CO57

Comparative Efficacy of First-line Therapies for Patients with Asymptomatic/ Mildly Symptomatic Metastatic Castration-resistant Prostate Cancer: An Updated Systematic Literature Review and Bayesian Network Meta-analyses

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Objective

To compare the efficacy of 1L treatments in an unselected mCRPC population, irrespective of gene status, using the latest available evidence in a network meta-analysis (NMA).

Conclusions

This NMA, incorporating the latest evidence, suggests that talazoparib + enzalutamide offers the greatest survival benefit among 1L treatments for mCRPC in the unselected population.

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Background

- Several therapies are available for first-line (1L) treatment of patients with metastatic castration-resistant prostate cancer (mCRPC). This disease is an area of active investigation, with new treatments and trials emerging to help fulfill an unmet need and with more mature survival data becoming available for earlier trials.
- Given a lack of head-to-head studies comparing 1L mCRPC treatments, a network meta-analysis (NMA) informed by a systematic literature review (SLR) was conducted to understand the relative efficacy of available treatments in an unselected mCRPC population, irrespective of gene status.

Materials and Methods

SYSTEMATIC LITERATURE REVIEW

- An SLR was conducted to identify evidence from inception through August 2024.
  - Methods aligned to latest guidance from Cochrane Handbook and PRISMA statement.[1,2,3]
  - Protocol was registered with PROSPERO (CRD42021283512).
- Sources included MEDLINE®, Embase, Cochrane via Ovid®, and key grey literature sources.
- Phase 2 or 3 randomized controlled trials (RCTs) of available therapies for 1L mCRPC were included.
- A feasibility assessment was conducted to confirm that RCTs were sufficiently similar to be included in a valid NMA.

NETWORK META-ANALYSIS

- Bayesian random-effects NMAs were conducted for radiographic progression-free survival (rPFS) and overall survival (OS), using vague priors for treatment effects.
  - Methods aligned to guidance from Dias et al.[4]
  - Continuous survival model (log hazard scale) was utilized.
  - For rPFS, we used the latest data cutoff available. In the event where rPFS by blinded independent central review (BICR) was not available, or was not the most recent data cutoff available, rPFS inputs assessed by investigator were used. For trials which did not specify the approach, BICR was assumed.
  - Placebo and steroid-based treatments were considered “best supportive care”. Prednisone and prednisolone were considered similar, as were regimens that were equal in their administration over 24 hours.
- Base case analyses excluded trials with clinical heterogeneity or violating proportional hazards assumptions.
  - Sensitivity analyses assessed the impact of including/excluding these trials from the base case.
- Hazard ratios (HR) and 95% credible intervals (CrI) were calculated for each outcome.
- Treatments were ranked using surface under the cumulative ranking curves (SUCRAs), with higher values indicating greater likelihood of being effective.
- Network diagrams were developed to reflect the evidence base for each NMA, and results were summarized using league tables and forest plots.

