

Supplementary appendix for

**Comparison of Doublet and Triplet Therapies for Metastatic Hormone-Sensitive Prostate Cancer: A Systematic Review and Network Meta-analysis**

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## Supplementary Material 1: Search strategy

### MEDLINE (PubMed interface)

#### Related to mHSPC

- #1 Prostatic Neoplasms[Mesh] OR (prostat\*[tw] AND cancer[tw])
- #2 prostat\*[tiab] AND (canc\*[tiab] OR tumor[tiab] OR carcinom\*[tiab] OR adeno\*[tiab] OR malignan\*[tiab] OR tumour\*[tiab] OR neoplas\*[tiab] )
- #3 #1 OR #2
- #4 metastasis[Mesh] OR metasta\*[tw] OR advanced[tw]
- #5 Hormones[Mesh] OR hormon\*[tw] OR castrat\*[tw] OR androgen\*[tw] OR testosterone[tw]
- #6 sensitive[tw] OR naive[tw] OR primary[tw] OR de novo[tw] OR newly diagnosed[tw]
- #7 #3 AND #4 AND #5 AND #6

#### Related to intervention

- #8 Docetaxel[tw] OR Docetaxol[tw] OR RP 56976[tw] OR RP56976[tw] OR Taxotere[tw] OR NSC 628503[tw] OR Daxotel[tw]
- #9 abiraterone[tw] OR CB-7598[tw] OR CB7598[tw]
- #10 MDV3100[tw] OR Enzalutamide[tw] OR MDV-3100[tw] OR x tandi[tw]
- #11 apalutamide[tw] OR ARN-509[tw] OR arn509[tw] OR erleada[tw]
- #12 darolutamide[tw] OR odm201[tw] OR ODM-201[tw]
- #13 Radiotherapy[Mesh] OR radiotherap\*[tw] OR radiation [tw] OR irradiation [tw]
- #14: #8 OR #9 OR #10 OR #11 OR #12 OR #13

#### Related to RCT

- #15 randomized controlled trial [pt]
- #16 controlled clinical trial [pt]
- #17 randomized [tiab]
- #18 placebo [tiab]
- #19 Drug therapy [sh]
- #20 Randomly [tiab]
- #21 Trial [tiab]
- #22 Groups [tiab]
- #23: #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22
- #24 Animals [mh] NOT humans [mh]
- #25: #23 NOT #24

#### Combined items

- #26: #7 AND #14 AND #25

### EMBASE

#### Related to prostate cancer

1. 'prostate carcinoma'/exp
2. 'prostate cancer'/exp

3. 'prostate tumor'/exp
4. (prostat\* NEAR/3 adeno\*):ti,ab,kw
5. (prostat\* NEAR/3 malignan\*):ti,ab,kw
6. (prostat\* NEAR/3 canc\*):ti,ab,kw
7. (prostat\* NEAR/3 carcinoma\*):ti,ab,kw
8. (prostat\* NEAR/3 tumo?r\*):ti,ab,kw
9. (prostat\* NEAR/3 neoplas\*):ti,ab,kw
10. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9

Related to metastasis

11. metasta\*/exp 1035036
12. (metast\* NEAR/3 prostat\*):ti,ab,kw
13. (advanc\* NEAR/3 prostat\*):ti,ab,kw
14. 11 OR 12 OR 13

Related to hormone-sensitive

15. (hormon\* NEAR/3 prostat\*):ti,ab,kw
16. (castrat\* NEAR/3 prostat\*):ti,ab,kw
17. (androgen NEAR/3 prostat\*):ti,ab,kw
18. 15 OR 16 OR 17
19. sensitive/exp
20. naive/exp
21. 19 OR 20
22. 18 AND 21
23. (primary NEAR/6 prostat\*):ti,ab,kw
24. ('de novo\*' NEAR/6 prostat\*):ti,ab,kw
25. (new\* diagnos\*):ti,ab,kw
26. 22 OR 23 OR 24 OR 25

Related to intervention

27. 'docetaxel'/exp OR (Docetaxel OR Docetaxol OR "RP 56976" OR RP56976 OR Taxotere OR "NSC 628503" OR nsc628503 OR Daxotel OR dexotel):ti,ab,kw
28. 'abiraterone'/exp OR (abiraterone OR 'CB-7598' OR CB7598):ti,ab,kw
29. 'enzalutamide'/exp OR (Enzalutamide OR 'MDV-3100' OR MDV3100 OR xtandi):ti,ab,kw
30. 'apalutamide'/exp OR (apalutamide OR 'ARN-509' OR arn509 OR erleada):ti,ab,kw
31. 'darolutamide'/exp OR (darolutamide OR 'ORM-16497' OR 'ORM-16555' OR 'ODM-201' OR odm201):ti,ab,kw
32. 'radiotherapy'/exp OR (radiotherapy OR 'radiotherap\*' OR 'radiation' OR 'irradiation'):ti,ab,kw
33. 27 OR 28 OR 29 OR 30 OR 31 OR 32

Related to randomised controlled trials

34. 'randomi\*ed controlled trial'/exp
35. 'controlled clinical trial'/exp
36. randomi\*ed:ti,ab,kw

37. placebo:ti,ab,kw
38. 'clinical trial':ti,ab,kw
39. randomly:ti,ab,kw
40. 'double blind':ti,ab,kw
41. trial:ti,ab
42. groups:ti,ab
43. 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42
44. ('animal'/exp OR 'animal experiment'/exp) NOT 'human'/exp
45. 43 NOT 44

Combining all terms

46. 10 AND 14 AND 26 AND 33 AND 45

#### Cochrane CENTRAL

Terms specific to prostate cancer:

1. MeSH descriptor: [Prostatic Neoplasms] explode all trees
2. (prostat\* near/3 malignan\*):ti,ab,kw
3. (prostat\* near/3 canc\*):ti,ab,kw
4. (prostat\* near/3 carcinoma\*):ti,ab,kw
5. (prostat\* near/3 tumor\*):ti,ab,kw
6. (prostat\* near/3 neoplas\*):ti,ab,kw
7. #1 or #2 or #3 or #4 or #5 or #6

Terms specific to metastatic disease:

8. MeSH descriptor: [Neoplasm Metastasis] explode all trees
9. (metast\* near/3 prostat\*):ti,ab,kw
10. (advanced\* near/3 prostat\*):ti,ab,kw
11. #8 or #9 or #10

Terms specific to hormonal sensitive:

12. hormon\*:ti,ab,kw
13. castra\*:ti,ab,kw
14. #12 OR #13
15. sensitive:ti,ab,kw
16. naive:ti,ab,kw
17. #15 OR #16
18. #14 AND #17
19. de-novo:ti,ab,kw
20. (new\* near/3 diagnos\*):ti,ab,kw
21. #19 OR #20
22. #18 OR #21

COMBINED



23. #7 and #11 and #22

ClinicalTrials.gov

Condition or disease: Prostate Cancer Metastatic

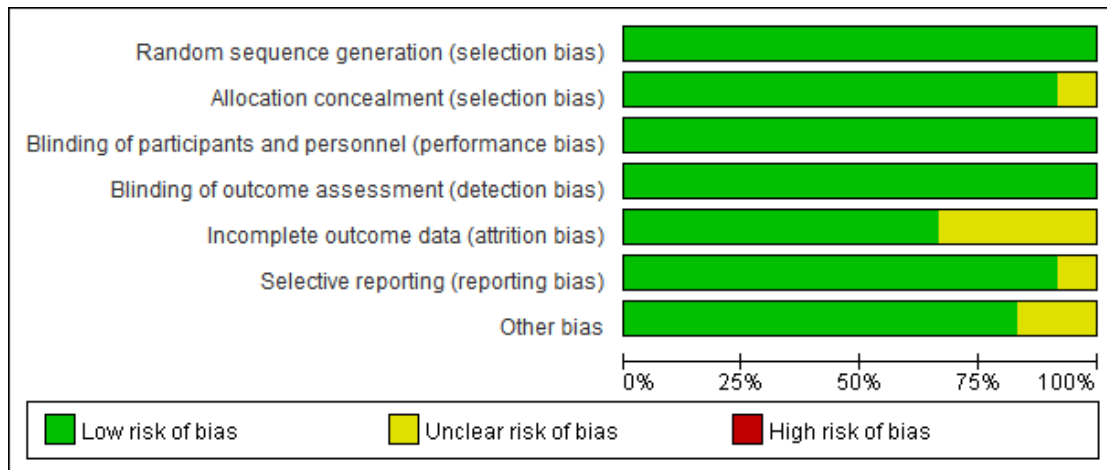
Study Type: Interventional Studies (Clinical Trials)

Study Results: Studies With Results

Last update posted: from 01/06/2017 to 01/06/2022

**Supplementary Material 2: Risk of study bias for OS (A) or PFS (B).**

	TITAN	STAMPEDE armH	STAMPEDE armG	STAMPEDE armC	PEACE-1	LATTITUDE	HORRAD	GETUG-AFU15	ENZAMET	CHAARTED	ARCHES	ARASENS
Random sequence generation (selection bias)	+	+	+	+	+	+	+	+	+	+	+	+
Allocation concealment (selection bias)	+	?	+	+	+	+	+	+	+	+	+	+
Blinding of participants and personnel (performance bias)	+	+	+	+	+	+	+	+	+	+	+	+
Blinding of outcome assessment (detection bias)	+	+	+	+	+	+	+	+	+	+	+	+
Incomplete outcome data (attrition bias)	+	+	?	+	+	?	+	?	+	+	?	+
Selective reporting (reporting bias)	+	+	+	+	+	+	+	?	+	+	+	+
Other bias	+	+	+	+	?	+	+	?	+	+	+	+



A



**Supplementary Material 3: Patients' supplementary information of included trials.**

Trial	Performance status (ECOG/WHO grade, %)	Age (Exp. vs. Ctrl, yrs)	PSA (Exp. vs. Ctrl, ng/ml)	Gleason score (Exp. vs. Ctrl, no. %)	Visceral metastases (Exp. vs. Ctrl, no. %).	Metastatic burden (CHAARTED definition, Exp. vs. Ctrl, no. %)	Metastases at initial diagnosis (Exp. vs. Ctrl, no. %)	Patients with planned/previous docetaxel use (Exp. vs. Ctrl, no. %)
GETUG -AFU15 <sup>[9, 35]</sup>	Grade 0, 97.5% Grade 1-2, 2.5%	Median(IQR): 63 (57-68) vs. 64 (58-70) Range: NR	Median(IQR): 26.7 (5-106) vs. 25.8 (5-126) Range: NR	≤7: 84(45) vs. 78(41) 8-10: 103(55) vs. 113(59) Unknown: 2 vs. 5	28 (15) vs. 23 (12)	LVD: 100(52) vs. 102(53) HVD:92(48) vs. 91(47) Unknown: 0	128(67) vs. 144(76)	none
CHAARTED <sup>[10, 36]</sup>	Grade 0, 69.5% Grade 1-2, 30.5%	Median(IQR): 64(NR) vs. 63(NR) Range: 36-91	Median(IQR): 50.9(NR) vs. 52.1(NR) Range: 0.1-8540	≤7: 117(33) vs.104(30) 8-10: 241(67) vs.243(70) Unknown: 46 vs. 39	57 (14) vs. 66 (17)	LVD:134(34) vs. 143(36) HVD:263(66) vs. 250(64) Unknown: 0	289(73) vs. 286(73)	none
STAMPEDE-arm C <sup>[11][29]</sup>	Grade 0, 72.8% Grade 1-2, 27.2%	Median(IQR): 65(60-70) vs. 65(60-71) Range: NR	Median(IQR): 97(40.5-340) vs. 102.5(32.8-354) Range: NR	≤7: 65(20) vs.158(25) 8-10: 253(80) vs. 480(75) Unknown: 44 vs. 86	Lung:13(4) vs.33(5) Liver: 6(2) vs. 15(2) Other: 25(7) vs. 46(6)	LVD:124(46) vs. 238(43) HVD:148(54) vs. 320(57) Unknown: 90 vs. 166	Total: 1037(95)	none
STAMPEDE-arm G <sup>[12, 28]</sup>	Grade 0, 74.6% Grade 1-2, 25.4%	Median(IQR): 67(NR) vs. 67(NR) Range: NR	Median(IQR): 51(19-158)vs. 56(19-165) Range: NR	≤7: 104(23) vs.110(24) 8-10: 345(77) vs.342(76) Unknown: 101	22 (5) vs. 19 (4)	LVD:206(46) vs. 196(43) HVD:243(54) vs. 256(57) Unknown: 101	Total: 859(95)	none
STAMPEDE-arm H <sup>[17]</sup>	Grade 0, 71.1% Grade 1-2, 28.9%	Median(IQR): 68(63-73) vs. 68(63-73) Range: 37-87	Median(IQR): 97(30-313) vs. 98(30-316) Range: 1-20590	≤7: 172(18) vs.173(17) 8-10: 810(82) vs.820(83) Unknown: 36 vs. 50	Lung:48(5) vs. 42(4) Liver: 19(2) vs. 23(2) Other: 33(3) vs. 35(3)	LVD:410(43) vs.409(42) HVD:553(57)vs. 567(58) Unknown: 69 vs. 53 52% high in HORRAD definition	Total: 2061(100)	183(18) vs. 184(18)
LATITUDE <sup>[13, 34]</sup>	Grade 0-1, 96.7% Grade 2, 3.3%	Median(IQR): 68(NR) vs. 67(NR) Range: 33-92	Median(IQR): NR(NR) vs. NR(NR) Range: NR	≤7: 13(2) vs.16(3) 8-10: 584(98) vs.586(97) Unknown: 0	114 (19) vs. 114 (19)	LVD:110(18) vs. 133(22) HVD:487(82) vs. 468(78) Unknown: 0 vs 1	Total: 1199(100)	none
ENZAMET <sup>[14]</sup>	Grade 0, 72.0% Grade 1-2, 28.0%	Median(IQR): 69(63-74) vs. 69(64-74) Range: NR	Median(IQR): NR(NR) vs. NR(NR) Range: NR	≤7: 152(31) vs.163(34) 8-10: 335(69) vs.321(66) Unknown: 76 vs 78	62 (11) vs. 67 (12)	LVD:272(48) vs. 265(47) HVD:291(52) vs. 297(53) Unknown: 0	325(58) vs. 327(58)	254(45) vs. 249(44)

ARCHES [15, 31, 33]	Grade 0, 77.5% Grade 1, 22.5%	Median(IQR): 70(NR) vs. 70(NR) Range: 42-92	Median(IQR): 5.4(NR) vs. 5.1(NR) Range: 0-19000	≤7: 171(31) vs.187(33) 8-10: 386(69) vs.373(67) Unknown: 16 vs. 17	NR	LVD:220(38) vs. 203(35) HVD:354(62) vs. 373(65) Unknown: 0	402(83) vs. 365(81) unknown: 89 vs. 125	103(18) vs. 102(18)
TITAN <sup>[16, 32]</sup>	Grade 0, 64.3% Grade 1, 35.7%	Median(IQR): 69(NR) vs. 68(NR) Range: 43-94	Median(IQR): 5.97(NR) vs. 4.02(NR) Range: 0-2682	≤7: 174(33) vs.169(32) 8-10: 351(67) vs.358(68) Unknown: 0	56 (11) vs. 72 (14)	LVD:200(38) vs. 192(36) HVD:325(62) vs. 335(64) Unknown: 0	411(83) vs. 441(88) unknown: 29 vs. 27	58(11) vs. 55(10)
HORRAD <sup>[41]</sup>	Grade 0, 84.0% Grade 1-3, 16.0%	Median(IQR): 67(61-71) vs. 67(61-71) Range: 47-85	Median(IQR): 125(48-433) vs. 149(50-483) Range: 4-14000	≤7: 73(34) vs.71(33) 8-10: 142(66) vs.144(67) Unknown: 1 vs 1	NR	LVD: NR; HVD: NR 82% high in HORRAD definition	Total: 432(100)	none
PEACE-1 <sup>[23]</sup> (Docetaxel population)	Grade 0, 69.9% Grade 1-2, 30.1%	Median(IQR): 66(60-70) vs. 66(59-70)	Median(IQR): 13.7 (2.4-58.9) vs. 12.0 (3.0-59.9)	≤7: 79(23) vs.71(20) 8-10:270(77) vs.276(80)	41(12) vs. 47(13)	LVD:131(37) vs. 123(35) HVD: 224(63) vs. 232(65)	Total: 710(100)	none
ARASENS <sup>[24]</sup>	Grade 0, 71.1% Grade 1, 28.9%	Median(Range): 67(41-89) vs. 67(42-86)	Median(Range): 30.3 (0-9219) vs. 24.2 (0-11947)	≤7: 122(18.7) vs.118(18) 8-10: 505(77.6) vs.516(78.9)	111(17) vs. 118(18)	NR	558(85.7) vs. 566(86.5) unknown: 6 vs 7	none

Ctrl: control group; ECOG: Eastern Cooperative Oncology Group; Exp.: experimental group; HVD: high volume disease; IQR: interquartile range; LVD: low volume disease; NR: not reported; PSA: prostatic specific antigen.

**Supplementary Material 4A: Hazard Ratio for OS and PFS in included trials or subgroups**

STUDY No.[Ref.]	Trial	Comparison	Patients number	HR (OS -total)	HVD-pts number	HR (OS-HVD)	LVD-pts number	HR (OS-LVD)	Visceral meta-pts	HR (OS-visc.)	PFS type	HR(PFS -total)
1 <sup>[10, 37]</sup>	GETUG -AFU15	DOC+ADT vs ADT	385	0.88, 0.68-1.14	183	0.78, 0.56-1.09	202	1.02, 0.67-1.55	NR	NR	rPFS cPFS	0.69, 0.55-0.87 0.75, 0.59-0.94
2 <sup>[11, 38]</sup>	CHAARTED	DOC+ADT vs ADT	790	0.72, 0.59-0.89	513	0.63, 0.50-0.79	277	1.04, 0.70-1.55	123 (15.6%)	0.53, 0.30-0.92	cPFS	0.62, 0.51-0.75
3 <sup>[12] [31]</sup>	STAMPEDE -arm C	DOC+ADT vs ADT	1086a	0.81, 0.69-0.95	468	0.81, 0.64-1.02	362	0.76, 0.54-1.07	NR	NR	PFS	0.69, 0.59-0.81
4 <sup>[14, 36]</sup>	LATITUDE	AAP+ADT vs ADT	1199	0.66, 0.56-0.78	955	0.62, 0.52-0.74	243	0.72, 0.47-1.10	228 (19.0%)	0.58, 0.41-0.83	rPFS	0.47, 0.39-0.55
5 <sup>[13, 30]</sup>	STAMPEDE -arm G	AAP+ADT vs ADT	1002 <sup>a</sup>	0.61, 0.49-0.75	499	0.60, 0.46-0.78	402	0.64, 0.42-0.97	NR	NR	PFS	0.45, 0.37-0.54
6 <sup>[32]</sup>	STAMPEDE, AAP vs. DOC	AAP+ADT vs DOC+ADT	342 <sup>b</sup>	1.13, 0.77-1.66	NR	NR	NR	NR	NR	NR	PFS	0.69, 0.50-0.95
7 <sup>[15]</sup>	ENZAMET <sup>c</sup>	ENZA+ADT vs ADT	622	0.53, 0.37-0.75	232	0.65, 0.42-0.99	390	0.38, 0.21-0.69	129 (11.5%)	1.05, 0.54-2.02	cPFS	0.34, 0.26-0.44
8 <sup>[15]</sup>	ENZAMET, DOC-sub	ENZA+DOC+ADT vs DOC+ ADT	503	0.90, 0.62-1.31	356	0.97, 0.64- 1.46	147	0.65, 0.25- 1.71				0.48, 0.37-0.62
9 <sup>[16, 33, 35]</sup>	ARCHES <sup>c</sup>	ENZA+ADT vs ADT	945	0.64, 0.51-0.81	727	0.66, 0.52-0.83	423	0.66, 0.43-1.03	128 (11.13%)	1.16, 0.67-2.00	rPFS	0.37, 0.28-0.49
10 <sup>[16, 33, 35]</sup>	ARCHES, DOC-sub	ENZA+DOC+ADT vs DOC+ ADT	205	0.74, 0.46-1.20								0.52, 0.30-0.89
11 <sup>[17, 34]</sup>	TITAN <sup>c</sup>	APA+ADT vs ADT	939	0.61, 0.50-0.76	660	0.70, 0.56-0.88	392	0.52, 0.35-0.79	128 (12.2%)	0.76, 0.47-1.23	rPFS	0.48, 0.39-0.60
	TITAN, DOC-sub		113	1.12 0.59-2.12								
12 <sup>[18]</sup>	STAMPEDE - arm H <sup>c</sup>	RT+ADT vs ADT	1691	0.93, 0.80-1.08	1120	1.07, 0.90-1.28	819	0.68, 0.52-0.90	NR	NR	PFS	0.96, 0.85-1.08
	STAMPEDE-arm H, DOC-sub		367	0.81 0.49-1.34								
13 <sup>[43]</sup>	HORRAD	RT+ADT vs ADT	432	0.90, 0.70-1.14	NR	NR	NR	NR	NR	NR	NR	NR
14 <sup>[25]</sup>	PEACE-1, DOC-sub	AAP+DOC+ADT vs DOC+ ADT	710	0.75, 0.59-0.95	456	0.72, 0.55-0.95	254	0.83, 0.50-1.38	88 (12.4%)	NR	rPFS	0.50, 0.40-0.62
15 <sup>[26]</sup>	ARASENS	DARO+DOC+ADT vs DOC+ ADT	1305	0.68, 0.57-0.80	NR	NR	NR	NR	229 (17.5%)	0.79, 0.55-1.14	NR	NR

<sup>a</sup> only metastatic patients were included; <sup>b</sup> direct comparison of abiraterone versus docetaxel from the multi-arm, multi-stage STAMPEDE trial; <sup>c</sup> patients with prior or concomitant docetaxel chemotherapy were excluded. AAP: abiraterone and prednisone; cPFS: clinical progression free survival; DOC: docetaxel; DOC-sub: subgroup with docetaxel population and available for triplet therapy analyses; HR: hazard ratio; HVD: high volume disease; LVD: low volume disease; NO.: number; NR: not reported; OS: overall survival; PFS: progression free survival; Ref.: reference; rPFS: radiographic progression free survival; visc.: visceral metastasis.

**Supplementary Material 4B: Hazard Ratio for OS in de novo and previous local treatment subgroups**

STUDY No.	1	2	3	4	5	6	7	9	11	12	13	14	15
Trial	GETUG-AFU15	CHAARTED	STAMPEDE-arm C	LATITUDE	STAMPEDE-arm G	STAMPEDE, abir vs. doce	ENZAMET	ARCHES	TITAN	STAMPED E-RT	HORRAD	PEACE-1, doce-sub	ARASENS
Patients number	385	790	1776*	1199	1917*	342 <sup>§</sup>	1125	1150	1052	2061	432	710	1305
HR (OS-total)	0.88, 0.68-1.14	0.72, 0.59-0.89	0.78, 0.66-0.93	0.66, 0.56-0.78	0.63, 0.52-0.76	1.13, 0.77-1.66	0.67, 0.52-0.86	0.66, 0.53-0.81	0.65, 0.53-0.79	0.92, 0.80-1.06	0.90, 0.70-1.14	0.75, 0.59-0.95	0.68, 0.57-0.80
De novo-pts number	144/190(76%) ADT:DOC 128/190(67%)	575/789 (73%)	1681/1776 (95%)	100%	1819/1917 (95%)	NA	652/1125 (58%)	890/1136 (78%)	852/996 (86%)	100%	100%	100%	1124/1292 (87%)
HR (OS-de novo)	0.93, 0.69-1.25	0.68, 0.54-0.85	0.78, 0.65-0.94	0.66, 0.56-0.78	0.61, 0.50-0.74	NA	0.65, 0.47-0.89	0.63, 0.50-0.79	0.68, 0.55-0.85	0.92, 0.80-1.06	0.90, 0.70-1.14	0.75, 0.59-0.95	0.71, 0.59-0.85
PLT-pts number	46/190(24%) ADT:DOC 62/190(33%)	214/789 (27%)	95/1776 (5%)	0	98/1917 (5%)	NA	473/1125 (42%)	246/1136 (22%)	144/996 (14%)	NA	NA	NA	168/1292 (13%)
HR (OS-PLT)	0.83, 0.47-1.47	0.97, 0.58-1.62	0.80, 0.26-2.48	NA	0.94, 0.35-2.52	NA	0.72, 0.47-1.09	0.71, 0.41-1.21	0.39, 0.22-0.69	NA	NA	NA	0.61, 0.35-1.05

\*Metastatic and localized patients were all included; <sup>§</sup> Direct comparison of abiraterone versus docetaxel from the multi-arm, multi-stage STAMPEDE trial; doce-sub: subgroup with docetaxel population and available for triple treatment analysis. PLT: previous local treatment.

