Supplementary Online Content

Riaz IB, Naqvi SAA, He H, et al. First-line systemic treatment options for metastatic castration-sensitive prostate cancer: a living systematic review and network meta-analysis. *JAMA Oncol*. Published online March 2, 2023. doi:10.1001/jamaoncol.2022.7762

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix. Detailed Search Strategy and Methodology

This systematic review and network meta-analysis was conducted using the 'living' interactive evidence (LIvE) synthesis framework. This framework was designed using six modules, each of which corresponds to a specific step in the process of conducting a systematic review. Each module can be executed across three pathways: (1) conventional pathway, (2) human-in-the-loop (HIL), or machine learning-powered pathway. The pathways are implemented through a five-layer system architecture consisting of an application, shared module, core service, middleware, and storage layers.

Literature Search

The search strategy was designed by an experienced medical librarian with input from the principal investigator. A comprehensive search of Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, and Daily; Ovid EMBASE; Ovid Cochrane Central Register of Controlled Trials; Ovid Cochrane Database of Systematic Reviews was conducted initially from each database's inception through June 16, 2021.

Subsequently, a "living" auto search has been created with weekly updates to identify new evidence as it becomes available. Every week, the system sends pre-specified queries to MEDLINE and actively pulls new citations. The metadata from each retrieved citation is then collected using the application programming interface by python packages "scrapy" and "request". The system also receives new citations from Ovid auto-alert system using a push retrieval mode. The retrieved citations are processed, and duplicates are removed through a rule-based algorithm. The deduplicated list of citations is then stored in a MySQL-based data repository and each citation is assigned a unique system identifier. The process of automated search is facilitated by the *Watcher* module.

Search Strategy

Database(s): Embase 1974 to 2021 June 16 , Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to June 16, 2021

#	Searches	Results
1	exp *Prostatic Neoplasms/	283331
2	exp Clinical Trial/	2498364
3	exp Meta-Analysis/	353101
4	1 and (2 or 3)	27693
5	exp animals/ not exp humans/	9641145
6	4 not 5	27634
7	limit 6 to (letter or editorial or erratum or note or addresses or autobiography or bibliography or biography or blogs or comment or dictionary or directory or interactive tutorial or interview or lectures or legal cases or legislation or news or newspaper article or overall or patient education handout or periodical index or portraits or published erratum or video-audio media or webcasts) [Limit not valid in Embase, Ovid MEDLINE(R), Ovid MEDLINE(R) Daily Update, Ovid MEDLINE(R) PubMed not MEDLINE, Ovid MEDLINE(R) In-Process, Ovid MEDLINE(R) Publisher; records were retained]	1039
8	6 not 7	26595

- ***Study Selection:***

Full-text or abstract publications of phase II/III RCTs evaluating contemporary treatment options (taxane-based chemotherapy, androgen pathway inhibitors) in patients with castrate-sensitive metastatic prostate cancer, were included in this review. Non-randomized, phase I, or single-arm studies and articles in non-English language were excluded. The process of study selection was conducted by two independent reviewers (IBR and SAAN). Discrepancies and conflicts between the two reviewers were resolved by consensus and input from the senior reviewer (AHB).

The central data repository channels new citations which are then processed by an ensemble classifier that combines natural language processing and machine learning techniques to facilitate the identification of randomized controlled trials (RCTs). The citations are then labeled accordingly and presented in an interactive web-assisted GUI which allows the citations to be screened at two levels, (1) titles and abstracts, and (2) full texts. Metadata for study selection at each level is processed and stored into a JavaScript object notation (JSON) file through a pre-defined data parser and is subsequently used to generate a 'living' interactive PRISMA using a web visualization application at the backend. The visualization application is built using JavaScript packages including D3.js and Vue.js. The process of study selection is facilitated by the *Scanner* module, and the final list of eligible studies is pushed to the next modular layer

Data Extraction and Quality Assessment:

The extracted data included but was not limited to:

(1) trial characteristics (first author's last name; trial name; national clinical registry number, PubMed identification; trial design and phase; type of report [original vs. updated follow-up])
(2) baseline population characteristics (number of included participants, overall and in each arm; median age, median on-treatment duration; median follow-up duration; the proportion of different prognostic subgroups)
(3) outcome results in the overall population and in clinically relevant subgroups.

