Supplementary data

NMA model description

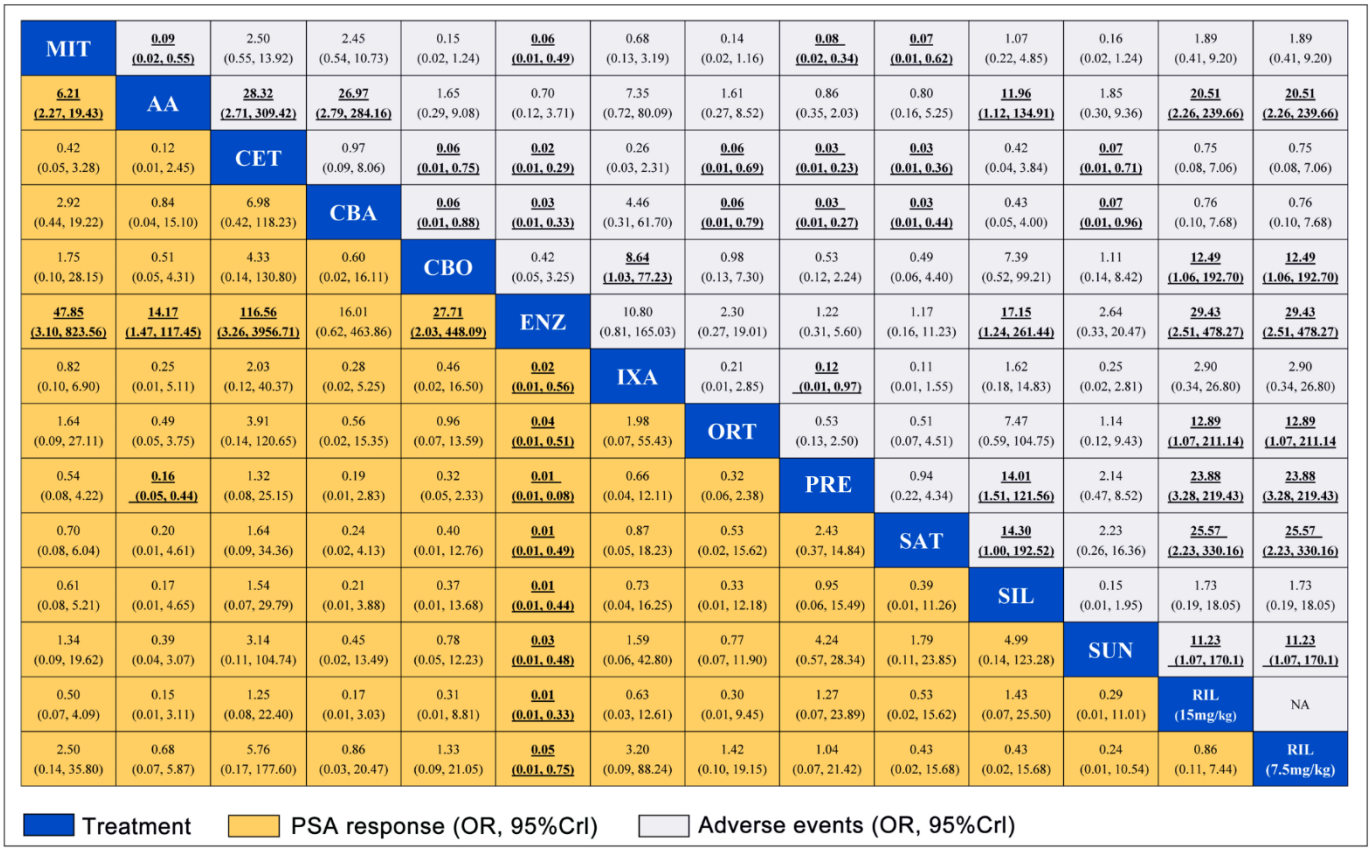
Fixed Effects Model in WinBUGS

```
model{
#Define Prior Distributions
#On tx effect mean
beta[1] < -0
for (tt in 2:nTx){
beta[tt]~dnorm(0,1.0E-6)
}
#On individual study baseline effect
for(ss in 1:nStudies){
alpha[ss] ~ dnorm(0,1.0E-6)
}
#Fit data
#For hazard ratio reporting studies
for(ii in 1:LnObs ){
Lmu[ii] < - alpha[Lstudy[ii]]*multi[ii] + beta[Ltx
[ii]] - beta[Lbase[ii]]
Lprec[ii] < - 1/pow(Lse[ii],2)
Lmean[ii] ~ dnorm(Lmu[ii],Lprec[ii])
}
#For binary data reporting studies
for(ss in 1:BnObs){
logCumHaz[ss] < - alpha[Bstudy[ss]] + beta[Btx
[ss]] - beta[Bbase[ss]]
cumFail[ss] < - 1-exp(-1*exp(logCumHaz[ss]))
Br[ss] ~ dbin(cumFail[ss], Bn[ss])
}
# Calculate HRs
for (hh in 1:nTx) {
hr[hh] < -exp(beta[hh])
}
# Ranking plot
for (ll in 1:nTx) {
for (mm in 1:nTx) {
rk[ll,mm] < - equals(ranked(beta[],mm),beta[ll])
}
}
}
```