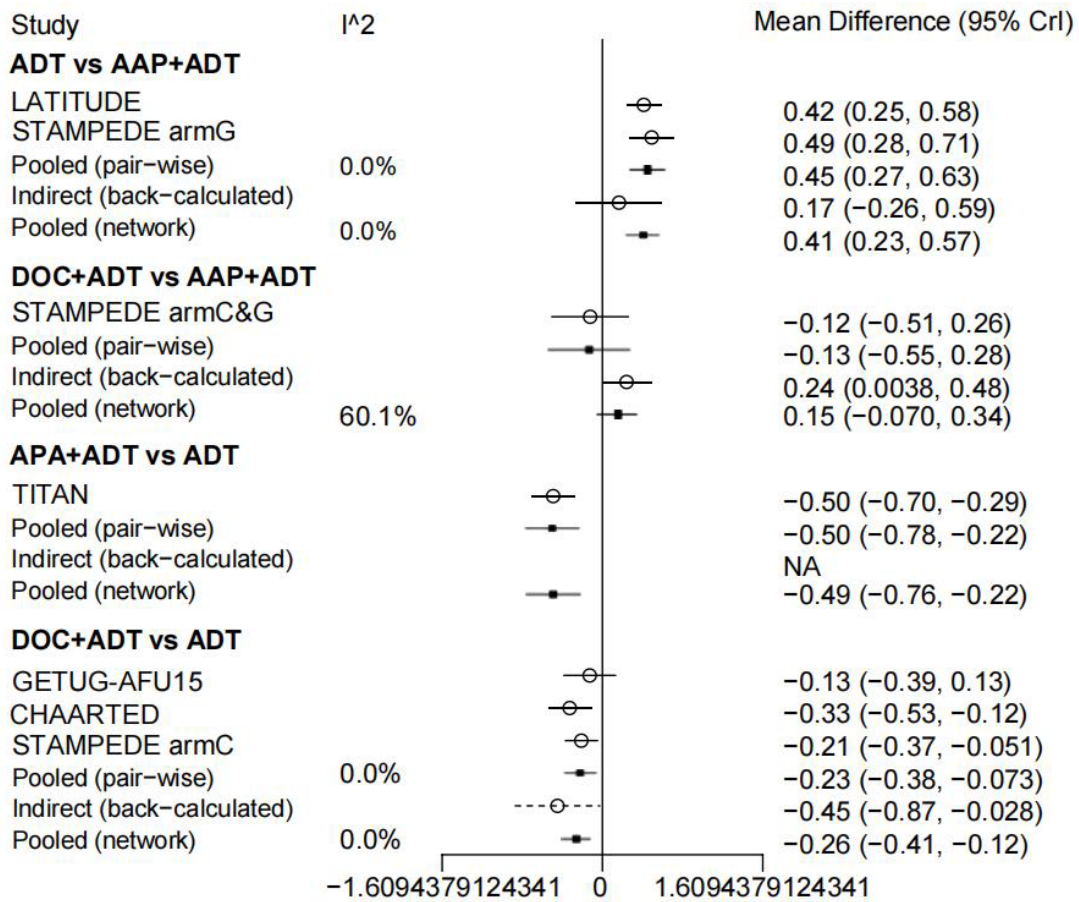
**Supplementary Material 5: Consistency test of closed-loop studies**

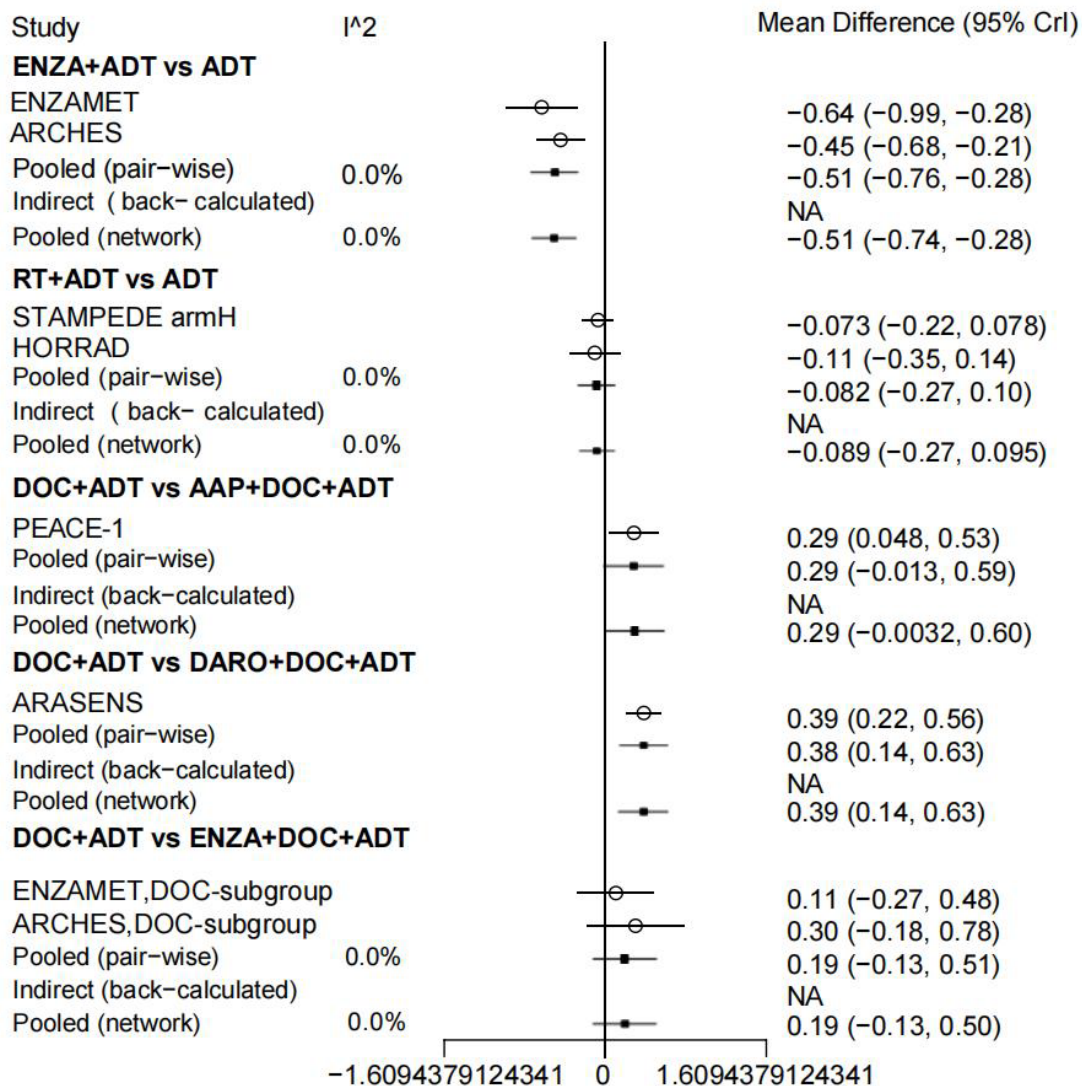
	comparison	p.value	CrI
1	d.ADT.DOC+ADT	0.162625	
2	-> direct		-0.23 (-0.38, -0.073)
3	-> indirect		-0.57 (-1.0, -0.11)
4	-> network		-0.26 (-0.41, -0.12)
5	d.ADT.AAP+ADT	0.173875	
6	-> direct		-0.45 (-0.63, -0.26)
7	-> indirect		-0.11 (-0.56, 0.34)
8	-> network		-0.41 (-0.57, -0.23)
9	d.DOC+ADT.AAP+ADT	0.156700	
10	-> direct		0.13 (-0.30, 0.55)
11	-> indirect		-0.22 (-0.46, 0.020)
12	-> network		-0.15 (-0.34, 0.076)



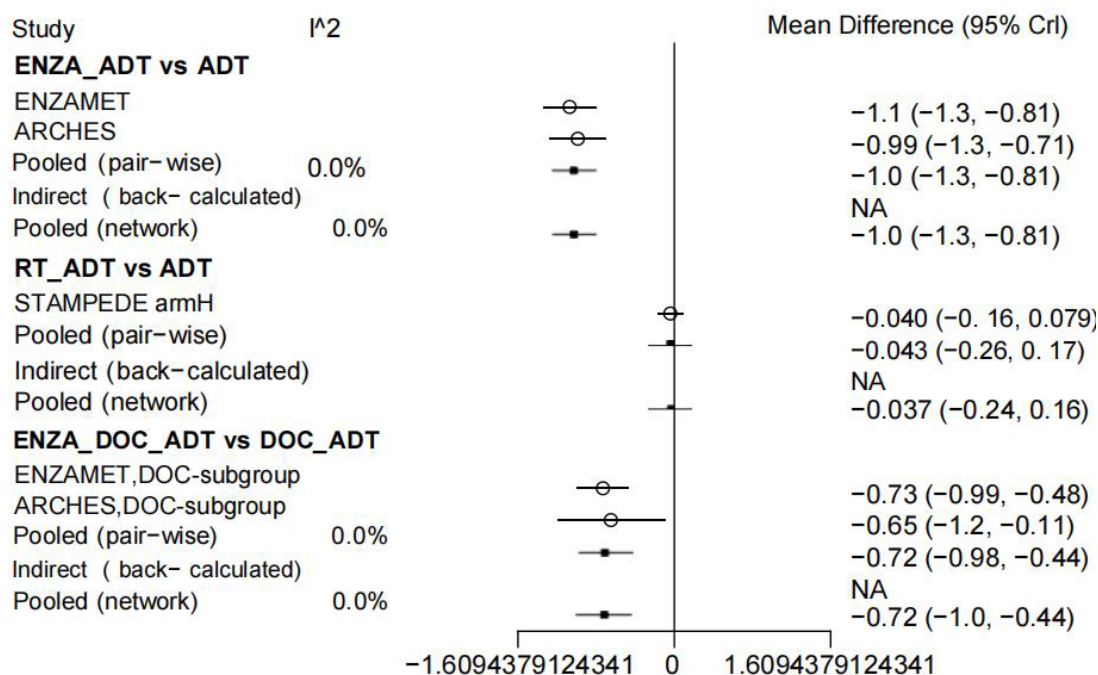
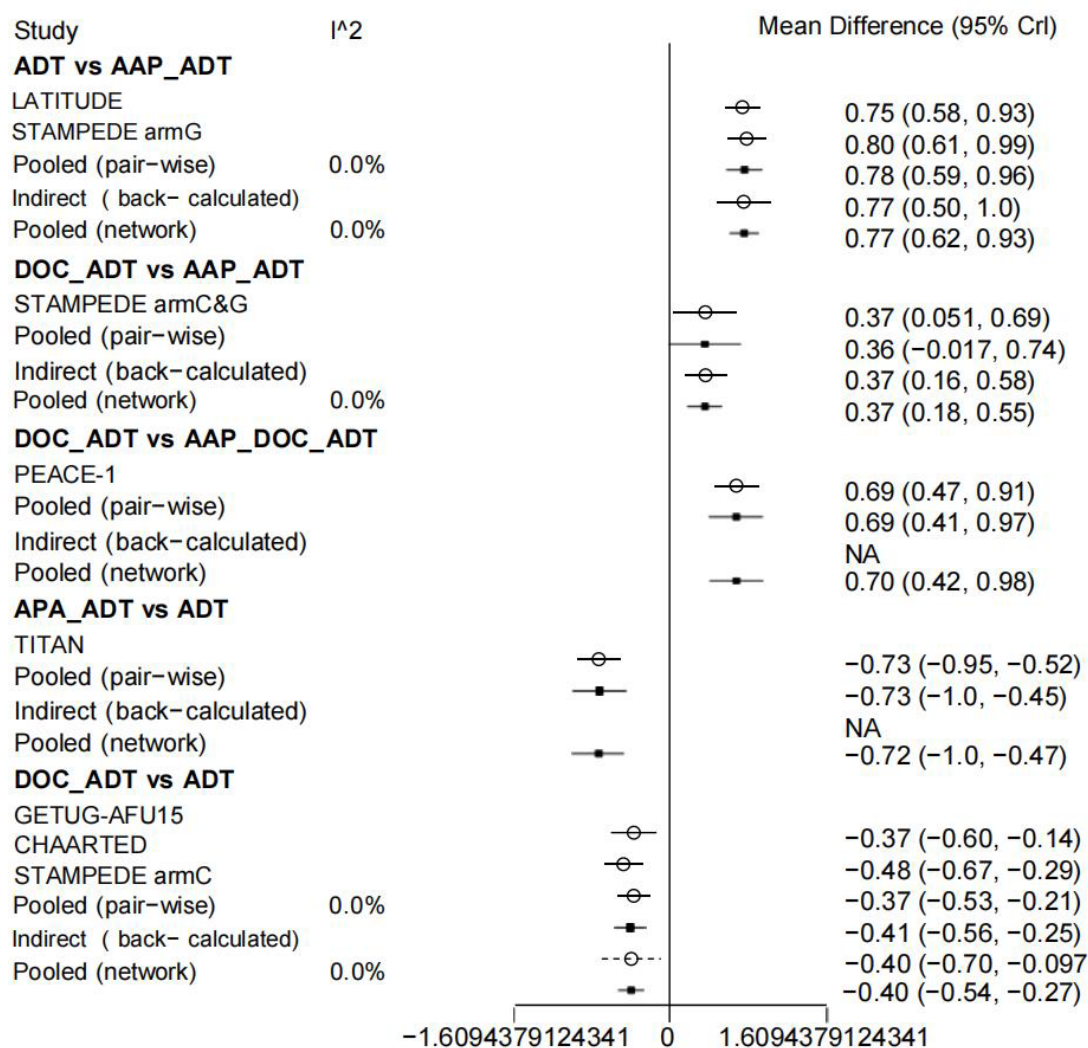
## Supplementary Material 6: Heterogeneity test

Heterogeneity test for OS for all population

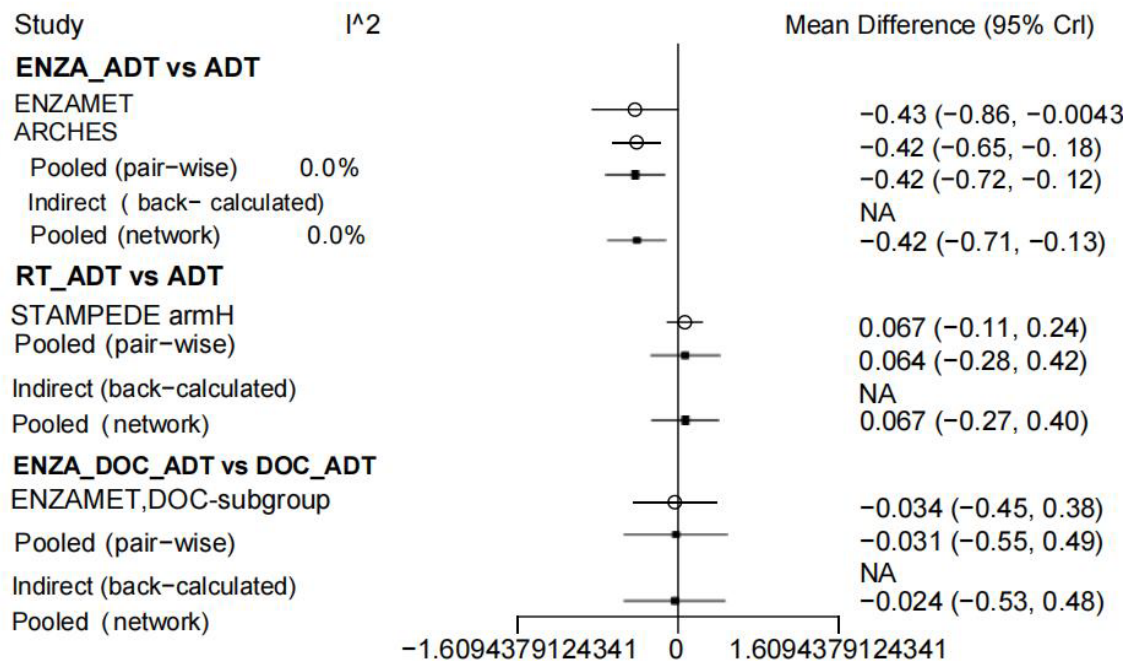
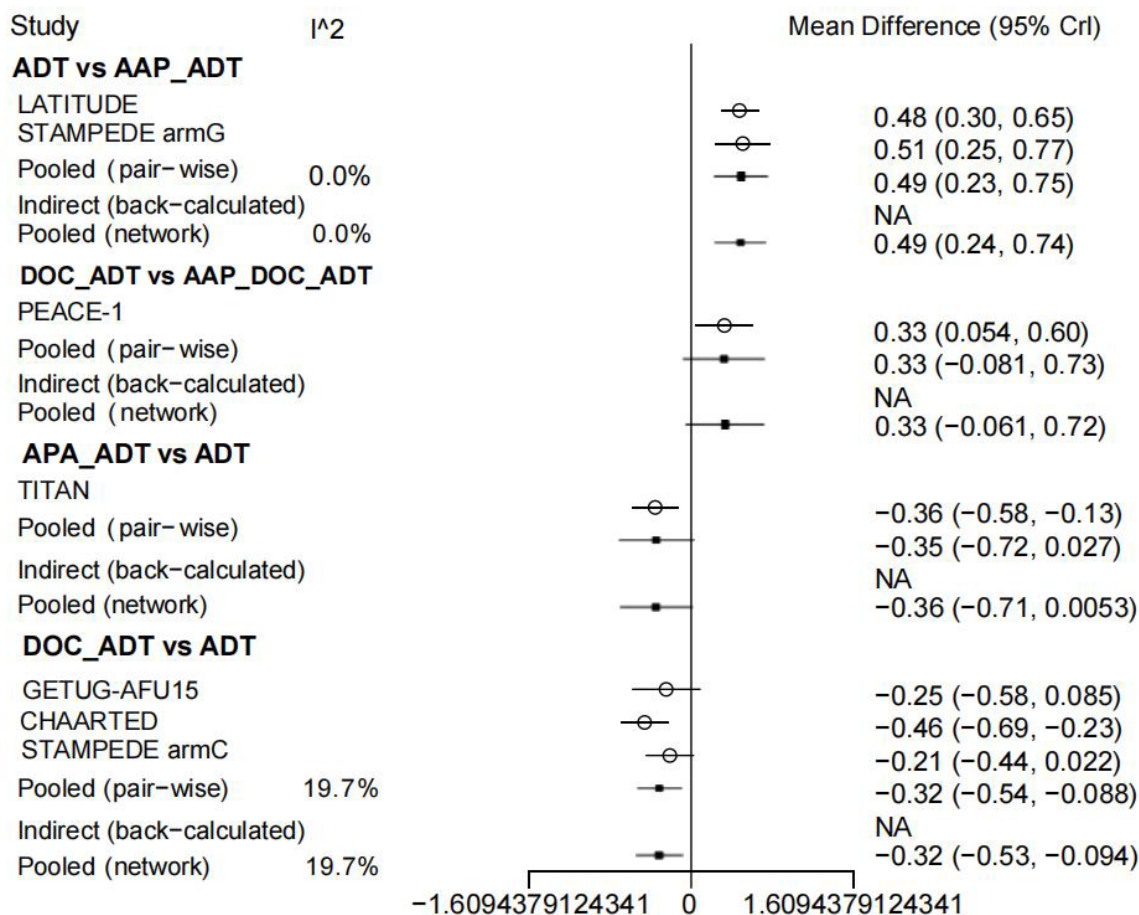




Heterogeneity test for PFS

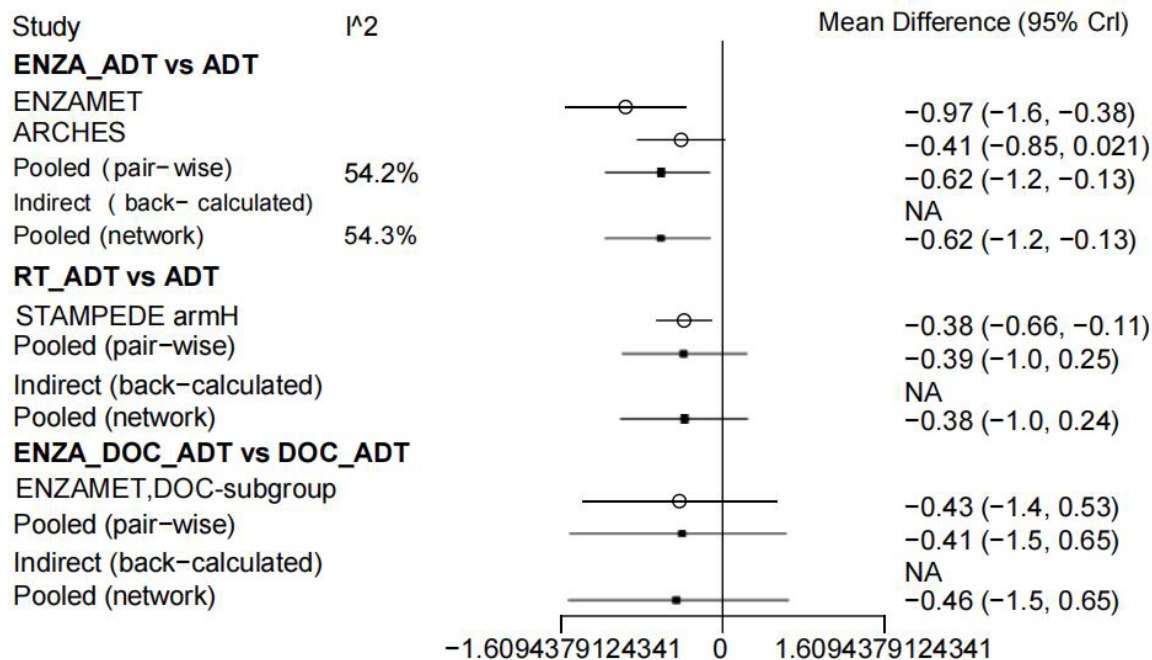
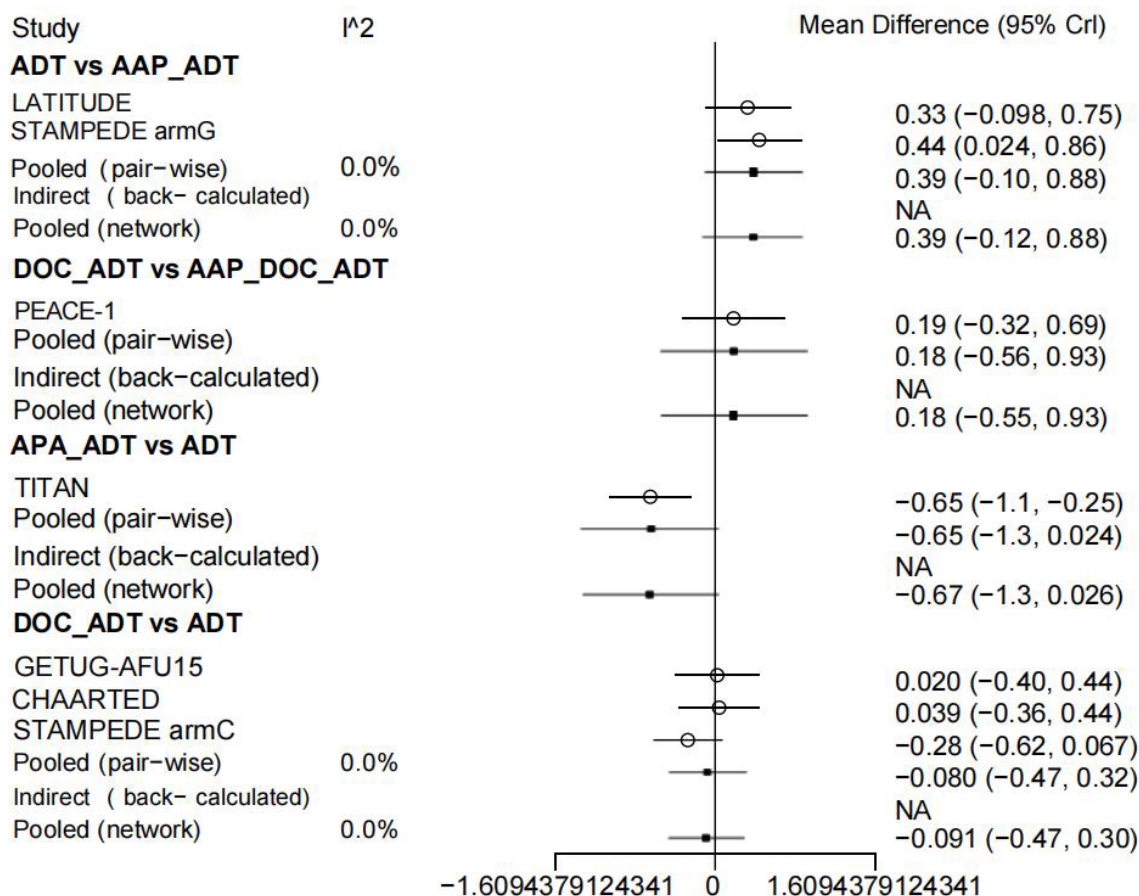