Results

RADIOGRAPHIC PROGRESSION-FREE SURVIVAL

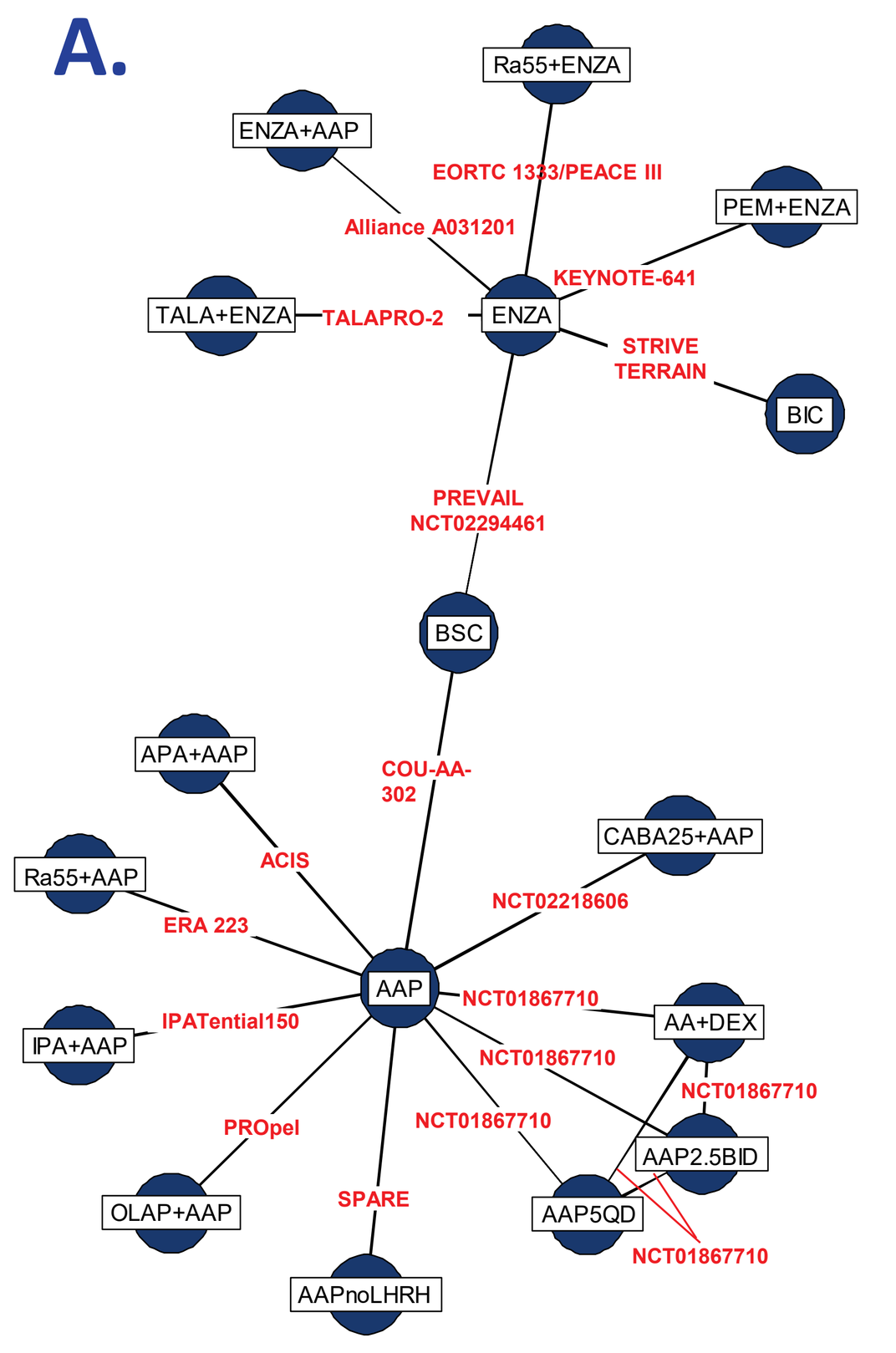
- In the base case, the rPFS network included 16 RCTs and 17 treatments (**Figure 1A**), while the sensitivity analysis included 15 RCTs and 16 treatments.
- In the base case, talazoparib + enzalutamide is the top-ranked treatment for rPFS (SUCRA = 89.6%).
- Talazoparib + enzalutamide is numerically superior to all 16 other treatments in the network (**Figure 1B and Figure 3A**).
- Talazoparib + enzalutamide is statistically superior to five treatments in the network (**Figure 1B and Figure 3A**).
- In the sensitivity analysis, the results remained consistent with the base case (SUCRA = 92.0% for talazoparib + enzalutamide).

OVERALL SURVIVAL

- In the base case, the OS network included 20 RCTs and 18 treatments (**Figure 2A**), while the sensitivity analysis included 22 RCTs and 20 treatments.
- In the base case, talazoparib + enzalutamide is the top-ranked treatment for OS (SUCRA = 84.4%).
- Talazoparib + enzalutamide is numerically superior to all 17 other treatments in the network (**Figure 2B and Figure 3B**).
- Talazoparib + enzalutamide is statistically superior to MIT14+HC and BSC in the network (**Figure 2B and Figure 3B**).
- In the sensitivity analysis, the results remained largely consistent with the base case (SUCRA = 78.7% for talazoparib + enzalutamide).

Figure 1. Base Case NMA Evidence Network (A) and League Table (B) for rPFS

A.



