Supplementary Methods: Systematic review

The following search strategy was employed on 8/13/2019: Three databases [MEDLINE/PubMed(NLM), EMBASE (Elsevier), Cochrane Central Register of Controlled Trials - CENTRAL (Wiley, Issue 8 of 12, August 2019)] were searched separately for each of the three agents of interest. Combined, these nine searches returned 494 records. The search strategy consisted of a string of synonyms (controlled terms combined with keywords using the Boolean operator "OR") for each individual agent combined (using the Boolean operator "AND") with a string of synonyms for "phase 3 clinical trials". Case reports, review articles, and conference proceedings were excluded (using each database's available search functionality and manually in Endnote in the case of CENTRAL results, from which 175 clinical trial registry and conference abstract records were removed). No date or language restrictions were applied. MEDLINE records were excluded from the EMBASE search results. Endnote citation management software (Clarivate Analytics) was used to manage the database search results and remove duplicates (103 duplicates). Screening (of 216 records) was carried out using Covidence systematic review software (Veritas Health Innovation) by two independent investigators.

Apalutamide; Total: 57 records

a) PubMed: 12 records; ("apalutamide"[Supplementary Concept] OR "apalutamide"[All Fields] OR "arn 509"[All Fields] OR "arn509"[All Fields] OR "erleada"[All Fields]) AND (Clinical Trial, Phase III[ptyp] OR "phase 3" OR "phase III") NOT (Case Reports[ptyp]) NOT (Review[ptyp])
b) EMBASE: 9 records; ('apalutamide'/exp OR 'apalutamide' OR 'arn 509' OR 'arn509' OR 'erleada') AND ('phase 3 clinical trial (topic)'/de OR "phase 3" OR "phase III") NOT 'case report'/de NOT 'review'/it NOT 'conference abstract'/it NOT [medline]/lim
c) Cochrane Library (CENTRAL): 36 records; ("apalutamide" OR "arn 509" OR "arn509" OR "erleada") AND ("phase 3" OR "phase III")

Enzalutamide; Total: 407 records

a) PubMed: 106 records; ("MDV 3100" [Supplementary Concept] OR "MDV-3100" OR "MDV3100" OR "Enzalutamide" OR "xtandi") AND (Clinical Trial, Phase III[ptyp] OR "phase 3" OR "phase III") NOT (Case Reports[ptyp]) NOT (Review[ptyp])
b) EMBASE: 98 records; ('enzalutamide'/exp OR 'mdv-3100' OR 'mdv3100' OR 'enzalutamide' OR 'xtandi') AND ('phase 3 clinical trial (topic)'/de OR 'phase 3' OR 'phase iii') NOT 'case report'/de NOT 'review'/it NOT 'conference abstract'/it NOT [medline]/lim
c) Cochrane Library (CENTRAL): 203 records; ("MDV-3100" OR "MDV3100" OR "Enzalutamide" OR "xtandi") AND ("phase 3" OR "phase III")

Darolutamide; Total: 30 records

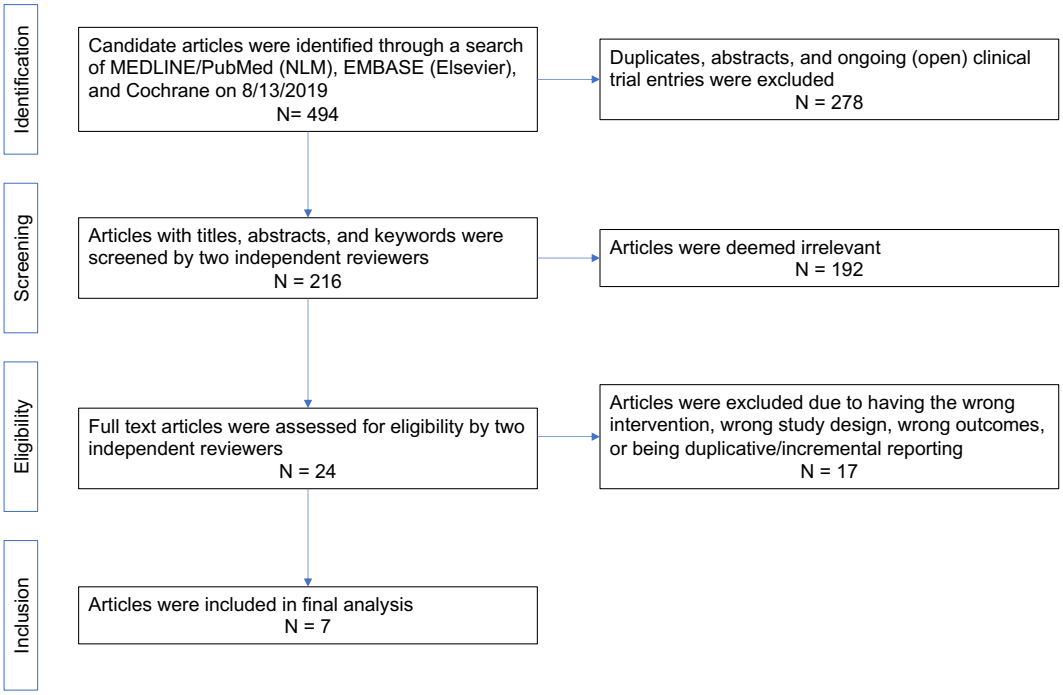
a) PubMed: 5 records; ("darolutamide" [Supplementary Concept] OR "darolutamide"[All Fields] OR "odm 201"[All Fields] OR "odm201" [All Fields]) AND (Clinical Trial, Phase III[ptyp] OR "phase 3" OR "phase III") NOT (Case Reports[ptyp]) NOT (Review[ptyp])
b) EMBASE: 5 records; ('darolutamide'/exp OR 'darolutamide' OR 'odm 201' OR 'odm201') AND ('phase 3 clinical trial (topic)'/de OR 'phase 3' OR 'phase iii') NOT 'case report'/de NOT 'review'/it NOT 'conference abstract'/it NOT [medline]/lim
c) Cochrane Library (CENTRAL): 20 records; ("darolutamide" OR "odm 201" OR "odm201") AND "phase 3" OR "phase III")

