL	Assessed with FACT-P and EQ-5D-3L
PROSPER	MFS	Time from randomization to radiographic progression or death. Assessment of bone disease will be done by bone scan. Radiographic progression for bone disease is defined as the appearance of one or more metastatic lesion on bone. Assessment of soft tissue disease will be done by CT or MRI. Radiographic progression for soft tissue disease is defined by RECIST 1.1
	OS	Time from randomization to death from any cause
	Time to PSA progression	Time from randomization to PSA progression by PCWG2
	PSA response rate	Percent of patients who achieved a 50% or greater reduction in PSA
	Time to the first use of a subsequent antineoplastic therapy	Time from randomization to the first use of new antineoplastic therapy for prostate cancer
	QoL	Assessed by the EQ-5D-5L and EORTC-QLQ-PR25
STRIVE	MFS (named as rPFS in STRIVE)	Time from randomization to first evidence of radiographic progression or death from any cause. For M0 patients, appearance of a metastasis is considered radiographic progression.
	PFS	Time from randomization to the earliest evidence of PSA progression by PCWG2, radiographic progression, or death from any cause
	Time to PSA progression	Time from randomization to PSA progression by PCWG2 criteria
	PSA response rate	Percentages of patients who achieved a 50% or greater, and 90% or greater reduction in PSA
	QoL	Assessed with FACT-P
ARAMIS	MFS	Time from randomization to evidence of metastasis by CT/MRI or bone scan, or death from any cause. Metastasis in bone is defined as appearance of 1 or more lesions. Metastasis in soft tissue is defined as the appearance of an abnormal lymph node (i.e. ≥2 cm in the short axis) or of any new visceral lesion(s) on CT/MRI
	OS	Time from randomization to death from any cause
	Time to pain progression	Time from randomization to an increase of ≥2 points from baseline in the score assessed with the BPI-SF questionnaire or initiation of opioid treatment for cancer pain
	Time to first symptomatic skeletal event	Time from randomization to external-beam radiation therapy to relieve skeletal symptoms, new symptomatic pathologic bone fracture, occurrence of spinal cord compression, or tumor-related orthopedic surgical intervention
	Time to first cytotoxic chemotherapy	Time from randomization to first cytotoxic chemotherapy
	PFS	Time from randomization to evidence of any radiographic disease progression, including local relapse or new pathologic lymph nodes, or death from any cause
	Time to first prostate cancer-related invasive procedure	Time from randomization to any procedure needed for alleviation of symptoms, signs or findings caused by progression of prostate cancer
	Time to initiation of subsequent antineoplastic therapy	Time from randomization to initiation of first antineoplastic therapy
	Time to PSA progression	Time from randomization to PSA progression by PCWG2 criteria
	PSA response rate	Percent of patients who achieved a 50% or greater reduction in PSA

Trial ID	Outcome	Outcome definition
	Deterioration in ECOG performance status	Percent of patients with an increase to a score of 3 or higher
	QoL	Assessed with FACT-P, EQ-5D-3L, and EORTC-QLQ-PR25
IMAAGEN	MFS (reported as time to radiographic evidence of disease progression in IMAAGEN; with available individual patient level data including time to death, we estimated MFS)	Time from randomization to first scan (bone scan or CT/MRI) showing disease progression according to the modified RECIST 1.1
	PSA response rate	Percentages of patients who achieved a 30% or greater, 50% or greater, and 90% or greater reduction in PSA by the end of cycle 6 (28-day treatment cycle); percent of patients who achieved a 50% or greater reduction in PSA by the end of cycle 3
	Time PSA progression	Time from randomization to PSA progression by PCWG2

[a]CT=computed tomography. ECOG=Eastern Cooperative Oncology Group. EORTC-QLQ-PR25=European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-Prostate Cancer Module. EQ-5D-3L=Three -level version of European Quality of Life-5 Dimensions. EQ-5D-5L=Five -level version of European Quality of Life-5 Dimensions. FACT-P=Functional Assessment of Cancer Therapy-Prostate. mCRPC=metastatic castration-resistant prostate cancer. MRI=magnetic resonance imaging. OS=overall survival. MFS=metastasis-free survival. PFS=progression-free survival. PCWG=Prostate Cancer Working Group. PSA=prostate-specific antigen. rPFS=radiographic progression-free survival. QoL=quality of life. RECIST=Response Evaluation Criteria in Solid Tumors.