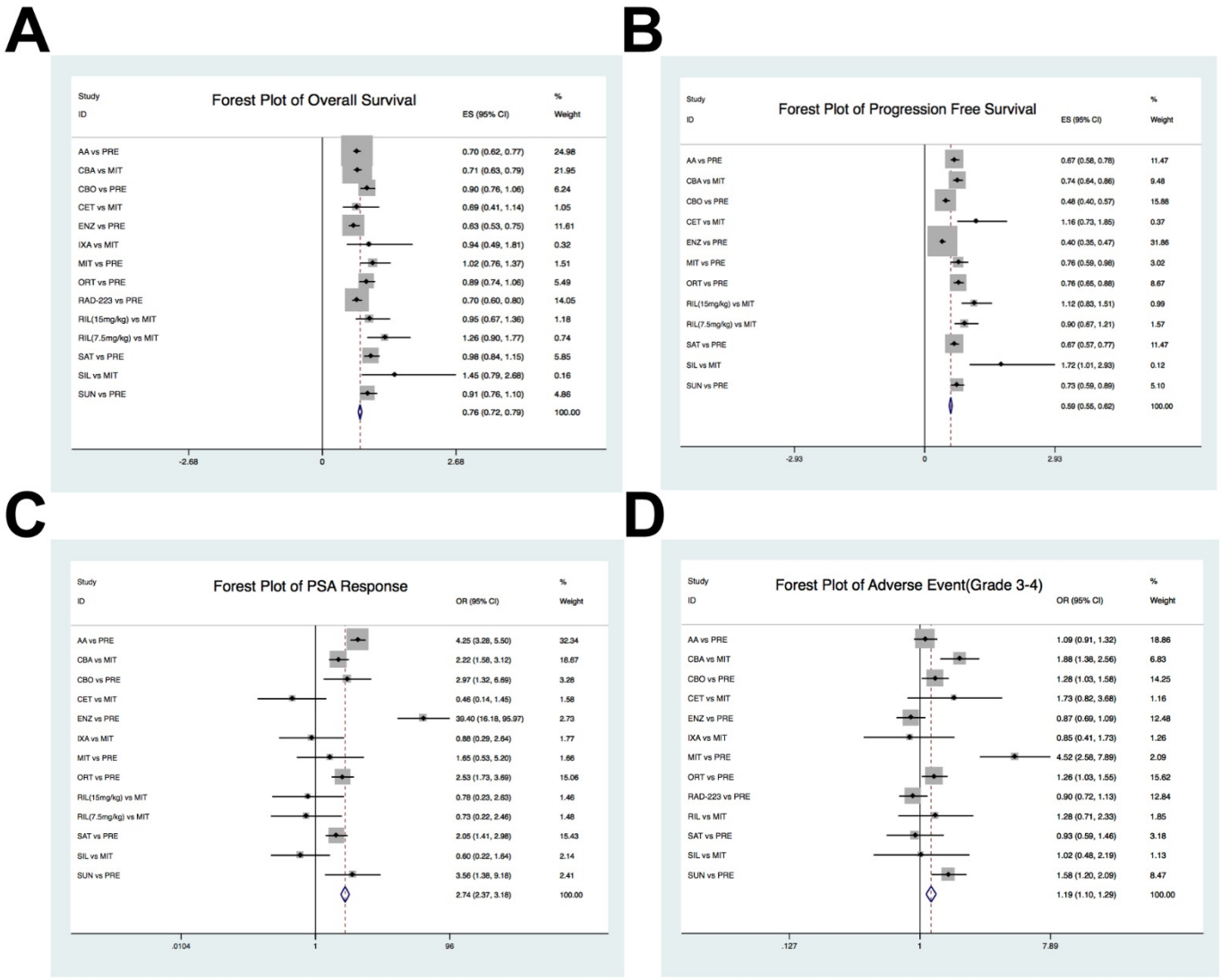
Random Effects Model in WinBUGS

```
model{
#Define Prior Distributions
#on random tx effect variance
sd~dunif(0,5)
reTau < - 2/pow(sd,2)
#On tx effect mean
beta[1] < -0
for (tt in 2:nTx){
beta[tt]~dnorm(0,1.0E-6)
}
#On individual study baseline effect
for(ss in 1:nStudies){
alpha[ss] ~ dnorm(0,1.0E-6)
}
#Define random effect
for (ss in 1:nStudies){
for(tt in 1:nTx){
re[ss,tt]~dnorm(0,reTau)
}
}
#Fit data
#For hazard ratio reporting studies
for(ii in 1:LnObs ){
Lmu[ii] < - alpha[Lstudy[ii]]*multi[ii] + re[Lstudy
[ii],Ltx[ii]] -
re[Lstudy[ii],Lbase[ii]] + beta[Ltx[ii]] - beta
[Lbase[ii]]
Lprec[ii] < - 1/pow(Lse[ii],2)
Lmean[ii] ~ dnorm(Lmu[ii],Lprec[ii])
}
#For binary data reporting studies
for(ss in 1:BnObs){
logCumHaz[ss] < - alpha[Bstudy[ss]] + re[Bstudy
[ss],Btx[ss]] -
re[Bstudy[ss],Bbase[ss]] + beta[Btx[ss]] - beta
[Bbase[ss]]
cumFail[ss] < - 1-exp(-1*exp(logCumHaz[ss]))
Br[ss] ~ dbin(cumFail[ss], Bn[ss])
}
# Calculate HRs
for (hh in 2:nTx) {
```

```
hr[hh] < -exp(beta[hh])
}
# Ranking plot
for (ll in 1:nTx) {
for (mm in 1:nTx) {
rk[ll,mm] < - equals(ranked(beta[],mm),beta[ll])
}
}
}
```