Heterogeneity test for OS-HVD

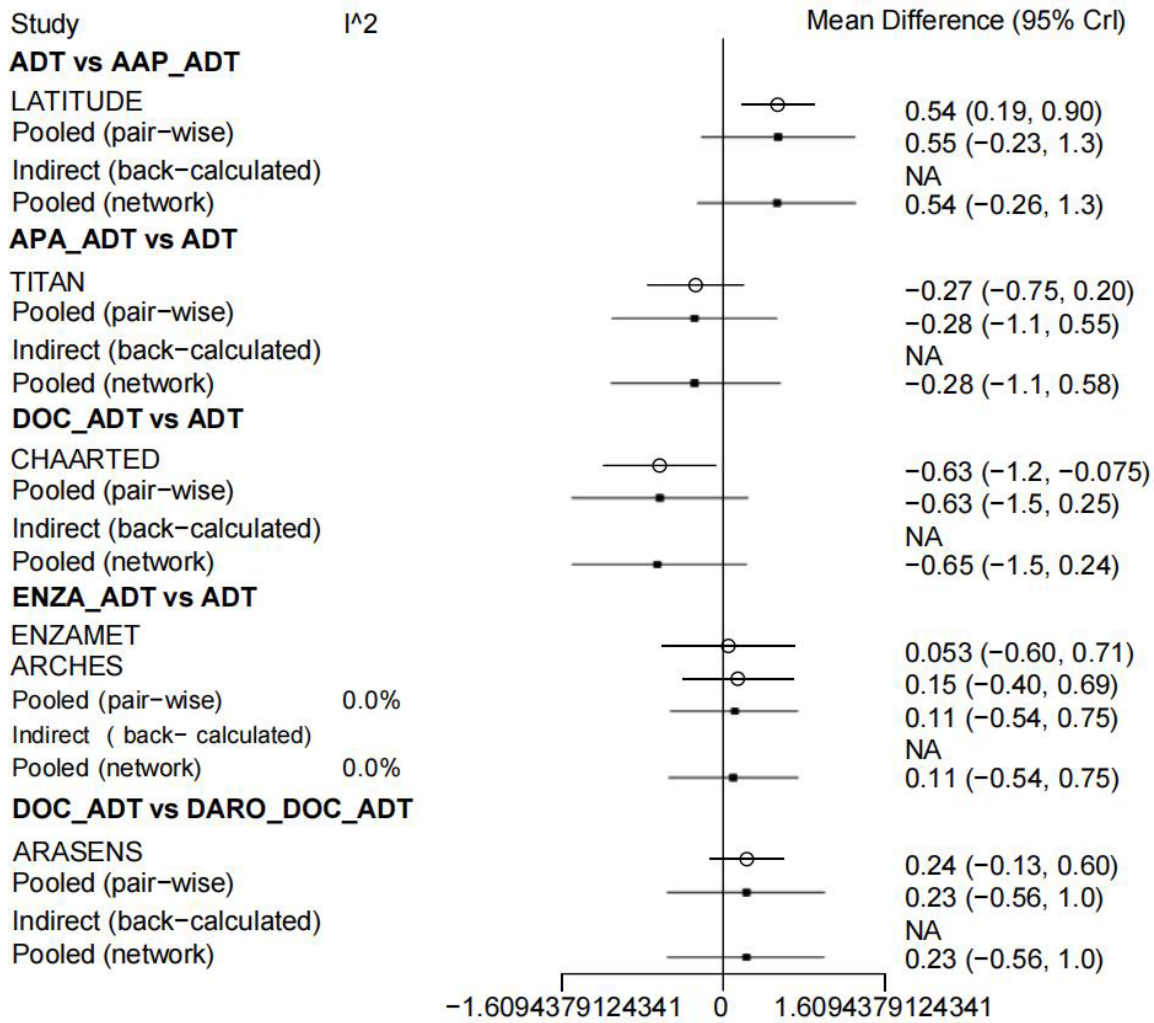




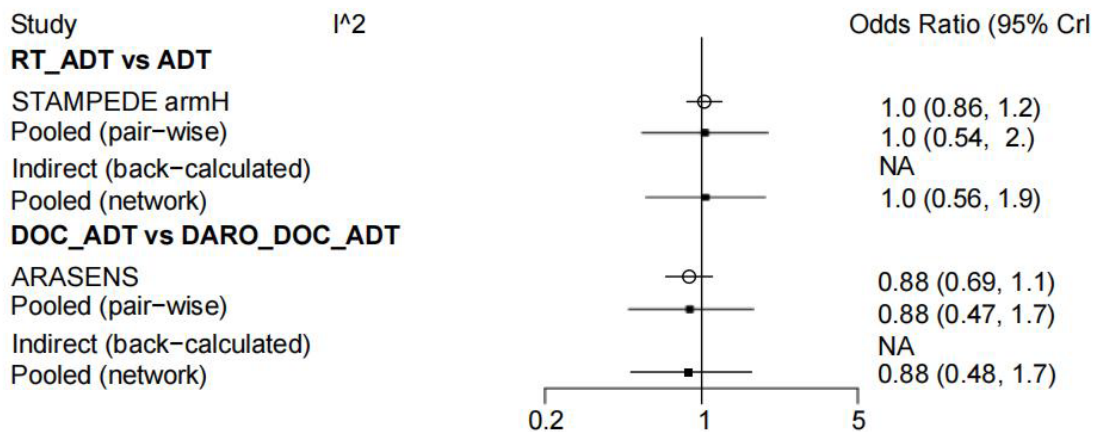
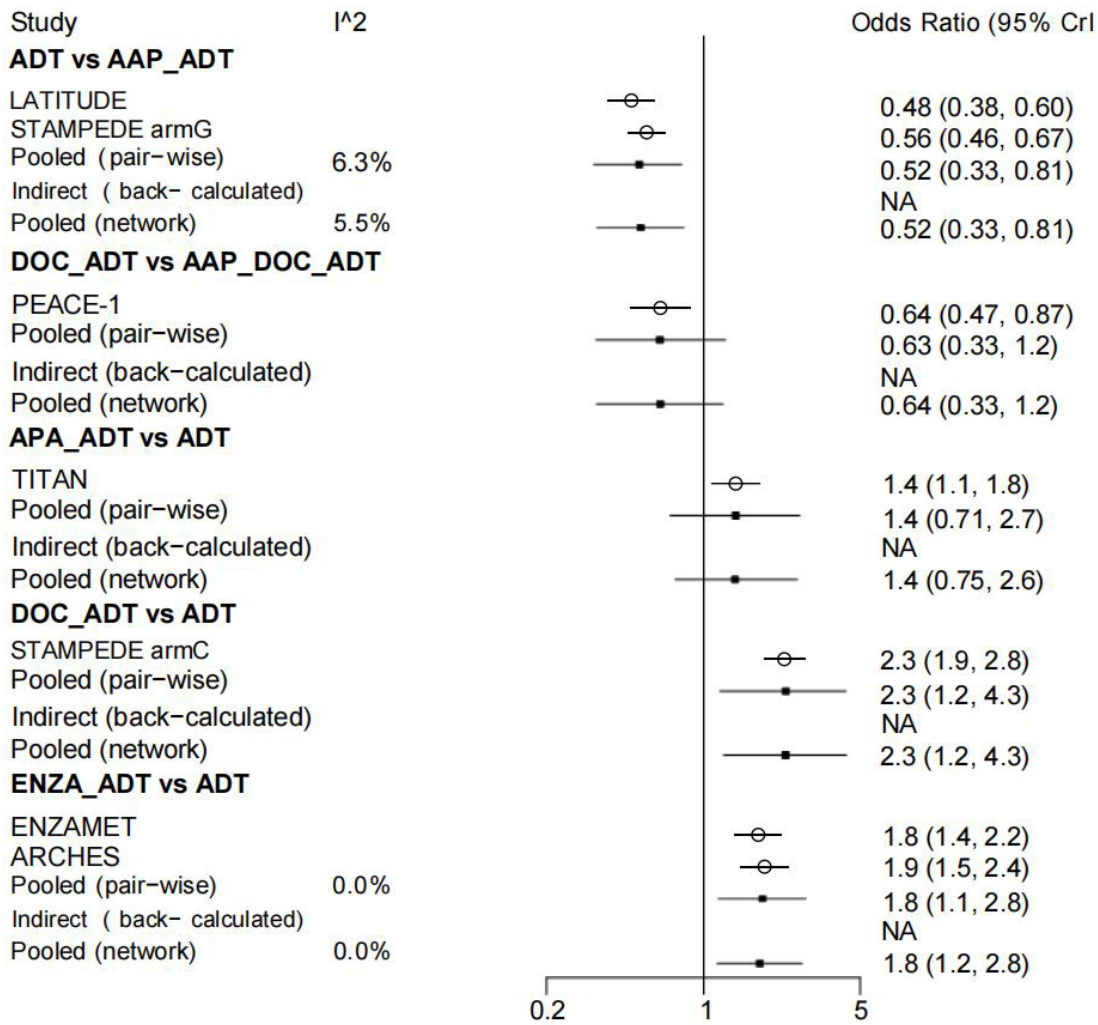
Heterogeneity test for OS-LVD



Heterogeneity test for OS-visceral metastasis

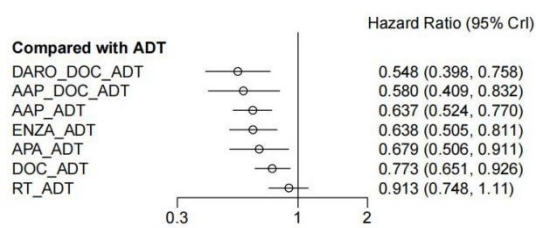


Heterogeneity test for high grade AE

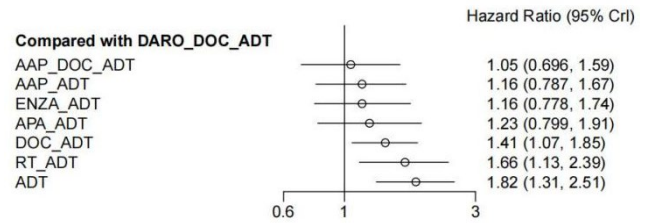


**Supplementary materials 7: Supplementary forest plots (for de novo and previous local treatment patients, as well as respective analyses for rPFS, PFS and cPFS)**

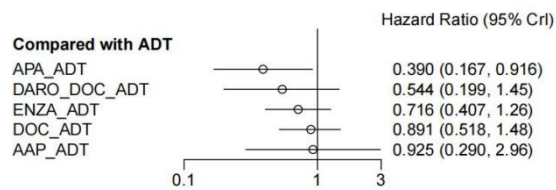
ADT: androgen deprivation treatment; DOC: docetaxel; AAP: abiraterone acetate and prednisone; ENZA: enzalutamide; APA: apalutamide; RT: radiotherapy; DARO: darolutamide. OS: overall survival; PFS: progression free survival; cPFS: clinical progression free survival; rPFS: radiographic progression free survival; The connector line “\_” represents combination of different treatment regimens.



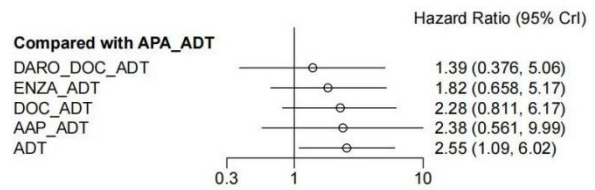
A: OS for de novo disease (vs. ADT)



B: OS for de novo disease (vs. DARO\_DOC\_ADT)

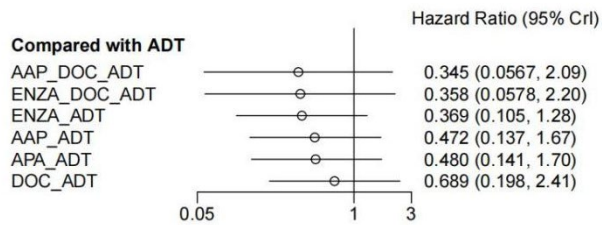


C: OS for patients with previous local treatment (vs. ADT)

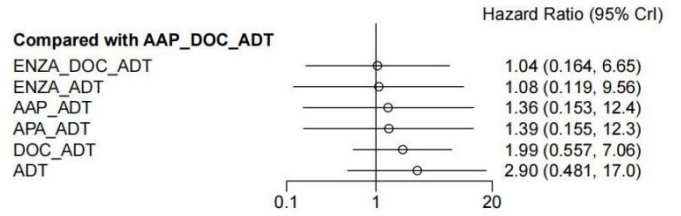


D: OS for patients with previous local treatment (vs. APA\_ADT)

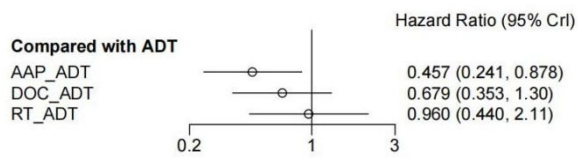




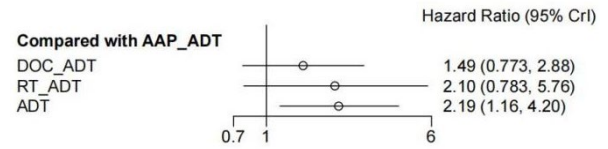
E: rPFS (vs.ADT)



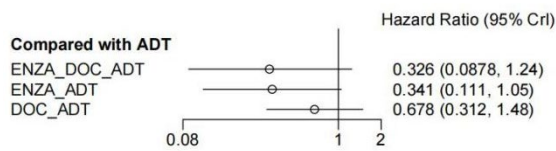
F: rPFS (vs.ENZA\_DOC\_ADT)



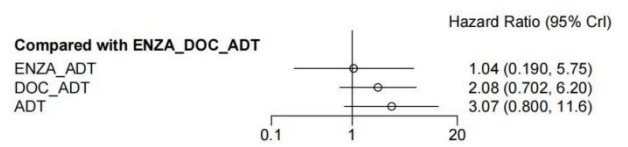
G: PFS (vs.ADT)



H: PFS (vs.AAP)



I: cPFS (vs.ADT)



J: cPFS (vs.ENZA\_DOC\_ADT)

**Supplementary Material 8: Relative effect estimates for all possible treatment comparisons**

Overall survival, hazard ratio (95% CI)

DARO+DOC+ADT								
0.91 (0.61, 1.34)	AAP+DOC+ADT							
0.81 (0.54, 1.23)	0.90 (0.58, 1.40)	ENZA+DOC+ADT						
<b>0.57 (0.40, 0.80)</b>	<b>0.63 (0.43, 0.92)</b>	0.70 (0.46, 1.03)	RT+ADT					
0.86 (0.57, 1.29)	0.95 (0.61, 1.47)	1.05 (0.67, 1.65)	1.51 (1.07, 2.12)	APA+ADT				
0.87 (0.60, 1.26)	0.96 (0.64, 1.45)	1.07 (0.70, 1.64)	1.53 (1.14, 2.06)	1.01 (0.71, 1.47)	ENZA+ADT			
0.79 (0.56, 1.08)	0.87 (0.60, 1.24)	0.97 (0.65, 1.41)	1.38 (1.06, 1.76)	0.92 (0.66, 1.26)	0.90 (0.67, 1.20)	AAP+ADT		
<b>0.68 (0.53, 0.88)</b>	0.75 (0.55, 1.01)	0.83 (0.60, 1.14)	1.20 (0.95, 1.52)	0.79 (0.58, 1.10)	0.78 (0.59, 1.04)	0.86 (0.71, 1.09)	DOC+ADT	
<b>0.52 (0.39, 0.70)</b>	<b>0.58 (0.41, 0.81)</b>	<b>0.64 (0.45, 0.92)</b>	0.92 (0.76, 1.11)	<b>0.61 (0.46, 0.81)</b>	<b>0.60 (0.47, 0.76)</b>	<b>0.67 (0.57, 0.80)</b>	<b>0.77 (0.66, 0.89)</b>	Placebo/No treatment /NSAA+ADT

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

AAP+DOC+ADT							
1.02 (0.70, 1.48)	ENZA+DOC+ADT						
<b>0.35 (0.24, 0.49)</b>	<b>0.34 (0.24, 0.48)</b>	RT+ADT					
0.69 (0.47, 1.03)	0.68 (0.45, 1.01)	2.00 (1.45, 2.77)	APA+ADT				
0.94 (0.65, 1.36)	0.92 (0.64, 1.34)	2.72 (2.03, 3.63)	1.36 (0.97, 1.91)	ENZA+ADT			
<b>0.72 (0.52, 0.99)</b>	<b>0.71 (0.51, 0.97)</b>	2.08 (1.64, 2.66)	1.05 (0.77, 1.42)	0.77 (0.59, 1.00)	AAP+ADT		
<b>0.50 (0.38, 0.65)</b>	<b>0.49 (0.37, 0.64)</b>	1.44 (1.14, 1.83)	<b>0.72 (0.54, 0.96)</b>	<b>0.53 (0.41, 0.68)</b>	<b>0.69 (0.58, 0.83)</b>	DOC+ADT	
<b>0.33 (0.25, 0.45)</b>	<b>0.32 (0.24, 0.44)</b>	0.96 (0.80, 1.16)	<b>0.48 (0.37, 0.63)</b>	<b>0.35 (0.28, 0.44)</b>	<b>0.46 (0.40, 0.53)</b>	<b>0.67 (0.59, 0.76)</b>	Placebo/No treatment /NSAA+ADT

Overall survival for patients with high volume disease, hazard ratio (95% CI)

AAP+DOC+ADT							
0.75 (0.39, 1.40)	ENZA+DOC+ADT						
<b>0.49 (0.28, 0.87)</b>	0.66 (0.35, 1.28)	RT+ADT					
0.75 (0.42, 1.34)	1.01 (0.52, 0.99)	1.52 (0.93, 2.54)	APA+ADT				
0.80 (0.47, 1.38)	1.08 (0.58, 2.01)	<b>1.63 (1.05, 2.55)</b>	1.06 (0.67, 1.71)	ENZA+ADT			
0.85 (0.51, 1.46)	1.15 (0.63, 2.11)	<b>1.75 (1.14, 2.70)</b>	1.14 (0.73, 1.78)	1.07 (0.72, 1.60)	AAP+ADT		
0.72 (0.49, 1.08)	0.97 (0.59, 1.61)	1.47 (0.96, 2.20)	0.96 (0.62, 1.48)	0.90 (0.62, 1.31)	0.84 (0.59, 1.18)	DOC+ADT	
<b>0.52 (0.33, 0.83)</b>	0.71 (0.41, 1.22)	1.07 (0.76, 1.51)	0.70 (0.48, 1.02)	<b>0.66 (0.49, 0.89)</b>	<b>0.61 (0.47, 0.79)</b>	<b>0.73 (0.58, 0.91)</b>	Placebo/No treatment /NSAA+ADT

Overall survival for patients with low volume disease, hazard ratio (95% CI)

AAP+DOC+ADT							
1.26 (0.33, 4.74)	ENZA+DOC+ADT						
1.13 (0.40, 3.21)	0.88 (0.24, 3.38)	RT+ADT					
1.47 (0.50, 4.34)	1.15 (0.30, 4.40)	1.30 (0.52, 3.38)	APA+ADT				
1.42 (0.54, 4.06)	1.11 (0.32, 4.20)	1.27 (1.57, 3.07)	0.97 (0.42, 2.45)	ENZA+ADT			
1.12 (0.43, 2.95)	0.87 (0.25, 3.13)	1.00 (0.45, 2.24)	0.77 (0.34, 1.78)	0.79 (0.37, 1.58)	AAP+ADT		
0.83 (0.40, 1.75)	0.65 (0.22, 1.94)	0.74 (0.35, 1.56)	0.57 (0.25, 1.25)	0.58 (0.30, 1.08)	0.74 (0.39, 1.37)	DOC+ADT	
0.77 (0.33, 1.78)	0.60 (0.19, 1.92)	0.68 (0.36, 1.28)	0.52 (0.26, 1.05)	<b>0.53 (0.31, 0.88)</b>	0.68 (0.41, 1.13)	0.92 (0.62, 1.37)	Placebo/No treatment /NSAA+ADT

Overall survival for patients with visceral metastasis, hazard ratio (95% CI)

DARO+DOC+ADT					
0.55 (0.13, 2.29)	APA+ADT				
0.38 (0.10, 1.44)	0.69 (0.24, 1.96)	ENZA+ADT			
0.73 (0.18, 3.02)	1.31 (0.43, 4.15)	1.91 (0.70, 5.18)	AAP+ADT		
0.79 (0.37, 1.74)	1.43 (0.42, 4.77)	2.11 (0.71, 6.07)	1.10 (0.34, 3.50)	DOC+ADT	
0.42 (0.13, 1.34)	0.76 (0.33, 1.75)	1.11 (0.58, 2.09)	0.58 (0.27, 1.26)	0.53 (0.22, 1.27)	Placebo/No treatment /NSAA+ADT

High grade AE, Odds ratio (95% CI)

DARO+DOC+ADT							
0.73 (0.31, 1.73)	AAP+DOC+ADT						
2.53 (0.84,6.90)	<b>3.46 (1.19, 9.92)</b>	RT+ADT					
1.85 (0.65, 5.17)	2.55 (0.90, 7.22)	0.73 (0.31, 1.64)	APA+ADT				
1.44 (0.56, 3.75)	1.98 (0.78, 5.27)	0.57 (0.28, 1.18)	0.78 (0.38, 1.62)	ENZA+ADT			
1.36 (0.53, 3.34)	1.86 (0.71, 4.66)	0.54 (0.26, 1.08)	0.73 (0.35, 1.49)	0.94 (0.52, 1.69)	AAP+ADT		
1.13 (0.63, 2.03)	1.56 (0.86, 2.85)	0.45 (0.20, 1.03)	0.61 (0.27, 1.37)	0.79 (0.39, 1.61)	0.84 (0.43, 1.72)	DOC+ADT	
<b>2.59 (1.11,6.09)</b>	<b>3.56 (1.51, 8.43)</b>	1.03 (0.57, 1.87)	1.39 (0.76, 2.55)	<b>1.81 (1.18, 2.77)</b>	<b>1.92 (1.27, 2.95)</b>	<b>2.28 (1.26, 4.16)</b>	Placebo/No treatment /NSAA+ADT

Overall survival for patients with de novo disease, hazard ratio (95% CI)

DARO+DOC+ADT							
0.95(0.63, 1.44)	AAP+DOC+ADT						
0.86 (0.59, 1.26)	0.91(0.61, 1.38)	AAP+ADT					
0.86 (0.58, 1.30)	0.91 (0.60, 1.40)	0.997 (0.73, 1.35)	ENZA+ADT				
0.81 (0.53, 1.26)	0.86 (0.54, 1.36)	0.94 (0.66, 1.33)	0.94 (0.64, 1.38)	APA+ADT			
<b>0.71 (0.54, 0.94)</b>	0.75 (0.55, 1.02)	0.83 (0.63, 1.06)	0.823 (0.61, 1.11)	0.88 (0.62, 1.24)	DOC+ADT		
<b>0.60 (0.41, 0.89)</b>	<b>0.64 (0.43, 0.96)</b>	<b>0.70 (0.53, 0.92)</b>	<b>0.70 (0.52, 0.95)</b>	0.74(0.52, 1.07)	0.85 (0.66, 1.11)	RT+ADT	
<b>0.55 (0.40, 0.76)</b>	<b>0.58 (0.41, 0.83)</b>	<b>0.64 (0.52, 0.77)</b>	<b>0.64 (0.51, 0.81)</b>	<b>0.68 (0.51, 0.91)</b>	<b>0.77 (0.65, 0.93)</b>	0.91 (0.75, 1.11)	Placebo/No treatment /NSAA+ADT

Overall survival for patients with previous local treatment, hazard ratio (95% CI)

APA+ADT					
0.72 (0.19, 2.71)	DARO+DOC+ADT				
0.54 (0.20, 1.50)	0.76 (0.24, 2.33)	ENZA+ADT			
0.44 (0.16, 1.20)	0.61 (0.26, 1.42)	0.81 (0.38, 1.74)	DOC+ADT		
0.41 (0.10, 1.80)	0.58 (0.13, 2.65)	0.76 (0.21, 2.78)	0.95 (0.26, 3.30)	AAP+ADT	
<b>0.39 (0.17, 0.92)</b>	0.54 (0.20, 1.45)	0.72 (0.41, 1.26)	0.89 (0.52, 1.48)	0.93 (0.29, 2.96)	Placebo/No treatment /NSAA+ADT

AAP: abiraterone acetate and prednisone; ADT: androgen deprivation therapy; APA: apalutamide; CI: confidence interval; DARO: darolutamide; DOC: docetaxel; ENZA: enzalutamide; NSAA: non-steroidal anti-androgen, including nilutamide, flutamide or bicalutamide; RT: radiotherapy.