Supplementary Table 3. Baseline Characteristics of Nonmetastatic Castration-resistant Patients in Trials Included in Network Meta-analysis[a]

Trial ID	Treatment	Age (yr), median (range)	Time from initial diagnosis (yr), median (range)	ECOG, score (%)	Gleason score, score (%)	PSA (ng/ml), median (range)	PSADT (mo), median (range)
SPARTAN	Apalutamide	74 (48-94)	8.0 (0.3-30.4)	0 (77) 1 (23)	≤7 (57) >7 (43)	7.8 (0.1-294.8)	4.4 (0.8-10.0)
	Placebo	74 (52-97)	7.9 (0.8-26.3)	0 (78) 1 (22)	≤7 (56) >7 (44)	8.0 (1.1-291.8)	4.5 (0.7-10.0)
PROSPER	Enzalutamide	74 (50-95)	7.5 (0.2-31.8)	0 (80) 1 (20)	≤7 (55) >7 (41) Missing (4)	11.1 (0.8-1071.1)	3.8 (0.4-37.4)
	Placebo	73 (53-92)	7.2 (0.2-23.0)	0 (82) 1 (18)	≤7 (52) >7 (44) Missing (4)	10.2 (0.2-457.5)	3.6 (0.5–71.8)
STRIVE (nmCRPC PSADT<=10 mo)	Enzalutamide	75 (50-89)	7.9 (1.0-33.4)	0 (82) 1 (18)	≤7 (47) >7 (37) Missing (16)	7.3 (1.8-83.7)	3.5 (0.6-9.8)
	Bicalutamide	78 (58-89)	8.1 (0.7-17.7)	0 (78) 1 (22)	≤7 (52) >7 (36) Missing (12)	6.5 (2.3-58.6)	4.5 (0.5-9.5)
ARAMIS	Darolutamide	74 (48-95)	7.2 (0.2-28.1)	0 (68) 1 (32)	≤7 (74) >7 (23) Missing (3)	9.0 (0.3-858.3)	4.4 (0.7-11.0)
	Placebo	74 (50-92)	7.0 (0.0-28.7)	0 (71) 1 (29)	≤7 (71) >7 (26) Missing (3)	9.7 (1.5-885.2)	4.7 (0.7-13.2)
IMAAGEN	Abiraterone acetate + Prednisone	72 (48-90)	10.2 (1.5-26.0)	0 (85) 1 (14) 2 (1)	≤7 (61) >7 (39)	11.9 (1.3-167.8)	3.4 (1.1-9.4)

[a]We chose SPARTAN from among the included randomized controlled trials for matching-adjusted indirect comparison with IMAAGEN, because PROSPER and ARAMIS populations had much more widely spread PSA and (or) PSADT than IMAAGEN population, which cannot be well balanced by reweighting. And the sample size of STRIVE trial (N=112) is much smaller than that of SPARTAN trial (N=1,207) for precise relative effect estimation.
ECOG=Eastern Cooperative Oncology Group. nmCRPC=nonmetastatic castration resistant prostate cancer. PSA=prostate-specific antigen. PSADT=PSA doubling time.