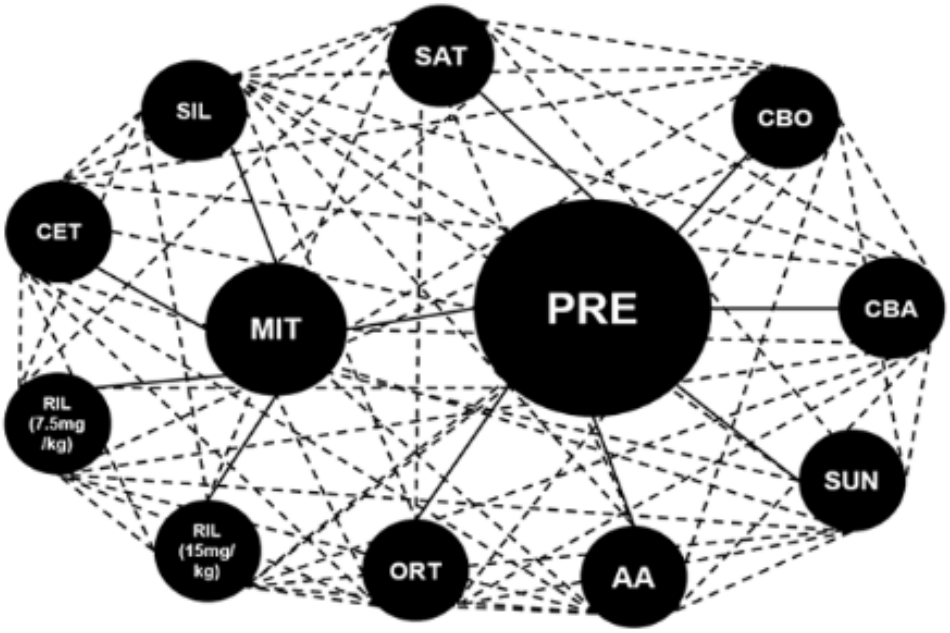


Supplementary Figure 1. Pooled relative ORs for PSA response (yellow region) and grade 3-4 adverse events (white region) based on mixed direct and indirect evidence from Bayesian network meta-analysis through fixed effects model with different pharmacological interventions in CRPC patients after docetaxel failure. The PSA response and safety estimates are located at the intersection of the column intervention and the row treatment (i.e., column intervention is reference for each comparison). To obtain ORs for comparisons in opposing direction, reciprocals should be applied. Results with statistic significant are in bold and underlined. Numbers in parentheses indicate 95% CrIs for network meta-analysis. MIT: Mitoxantrone; CBA: Cabazitaxel; PRE: Prednisone plus Placebo; ABA: Abiraterone acetate; SIL: Siltuximab; ORT: Orteronel; CET: Cetuximab; RAD: Radium-223; SUN: Sunitinib; IXA: Ixabepilone; RIL: Rilotumumab; ENZ: Enzalutamide; CBO: Cabozantinib; SAT: Satraplatin; NA: not applicable; OR: odds ratio; PSA: prostatic specific antigen.



Supplementary Figure 2. Pair-wise meta-analyses of included interventions for OS (A), PFS (B), PSA response (C) and grade 3-4 adverse events (D) in mCRPC patients after docetaxel failure. Pooled hazard ratios (HRs) with corresponding 95% credible intervals (CrIs) are applied to evaluate OS and PFS, while Pooled odds ratios (ORs) with corresponding 95% credible intervals (CrIs) are used to evaluate PSA response and adverse events (grade 3-4). MIT: Mitoxantrone; CBA: Cabazitaxel; PRE: Prednisone plus Placebo; ABA: Abiraterone acetate; SIL: Siltuximab; ORT: Orteronel; CET: Cetuximab; RAD: Radium-223; SUN: Sunitinib; IXA: Ixabepilone; RIL: Rilotumumab; ENZ: Enzalutamide; CBO: Cabozantinib; SAT: Satraplatin; NA: not applicable; OS: overall survival; PFS: progression free survival; HR: hazard ratio; OS: overall survival; PFS: progression free survival; PSA: prostatic specific antigen.