**Supplementary Material 9: OS/PFS ranking and ranking probability of competing interventions based on overall population**

A. OS for overall population

Probability for place		1st	2nd	3rd	4th	5th	6th	7th	8th	9th
Rank	Treatment									
1	DARO+DOC+ADT	0.49	0.26	0.13	0.07	0.03	0.01	0	0	0
2	AAP+DOC+ADT	0.20	0.23	0.20	0.15	0.11	0.08	0.02	0	0
3	ENZA+ADT	0.11	0.19	0.24	0.21	0.15	0.08	0.02	0	0
4	APA+ADT	0.11	0.16	0.20	0.20	0.17	0.08	0.02	0	0
5	ENZA+DOC+ADT	0.08	0.12	0.15	0.16	0.17	0.20	0.10	0.03	0.01
6	AAP+ADT	0.01	0.03	0.09	0.20	0.32	0.28	0.06	0.01	0
7	DOC+ADT	0	0	0	0.01	0.04	0.22	0.68	0.04	0
8	RT+ADT	0	0	0	0	0.01	0.02	0.07	0.74	0.16
9	ADT alone	0	0	0	0	0	0	0	0.17	0.83

B. Generalized PFS for overall population

Probability for place		1st	2nd	3rd	4th	5th	6th	7th	8th
Rank	Treatment								
1	ENZA+DOC+ADT	0.45	0.33	0.20	0.02	0.01	0	0	0
2	AAP+DOC+ADT	0.36	0.35	0.25	0.03	0.01	0	0	0
3	ENZA+ADT	0.19	0.30	0.46	0.04	0.01	0	0	0
4	AAP+ADT	0	0.01	0.04	0.59	0.37	0	0	0
5	APA+ADT	0	0.01	0.01	0.32	0.59	0.02	0	0
6	DOC+ADT	0	0	0	0	0.02	0.98	0	0
7	RT+ADT	0	0	0	0	0	0	0.69	0.31
8	ADT alone	0	0	0	0	0	0	0.31	0.69

C. OS for patients with high volume disease

Probability for place		1st	2nd	3rd	4th	5th	6th	7th	8th
Rank	Treatment								
1	AAP+DOC+ADT	0.61	0.18	0.10	0.06	0.03	0.02	0	0
2	AAP+ADT	0.15	0.33	0.26	0.15	0.07	0.03	0	0
3	ENZA+ADT	0.08	0.19	0.24	0.21	0.16	0.11	0.01	0
4	APA+ADT	0.06	0.11	0.16	0.20	0.19	0.23	0.03	0.01
5	ENZA+DOC+ADT	0.10	0.16	0.12	0.13	0.14	0.23	0.06	0.06
6	DOC+ADT	0	0.02	0.10	0.24	0.38	0.24	0.01	0
7	ADT alone	0	0	0	0	0.01	0.08	0.65	0.25
8	RT+ADT	0	0	0.01	0.01	0.02	0.06	0.24	0.66



D. OS for patients with low volume disease

Probability for place		1st	2nd	3rd	4th	5th	6th	7th	8th
Rank	Treatment								
1	APA+ADT	0.31	0.26	0.17	0.23	0.07	0.04	0.02	0.02
2	ENZA+ADT	0.24	0.30	0.22	0.13	0.07	0.03	0.01	0
3	ENZA+DOC+ADT	0.29	0.13	0.11	0.10	0.09	0.08	0.06	0.14
4	AAP+ADT	0.04	0.10	0.19	0.24	0.22	0.12	0.06	0.02
5	RT+ADT	0.05	0.11	0.18	0.23	0.20	0.12	0.06	0.04
6	AAP+DOC+ADT	0.06	0.09	0.11	0.14	0.16	0.16	0.11	0.16
7	DOC+ADT	0	0	0.01	0.04	0.13	0.29	0.38	0.15
8	ADT alone	0	0	0	0.01	0.06	0.16	0.30	0.47

E. OS for patients with vesical metastasis

Probability for place		1st	2nd	3rd	4th	5th	6th
Rank	Treatment						
1	DARO+DOC+ADT	0.59	0.20	0.11	0.05	0.03	0.03
2	DOC+ADT	0.11	0.46	0.26	0.11	0.04	0.02
3	AAP+ADT	0.21	0.20	0.35	0.16	0.04	0.03
4	APA+ADT	0.08	0.11	0.19	0.35	0.13	0.13
5	ADT alone	0	0	0.04	0.18	0.53	0.24
6	ENZA+ADT	0.01	0.02	0.05	0.14	0.23	0.55

F. Grade 3-5 AEs for overall population

Probability for place		1st	2nd	3rd	4th	5th	6th	7th	8th
Rank	Treatment								
1	ADT alone	0.51	0.42	0.05	0.01	0	0	0	0
2	RT+ADT	0.41	0.44	0.10	0.03	0.01	0.01	0.01	0
3	APA+ADT	0.05	0.09	0.64	0.11	0.05	0.02	0.02	0.01
4	ENZA+ADT	0.01	0.02	0.10	0.46	0.27	0.08	0.05	0.02
5	AAP+ADT	0	0.01	0.06	0.27	0.44	0.12	0.08	0.03
6	DOC+ADT	0	0.01	0.02	0.06	0.14	0.58	0.18	0.01
7	DARO+DOC+ADT	0.01	0.01	0.02	0.05	0.07	0.16	0.55	0.13
8	AAP+DOC+ADT	0	0	0.01	0.01	0.02	0.03	0.12	0.80

G. OS for de novo patients

Probability for place		1st	2nd	3rd	4th	5th	6th	7th	8th
Rank	Treatment								
1	DARO+DOC+ADT	0.48	0.28	0.12	0.07	0.04	0.01	0	0
2	AAP+DOC+ADT	0.30	0.29	0.16	0.12	0.09	0.02	0.01	0
3	AAP+ADT	0.07	0.16	0.30	0.29	0.16	0.03	0	0
4	ENZA+ADT	0.10	0.17	0.25	0.25	0.18	0.05	0.01	0
5	APA+ADT	0.06	0.10	0.16	0.21	0.29	0.15	0.03	0.01
6	DOC+ADT	0	0	0.01	0.06	0.21	0.65	0.07	0
7	RT+ADT	0	0	0	0.01	0.02	0.09	0.74	0.14
8	ADT alone	0	0	0	0	0	0.01	0.15	0.84

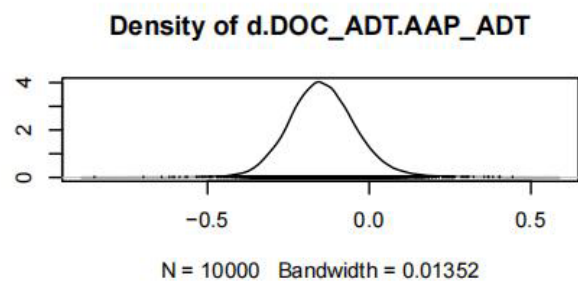
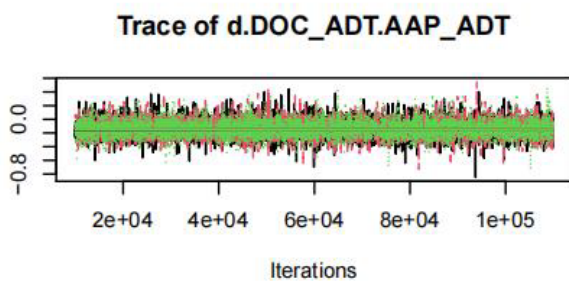
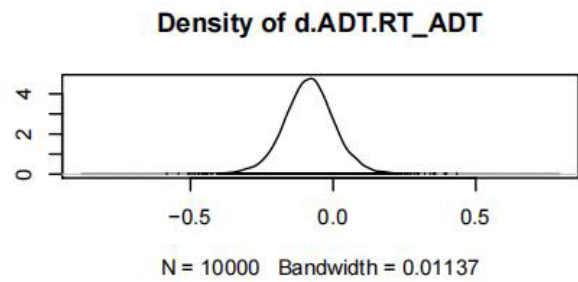
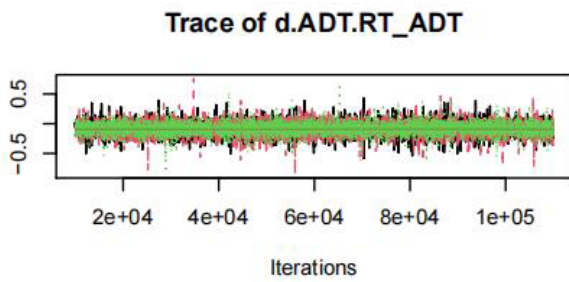
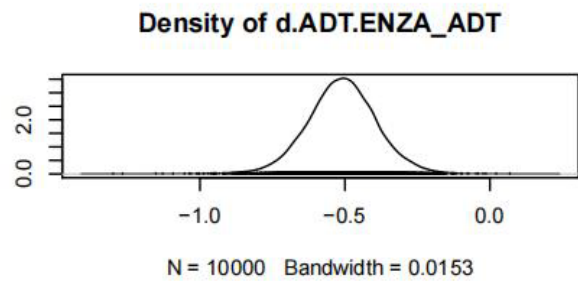
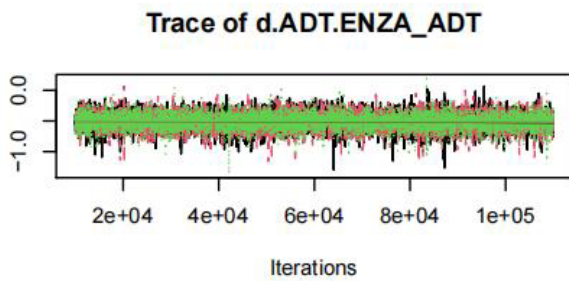
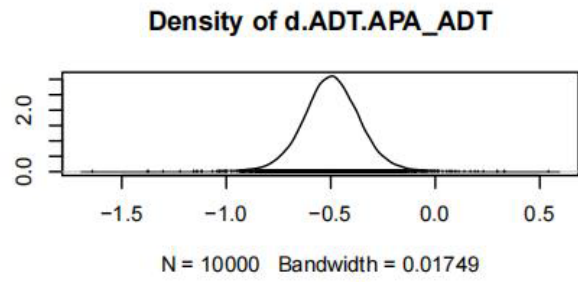
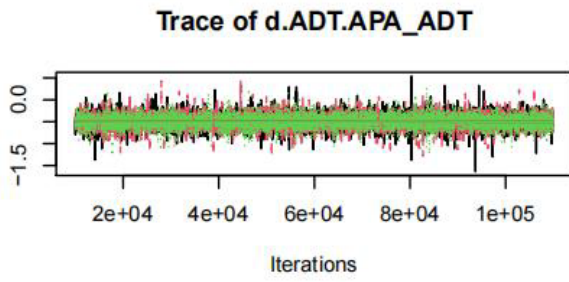
H. OS for patients with previous local treatment

Probability for place		1st	2nd	3rd	4th	5th	6th
Rank	Treatment						
1	APA+ADT	0.65	0.23	0.07	0.03	0.01	0.01
2	DARO+DOC+ADT	0.25	0.39	0.19	0.09	0.05	0.04
3	ENZA+ADT	0.04	0.21	0.37	0.24	0.10	0.04
4	DOC+ADT	0	0.04	0.17	0.32	0.29	0.17
5	ADT alone	0	0.01	0.04	0.18	0.44	0.33
6	AAP+ADT	0.06	0.13	0.15	0.14	0.11	0.41

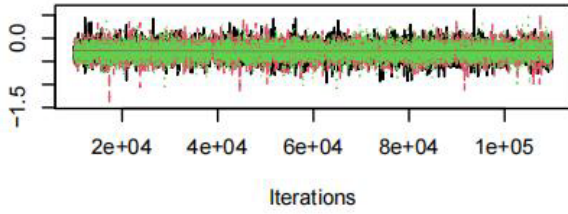
AAP: abiraterone acetate and prednisone; ADT: androgen deprivation therapy; APA: apalutamide; DARO: darolutamide; DOC: docetaxel; ENZA: enzalutamide; OS: overall survival; PFS: progression free survival; RT: radiotherapy.

## Supplementary Material 10: Trace and density plots

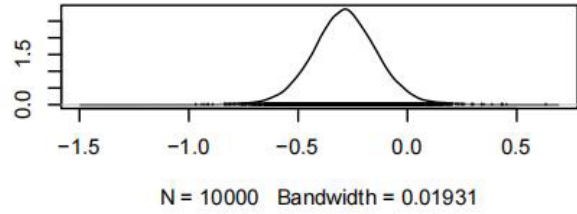
A: Trace and density plots for OS for all population



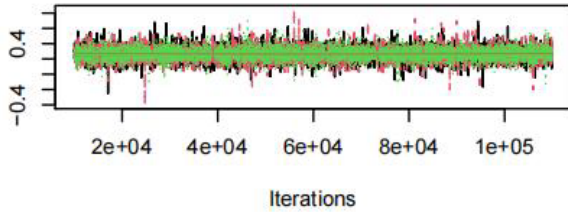
**Trace of d.DOC\_ADT.AAP\_DOC\_ADT**



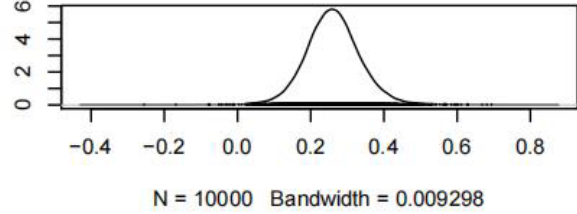
**Density of d.DOC\_ADT.AAP\_DOC\_ADT**



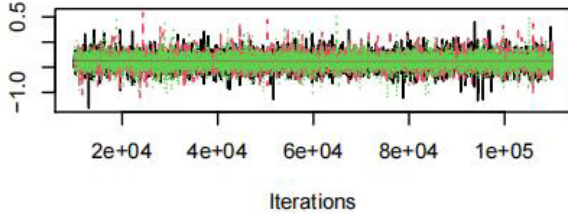
**Trace of d.DOC\_ADT.ADT**



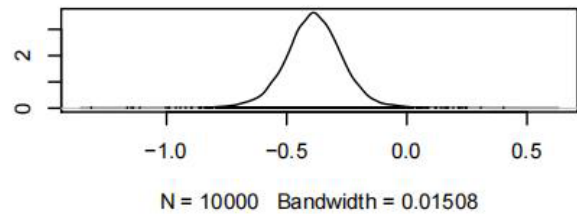
**Density of d.DOC\_ADT.ADT**



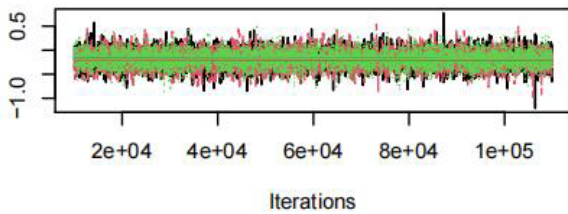
**Trace of d.DOC\_ADT.DARO\_DOC\_ADT**



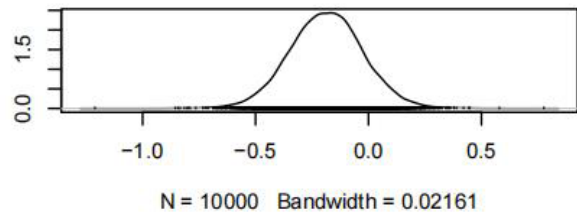
**Density of d.DOC\_ADT.DARO\_DOC\_ADT**



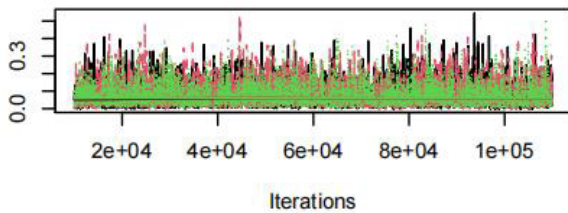
**Trace of d.DOC\_ADT.ENZA\_DOC\_ADT**



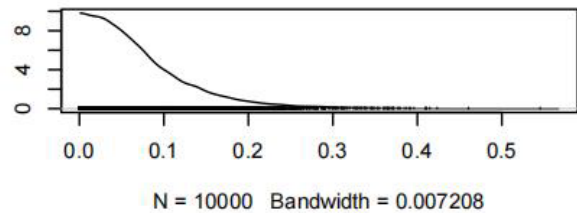
**Density of d.DOC\_ADT.ENZA\_DOC\_ADT**



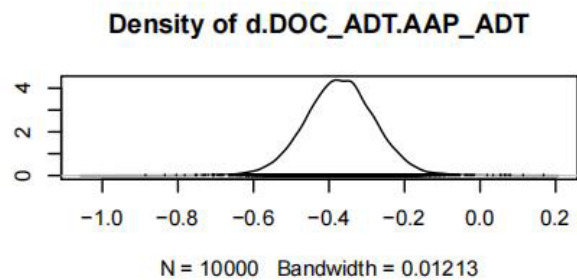
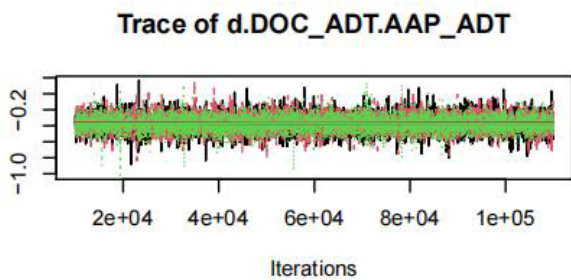
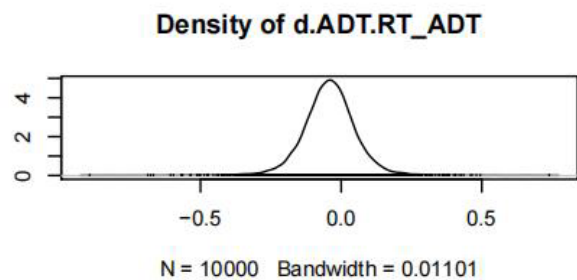
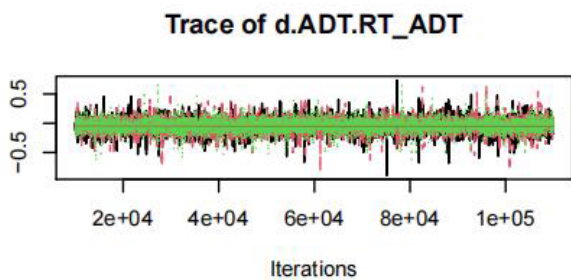
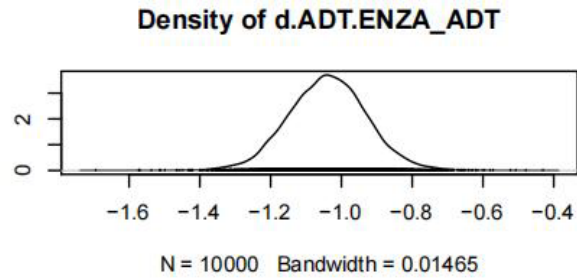
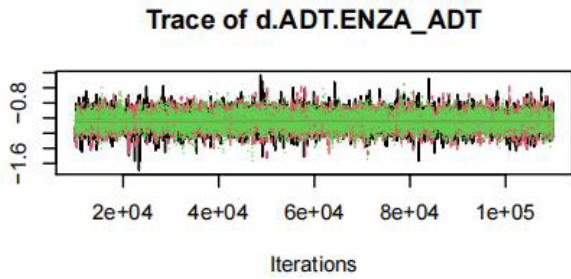
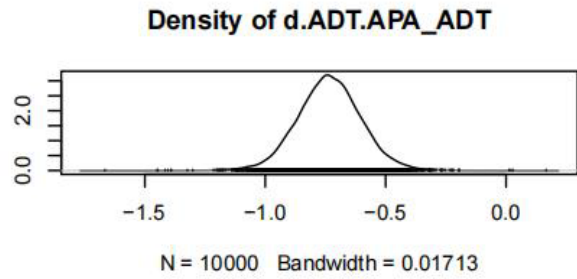
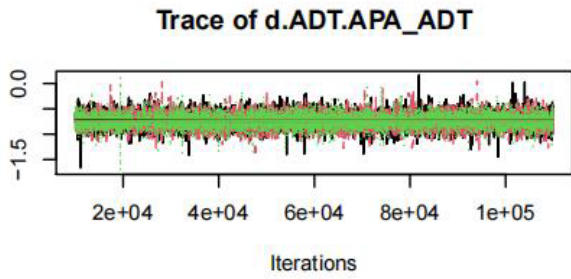
**Trace of sd.d**