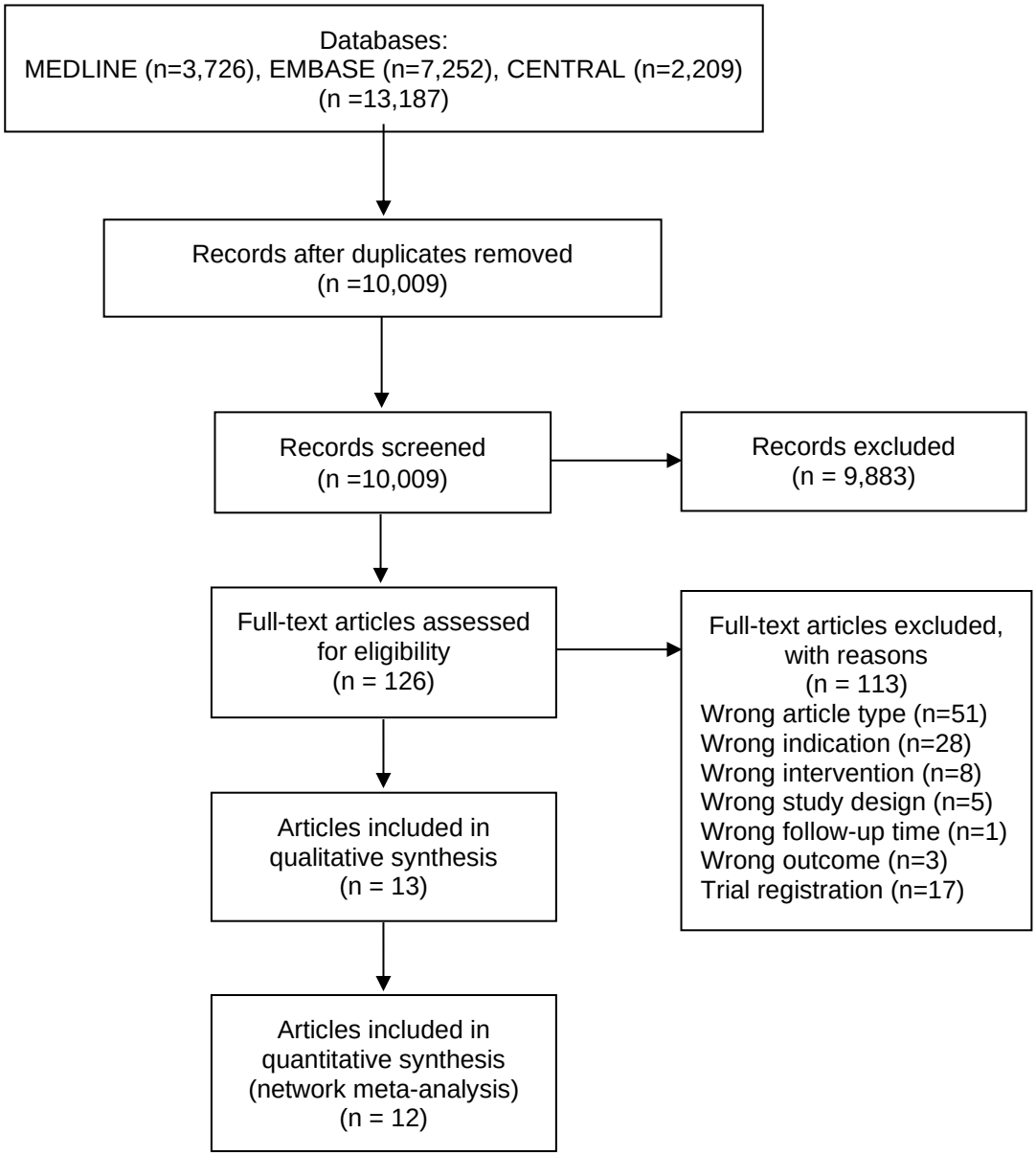
Supplementary Table 4. Relative Effect Estimates for All Possible Pairwise Treatment Comparisons

Outcome, treatment effect (95% CrI[a])	Comparator	Intervention					
Metastasis-free survival, hazard ratio		Abiraterone acetate					
	Apalutamide	0.79 (0.41-1.50)	Apalutamide				
	Enzalutamide	0.74 (0.39-1.40)	0.93 (0.71-1.22)	Enzalutamide			
	Darolutamide	0.54 (0.28-1.02)	0.68 (0.52-0.90)	0.73 (0.56-0.95)	Darolutamide		
	Bicalutamide	0.22 (0.08-0.63)	0.28 (0.12-0.68)	0.30 (0.13-0.69)	0.41 (0.17-0.98)	Bicalutamide	
	Placebo	0.22 (0.12-0.41)	0.28 (0.23-0.34)	0.30 (0.25-0.36)	0.41 (0.34-0.49)	1.01 (0.43-2.38)	Placebo
Overall survival, hazard ratio		Darolutamide					
	Enzalutamide	0.95 (0.69-1.29)	Enzalutamide				
	Apalutamide	0.92 (0.64-1.31)	0.97 (0.72-1.31)	Apalutamide			
	Placebo	0.69 (0.53-0.89)	0.73 (0.61-0.87)	0.75 (0.59-0.95)	Placebo		
Serious adverse events, odds ratio		Darolutamide					
	Enzalutamide	0.92 (0.63-1.34)	Enzalutamide				
	Bicalutamide	0.81 (0.29-2.33)	0.88 (0.34-2.28)	Bicalutamide			
	Apalutamide	0.83 (0.58-1.19)	0.91 (0.62-1.32)	1.03 (0.37-2.89)	Apalutamide		
	Abiraterone acetate	0.68 (0.39-1.19)	0.74 (0.42-1.31)	0.84 (0.28-2.56)	0.81 (0.47-1.43)	Abiraterone acetate	
	Placebo	1.32 (1.02-1.70)	1.44 (1.08-1.89)	1.63 (0.61-4.41)	1.58 (1.23-2.03)	1.94 (1.17-3.22)	Placebo