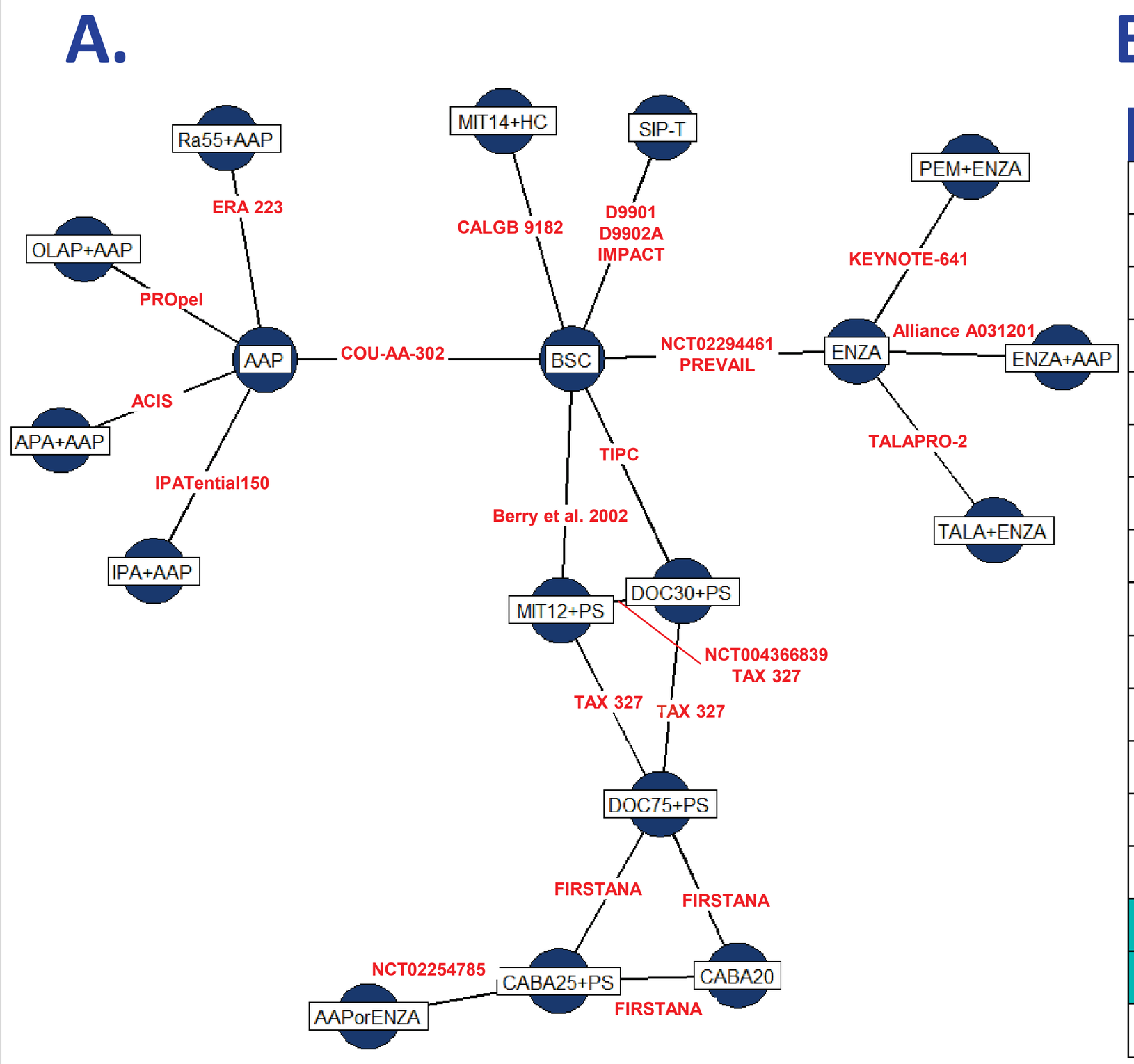
B.