**Density of sd.d**

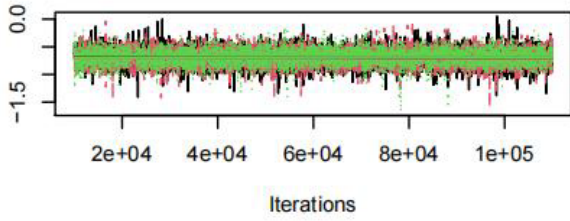


B: Trace and density plots for generalized PFS for all population

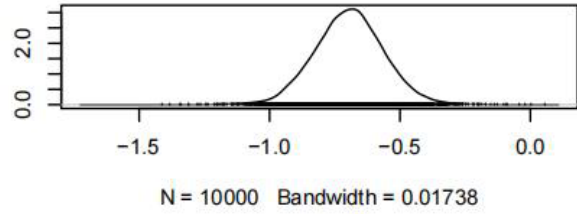




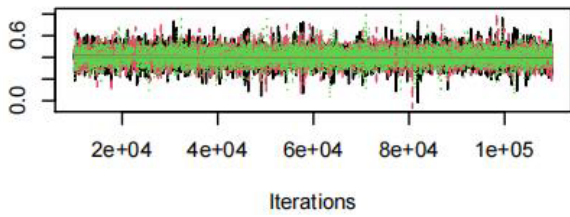
**Trace of d.DOC\_ADT.AAP\_DOC\_ADT**



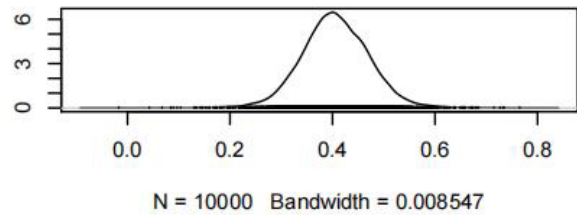
**Density of d.DOC\_ADT.AAP\_DOC\_ADT**



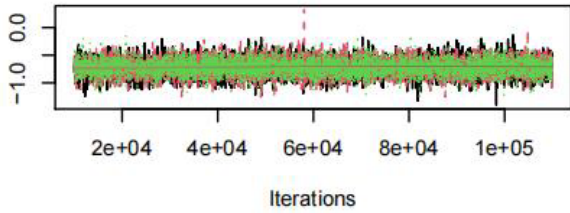
**Trace of d.DOC\_ADT.ADT**



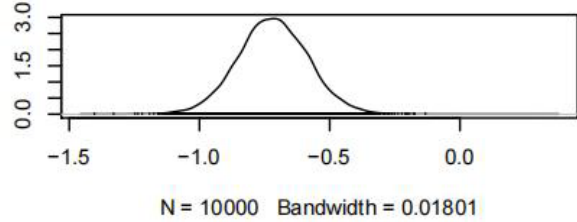
**Density of d.DOC\_ADT.ADT**



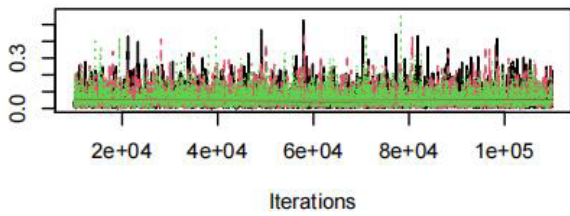
**Trace of d.DOC\_ADT.ENZA\_DOC\_ADT**



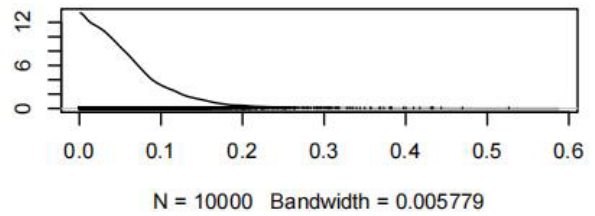
**Density of d.DOC\_ADT.ENZA\_DOC\_ADT**



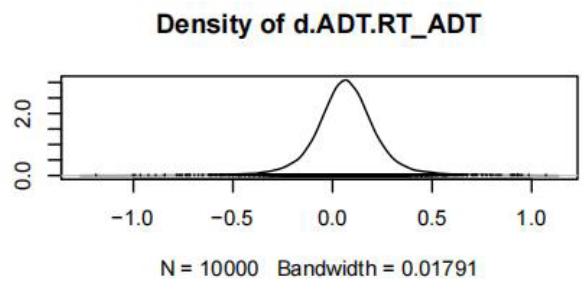
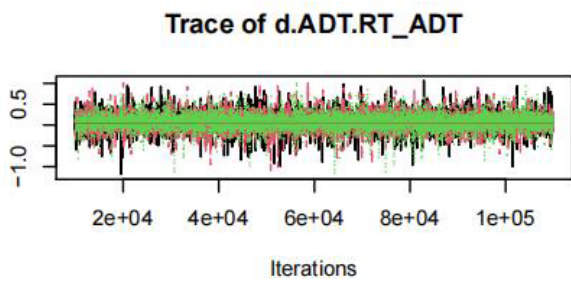
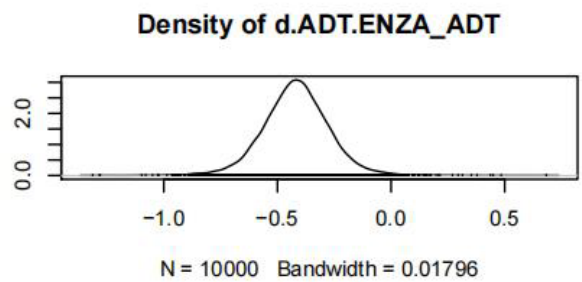
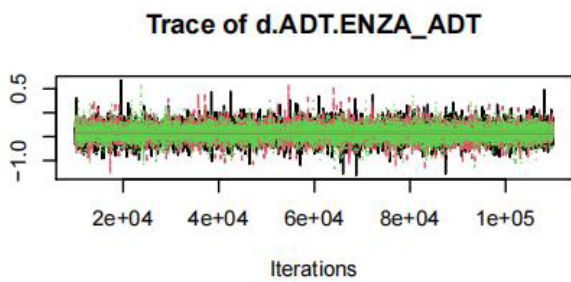
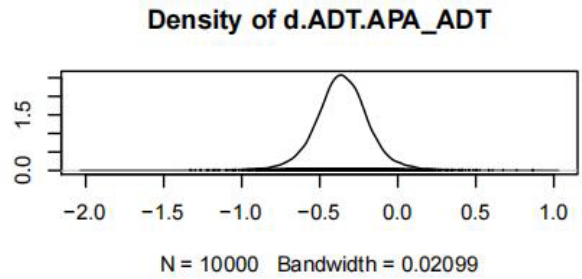
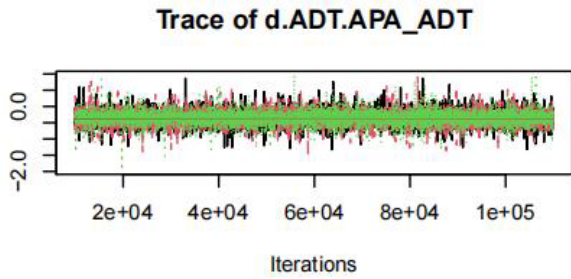
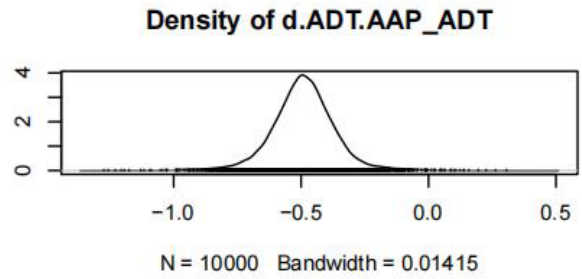
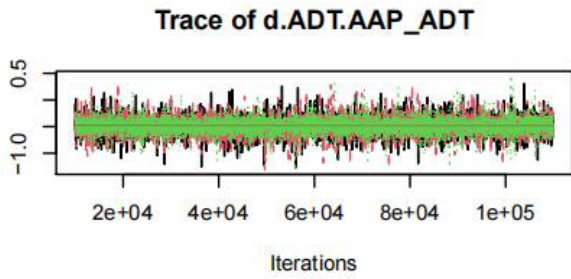
**Trace of sd.d**



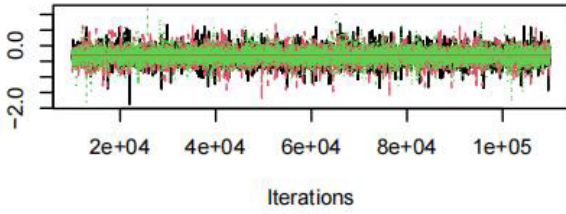
**Density of sd.d**



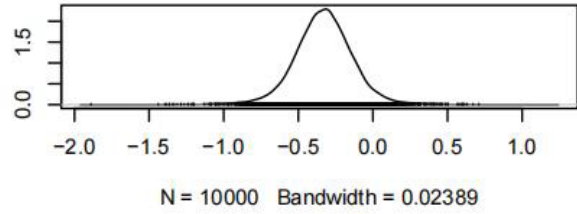
C: Trace and density plots for OS for high volume disease



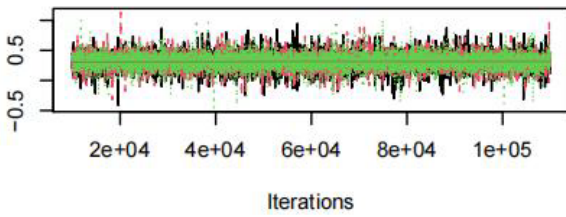
**Trace of d.DOC\_ADT.AAP\_DOC\_ADT**



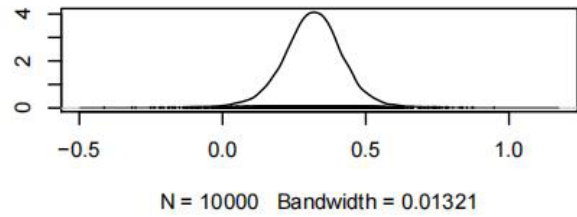
**Density of d.DOC\_ADT.AAP\_DOC\_ADT**



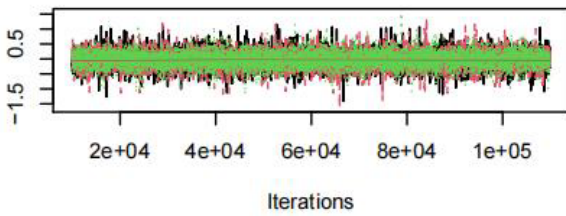
**Trace of d.DOC\_ADT.ADT**



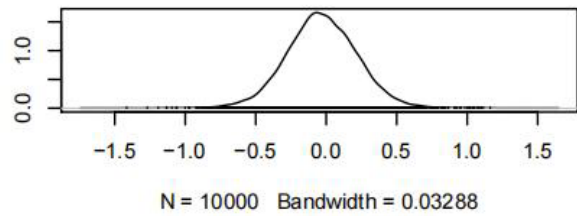
**Density of d.DOC\_ADT.ADT**



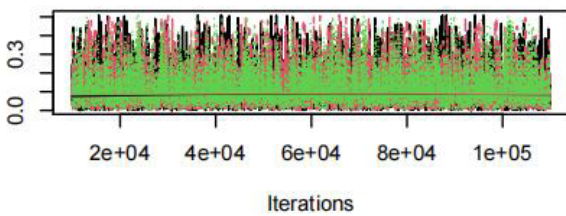
**Trace of d.DOC\_ADT.ENZA\_DOC\_ADT**



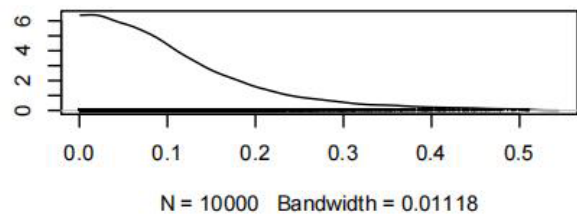
**Density of d.DOC\_ADT.ENZA\_DOC\_ADT**



**Trace of sd.d**

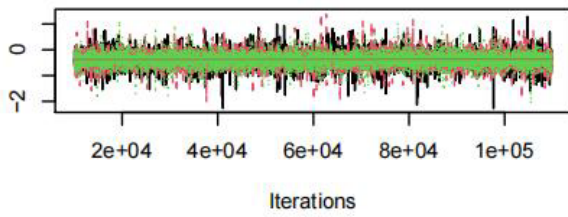


**Density of sd.d**

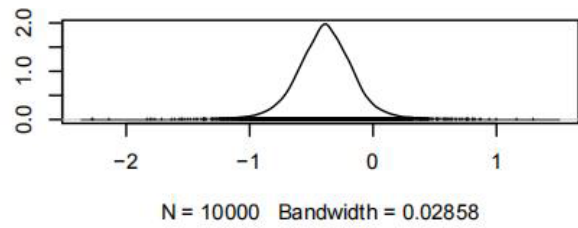


D: Trace and density plots for OS for low volume disease

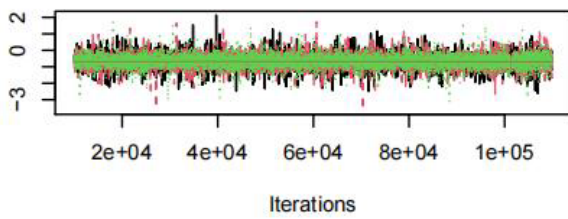
**Trace of d.ADT.AAP\_ADT**



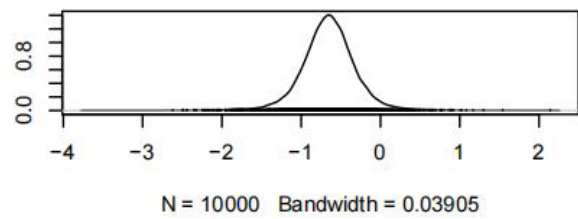
**Density of d.ADT.AAP\_ADT**



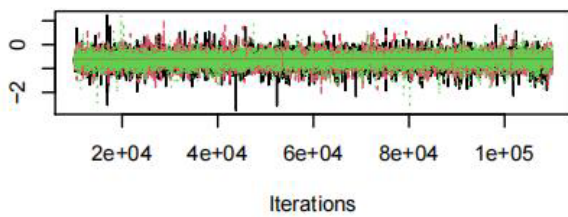
**Trace of d.ADT.APA\_ADT**



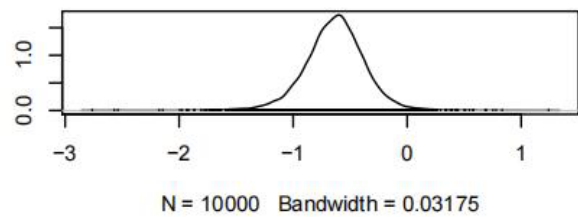
**Density of d.ADT.APA\_ADT**



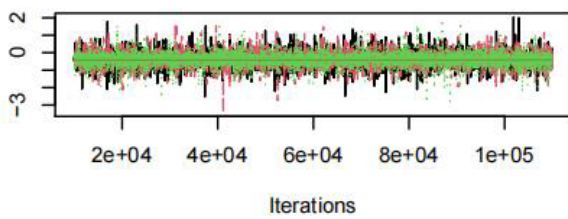
**Trace of d.ADT.ENZA\_ADT**



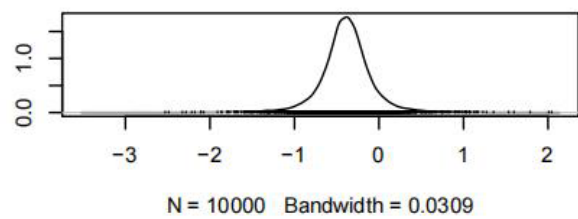
**Density of d.ADT.ENZA\_ADT**



**Trace of d.ADT.RT\_ADT**

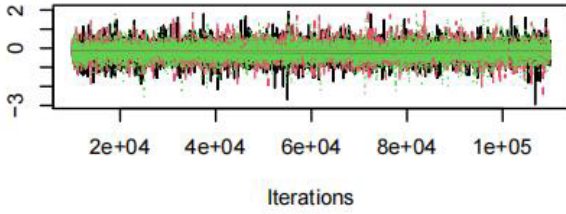


**Density of d.ADT.RT\_ADT**

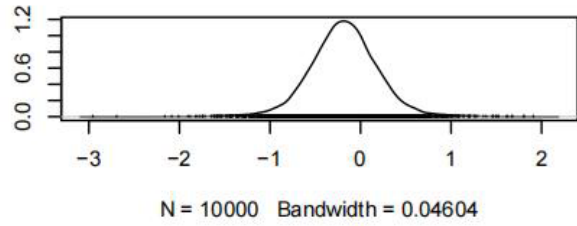




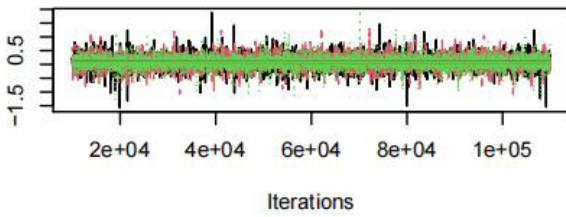
**Trace of d.DOC\_ADT.AAP\_DOC\_ADT**



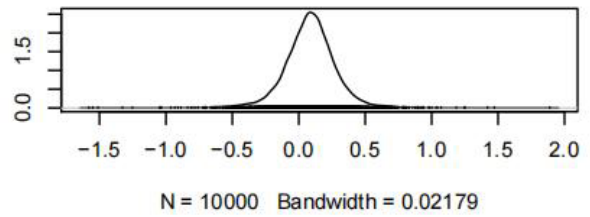
**Density of d.DOC\_ADT.AAP\_DOC\_ADT**



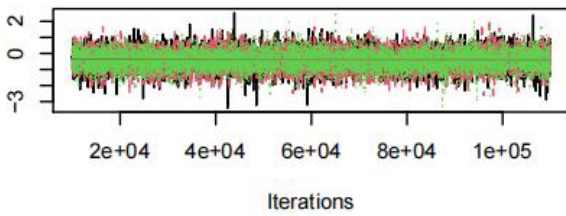
**Trace of d.DOC\_ADT.ADT**



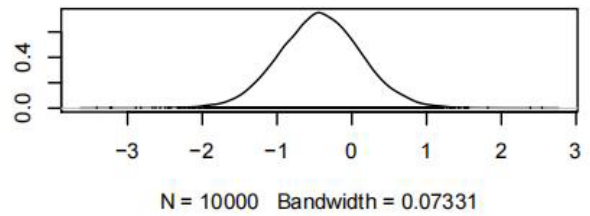
**Density of d.DOC\_ADT.ADT**



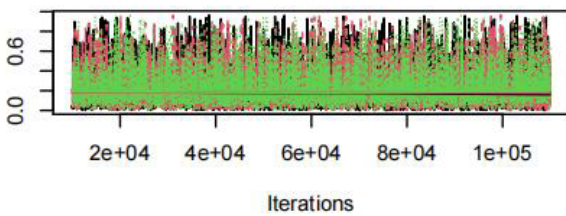
**Trace of d.DOC\_ADT.ENZA\_DOC\_ADT**



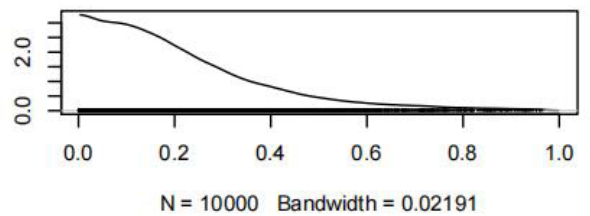
**Density of d.DOC\_ADT.ENZA\_DOC\_ADT**



**Trace of sd.d**

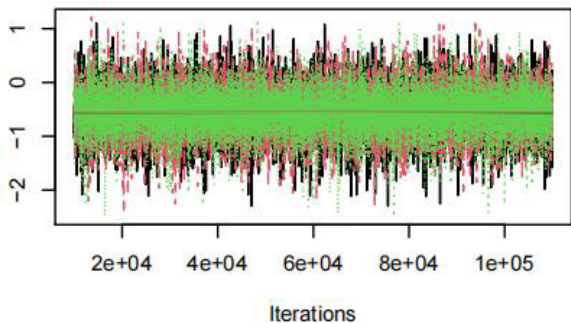


**Density of sd.d**

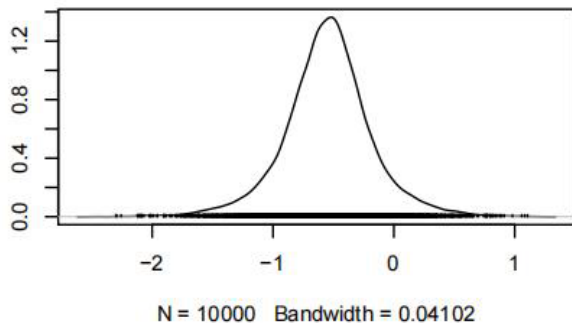


E: Trace and density plots for OS for visceral metastasis

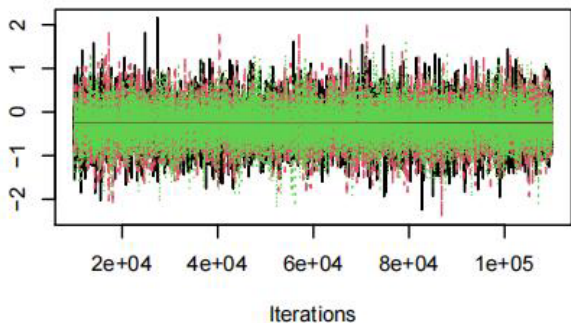
**Trace of d.ADT.AAP\_ADT**



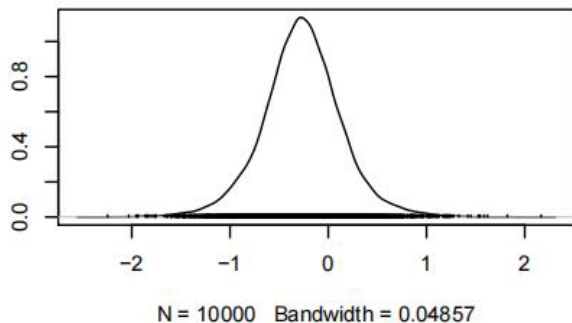
**Density of d.ADT.AAP\_ADT**



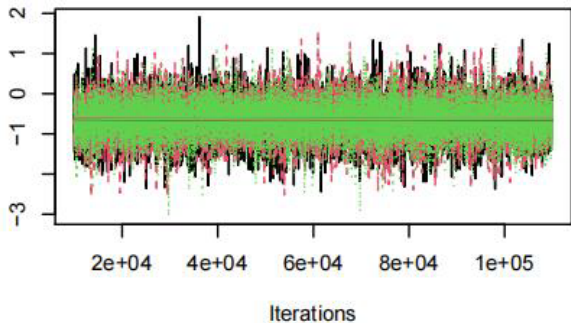
**Trace of d.ADT.APA\_ADT**



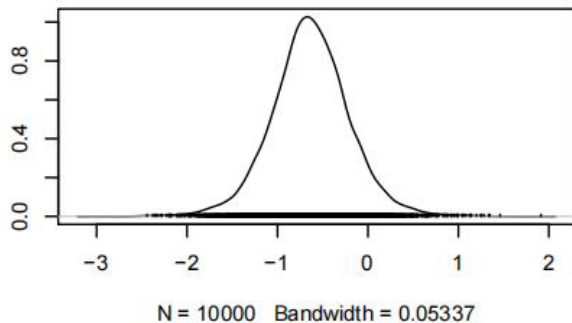
**Density of d.ADT.APA\_ADT**



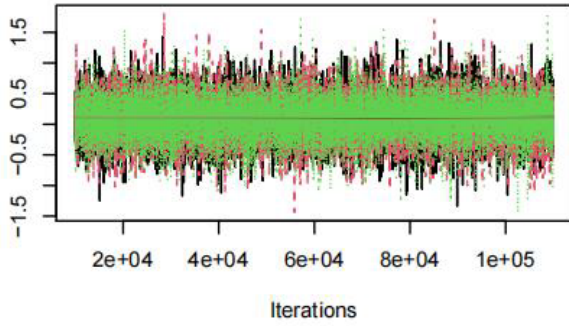
**Trace of d.ADT.DOC\_ADT**



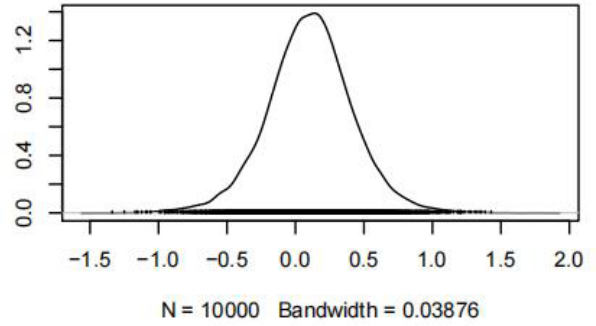
**Density of d.ADT.DOC\_ADT**



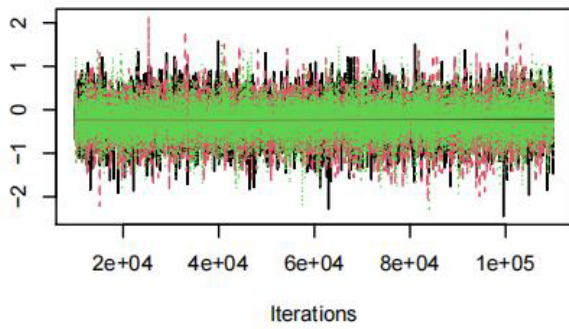
**Trace of d.ADT.ENZA\_ADT**



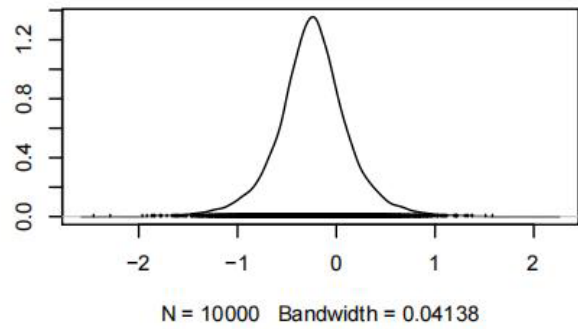
**Density of d.ADT.ENZA\_ADT**



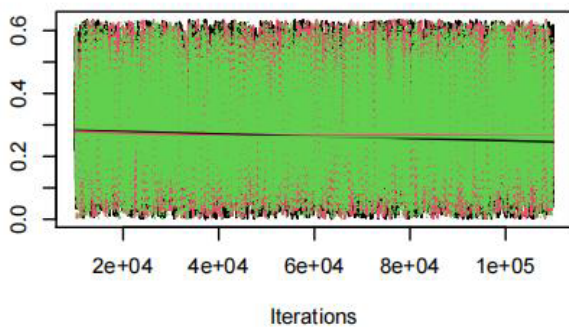
**Trace of d.DOC\_ADT.DARO\_DOC\_ADT**



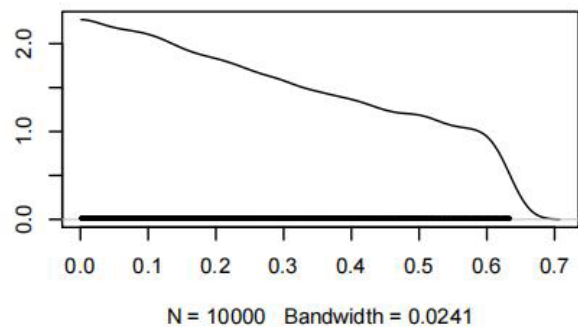
**Density of d.DOC\_ADT.DARO\_DOC\_ADT**