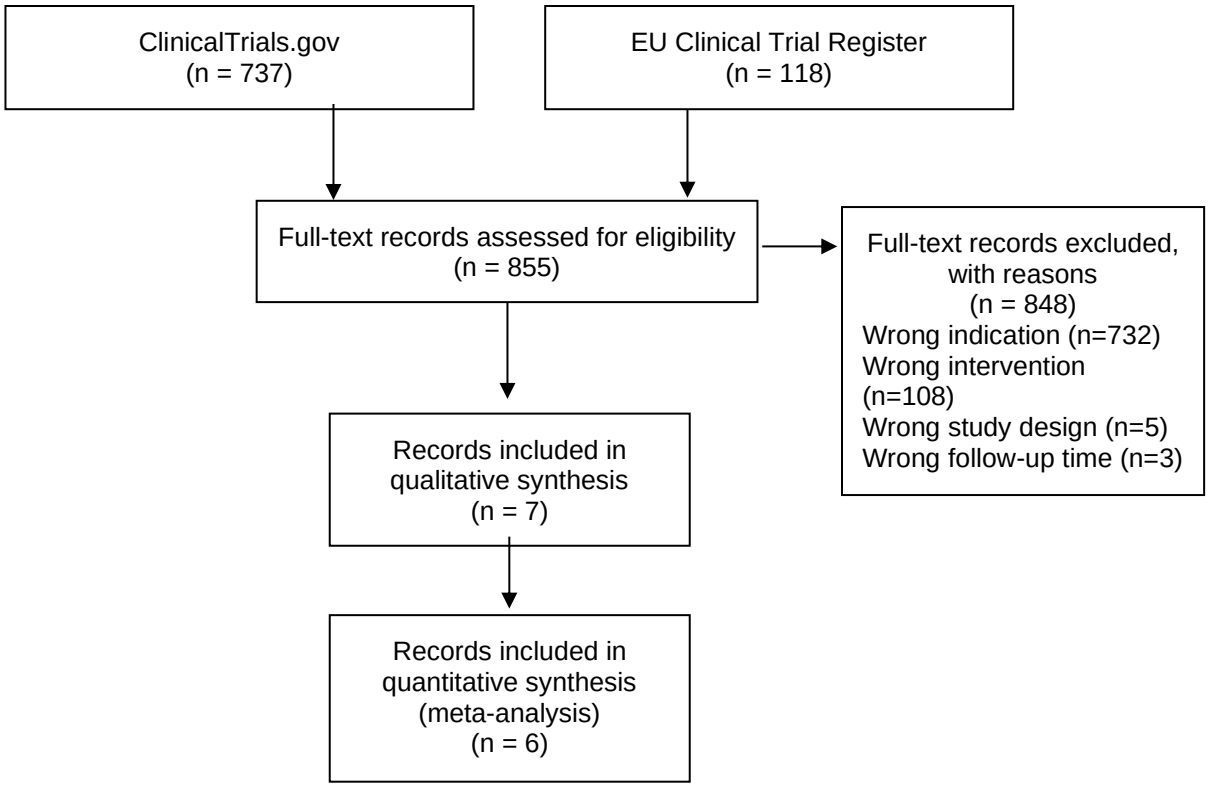
[a]CrI=credible interval.