Clinically relevant subgroups were mainly defined by the mode of metastatic presentation (synchronous [*de novo*], metachronous [recurrent]) and volume of disease (high, low). In instances where an eligible trial had multiple reports, data from the most updated or longest follow-up were included in the analysis. Moreover, the quality of included trials was assessed using the Cochrane Risk of Bias tool version 2. This process of data extraction and quality assessment was carried out by two independent reviewers (IBR and SAAN). Discrepancies in the process were resolved by consensus and input from a third review (AHB).

Data extraction from eligible studies is facilitated by the *Extractor* module which consists of submodular layers: outline layer, tabular layer, and interactive abstraction layer. First, the data extraction instrument is structured using the outline layer. Second, the metadata of each eligible study is automatically populated using the tabular layer. Finally, the interactive abstraction layer enables annotation-assisted data extraction from eligible studies. The relevant PDFs are managed using a PDF file management system and the corresponding abstract and PDFs are displayed in a floating panel that allows fragment text annotations. The selected text fragments are passed to an NLP identifier model that predicts what attribute of data the selected fragment belongs to. The extracted data is parsed and stored in JSON and subsequently tabulated by the web visualization application as an interactive summary table.

- ***Patient important outcomes***

Patient important outcomes included overall survival (OS), radiographic or clinical progression-free survival (PFS), grade 3 or higher adverse events, and health-related quality of life (HrQoL). These outcomes were defined in accordance with definitions in the included clinical trials (**eTable 1**).

Data extracted for each patient important outcome is pushed to the next modular layer for statistical analyses.

- ***Statistical Analysis***

Pairwise Meta-Analysis

Pre-computed hazard ratios (HR) with corresponding 95% confidence intervals (CI) were pooled using an inverse-variance approach after logarithmic transformation. Binary raw outcome data was expressed as relative risks (RR) and was subsequently pooled using a Mantel-Haenszel approach. A DerSimonian and Laird random-effects meta-analysis was conducted to make direct (pairwise) comparisons. Cochran's Q statistical test was used to assess statistically significant heterogeneity not explained by chance, while the I^2 statistical test was used to quantify the total observed variability, due to between-study heterogeneity. I^2 values >50% indicated substantial heterogeneity.

Network Meta-Analysis

Direct and indirect evidence were used to compute mixed treatment comparisons using a multivariate meta-regression within the frequentist framework. Both fixed-effect and random-effects models were fitted; however, the final choice of model was made based on a priori criteria and the fixed effect model was used if the network was open and sparse given that the common between-study heterogeneity cannot be estimated reliably in such networks. Relative treatment rankings for each patient-important outcome were assessed using a P-score and were evaluated based on their congruence with pairwise estimates. A higher relative treatment rank indicated potentially better efficacy and safety. In the case of a closed loop network, statistical consistency between direct and indirect evidence was assessed using the node-split method. In instances, where there were two sub-networks, the larger sub-network was used for the analysis.

Secondary Analyses

For direct comparisons between doublet therapy and ADT, pre-specified subgroup analyses were also performed to explore if the treatment effect varied (effect modification) across various clinically relevant subgroups stratified by the following co-variables:

1. Volume of disease (high and low)
2. Time of metastatic presentation (synchronous [de novo] and metachronous [recurrent])
3. Gleason score (GS ≥ 8 and <8),
4. Performance status (PS 0 and 1-2)
5. Age in years (older defined as either >65 or >70 years and younger defined as either <65 or <70 years).

The P-value of heterogeneity was computed to assess if there were any significant interaction between the subgroups. A two-sided P value of <0.10 was considered statistically significant. These analyses were subject to the availability of the data.

For mixed treatment comparisons, sensitivity analyses were also conducted for the subgroups of interest (mentioned above). It was also observed that three trials, assessing API doublet therapies as compared to ADT alone, allowed the use of either concurrent or prior docetaxel in a subset of patients. Hence, post-hoc sensitivity analyses were performed which excluded patients who received concurrent or prior docetaxel in these trials.

The statistical analysis is enabled by the *Analyzer* module. The extracted data is pre-processed using Python packages, Pandas (version 1.0.3), and NumPy (version 1.18.4). Domain and statistical experts pre-specify analysis parameters. Pairwise and network meta-analyses are conducted using R packages, meta (version 5.1-1), and netmeta (version 2.0-1), respectively. Crude results generated from the R script are parsed and stored in JSON files. Data from JSON files are then pushed to the web visualization application to generate interactive figures and plots. Results from pairwise meta-analyses are visualized using interactive forest plots while results from network meta-analyses are visualized using league tables, ranking plots, and forest plots. League tables are color coded and provide mixed treatment comparisons where each cell indicates a comparison between treatment (column) and comparator (row). The green color indicates benefit, and the red color indicates harm. Darker shade corresponds to a significant effect while lighter shade corresponds to a non-significant effect.