	TALA+ENZA	Ra55+ENZA	CABA25+AAP	ENZA+AAP	AA+DEX	ENZA	AAPnoLHRH	OLAP+AAP	PEM+ENZA	APA+AAP	IPA+AAP	AAP	AAP5QD	Ra55+AAP	AAP2.5BID	BIC
Ra55+ENZA	0.966 (0.523 to 1.792)															
CABA25+AAP	0.823 (0.321 to 2.078)	0.850 (0.328 to 2.158)														
ENZA+AAP	0.775 (0.432 to 1.397)	0.802 (0.440 to 1.459)	0.942 (0.379 to 2.394)													
AA+DEX	0.752 (0.276 to 2.023)	0.779 (0.281 to 2.117)	0.915 (0.336 to 2.506)	0.971 (0.359 to 2.574)												
ENZA	0.667 (0.437 to 1.020)	0.690 (0.442 to 1.077)	0.810 (0.356 to 1.880)	0.860 (0.575 to 1.288)	0.887 (0.361 to 2.207)											
AAPnoLHRH	0.636 (0.183 to 2.192)	0.659 (0.187 to 2.294)	0.771 (0.223 to 2.723)	0.821 (0.238 to 2.805)	0.843 (0.228 to 3.124)	0.955 (0.294 to 3.062)										
OLAP+AAP	0.601 (0.272 to 1.330)	0.621 (0.276 to 1.384)	0.731 (0.337 to 1.596)	0.775 (0.354 to 1.691)	0.797 (0.341 to 1.882)	0.901 (0.460 to 1.764)	0.945 (0.307 to 2.943)									
PEM+ENZA	0.585 (0.318 to 1.081)	0.606 (0.324 to 1.131)	0.711 (0.280 to 1.837)	0.754 (0.416 to 1.378)	0.776 (0.287 to 2.147)	0.877 (0.564 to 1.366)	0.919 (0.265 to 3.229)	0.974 (0.438 to 2.170)								
APA+AAP	0.583 (0.265 to 1.284)	0.603 (0.270 to 1.341)	0.710 (0.330 to 1.537)	0.752 (0.345 to 1.636)	0.775 (0.330 to 1.832)	0.874 (0.449 to 1.703)	0.919 (0.298 to 2.846)	0.971 (0.539 to 1.749)	0.997 (0.448 to 2.204)							
IPA+AAP	0.486 (0.219 to 1.079)	0.503 (0.224 to 1.116)	0.592 (0.274 to 1.290)	0.628 (0.285 to 1.374)	0.646 (0.275 to 1.526)	0.730 (0.371 to 1.430)	0.766 (0.246 to 2.386)	0.810 (0.447 to 1.464)	0.832 (0.370 to 1.854)	0.834 (0.462 to 1.495)						
AAP	**0.408 (0.208 to 0.805)**	**0.422 (0.212 to 0.836)**	**0.497 (0.259 to 0.965)**	0.527 (0.271 to 1.020)	0.543 (0.256 to 1.155)	0.612 (0.362 to 1.033)	0.642 (0.223 to 1.855)	0.680 (0.446 to 1.033)	0.697 (0.351 to 1.378)	0.700 (0.461 to 1.059)	0.839 (0.555 to 1.276)					
AAP5QD	0.405 (0.154 to 1.053)	0.418 (0.158 to 1.098)	0.494 (0.187 to 1.288)	0.523 (0.200 to 1.339)	0.538 (0.233 to 1.251)	0.608 (0.253 to 1.435)	0.637 (0.178 to 2.274)	0.674 (0.296 to 1.514)	0.692 (0.258 to 1.820)	0.694 (0.307 to 1.551)	0.833 (0.370 to 1.866)	0.993 (0.488 to 1.997)				
Ra55+AAP	**0.354 (0.160 to 0.785)**	**0.367 (0.164 to 0.817)**	**0.431 (0.200 to 0.938)**	**0.457 (0.209 to 1.000)**	0.470 (0.201 to 1.113)	0.532 (0.271 to 1.038)	0.559 (0.180 to 1.739)	0.590 (0.326 to 1.064)	0.605 (0.270 to 1.344)	0.607 (0.337 to 1.099)	0.729 (0.405 to 1.319)	0.868 (0.571 to 1.327)	0.874 (0.390 to 1.990)			
AAP2.5BID	**0.301 (0.117 to 0.780)**	**0.312 (0.120 to 0.809)**	**0.367 (0.144 to 0.954)**	**0.388 (0.152 to 0.988)**	**0.400 (0.178 to 0.897)**	0.451 (0.193 to 1.060)	0.477 (0.134 to 1.662)	0.502 (0.228 to 1.113)	0.514 (0.198 to 1.350)	0.516 (0.236 to 1.144)	0.620 (0.282 to 1.368)	0.738 (0.375 to 1.465)	0.743 (0.351 to 1.597)	0.850 (0.386 to 1.888)		
BIC	**0.278 (0.156 to 0.485)**	**0.288 (0.158 to 0.509)**	**0.339 (0.135 to 0.843)**	**0.359 (0.204 to 0.615)**	**0.369 (0.138 to 0.986)**	**0.417 (0.282 to 0.605)**	0.436 (0.128 to 1.501)	0.463 (0.211 to 0.987)	**0.475 (0.262 to 0.843)**	0.477 (0.219 to 1.009)	0.572 (0.262 to 1.221)	0.681 (0.353 to 1.278)	0.687 (0.265 to 1.766)	0.785 (0.360 to 1.669)	0.924 (0.359 to 2.317)	
BSC	**0.212 (0.124 to 0.361)**	**0.219 (0.126 to 0.378)**	**0.258 (0.120 to 0.560)**	**0.274 (0.163 to 0.456)**	**0.282 (0.120 to 0.660)**	**0.318 (0.230 to 0.437)**	0.333 (0.108 to 1.034)	**0.353 (0.195 to 0.635)**	**0.362 (0.208 to 0.624)**	0.363 (0.203 to 0.651)	**0.436 (0.242 to 0.785)**	**0.519 (0.343 to 0.783)**	0.523 (0.234 to 1.182)	0.598 (0.331 to 1.074)	0.704 (0.318 to 1.550)	0.762 (0.468 to 1.266)

- League tables contain HRs for relative efficacy for all possible pairs of treatments in the network.
- HR < 1 implies that column is better than row.
- Teal squares indicate statistical significance.