Supplementary Figure 1. Flowchart of Study Selection

Bibliographic databases



Trial registries



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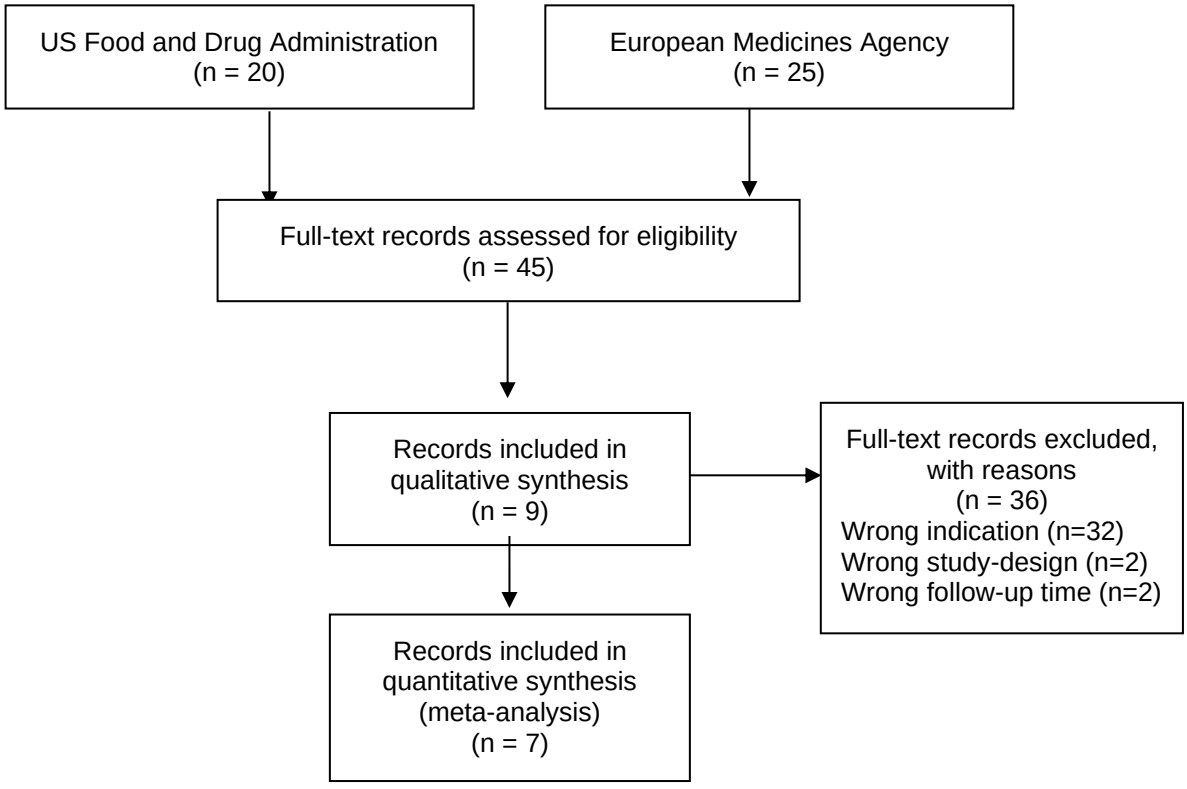
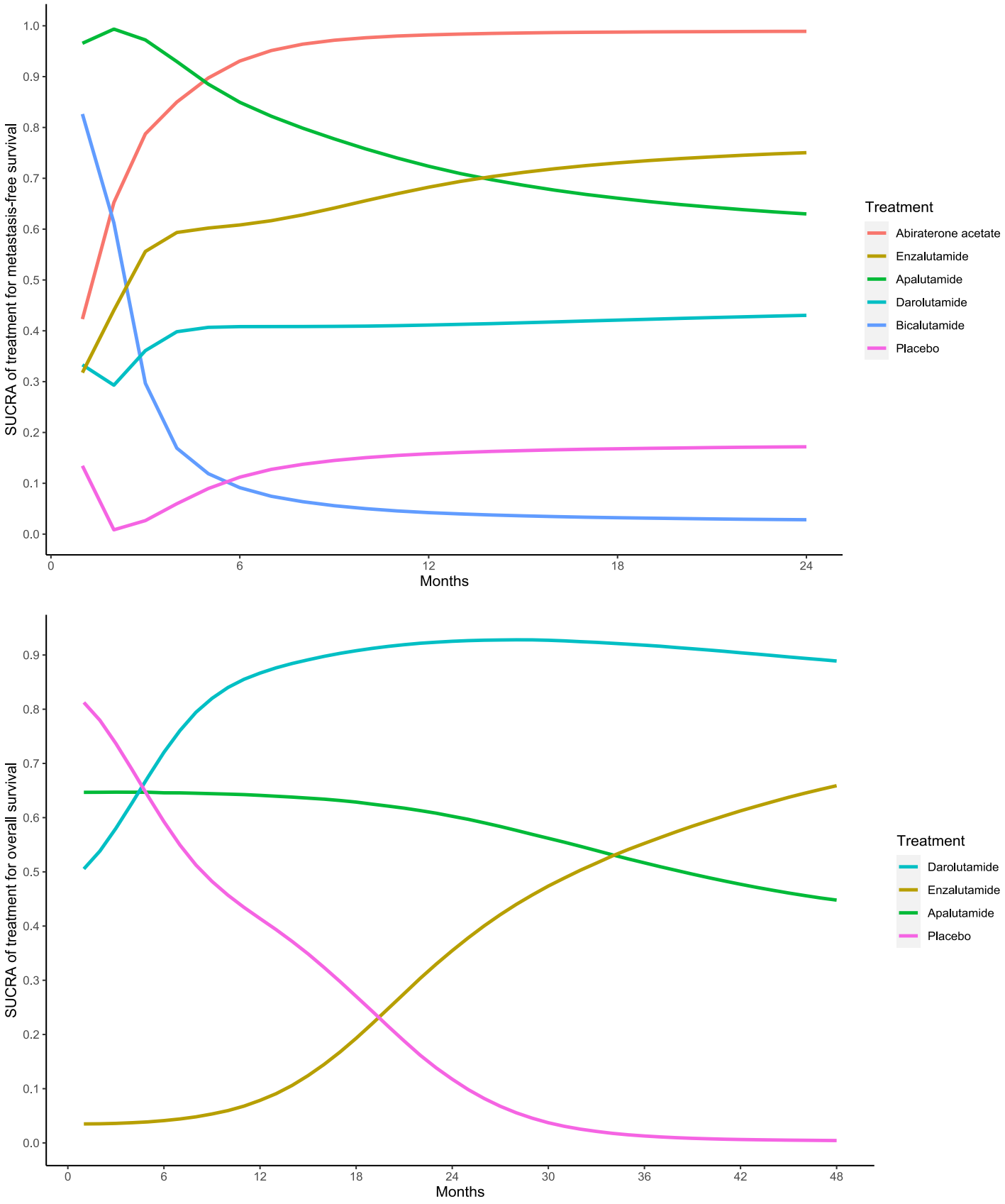