- ***Certainty of Evidence***

The relative effect estimates along with their 95% confidence intervals pushed from the analysis module to the *Tabulator* module are translated into intervention risk, and absolute risk differences using relative estimates and assumed baseline event risk.

The absolute risk difference per 1000 patients using relative risk (RR) is calculated as:

$$ARD = 1000 \times baseline\ event\ risk\ (RR - 1)$$

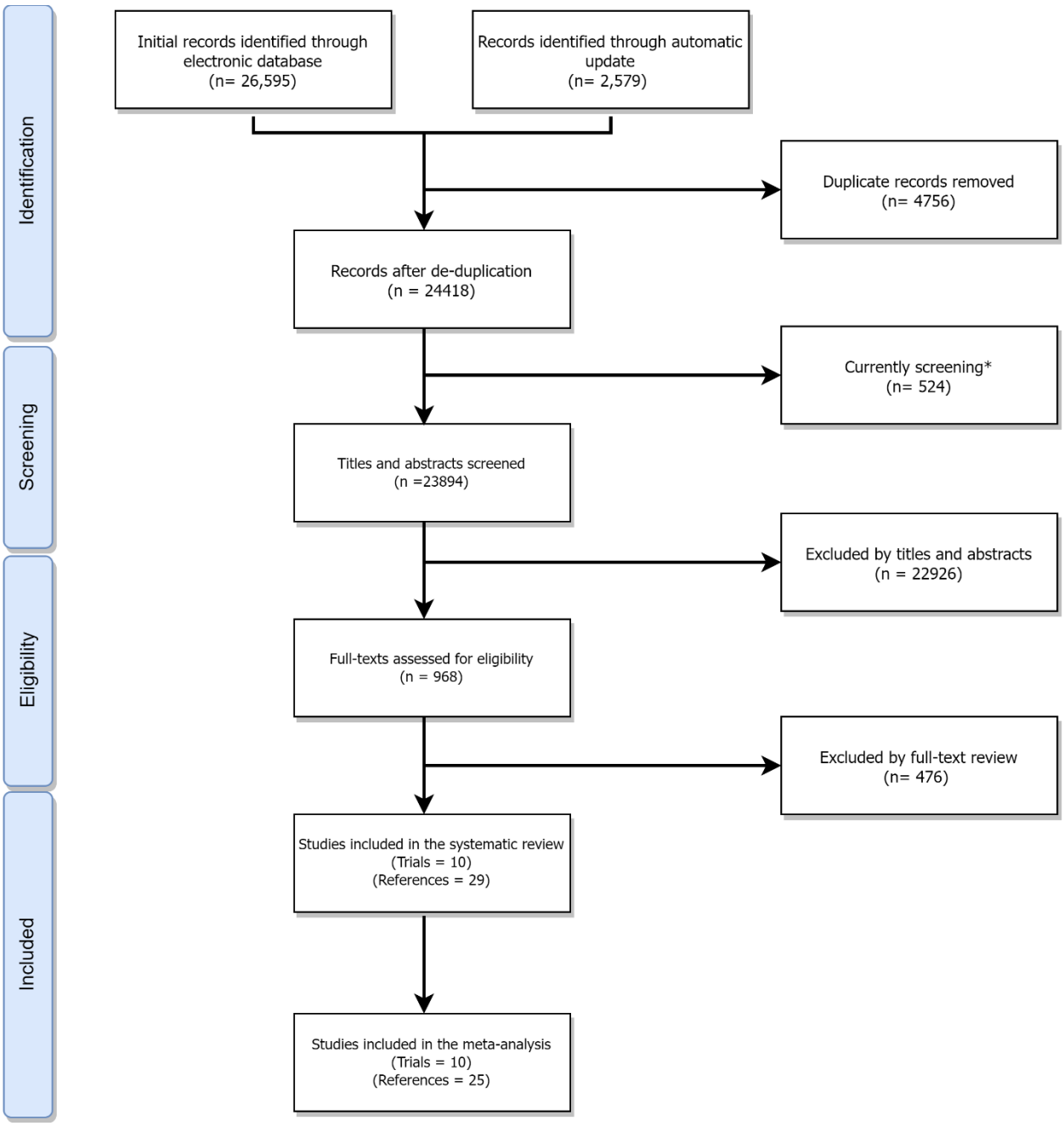
The absolute risk difference per 1000 patients using hazard ratio (HR) is calculated as:

$$RR = \frac{(1 - e^{HR \times \ln(1 - baseline\ event\ risk)})}{baseline\ event\ risk}$$

$$ARD = 1000 \times baseline\ event\ risk \times (RR - 1)$$

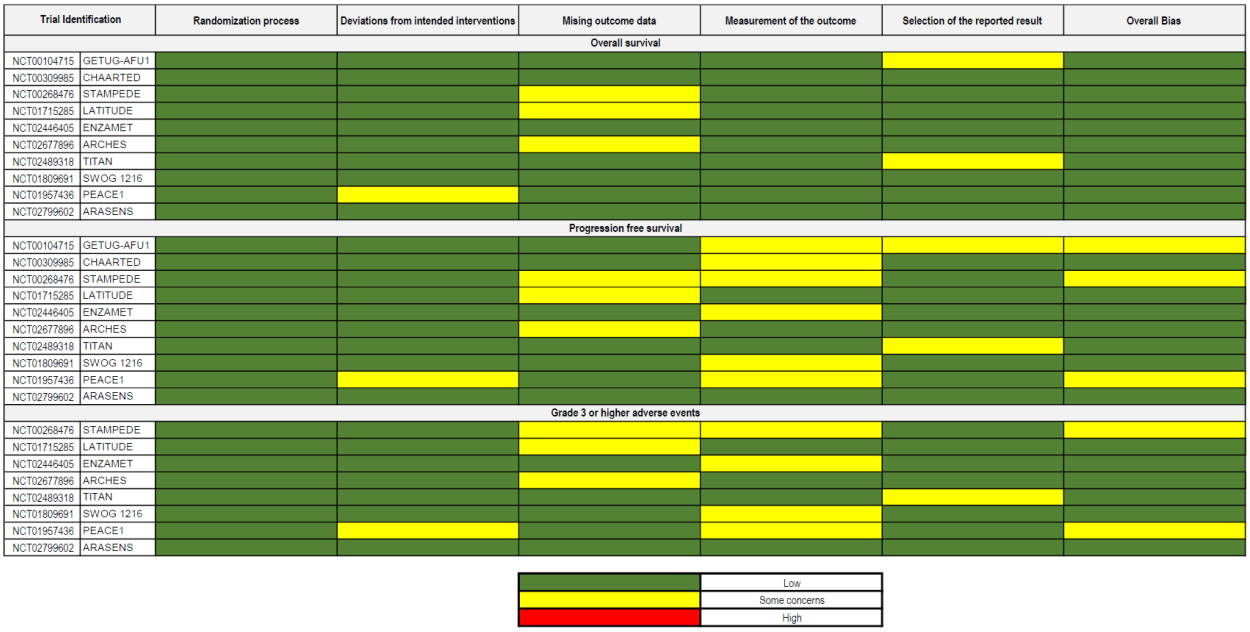
The grading of recommendation, assessment, development, and evaluation (GRADE) approach is then used to assess the certainty of evidence. Direct evidence was assessed for overall risk of bias, inconsistency, indirectness, and suspicion of publication bias, and indirect evidence was assessed for intransitivity. Network estimates were additionally assessed on incoherence and imprecision. Imprecision was assessed using a non-contextualized approach with null effect as the threshold of importance. These responses were recorded in a systematically structured instrument and the level of certainty was adjudicated by a rule-based algorithm as high, moderate, low, and very low. These results are presented as an interactive evidence profile (summary of findings table) and are visualized as evidence maps using plotly (version 4.12.0)

eFigure 1. PRISMA Flowchart Outlining the Process of Study Selection



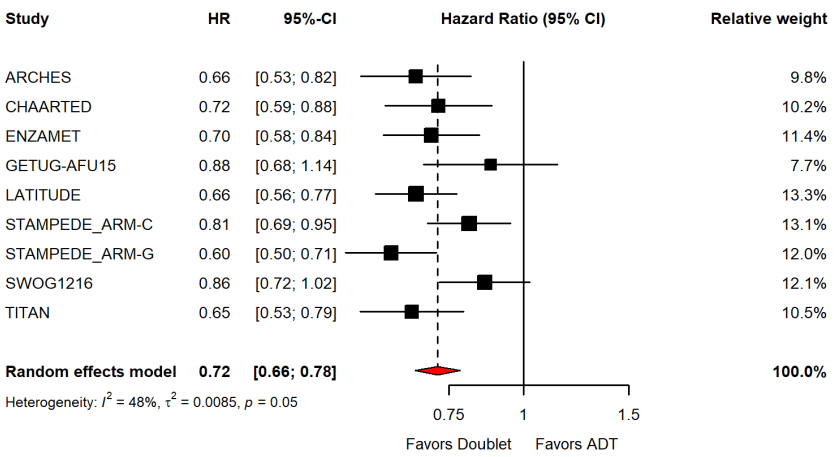
*New citations are constantly assessed for inclusion using an automated workflow. 524 citations are unscreened as of July 10th,2022.