**Trace of sd.d**

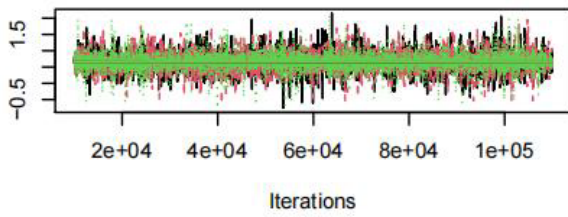


**Density of sd.d**

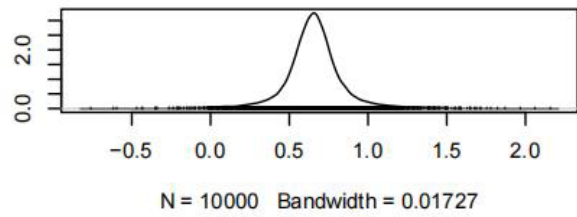


F: Trace and density plots for high grade AE

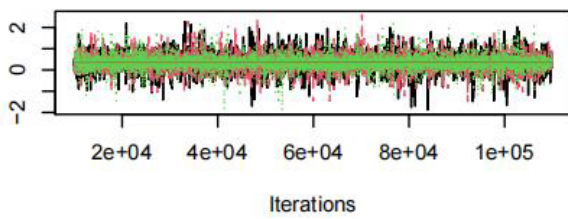
**Trace of d.ADT.AAP\_ADT**



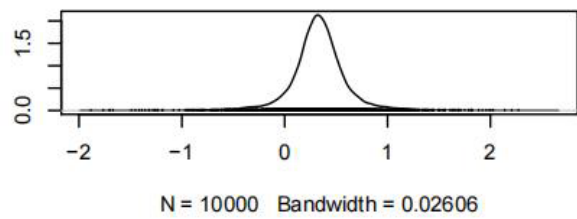
**Density of d.ADT.AAP\_ADT**



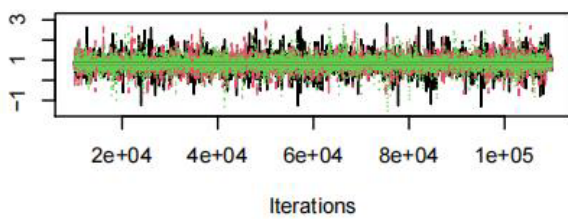
**Trace of d.ADT.APA\_ADT**



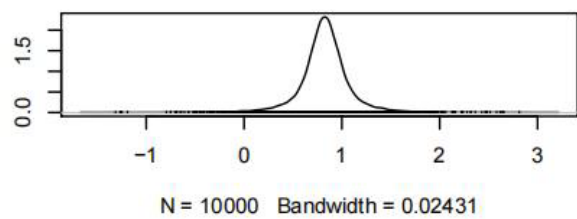
**Density of d.ADT.APA\_ADT**



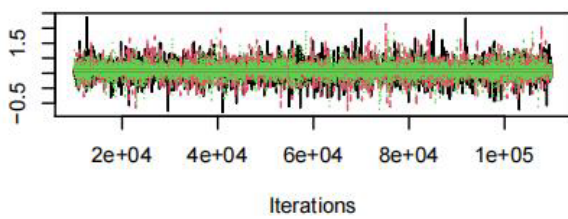
**Trace of d.ADT.DOC\_ADT**



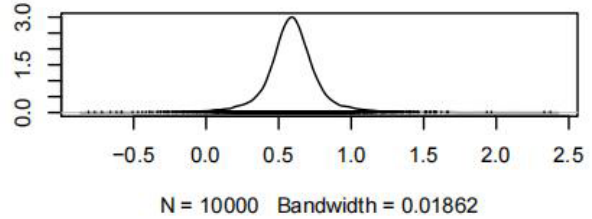
**Density of d.ADT.DOC\_ADT**



**Trace of d.ADT.ENZA\_ADT**

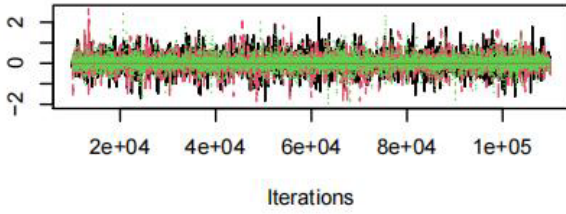


**Density of d.ADT.ENZA\_ADT**

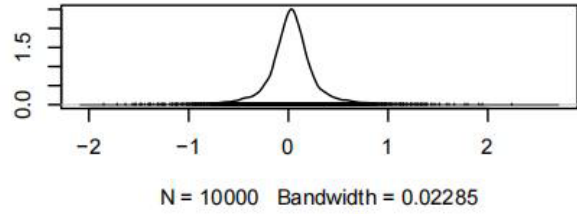




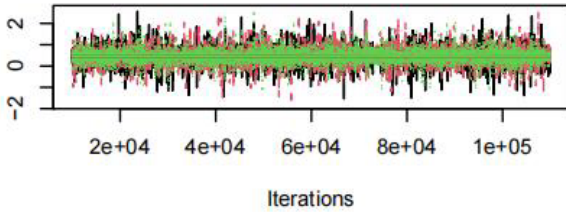
**Trace of d.ADT.RT\_ADT**



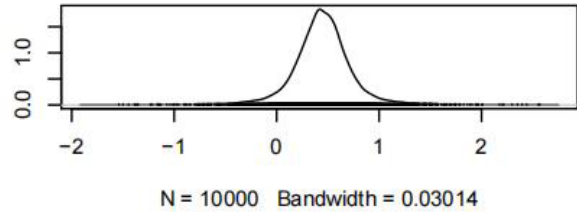
**Density of d.ADT.RT\_ADT**



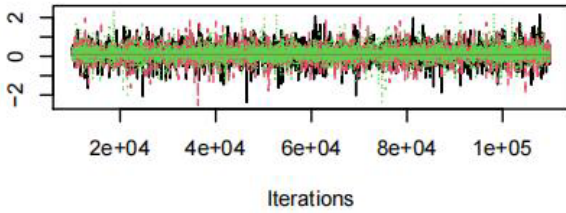
**Trace of d.DOC\_ADT.AAP\_DOC\_ADT**



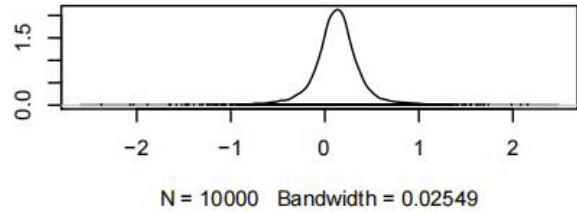
**Density of d.DOC\_ADT.AAP\_DOC\_ADT**



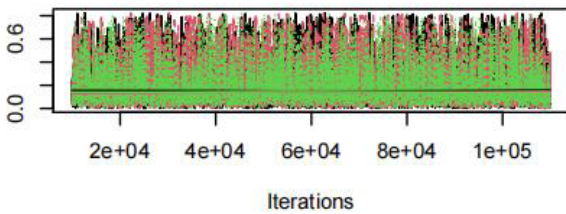
**Trace of d.DOC\_ADT.DARO\_DOC\_ADT**



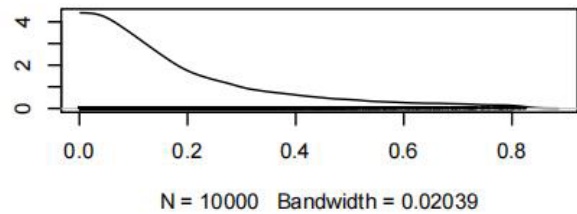
**Density of d.DOC\_ADT.DARO\_DOC\_ADT**



**Trace of sd.d**



**Density of sd.d**



**Supplementary Material 11: Summary of grade 3-5 adverse events in reported trials and corresponding odds ratio**

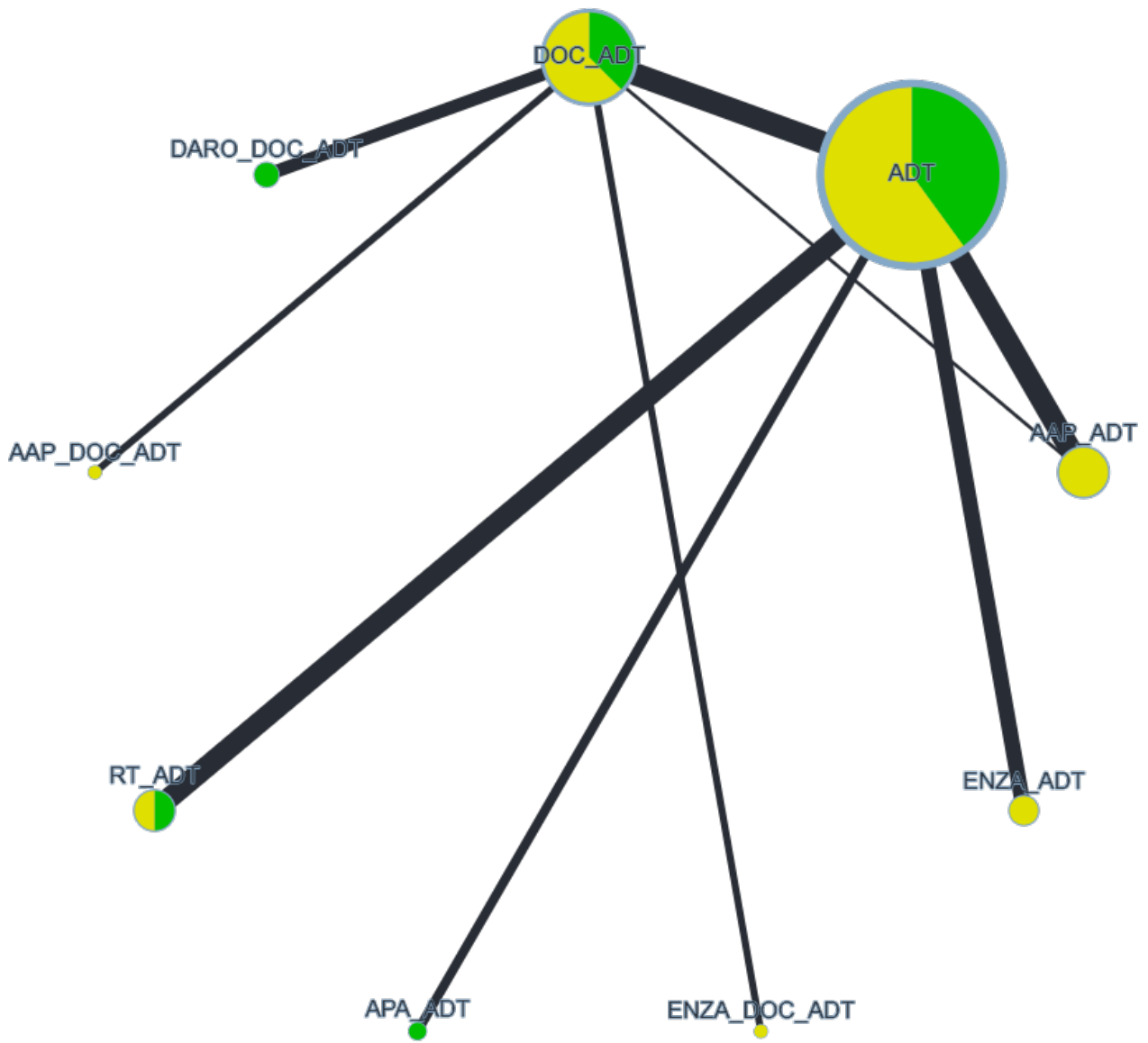
STUDY No.	3	4	5	7	9	11	12	14	15
Trial	STAMPEDE-arm C	LATITUDE	TAMPEDE-arm G	ENZAMET	ARCHES	TITAN	STAMPEDE-RT	PEACE-1	ARASENS
G3-5 AE (Exp.)	288/550 (52%)	411/597 (69%)	443/948 (47%)	321/563 (57.0%)	254/572 (44.4%)	279/524 (53.2%)	380/985 (39%)	217/347 (62.5%)	458/652 (70.2%)
G3-5 AE (Control)	399/1228 (32%)	309/602 (51%)	315/960 (33%)	241/558 (43.2%)	172/574 (30.0%)	237/527 (45.0%)	398/1050 (38%)	181/350 (51.7%)	439/650 (67.5%)
OR	2.28 (1.86-2.81)	2.10 (1.66-2.65)	1.80 (1.49-2.16)	1.74 (1.38-2.21)	1.87 (1.46-2.38)	1.39 (1.09-1.78)	1.03 (0.86-1.23)	1.56 (1.15-2.11)	1.13 (0.90-1.44)
		1.86(1.61-2.14)		1.79(1.51-2.11)					

AE: adverse event; Exp.: experimental group; OR: odds ratio.

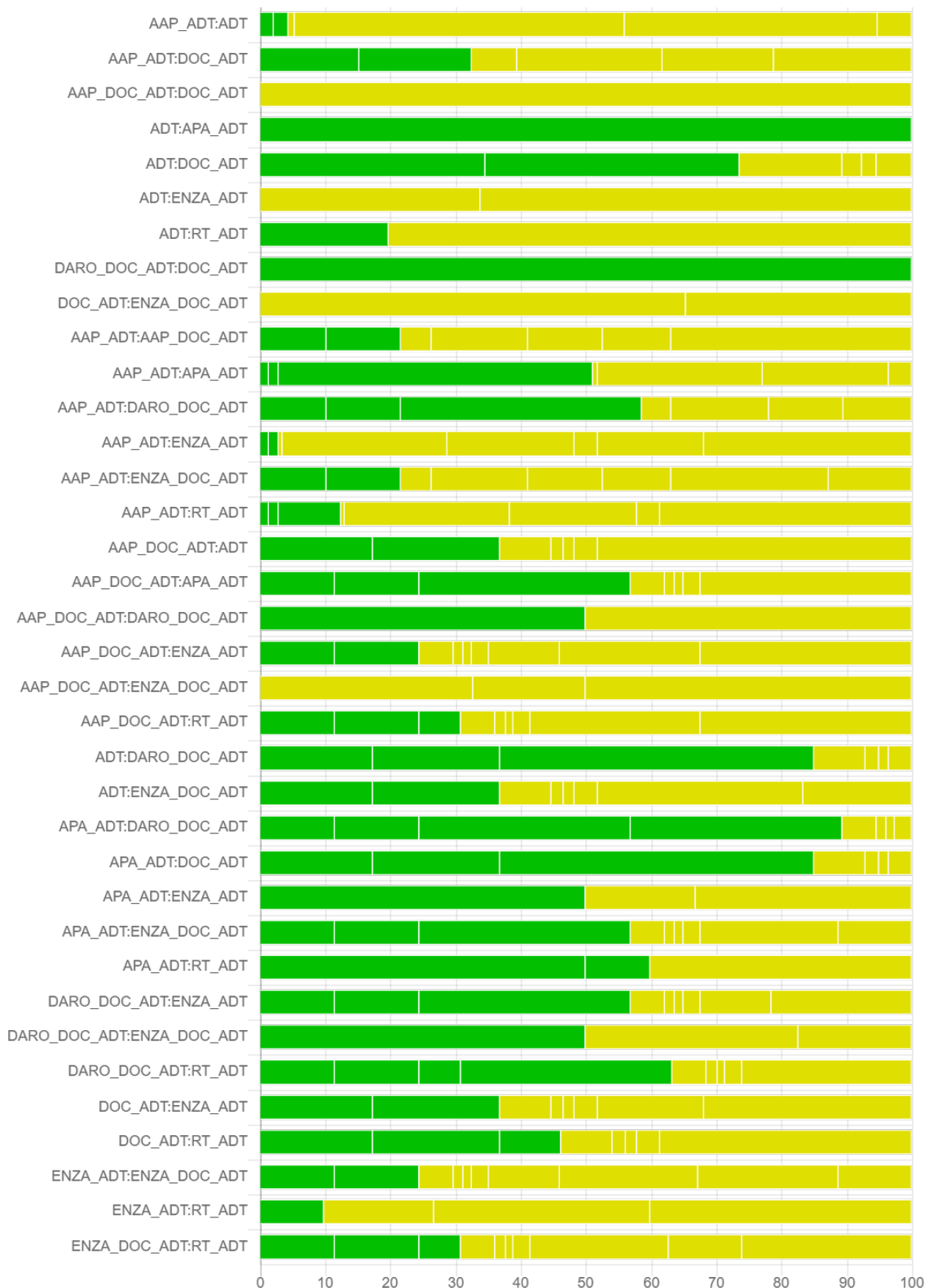
Supplementary Material 12: Assessment of the certainty of evidence using the confidence in network meta-analysis (CINeMA)

1. Efficacy-OS for all population

1.1 network plot drawn by CINeMA



1.2 Risk of Bias Chart showing the contribution of low, moderate or high RoB comparisons to each network estimate



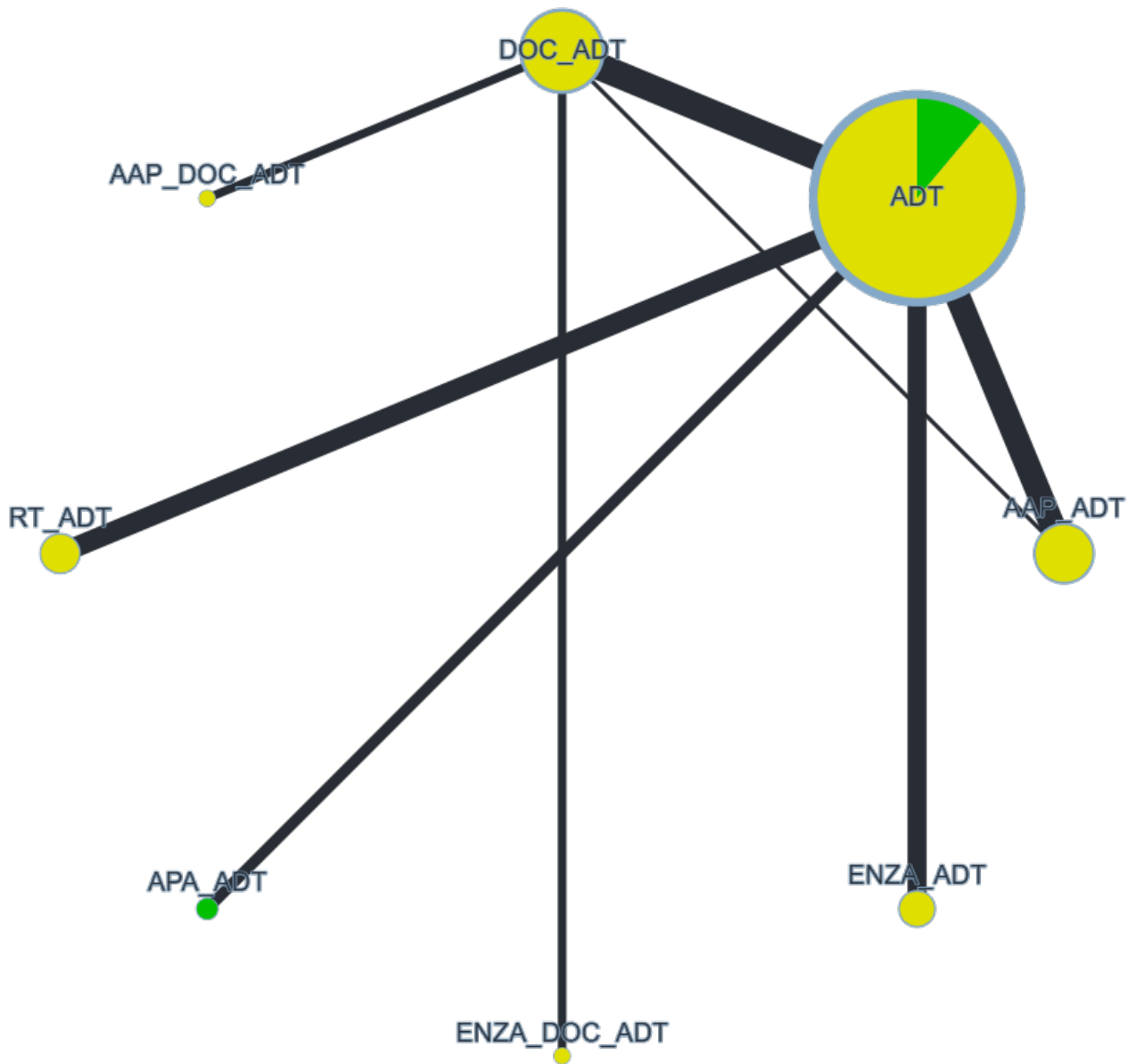
### 1.3 Evaluation of the Certainty of evidence Using CINEMA Framework, mixed evidence

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
AAP_ADT:ADT	2	Some concerns	Low risk	No concerns	No concerns	No concerns	Major concerns	Very low
AAP_ADT:DOC_ADT	1	Some concerns	Low risk	No concerns	Some concerns	No concerns	Major concerns	Very low
AAP_DOC_ADT:DOC_ADT	1	Some concerns	Low risk	No concerns	No concerns	Some concerns	Some concerns	Very low
ADT:APA_ADT	1	No concerns	Low risk	No concerns	No concerns	No concerns	Some concerns	Moderate
ADT:DOC_ADT	3	No concerns	Low risk	No concerns	No concerns	No concerns	Some concerns	Moderate
ADT:ENZA_ADT	2	Some concerns	Low risk	No concerns	No concerns	No concerns	Some concerns	Low
ADT:RT_ADT	2	Some concerns	Low risk	No concerns	Some concerns	No concerns	Some concerns	Low
DARO_DOC_ADT:DOC_ADT	1	No concerns	Low risk	No concerns	No concerns	No concerns	Some concerns	Moderate
DOC_ADT:ENZA_DOC_ADT	2	Some concerns	Low risk	No concerns	Some concerns	Some concerns	Some concerns	Very low
AAP_ADT:AAP_DOC_ADT	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	Some concerns	Very low
AAP_ADT:APA_ADT	0	No concerns	Low risk	No concerns	Some concerns	Some concerns	Some concerns	Very low
AAP_ADT:DARO_DOC_ADT	0	No concerns	Low risk	No concerns	No concerns	Some concerns	Some concerns	Low
AAP_ADT:ENZA_ADT	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	Some concerns	Very low
AAP_ADT:ENZA_DOC_ADT	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	Some concerns	Very low
AAP_ADT:RT_ADT	0	Some concerns	Low risk	No concerns	No concerns	No concerns	Some concerns	Low
AAP_DOC_ADT:ADT	0	Some concerns	Low risk	No concerns	No concerns	No concerns	Some concerns	Low
AAP_DOC_ADT:APA_ADT	0	No concerns	Low risk	No concerns	Major concerns	No concerns	Some concerns	High
AAP_DOC_ADT:DARO_DOC_ADT	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	Some concerns	Very low
AAP_DOC_ADT:ENZA_ADT	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	Some concerns	Very low
AAP_DOC_ADT:ENZA_DOC_ADT	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	Some concerns	Very low
AAP_DOC_ADT:RT_ADT	0	Some concerns	Low risk	No concerns	No concerns	No concerns	Some concerns	Low
ADT:DARO_DOC_ADT	0	No concerns	Low risk	No concerns	No concerns	No concerns	Some concerns	Moderate
ADT:ENZA_DOC_ADT	0	Some concerns	Low risk	No concerns	No concerns	No concerns	Some concerns	Low
APA_ADT:DARO_DOC_ADT	0	No concerns	Low risk	No concerns	Some concerns	Some concerns	Some concerns	Very low
APA_ADT:DOC_ADT	0	No concerns	Low risk	No concerns	Some concerns	No concerns	Some concerns	Low
APA_ADT:ENZA_ADT	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	Some concerns	Very low