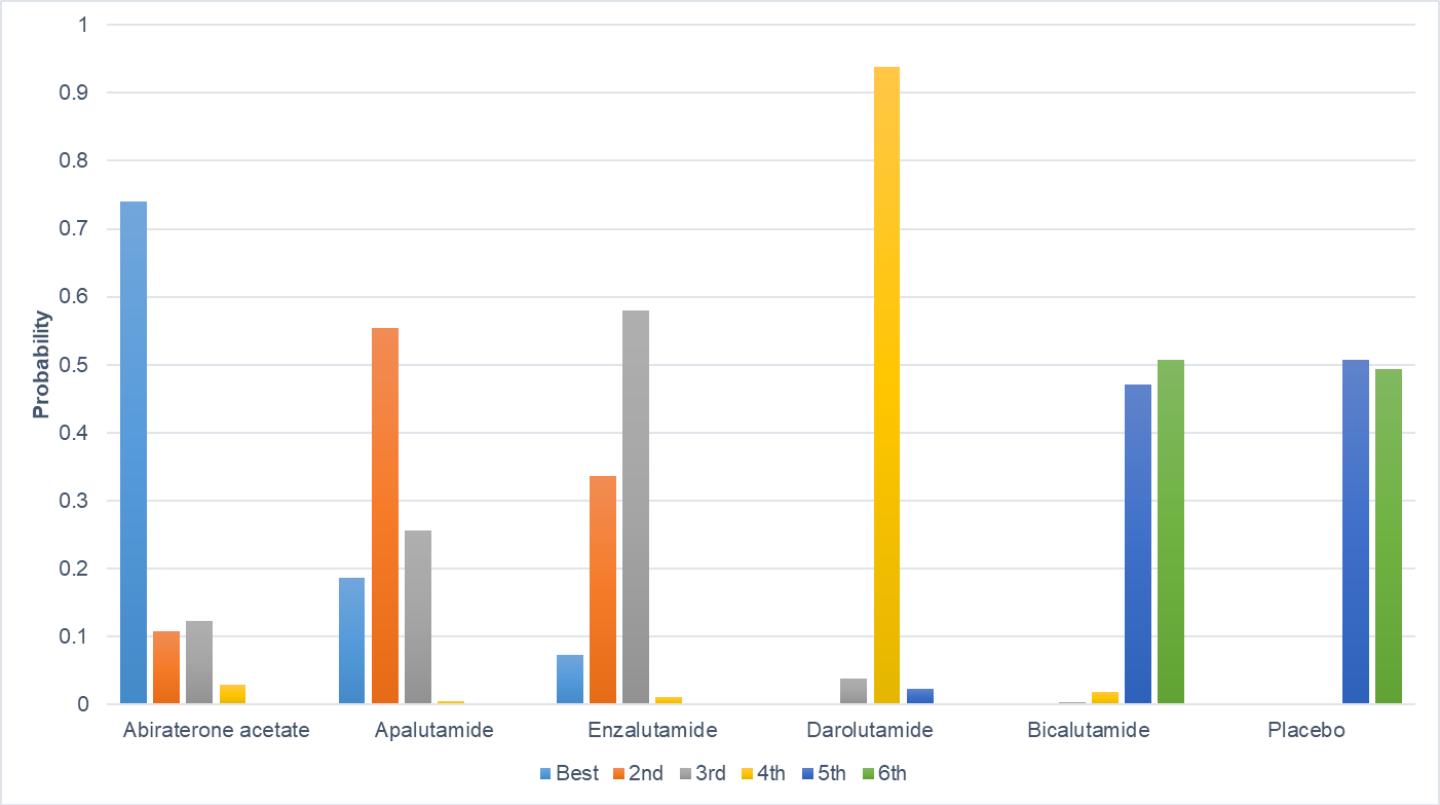
Supplementary Figure 2. SUCRA over time derived from parametric survival network meta-analysis