eFigure 2. Risk of Bias for Included Trials Assessing Patient-Important Outcomes

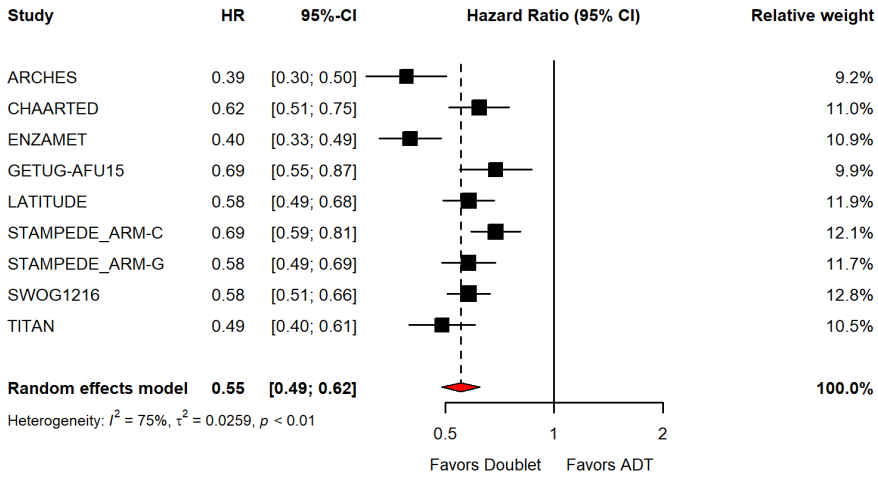


Risk of bias was assessed using Cochrane risk of bias for randomized controlled trials guidelines (v2) for each trial across patient important outcomes (overall survival, progression free survival, and grade 3 or higher adverse events). Overall bias for each trial was deemed to be low if there were low risk of bias in all domains or some concerns in one domain. PEACE-1 trial raised some concerns over the deviation from intended intervention considering the trial protocol was modified to include docetaxel for some patients owing to change in standard of care. For STAMPEDE, LATITUDE, and ARCHES some concerns were raised for potential missing outcome data in at least 10% of the total population. Some concerns were raised for trials assessing progression free survival and adverse events which followed an open-label design and did not mask the outcome assessment. Only four trials followed a double-blind design. The outcome assessment for overall survival was deemed to be void of any potential biases due to unblinded assessment.

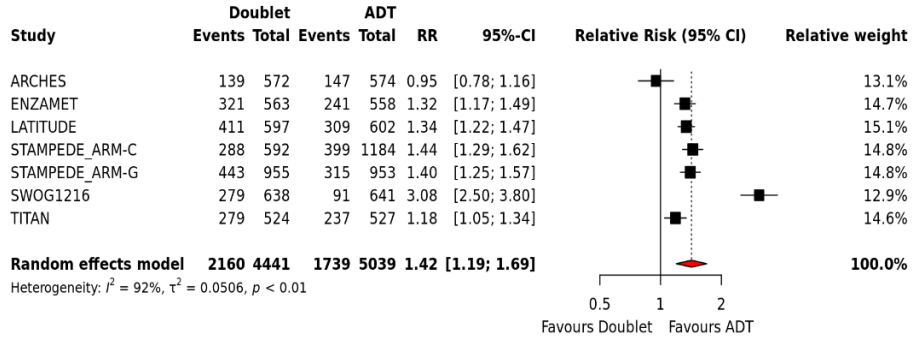
eFigure 3. Forest Plot Showing Overall Survival in the Overall Patient Population