Figure 2. Base Case NMA Evidence Network (A) and League Table (B) for OS

A.



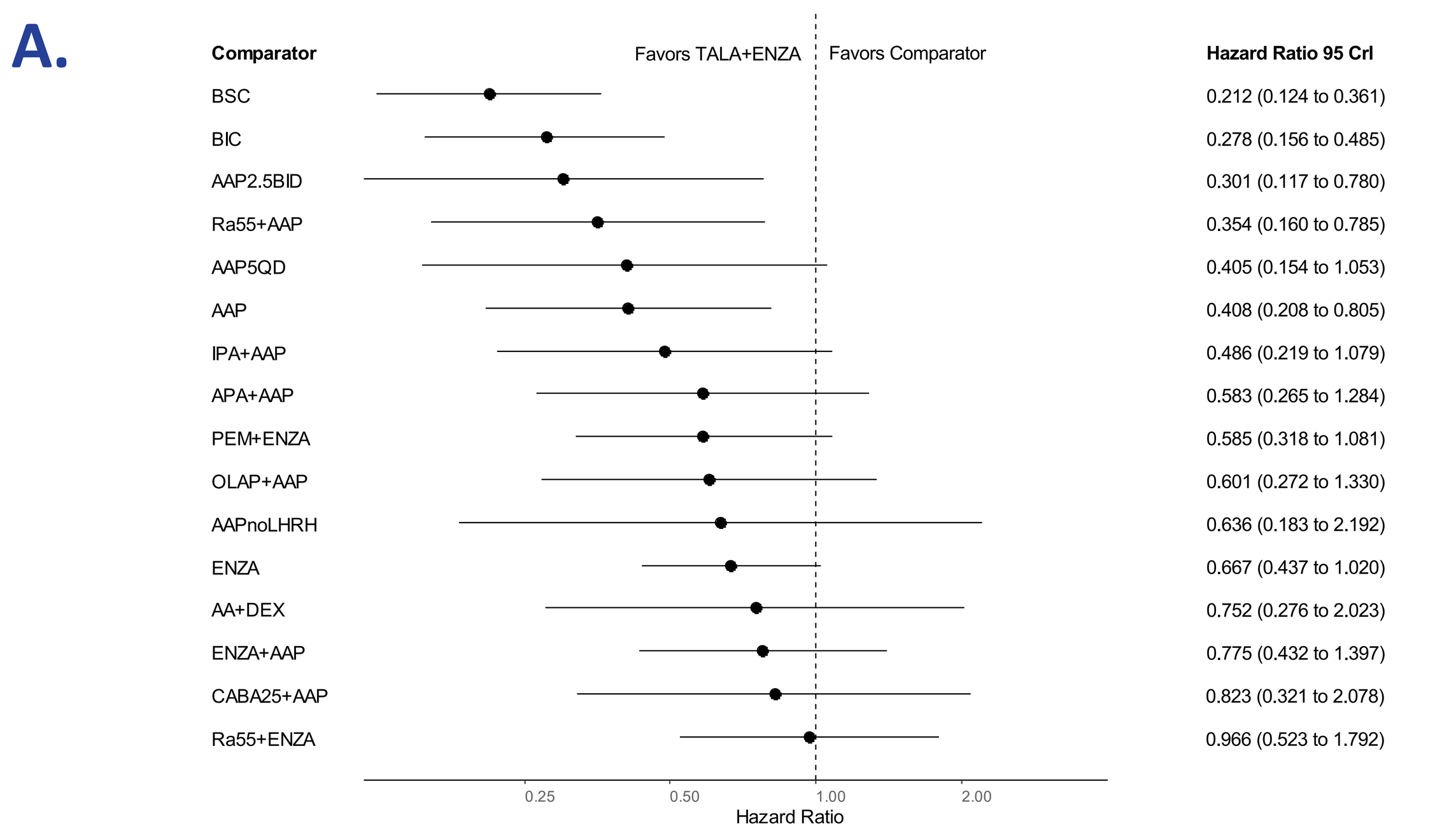
B.