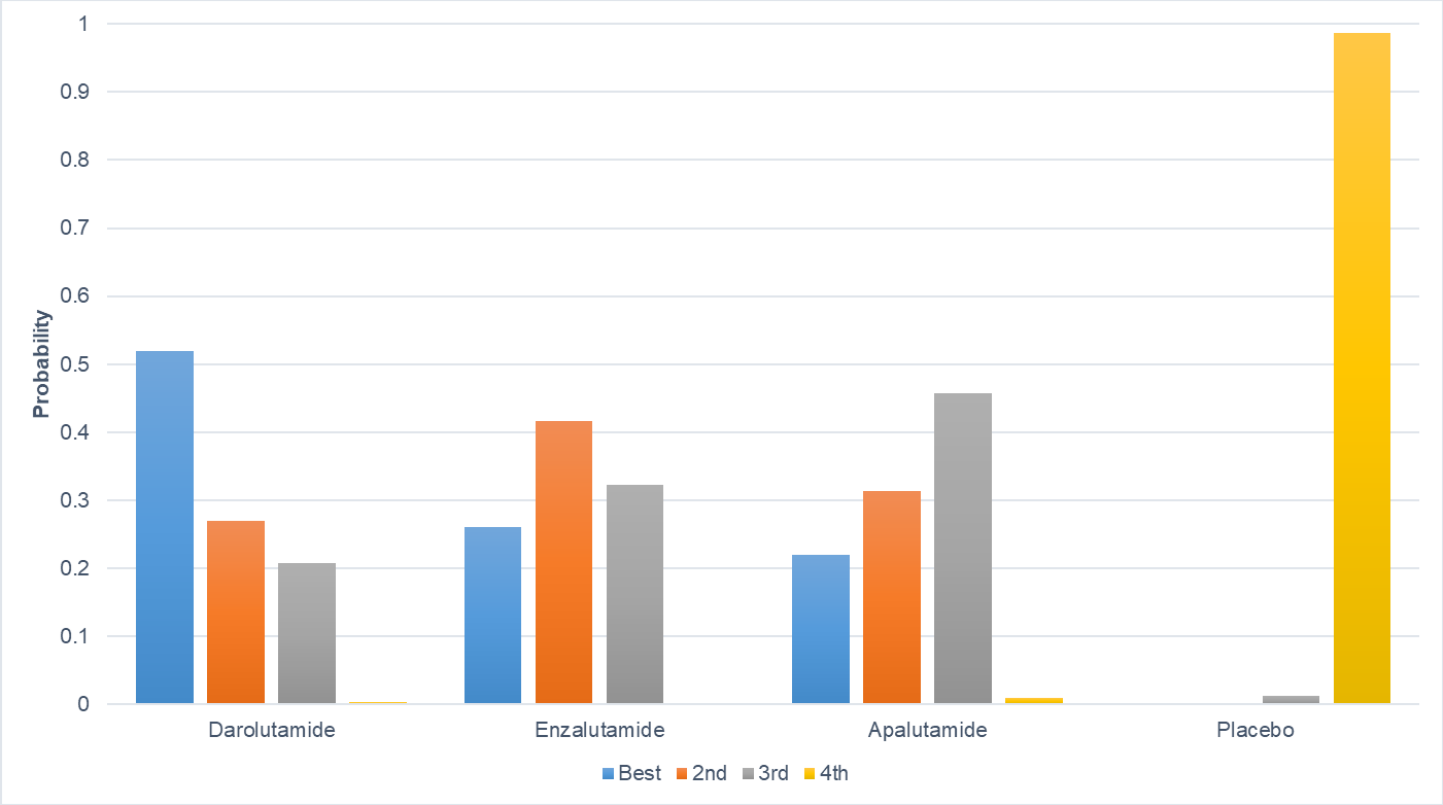
SUCRA=the surface under the cumulative ranking line (SUCRA). SUCRA was used to summarize treatment rankings. SUCRA ranges from 0 to 1. The closer SUCRA to 1, the higher the treatment rank.