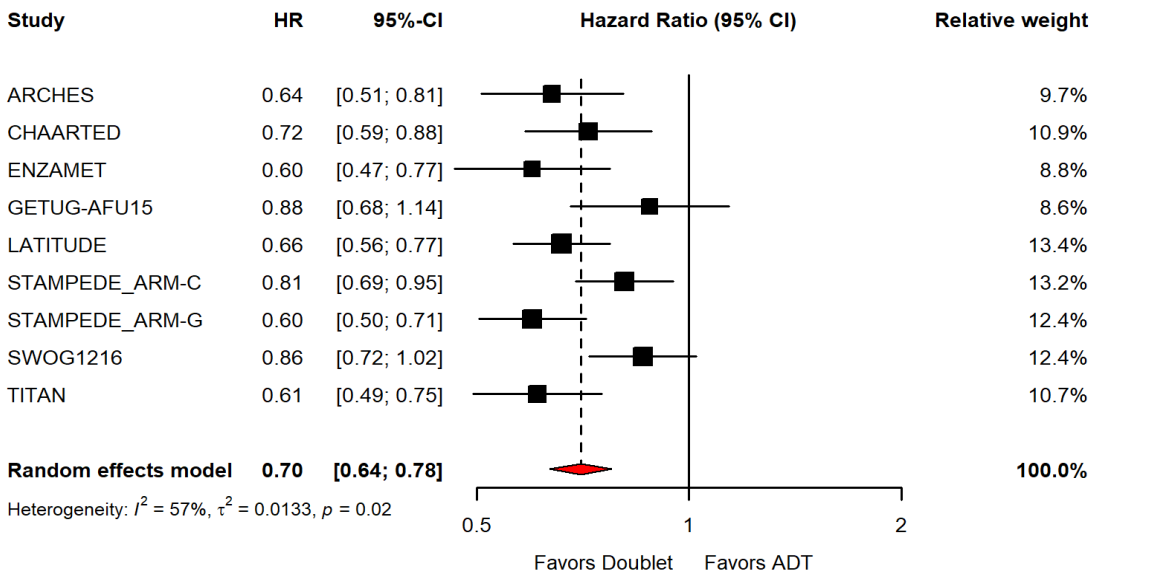
eFigure 4. Forest Plot Showing Progression-Free Survival in the Overall Patient Population



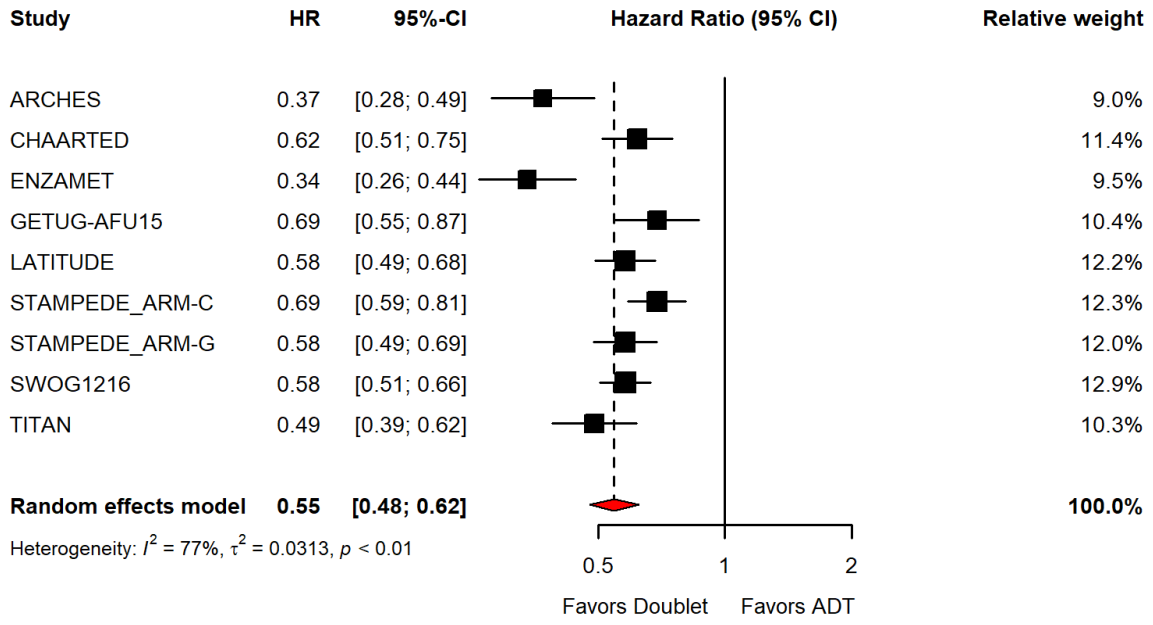
eFigure 5. Forest Plot Showing Adverse Events (Grade 3 or Higher)