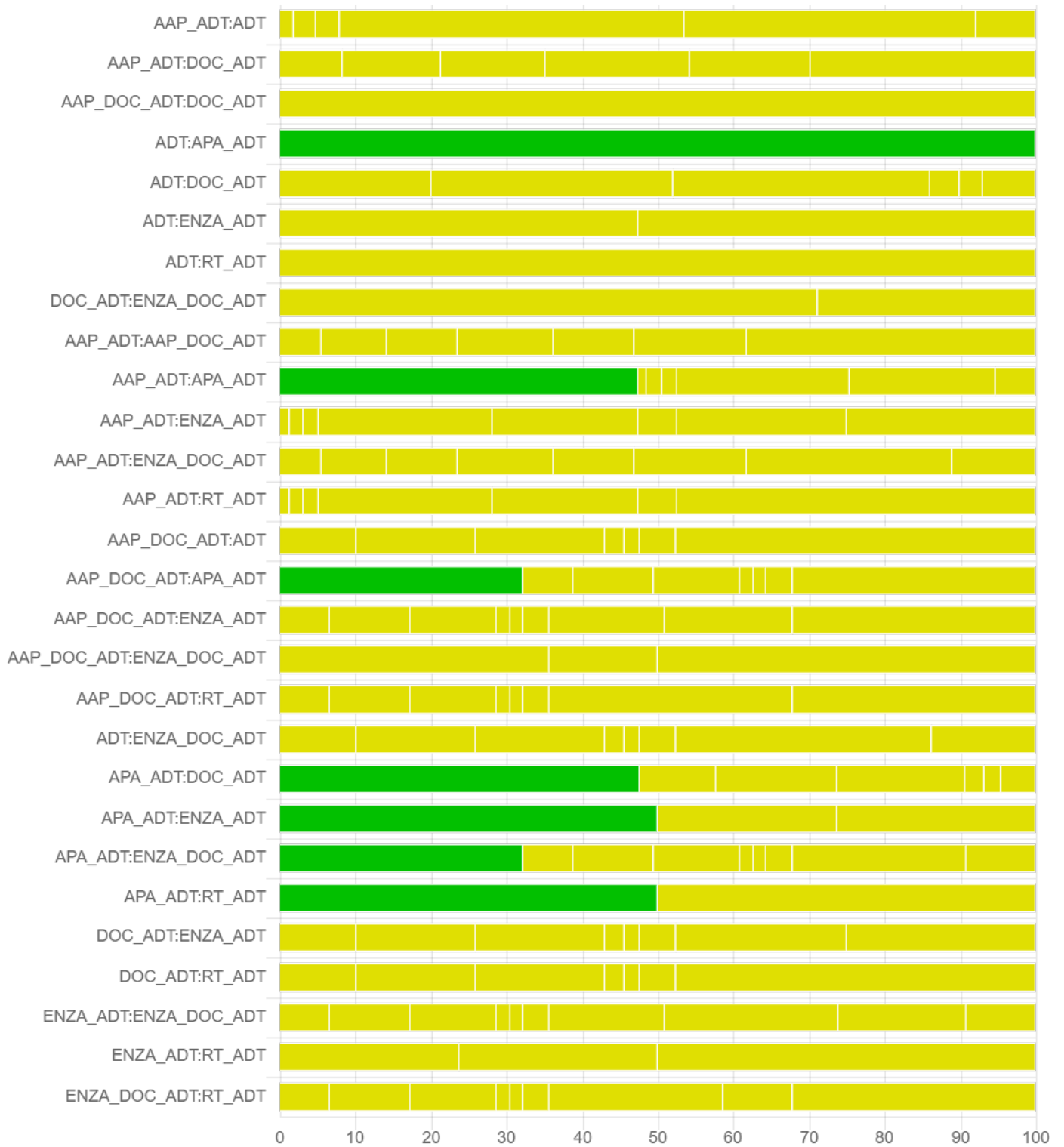
APA_ADT:ENZA_DOC_ADT	0	No concerns	Low risk	No concerns	Major concerns	No concerns	Some concerns	Very low
APA_ADT:RT_ADT	0	No concerns	Low risk	No concerns	No concerns	No concerns	Some concerns	Moderate
DARO_DOC_ADT:ENZA_ADT	0	No concerns	Low risk	No concerns	Some concerns	No concerns	Some concerns	Low
DARO_DOC_ADT:ENZA_DOC_ADT	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	Some concerns	Very low
DARO_DOC_ADT:RT_ADT	0	No concerns	Low risk	No concerns	No concerns	No concerns	Some concerns	Moderate
DOC_ADT:ENZA_ADT	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	Some concerns	Very low
DOC_ADT:RT_ADT	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	Some concerns	Very low
ENZA_ADT:ENZA_DOC_ADT	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	Some concerns	Very low
ENZA_ADT:RT_ADT	0	Some concerns	Low risk	No concerns	No concerns	No concerns	Some concerns	Low
ENZA_DOC_ADT:RT_ADT	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	Some concerns	Very low

2. Efficacy- generalized PFS for all population

2.1 network plot drawn by CINeMA



2.2 Risk of Bias Chart showing the contribution of low, moderate or high RoB comparisons to each network estimate



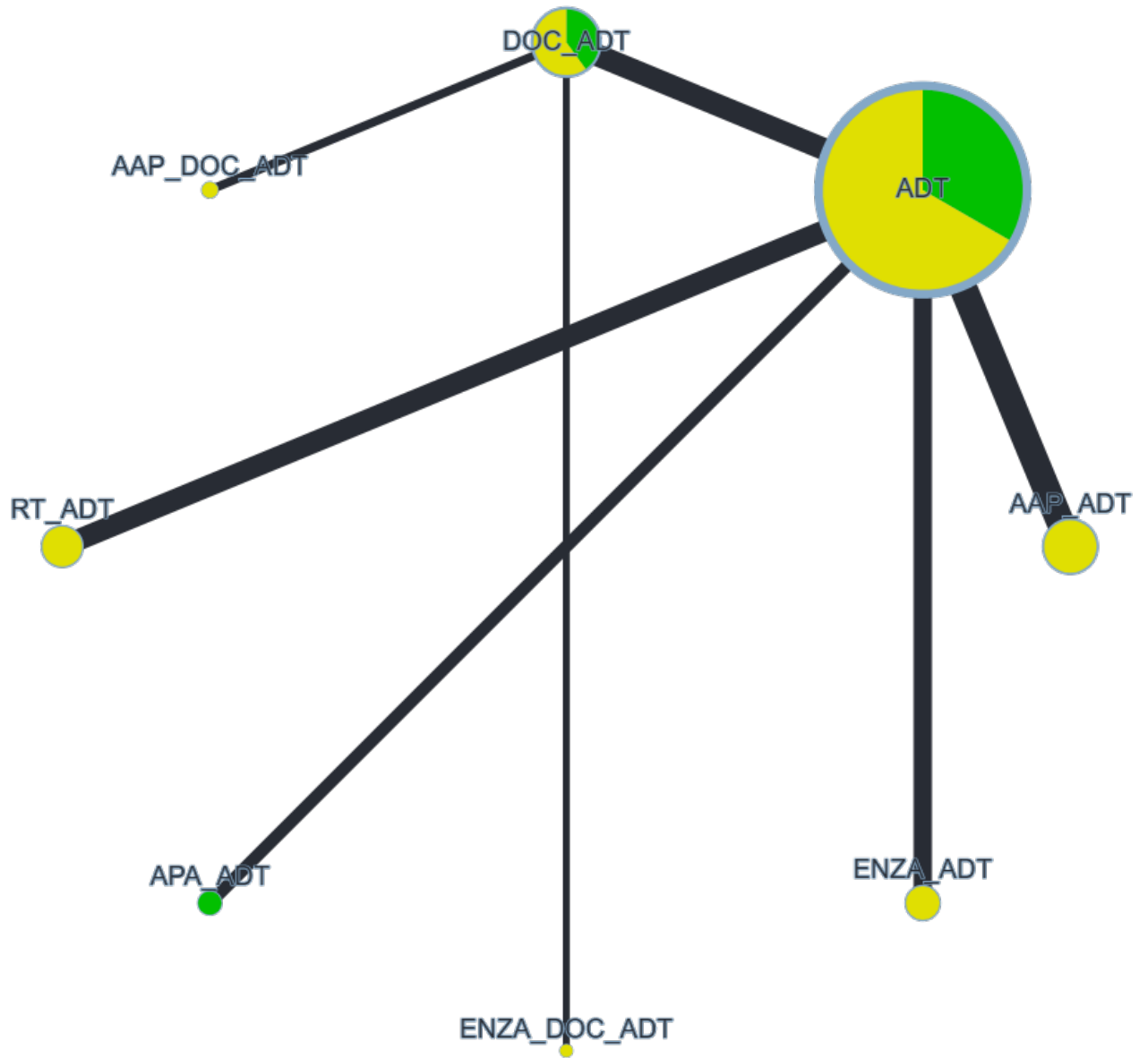


## 2.3 Evaluation of the Certainty of evidence Using CINEMA Framework, mixed evidence

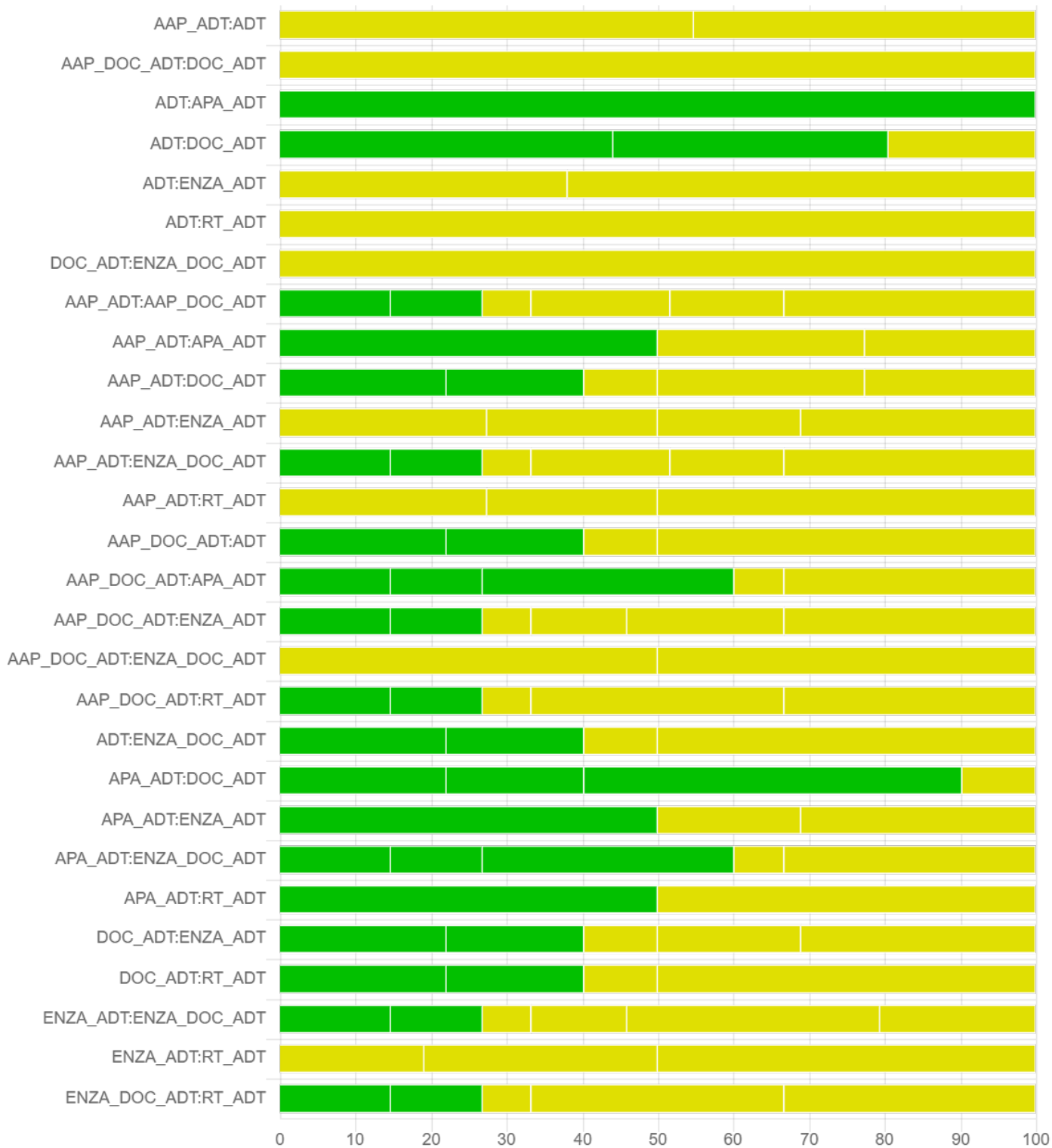
Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
AAP_ADT:ADT	2	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate
AAP_ADT:DOC_ADT	1	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Low
AAP_DOC_ADT:DOC_ADT	1	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate
ADT:APA_ADT	1	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
ADT:DOC_ADT	3	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate
ADT:ENZA_ADT	2	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate
ADT:RT_ADT	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
DOC_ADT:ENZA_DOC_ADT	2	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate
AAP_ADT:AAP_DOC_ADT	0	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Low
AAP_ADT:APA_ADT	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
AAP_ADT:ENZA_ADT	0	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Low
AAP_ADT:ENZA_DOC_ADT	0	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Low
AAP_ADT:RT_ADT	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate
AAP_DOC_ADT:ADT	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate
AAP_DOC_ADT:APA_ADT	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Very low
AAP_DOC_ADT:ENZA_ADT	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
AAP_DOC_ADT:ENZA_DOC_ADT	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
AAP_DOC_ADT:RT_ADT	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate
ADT:ENZA_DOC_ADT	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate
APA_ADT:DOC_ADT	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Very low
APA_ADT:ENZA_ADT	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Very low
APA_ADT:ENZA_DOC_ADT	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Very low
APA_ADT:RT_ADT	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate
DOC_ADT:ENZA_ADT	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate
DOC_ADT:RT_ADT	0	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Low
ENZA_ADT:ENZA_DOC_ADT	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
ENZA_ADT:RT_ADT	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate
ENZA_DOC_ADT:RT_ADT	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate

3. Efficacy-OS for HVD

3.1 network plot drawn by CINeMA



3.2 Risk of Bias Chart showing the contribution of low, moderate or high RoB comparisons to each network estimate

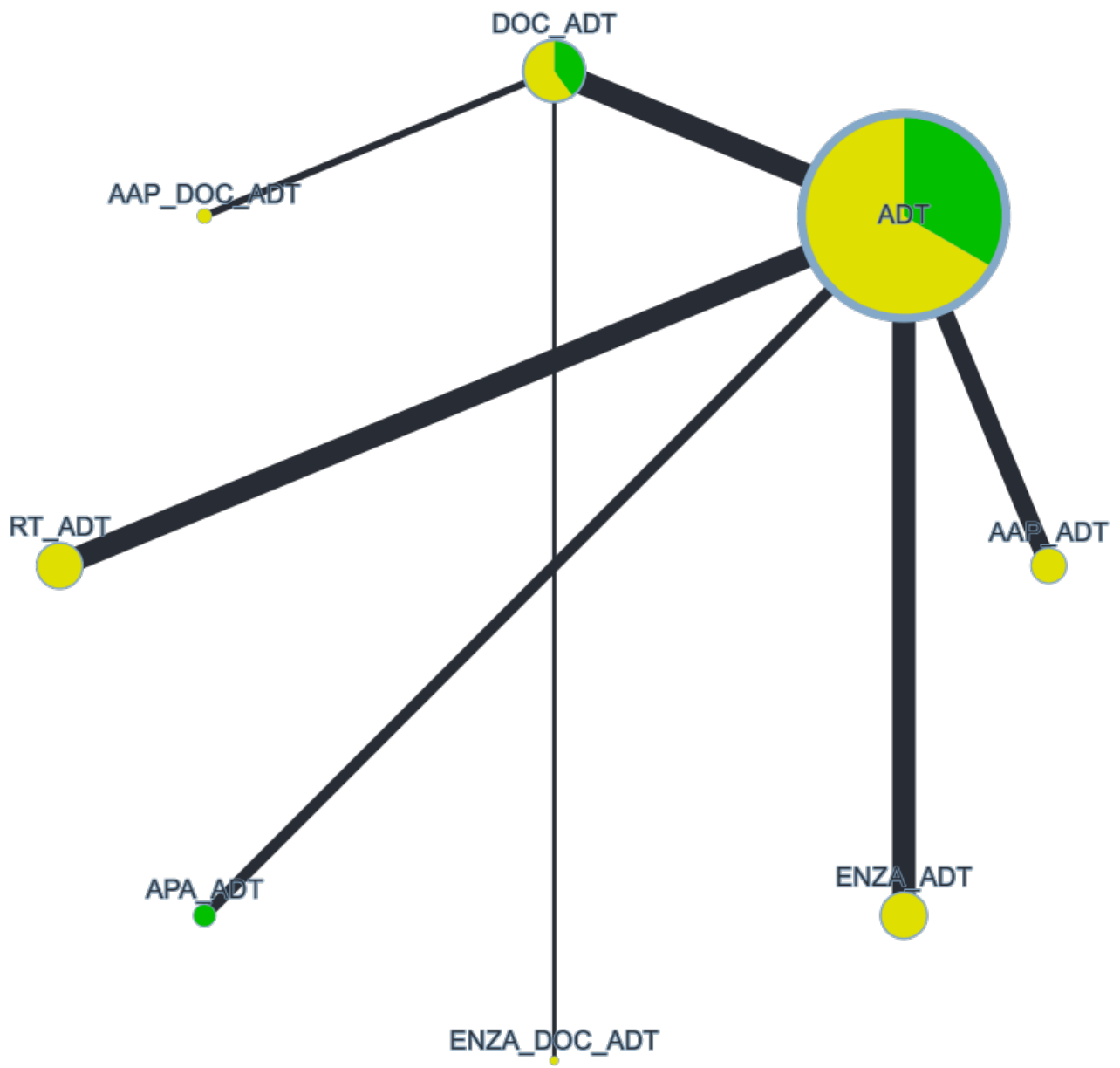


### 3.3 Evaluation of the Certainty of evidence Using CINEMA Framework, mixed evidence

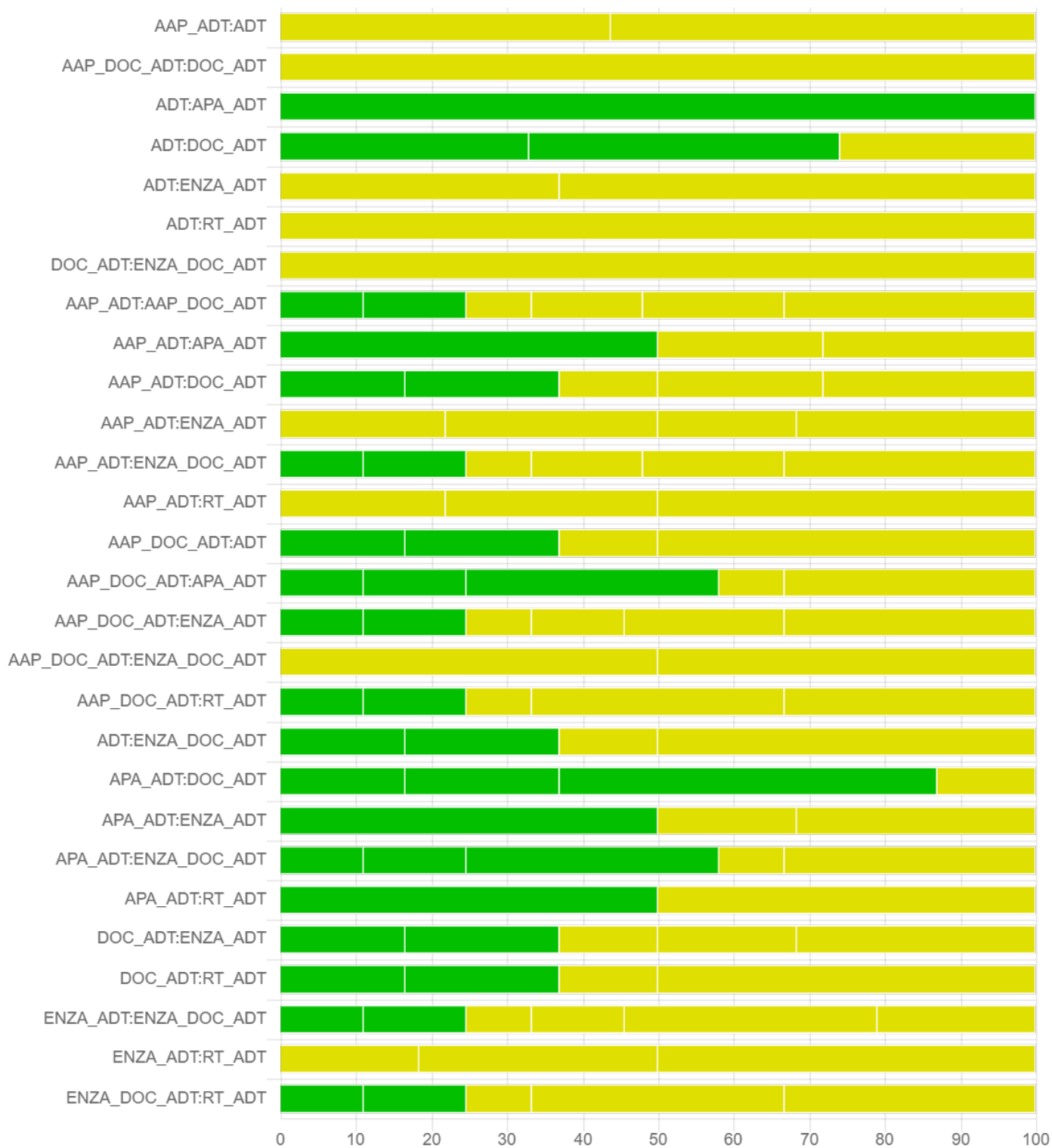
Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
AAP_ADT:ADT	2	Some concerns	Low risk	No concerns	No concerns	No concerns	Major concerns	Very low
AAP_DOC_ADT:DOC_ADT	1	Some concerns	Low risk	No concerns	No concerns	Some concerns	Major concerns	Very low
ADT:APA_ADT	1	No concerns	Low risk	No concerns	No concerns	Some concerns	Major concerns	Very low
ADT:DOC_ADT	3	No concerns	Low risk	No concerns	No concerns	No concerns	Major concerns	Low
ADT:ENZA_ADT	2	Some concerns	Low risk	No concerns	No concerns	Some concerns	Major concerns	Very low
ADT:RT_ADT	1	Some concerns	Low risk	No concerns	Some concerns	Some concerns	Major concerns	Very low
DOC_ADT:ENZA_DOC_ADT	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low
AAP_ADT:AAP_DOC_ADT	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	Major concerns	Very low
AAP_ADT:APA_ADT	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low
AAP_ADT:DOC_ADT	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low
AAP_ADT:ENZA_ADT	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	Major concerns	Very low
AAP_ADT:ENZA_DOC_ADT	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low
AAP_ADT:RT_ADT	0	Some concerns	Low risk	No concerns	No concerns	No concerns	Major concerns	Very low
AAP_DOC_ADT:ADT	0	Some concerns	Low risk	No concerns	No concerns	No concerns	Major concerns	Very low
AAP_DOC_ADT:APA_ADT	0	No concerns	Low risk	No concerns	Some concerns	Some concerns	Major concerns	Very low
AAP_DOC_ADT:ENZA_ADT	0	Some concerns	Low risk	No concerns	No concerns	Major concerns	Major concerns	Very low
AAP_DOC_ADT:ENZA_DOC_ADT	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	Major concerns	Very low
AAP_DOC_ADT:RT_ADT	0	Some concerns	Low risk	No concerns	No concerns	No concerns	Major concerns	Very low
ADT:ENZA_DOC_ADT	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	Major concerns	Very low
APA_ADT:DOC_ADT	0	No concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low
APA_ADT:ENZA_ADT	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low
APA_ADT:ENZA_DOC_ADT	0	No concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low
APA_ADT:RT_ADT	0	Some concerns	Low risk	No concerns	No concerns	Some concerns	Major concerns	Very low
DOC_ADT:ENZA_ADT	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low
DOC_ADT:RT_ADT	0	Some concerns	Low risk	No concerns	No concerns	No concerns	Major concerns	Very low
ENZA_ADT:ENZA_DOC_ADT	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low
ENZA_ADT:RT_ADT	0	Some concerns	Low risk	No concerns	No concerns	Some concerns	Major concerns	Very low
ENZA_DOC_ADT:RT_ADT	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	Major concerns	Very low