	TALA+ENZA	CABA25+PS	ENZA+AAP	DOC75+PS	CABA20	OLAP+AAP	ENZA	DOC30+PS	PEM+ENZA	SIP-T	IPA+AAP	APA+AAP	AAP	MIT12+PS	Ra55+AAP	MIT14+HC	BSC
CABA25+PS	0.896 (0.380 to 1.873)																
ENZA+AAP	0.895 (0.528 to 1.517)	0.998 (0.482 to 2.327)															
DOC75+PS	0.878 (0.412 to 1.673)	0.980 (0.673 to 1.433)	0.983 (0.465 to 1.853)														
CABA20	0.869 (0.371 to 1.818)	0.970 (0.666 to 1.416)	0.972 (0.415 to 2.013)	0.990 (0.677 to 1.443)													
OLAP+AAP	0.814 (0.354 to 1.588)	0.905 (0.399 to 2.038)	0.910 (0.402 to 1.751)	0.922 (0.447 to 1.886)	0.932 (0.411 to 2.092)												
ENZA	0.796 (0.543 to 1.167)	0.889 (0.466 to 1.896)	0.890 (0.620 to 1.284)	0.908 (0.530 to 1.723)	0.917 (0.481 to 1.958)	0.979 (0.558 to 2.023)											
DOC30+PS	0.779 (0.377 to 1.443)	0.870 (0.520 to 1.448)	0.870 (0.424 to 1.591)	0.887 (0.631 to 1.244)	0.896 (0.538 to 1.490)	0.962 (0.485 to 1.934)	0.976 (0.535 to 1.616)										
PEM+ENZA	0.780 (0.445 to 1.371)	0.871 (0.409 to 2.083)	0.872 (0.505 to 1.512)	0.888 (0.457 to 1.931)	0.896 (0.421 to 2.155)	0.959 (0.483 to 2.227)	0.980 (0.650 to 1.482)	1.002 (0.530 to 2.112)									
SIP-T	0.733 (0.381 to 1.225)	0.816 (0.416 to 1.579)	0.820 (0.432 to 1.342)	0.832 (0.477 to 1.432)	0.841 (0.428 to 1.626)	0.901 (0.495 to 1.654)	0.919 (0.554 to 1.336)	0.939 (0.556 to 1.562)	0.938 (0.480 to 1.600)								
IPA+AAP	0.733 (0.320 to 1.412)	0.812 (0.360 to 1.821)	0.820 (0.363 to 1.568)	0.829 (0.405 to 1.681)	0.837 (0.372 to 1.865)	0.900 (0.522 to 1.554)	0.921 (0.448 to 1.594)	0.935 (0.469 to 1.839)	0.938 (0.406 to 1.845)	0.998 (0.548 to 1.810)							
APA+AAP	0.694 (0.304 to 1.337)	0.770 (0.343 to 1.723)	0.777 (0.345 to 1.476)	0.786 (0.384 to 1.585)	0.794 (0.354 to 1.766)	0.853 (0.499 to 1.464)	0.872 (0.426 to 1.502)	0.886 (0.446 to 1.744)	0.889 (0.387 to 1.743)	0.946 (0.519 to 1.712)	0.947 (0.559 to 1.612)						
AAP	0.659 (0.319 to 1.151)	0.731 (0.357 to 1.495)	0.739 (0.363 to 1.269)	0.745 (0.404 to 1.359)	0.754 (0.368 to 1.535)	0.810 (0.549 to 1.197)	0.828 (0.458 to 1.268)	0.842 (0.473 to 1.482)	0.845 (0.406 to 1.506)	0.898 (0.564 to 1.425)	0.900 (0.618 to 1.313)	0.950 (0.653 to 1.375)					
MIT12+PS	0.640 (0.305 to 1.160)	0.715 (0.435 to 1.124)	0.716 (0.346 to 1.282)	**0.729 (0.538 to 0.947)**	0.737 (0.449 to 1.154)	0.790 (0.394 to 1.548)	0.802 (0.433 to 1.306)	0.823 (0.583 to 1.106)	0.821 (0.383 to 1.516)	0.875 (0.525 to 1.443)	0.879 (0.442 to 1.704)	0.927 (0.467 to 1.798)	0.976 (0.551 to 1.692)				
Ra55+AAP	0.552 (0.240 to 1.087)	0.612 (0.267 to 1.383)	0.617 (0.269 to 1.202)	0.624 (0.300 to 1.288)	0.631 (0.277 to 1.431)	0.677 (0.388 to 1.185)	0.693 (0.333 to 1.223)	0.704 (0.349 to 1.412)	0.706 (0.302 to 1.408)	0.752 (0.406 to 1.387)	0.753 (0.434 to 1.307)	0.795 (0.458 to 1.376)	0.837 (0.560 to 1.255)	0.857 (0.438 to 1.737)			
MIT14+HC	**0.533 (0.254 to 0.947)**	0.594 (0.280 to 1.212)	0.597 (0.288 to 1.043)	0.605 (0.318 to 1.118)	0.612 (0.289 to 1.255)	0.657 (0.331 to 1.280)	0.670 (0.361 to 1.056)	0.683 (0.370 to 1.228)	0.683 (0.319 to 1.243)	0.728 (0.439 to 1.184)	0.730 (0.370 to 1.410)	0.770 (0.391 to 1.488)	0.810 (0.462 to 1.400)	0.831 (0.461 to 1.498)	0.968 (0.484 to 1.906)		
BSC	**0.533 (0.292 to 0.822)**	0.593 (0.317 to 1.075)	**0.597 (0.330 to 0.898)**	**0.604 (0.369 to 0.963)**	0.611 (0.327 to 1.105)	0.655 (0.381 to 1.113)	**0.669 (0.436 to 0.871)**	0.681 (0.435 to 1.044)	0.682 (0.368 to 1.080)	**0.726 (0.545 to 0.953)**	0.728 (0.425 to 1.226)	0.769 (0.450 to 1.291)	0.809 (0.554 to 1.164)	0.830 (0.543 to 1.269)	0.966 (0.554 to 1.662)	0.998 (0.662 to 1.504)	
AAPorENZA	0.506 (0.140 to 1.719)	0.569 (0.212 to 1.504)	0.566 (0.159 to 1.889)	0.579 (0.202 to 1.640)	0.586 (0.204 to 1.654)	0.628 (0.178 to 2.265)	0.635 (0.187 to 2.040)	0.654 (0.217 to 1.954)	0.649 (0.178 to 2.221)	0.699 (0.215 to 2.271)	0.699 (0.199 to 2.454)	0.738 (0.210 to 2.596)	0.775 (0.234 to 2.612)	0.799 (0.271 to 2.354)	0.925 (0.263 to 3.314)	0.958 (0.287 to 3.264)	0.961 (0.307 to 3.036)