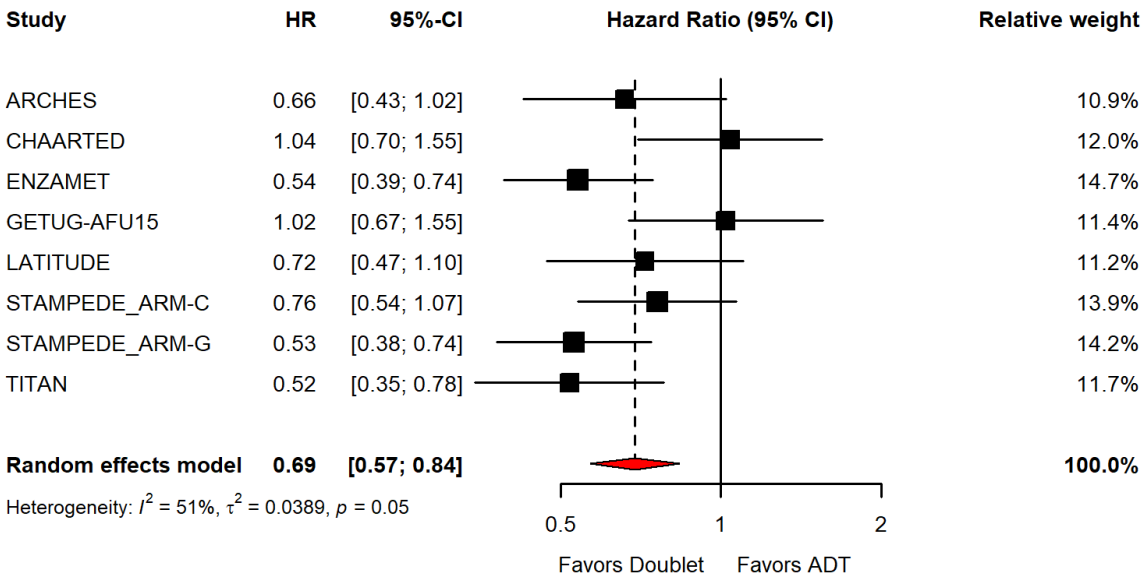
eFigure 6. Forest Plot Showing Overall Survival in the Overall Patient Population (Excluding Patients Who Received Docetaxel in 3 Trials)



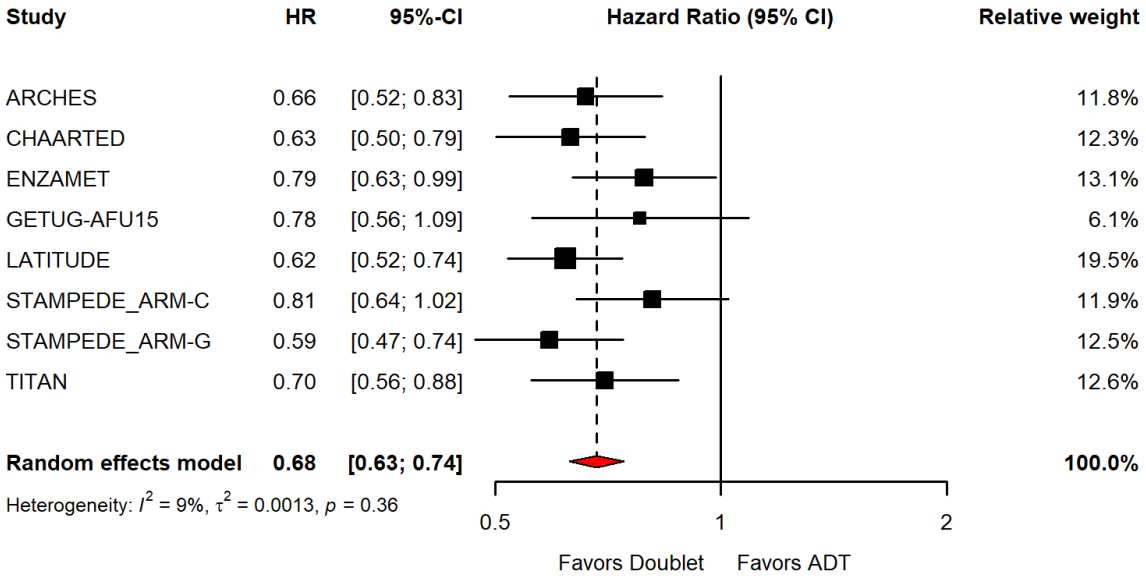
eFigure 7. Forest Plot Showing Progression-Free Survival in the Overall Patient Population (Excluding Patients Who Received Docetaxel in 3 Trials)