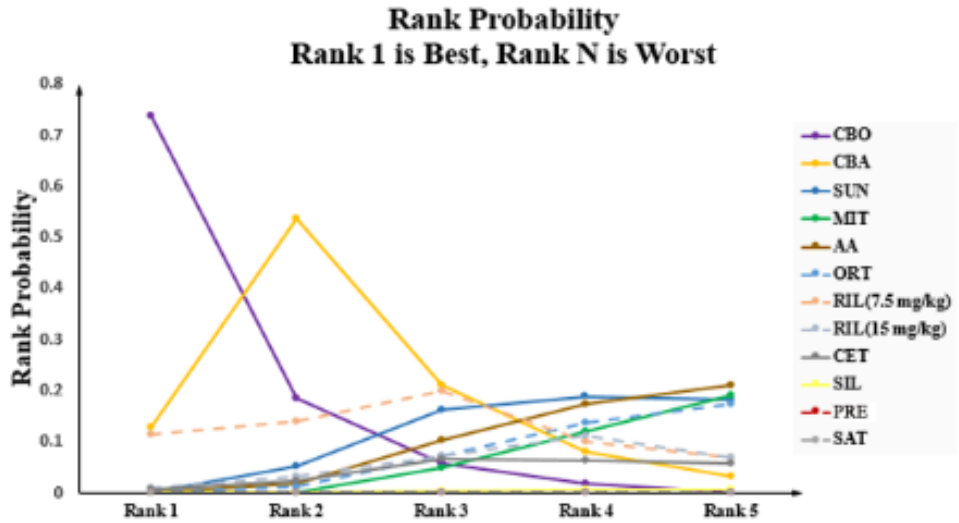
A



B

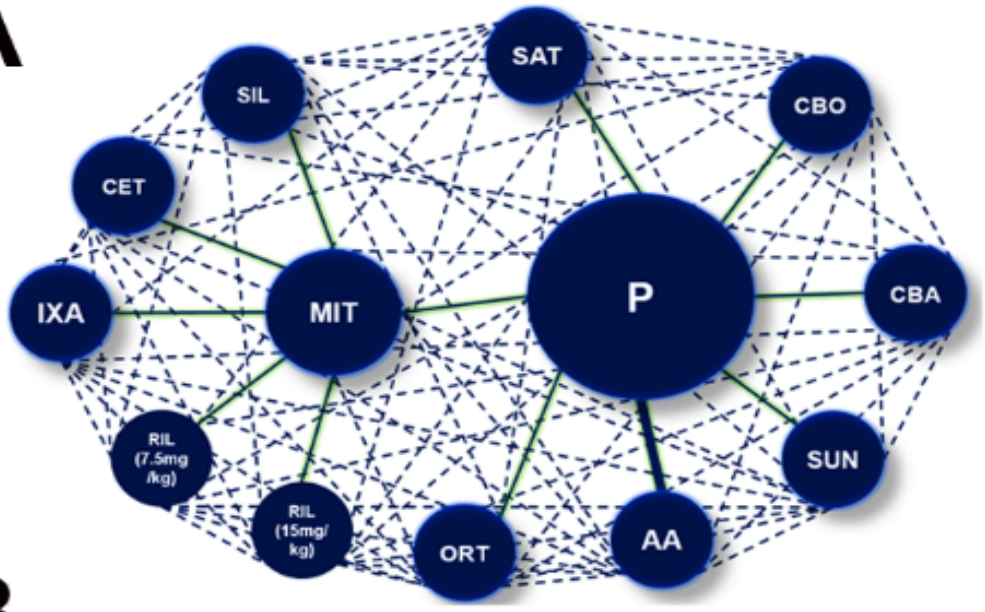
Comparison	HR	95%CrI-Low	95%CrI-High
AA vs PRE	0.7413	0.6558	0.8332
CBA vs PRE	0.5742	0.4258	0.7601
ORT vs PRE	0.7636	0.6543	0.8891
CBO vs PRE	0.4815	0.4011	0.5703
SUN vs PRE	0.7284	0.5904	0.8853
MIT vs PRE	0.773	0.5978	0.9836
SAT vs PRE	1.002	0.8561	1.168
RIL(7.5mg/kg) vs PRE	0.8871	0.4721	1.548
RIL(15mg/kg) vs PRE	0.7133	0.3802	1.219
SIL vs PRE	1.379	0.7216	2.4
CET vs PRE	0.924	0.5272	1.512

C



Supplementary Figure 3. The network meta-analysis outcomes of eligible comparisons of PFS excluding studies with control arm of placebo: network diagram (A), relative HRs (B) and rank probability (C) based on mixed direct and indirect evidence from Bayesian network meta-analysis through fixed effects model with different pharmacological interventions in CRPC patients after docetaxel failure.