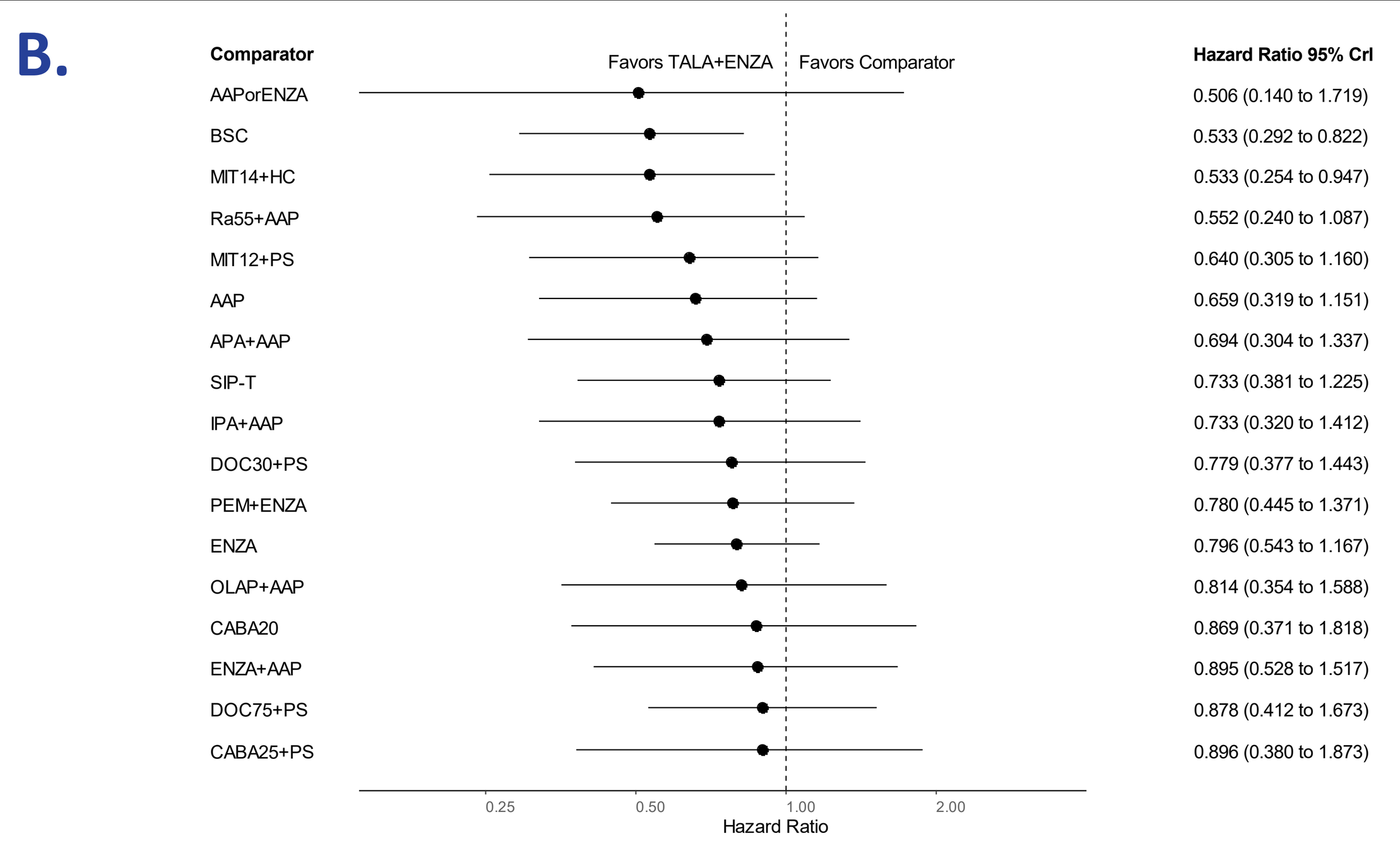
- League tables contain HRs for relative efficacy for all possible pairs of treatments in the network.
- HR < 1 implies that column is better than row.
- Teal squares indicate statistical significance.