#### 4. Efficacy-OS for LVD

##### 4.1 network plot drawn by CINeMA



4.2 Risk of Bias Chart showing the contribution of low, moderate or high RoB comparisons to each network estimate

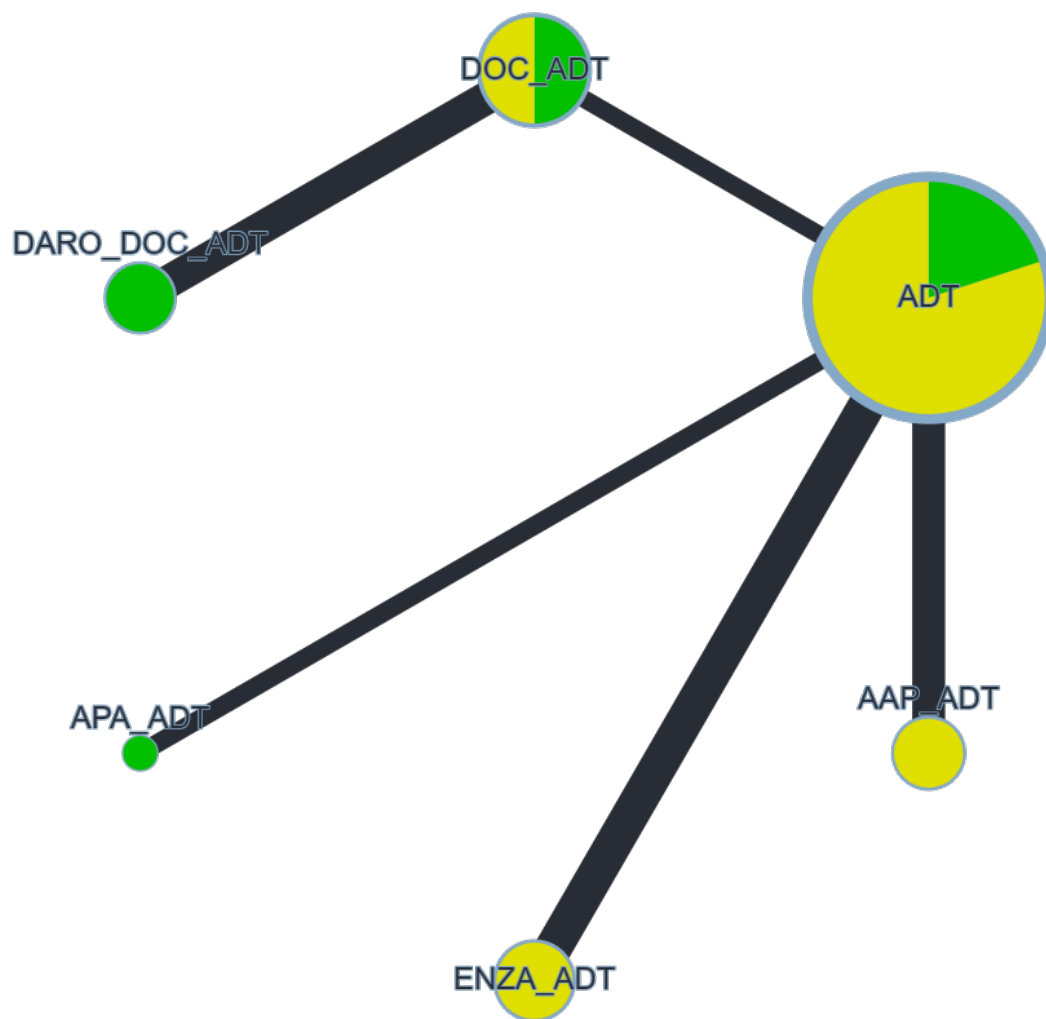


### 4.3 Evaluation of the Certainty of evidence Using CINEMA Framework, mixed evidence

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
AAP_ADT:ADT	2	Some concerns	Low risk	No concerns	No concerns	Some concerns	Major concerns	Very low
AAP_DOC_ADT:DOC_ADT	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low
ADT:APA_ADT	1	No concerns	Low risk	No concerns	Some concerns	Some concerns	Major concerns	Very low
ADT:DOC_ADT	3	No concerns	Low risk	No concerns	Some concerns	Some concerns	Major concerns	Very low
ADT:ENZA_ADT	2	Some concerns	Low risk	No concerns	No concerns	No concerns	Major concerns	Very low
ADT:RT_ADT	1	Some concerns	Low risk	No concerns	No concerns	Some concerns	Major concerns	Very low
DOC_ADT:ENZA_DOC_ADT	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low
AAP_ADT:AAP_DOC_ADT	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low
AAP_ADT:APA_ADT	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low
AAP_ADT:DOC_ADT	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	Major concerns	Very low
AAP_ADT:ENZA_ADT	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low
AAP_ADT:ENZA_DOC_ADT	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low
AAP_ADT:RT_ADT	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low
AAP_DOC_ADT:ADT	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low
AAP_DOC_ADT:APA_ADT	0	No concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low
AAP_DOC_ADT:ENZA_ADT	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low
AAP_DOC_ADT:ENZA_DOC_ADT	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low
AAP_DOC_ADT:RT_ADT	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low
ADT:ENZA_DOC_ADT	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low
APA_ADT:DOC_ADT	0	No concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low
APA_ADT:ENZA_ADT	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low
APA_ADT:ENZA_DOC_ADT	0	No concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low
APA_ADT:RT_ADT	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low
DOC_ADT:ENZA_ADT	0	Some concerns	Low risk	No concerns	No concerns	Some concerns	Major concerns	Very low
DOC_ADT:RT_ADT	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	Major concerns	Very low
ENZA_ADT:ENZA_DOC_ADT	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low
ENZA_ADT:RT_ADT	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	Major concerns	Very low
ENZA_DOC_ADT:RT_ADT	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low

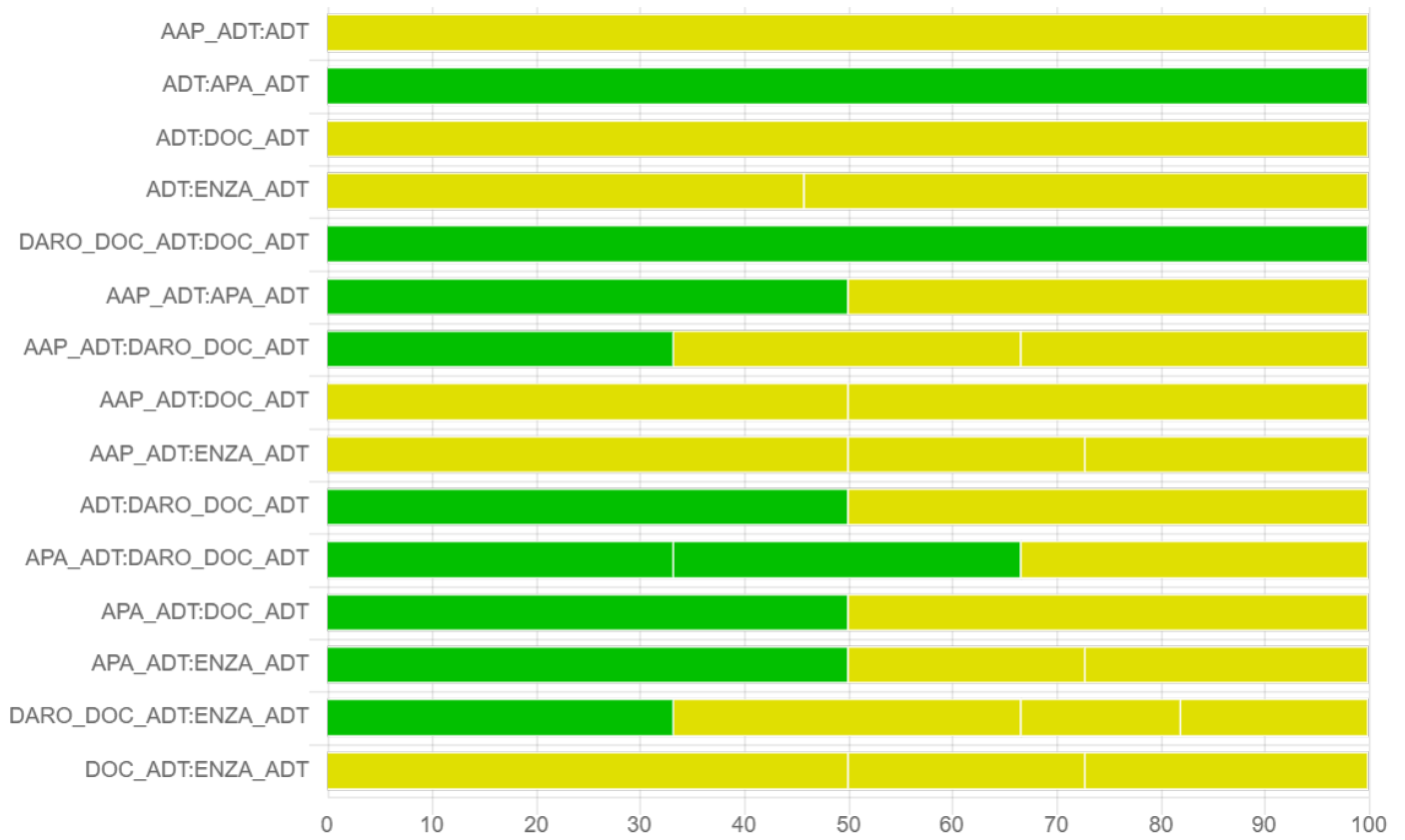
5. Efficacy-OS for visceral metastasis

5.1 network plot drawn by CINeMA





5.2 Risk of Bias Chart showing the contribution of low, moderate or high RoB comparisons to each network estimate

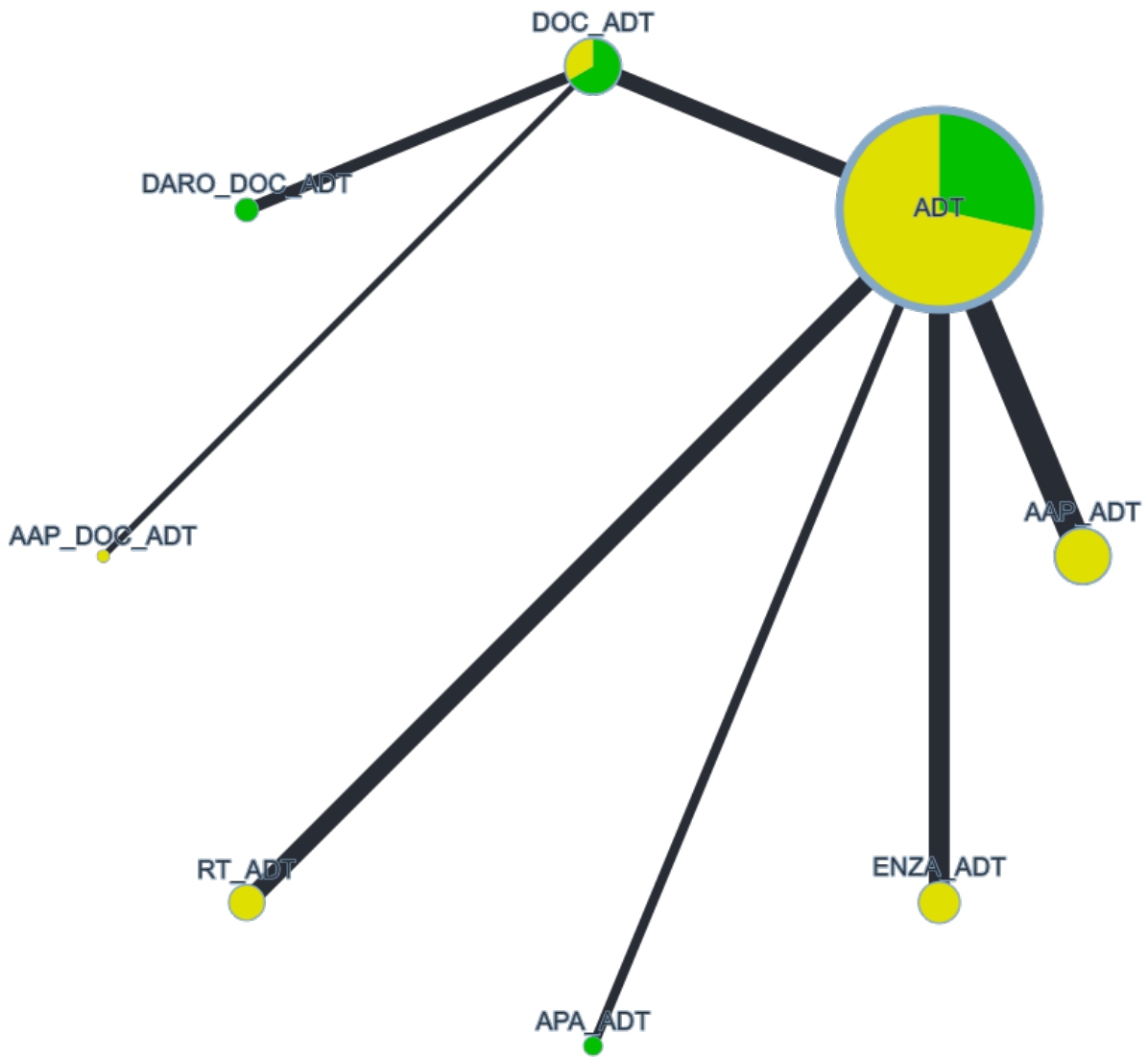


### 5.3 Evaluation of the Certainty of evidence Using CINEMA Framework, mixed evidence

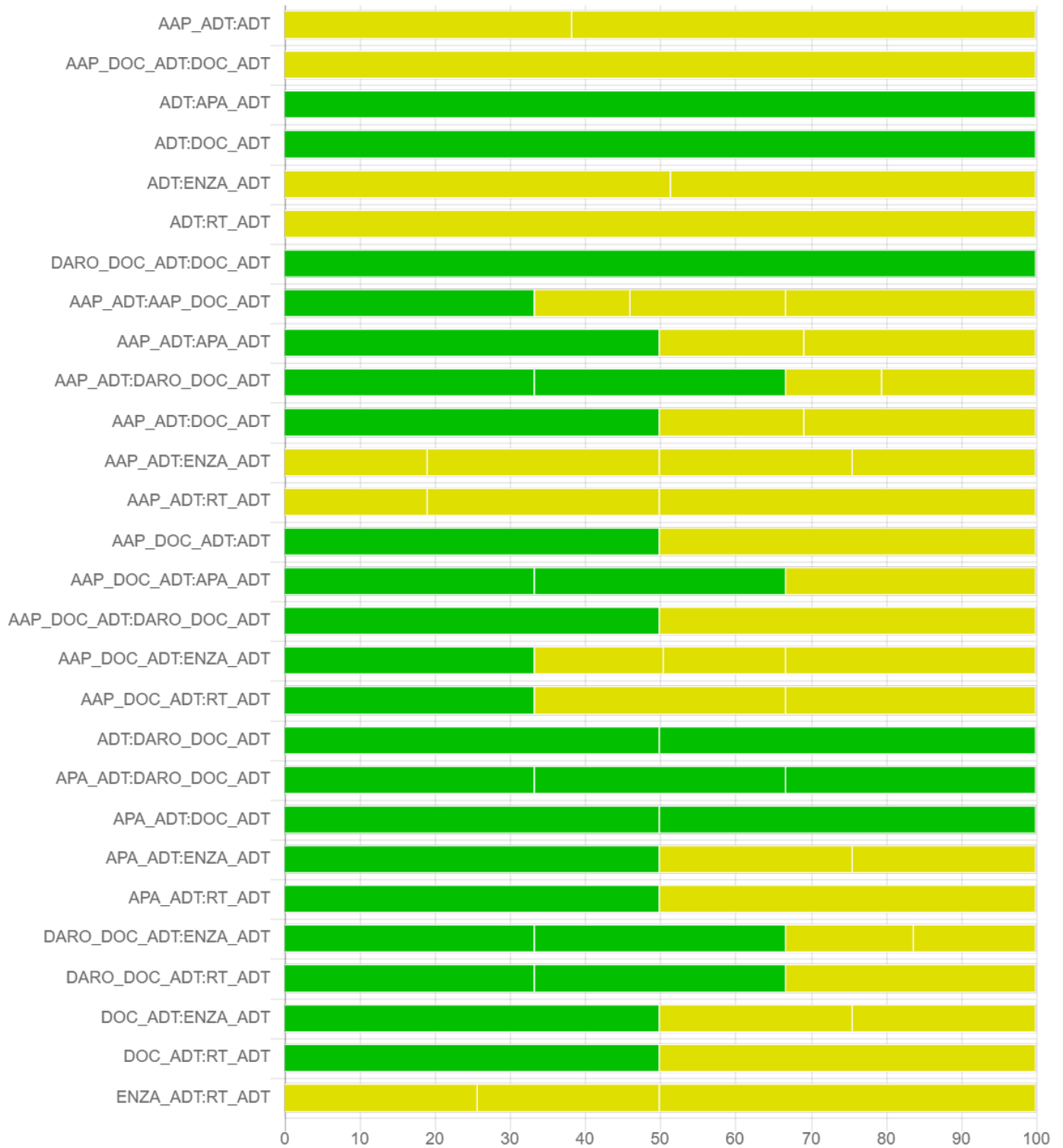
Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
AAP_ADT:ADT	1	Some concerns	Low risk	No concerns	No concerns	Major concerns	Major concerns	Very low
ADT:APA_ADT	1	No concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low
ADT:DOC_ADT	1	Some concerns	Low risk	No concerns	Some concerns	Some concerns	Major concerns	Very low
ADT:ENZA_ADT	2	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low
DARO_DOC_ADT:DOC_ADT	1	No concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low
AAP_ADT:APA_ADT	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low
AAP_ADT:DARO_DOC_ADT	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low
AAP_ADT:DOC_ADT	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low
AAP_ADT:ENZA_ADT	0	Some concerns	Low risk	No concerns	No concerns	Major concerns	Major concerns	Very low
ADT:DARO_DOC_ADT	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	Major concerns	Very low
APA_ADT:DARO_DOC_ADT	0	No concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low
APA_ADT:DOC_ADT	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low
APA_ADT:ENZA_ADT	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	Major concerns	Very low
DARO_DOC_ADT:ENZA_ADT	0	Some concerns	Low risk	No concerns	No concerns	Major concerns	Major concerns	Very low
DOC_ADT:ENZA_ADT	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	Major concerns	Very low

6.Safety-Grade 3-5 adverse events

6.1 network plot drawn by CINeMA



6.2 Risk of Bias Chart showing the contribution of low, moderate or high RoB comparisons to each network estimate



### 6.3 Evaluation of the Certainty of evidence Using CINEMA Framework, mixed evidence

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
AAP_ADT:ADT	2	Some concerns	Low risk	No concerns	No concerns	Major concerns	Major concerns	Very low
AAP_DOC_ADT:DOC_ADT	1	Some concerns	Low risk	No concerns	No concerns	Major concerns	Major concerns	Very low
ADT:APA_ADT	1	No concerns	Low risk	No concerns	No concerns	Major concerns	Major concerns	Very low
ADT:DOC_ADT	1	No concerns	Low risk	No concerns	No concerns	Major concerns	Major concerns	Very low
ADT:ENZA_ADT	2	Some concerns	Low risk	No concerns	No concerns	Major concerns	Major concerns	Very low
ADT:RT_ADT	1	Some concerns	Low risk	No concerns	No concerns	Major concerns	Major concerns	Very low
DARO_DOC_ADT:DOC_ADT	1	No concerns	Low risk	No concerns	Some concerns	Some concerns	Major concerns	Very low
AAP_ADT:AAP_DOC_ADT	0	Some concerns	Low risk	No concerns	No concerns	Major concerns	Major concerns	Very low
AAP_ADT:APA_ADT	0	Some concerns	Low risk	No concerns	No concerns	Major concerns	Major concerns	Very low
AAP_ADT:DARO_DOC_ADT	0	No concerns	Low risk	No concerns	Some concerns	Some concerns	Major concerns	Very low
AAP_ADT:DOC_ADT	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	Major concerns	Very low
AAP_ADT:ENZA_ADT	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	Major concerns	Very low
AAP_ADT:RT_ADT	0	Some concerns	Low risk	No concerns	No concerns	Major concerns	Major concerns	Very low
AAP_DOC_ADT:ADT	0	Some concerns	Low risk	No concerns	No concerns	Major concerns	Major concerns	Very low
AAP_DOC_ADT:APA_ADT	0	No concerns	Low risk	No concerns	No concerns	Major concerns	Major concerns	Very low
AAP_DOC_ADT:DARO_DOC_ADT	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	Major concerns	Very low
AAP_DOC_ADT:ENZA_ADT	0	Some concerns	Low risk	No concerns	No concerns	Major concerns	Major concerns	Very low
AAP_DOC_ADT:RT_ADT	0	Some concerns	Low risk	No concerns	No concerns	Major concerns	Major concerns	Very low
ADT:DARO_DOC_ADT	0	No concerns	Low risk	No concerns	No concerns	Major concerns	Major concerns	Very low
APA_ADT:DARO_DOC_ADT	0	No concerns	Low risk	No concerns	No concerns	Major concerns	Major concerns	Very low
APA_ADT:DOC_ADT	0	No concerns	Low risk	No concerns	No concerns	Major concerns	Major concerns	Very low
APA_ADT:ENZA_ADT	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	Major concerns	Very low
APA_ADT:RT_ADT	0	Some concerns	Low risk	No concerns	No concerns	Major concerns	Major concerns	Very low
DARO_DOC_ADT:ENZA_ADT	0	No concerns	Low risk	No concerns	No concerns	Major concerns	Major concerns	Very low
DARO_DOC_ADT:RT_ADT	0	No concerns	Low risk	No concerns	No concerns	Major concerns	Major concerns	Very low
DOC_ADT:ENZA_ADT	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	Major concerns	Very low
DOC_ADT:RT_ADT	0	Some concerns	Low risk	No concerns	No concerns	Major concerns	Major concerns	Very low
ENZA_ADT:RT_ADT	0	Some concerns	Low risk	No concerns	No concerns	Major concerns	Major concerns	Very low

The end.