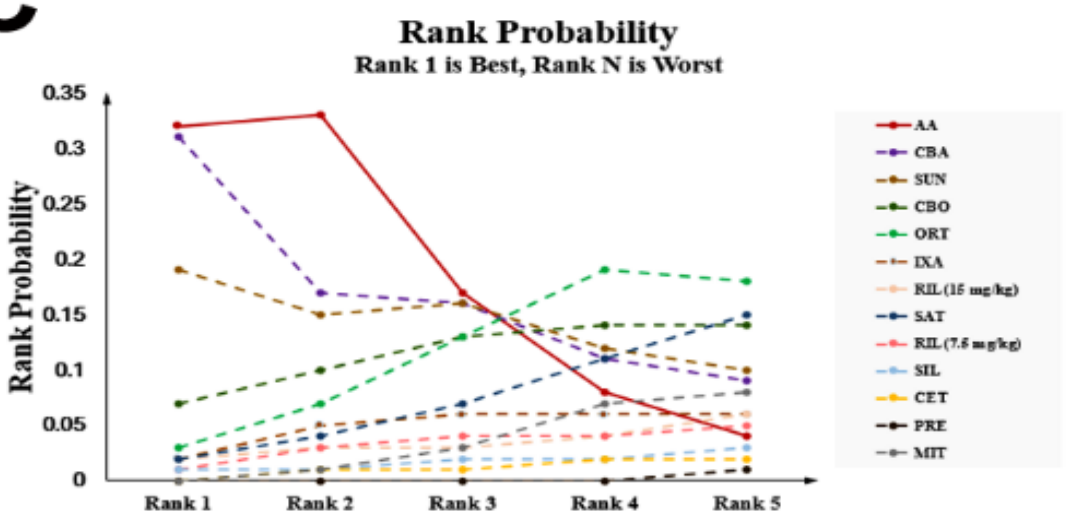
A



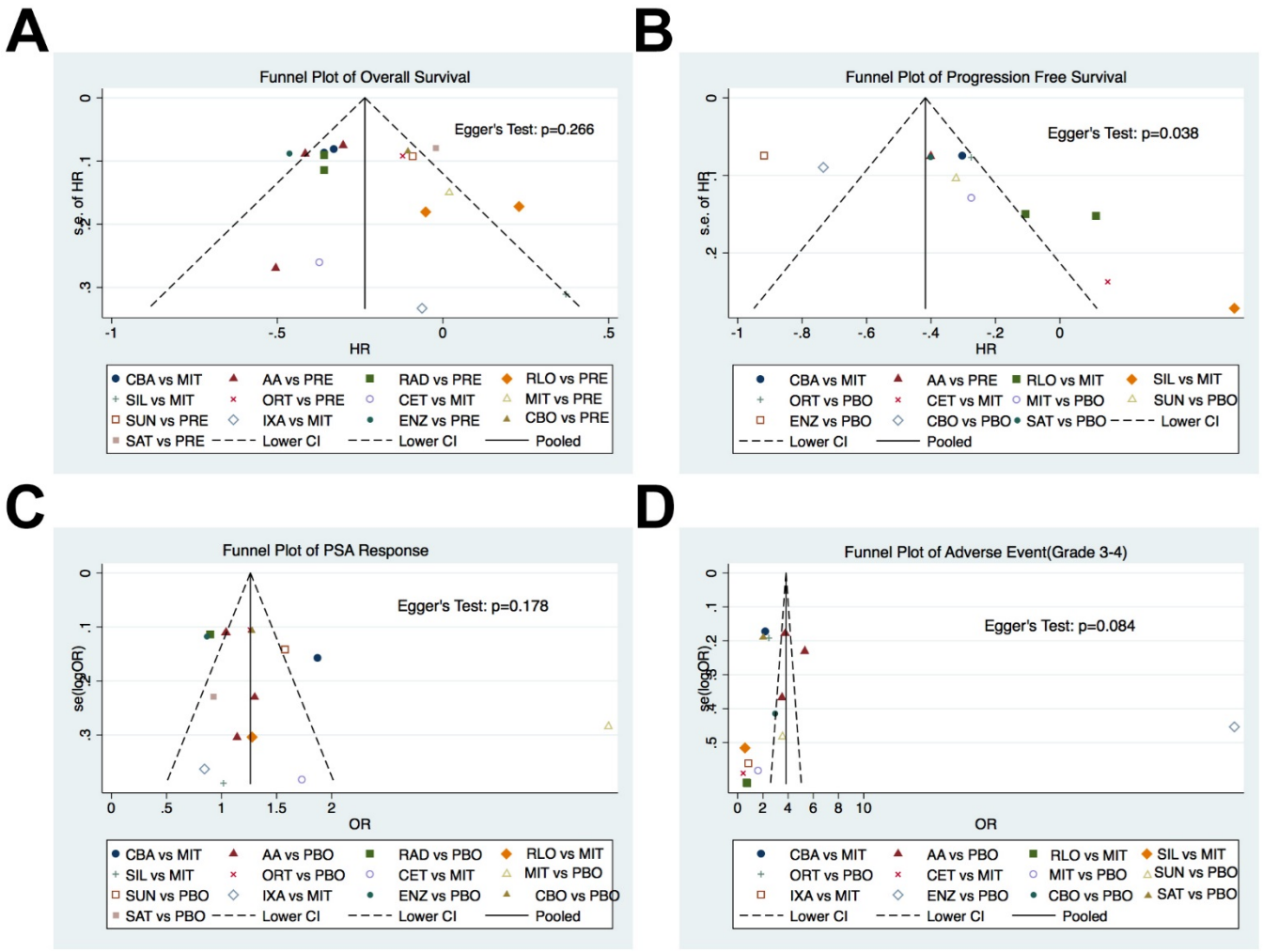
B

Comparison	OR	95%CrI-Low	95%CrI-High
AA vs PRE	6.17	2.83	13.59
CBA vs PRE	5.12	0.67	42.49
ORT vs PRE	0.33	0.09	1.22
CBO vs PRE	3.13	0.81	14.42
SUN vs PRE	4.19	0.92	21.08
MIT vs PRE	0.55	0.10	2.83
SAT vs PRE	0.41	0.11	1.41
RIL(7.5mg/kg) vs PRE	1.19	0.12	12.65
RIL(15mg/kg) vs PRE	1.39	0.13	14.83
SIL vs PRE	0.92	0.10	9.17
CET vs PRE	0.73	0.07	7.77

C



Supplementary Figure 4. The network meta-analysis outcomes of eligible comparisons of PSA Response excluding studies with control arm of placebo: network diagram (A), relative ORs (B) and rank probability (C) based on mixed direct and indirect evidence from Bayesian network meta-analysis through fixed effects model with different pharmacological interventions in CRPC patients after docetaxel failure. MIT: Mitoxantrone; CBA: Cabazitaxel; PRE: Prednisone plus Placebo; ABA: Abiraterone acetate; SIL: Siltuximab; ORT: Orteronel; CET: Cetuximab; SUN: Sunitinib; IXA: Ixabepilone; RIL: Rilotumumab; CBO: Cabozantinib; SAT: Satraplatin; NA: not applicable; OR: odds ratio; PSA: prostatic specific antigen.