Figure 3. Base Case Forest Plots of Talazoparib plus Enzalutamide vs Comparators for (A) rPFS and (B) OS

A.



B.



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Abbreviations: AAP = Abiraterone acetate PO QD 1000mg + Prednisone/Prednisolone 5mg PO BID/10mg PO QD; AAP2.5BID = Abiraterone acetate PO QD 1000mg + Prednisone 2.5mg BID; AAP5QD = Abiraterone acetate 1000mg PO QD + Prednisone 5mg PO QD; AAPnoLHRH = Abiraterone acetate 1000 mg PO QD + Prednisone 5 mg PO BID with no LHRH therapy; AAPorENZA = Abiraterone acetate 1000mg PO QD + Prednisone 5mg PO BID or Enzalutamide 160mg PO QD; AA+DEX = Abiraterone acetate 1000mg PO QD + Dexamethasone 0.5mg PO QD; APA+AAP = Apalutamide 240mg PO QD + Abiraterone acetate 1000mg PO QD + Prednisone 5mg PO BID; BIC = Bicalutamide 50mg PO QD; BSC = Best supportive care (Placebo, Prednisone 5mg PO BID, Hydrocortisone 40mg PO QD, and Prednisolone 5mg PO BID); CABA20 = Cabazitaxel 20mg/m² IV Q3W + Prednisone 10mg PO QD; CABA25+AAP = Cabazitaxel 25mg/m² IV Q3W + Abiraterone Acetate 1000mg PO QD + Prednisone 5mg PO BID; CABA25+PS = Cabazitaxel 25mg/m² IV Q3W + Prednisone 5mg PO BID/10mg PO QD; DOC30+PS = Docetaxel 30mg/m² IV Q1W + Prednisone/ Prednisolone 5mg PO BID; DOC75+PS = Docetaxel 75mg/m² IV Q3W + Prednisone/Prednisolone 5mg PO BID/10mg PO QD; ENZA = Enzalutamide 160mg PO QD; ENZA+AAP = Enzalutamide 160mg PO QD + Abiraterone acetate PO QD 1000mg + Prednisone 5mg PO BID; HR = hazard ratio; IPA+AAP = Ipatasertib 400mg PO QD + Abiraterone acetate 1000mg PO QD + Prednisone/Prednisolone 5mg PO BID; MIT12+PS = Mitoxantrone 12mg/m² IV Q3W + Prednisone/Prednisolone 5mg PO BID/10mg PO QD; MIT14+HC = Mitoxantrone 14mg/m² IV Q3W + Hydrocortisone 40mg PO QD; OLAP+AAP = Olaparib 300mg PO BID + Abiraterone acetate 1000mg PO QD + Prednisone/Prednisolone 5 mg PO BID; OS = overall survival; PEM+ENZA = Pembrolizumab 200mg IV Q3W + Enzalutamide 160mg PO QD; Ra55+AAP = Radium-223 55 kBq/kg Q4W + Abiraterone acetate 1000mg PO QD + Prednisone/Prednisolone 5mg PO BID; Ra55+ENZA = Radium-223 55 kBq/kg Q4W + Enzalutamide 160mg PO QD; rPFS = radiographic progression-free survival; SIP-T = Sipuleucel-T (1 infusion every 2 weeks for 6 weeks); TALA+ENZA = Talazoparib 0.5mg QD + Enzalutamide 160mg PO QD.

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