Supplementary Table 1. Scheduled study visits as per study protocols.

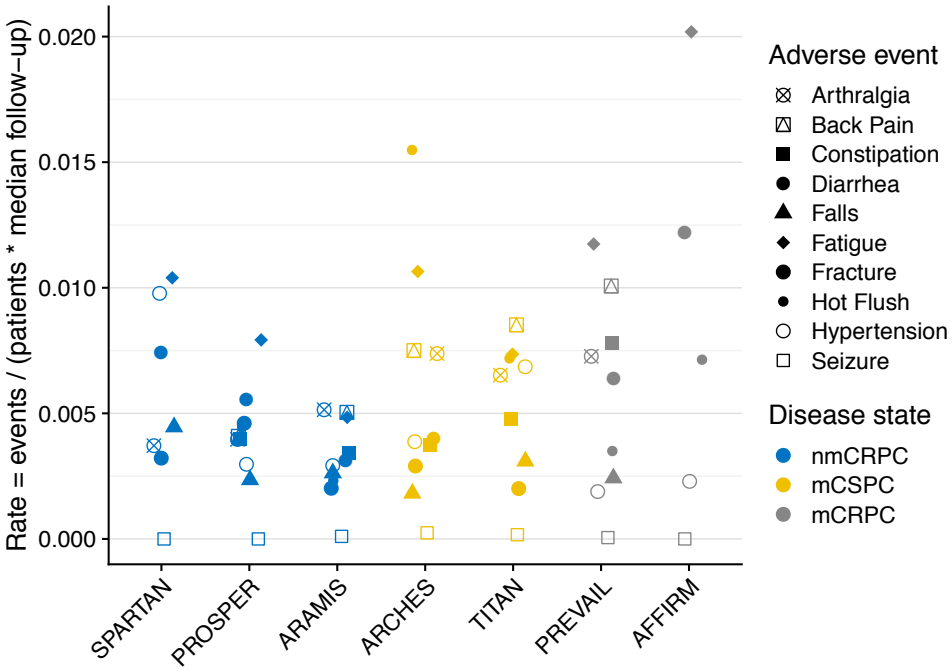
Trial	Schedule	Derived visit schedule in weeks within the first 3 years (156 weeks)	Median follow-up (weeks)	Visits within the median follow-up
SPARTAN	Original: Q4 weeks (not used) Per 1 June 2016 Amendment: Q4 weeks x6, then Q8 weeks x6, then Q16 weeks	4, 8, 12, 16, 20, 24, 32, 40, 48, 56, 64, 72, 88, 104, 120, 136, 152	88	12
PROSPER	Q4 weeks x1, then Q16 weeks	4, 20, 36, 52, 68, 84, 100, 116, 132, 148	75[1]	6
ARAMIS	Q2 weeks x2, then Q16 weeks	2, 4, 20, 36, 52, 68, 84, 100, 116, 132, 148	76	6
ARCHES	Q4 weeks x1, then Q 12 weeks	4, 16, 28, 40, 52, 64, 76, 88, 100, 112, 124, 136, 148	62	6
TITAN	Q4 weeks x12, then Q8 weeks	4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 56, 64, 72, 80, 88, 96, 104, 112, 120, 128, 136, 144, 152	98	14
PREVAIL	Q4 weeks x48, then Q12 weeks	4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92, 96, 100, 104, 108, 112, 116, 120, 124, 128, 132, 136, 140, 144, 148, 152, 156	95	19
AFFIRM	Q2 weeks x1, then Q4 weeks x6, then Q12 weeks	2, 6, 10, 14, 18, 22, 26, 38, 50, 62, 74, 86, 98, 110, 122, 134, 146	62	11

[a] In PROSPER, median follow-up was reported separately for drug and placebo arms only. The weighted mean of the median follow-up in each arm was used for the entire trial in all relevant analyses.

Supplementary Figure 1. Literature review flow chart.



Supplementary Figure 2. Estimated AE rates in placebo arms, by trial. Rates, which differ from risks by considering length of follow-up, were calculated based on estimated median follow-up because only 3 trials actually reported rates.



Supplementary Figure 3. Absolute AE risks in the placebo arms of each trial, comparing crude risks and risks standardized to the same number of scheduled follow up visits per trial. The plot is restricted to AE types reported by at least five of the seven trials. The left panel shows the observed risk; the right panel shows the risk standardized to visit count, *i.e.*, observed risk / number of visits per trial * 11, with 11 being the median number of visits across trials.