Supplementary Figure 5. Comparison-adjusted funnel plot for OS (A), PFS (B), PSA response (C) and adverse event (D) in CRPC patients after docetaxel failure. The Egger's regression test was applied to evaluate the publication bias. MIT: Mitoxantrone; CBA: Cabazitaxel; PRE: Prednisone plus Placebo; ABA: Abiraterone acetate; SIL: Siltuximab; ORT: Orteronel; CET: Cetuximab; RAD: Radium-223; SUN: Sunitinib; IXA: Ixabepilone; RIL: Rilotumumab; ENZ: Enzalutamide; CBO: Cabozantinib; SAT: Satraplatin; NA: not applicable; OR: odds ratio.

Supplementary Table 1. Primary endpoint and main secondary efficacy endpoints

Reference	Group	Number of patients	OS (HR 95%CI)	PFS (HR 95%CI)	PSA response	Adverse events (Grade 3-4)
(Bahl et al., 2013)	MIT	377	Control	NA	NA	NA
	CBA	378	0.72(0.61-0.84)	NA	NA	NA
(de Bono et al., 2010)	MIT	377	Control	Control	58	77
	CBA	378	0.7(0.59-0.83)	0.74(0.64-0.86)	129	145
(de Bono et al., 2011)	PRE	398	Control	Control	40	175
	AA	797	0.66(0.55-0.78)	0.67(0.58-0.78)	303	365
(Fizazi et al., 2012a)	MIT	49	Control	Control	12	18
	SIL	48	1.45 (0.79-2.68)	1.72 (1.01-2.93)	7	18
(Fizazi et al., 2012b)	PRE	398	Control	NA	22	28
	AA	797	0.74(0.64-0.86)	NA	235	73
(Fizazi et al., 2015)	PRE	365	control	Control	36	199
	ORT	734	0.886(0.739-1.062)	0.760(0.653-0.885)	183	506
(Fleming et al., 2012)	MIT	40	Control	Control	7	12
	CET	75	0.69(0.41-1.14)	1.16(0.73-1.85)	6	39
(Hoskin et al., 2014)	PRE	174	Control	NA	NA	NA
	RAD	352	0.70(0.56-0.88)	NA	NA	NA
(Kantoff et al., 1999)	PRE	123	Control	Control	5	19
	MIT	119	1.02(0.76-1.37)	0.76(0.59-0.98)	8	83
(Michaelson et al., 2014)	PRE	289	Control	Control	5	86
	SUN	584	0.914(0.762,1.097)	0.725(0.591, 0.89)	36	275
(Parker et al., 2013)	PRE	307	Control	NA	NA	188
	RAD	614	0.7(0.58-0.83)	NA	NA	339
(Rosenberg et al., 2007)	MIT	41	Control	NA	8	26
	IXA	41	0.94(0.49-1.81)	NA	7	22
(Ryan et al., 2013)	MIT	49	Control	Control	7	23
	RIL (7.5 mg/kg)	48	1.26 (0.90–1.77)	0.90 (0.67–1.21)	5	56
	RIL (15 mg/kg)	45	0.95 (0.67–1.36)	1.12 (0.83–1.51	5	

(Scher et al., 2012)	PRE ENZ	399 800	Control 0.63(0.53-0.75)	Control 0.4(0.35-0.47)	5 395	154 268
(Smith et al., 2016)	PRE CBO	346 682	Control 0.9(0.76-1.06)	Control 0.48(0.40-0.57)	7 41	191 481
(Sternberg et al., 2009)	PRE SAT	315 635	Control 0.98(0.84-1.15)	Control 0.67(0.57-0.77)	39 161	32 60
(Sun et al., 2016)	PRE AA	71 143	Control 0.604(0.356-1.026)	NA NA	10 71	20 46

MIT: Mitoxantrone; CBA: Cabazitaxel; PRE: Prednisone plus Placebo; AA: Abiraterone acetate; SIL: Siltuximab; ORT: Orteronel; CET: Cetuximab; RAD: Radium-223; SUN: Sunitinib; IXA: Ixabepilone; RIL: Rilotumumab; ENZ: Enzalutamide; CBO: Cabozantinib; SAT: Satraplatin; NA: not applicable; OS: overall survival; PFS: progression free survival; HR: hazard ratio.