Supplementary Figure 3. Treatment Ranking Probabilities for Metastasis-free Survival, Overall Survival, and Serious Adverse Events

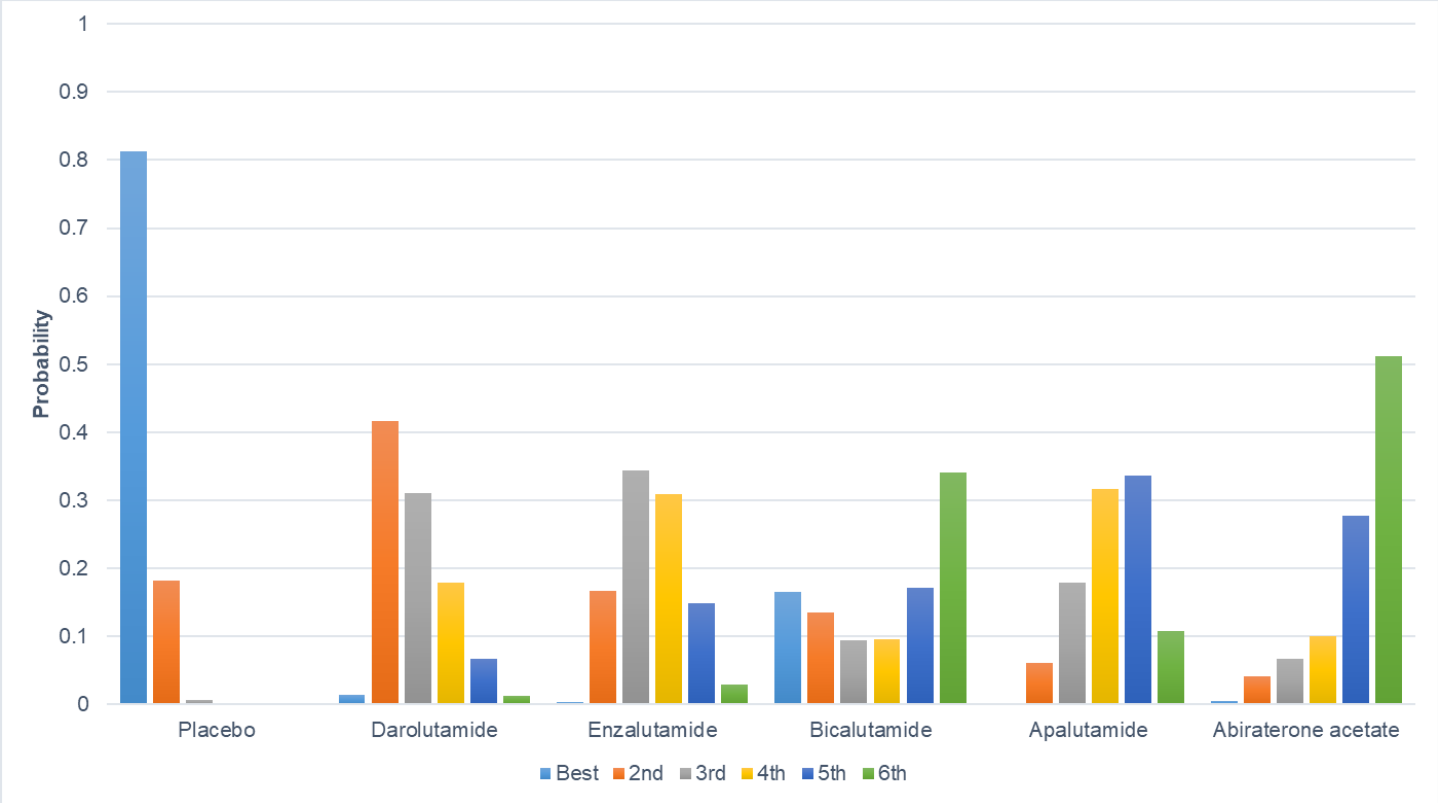
Metastasis-free survival



Overall survival



Serious Adverse Events



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