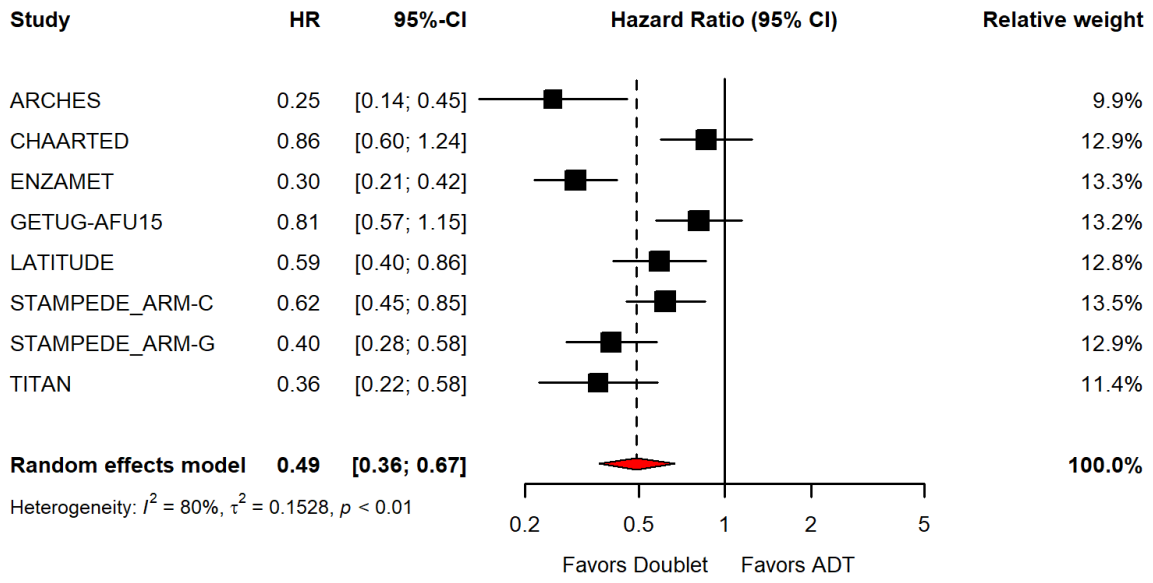
eFigure 8. Forest Plot Showing Overall Survival in Low-Volume Disease



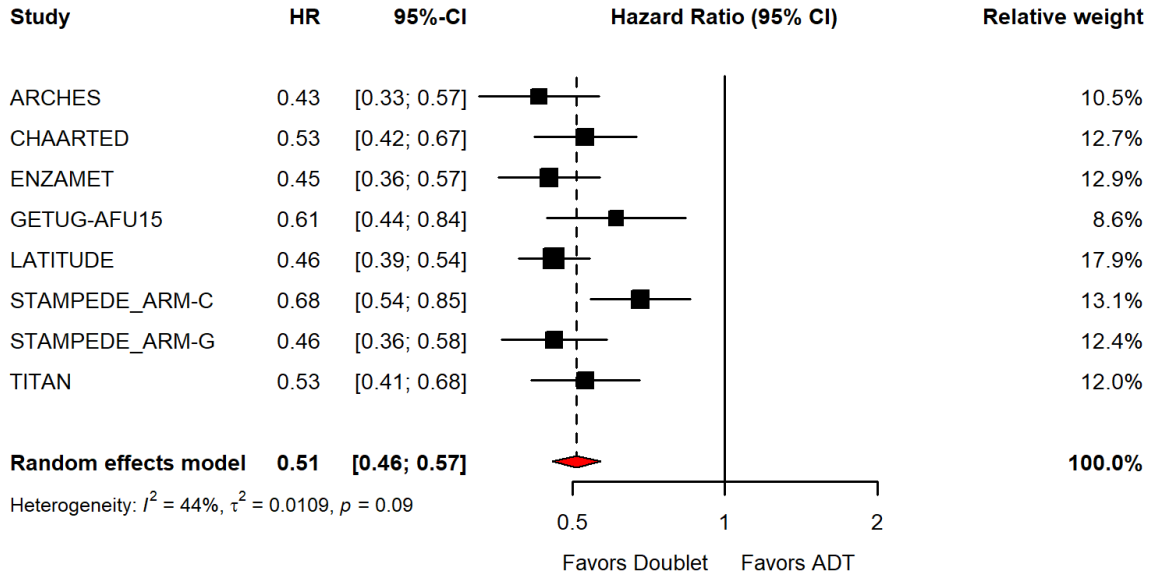
eFigure 9. Forest Plot Showing Overall Survival in High-Volume Disease



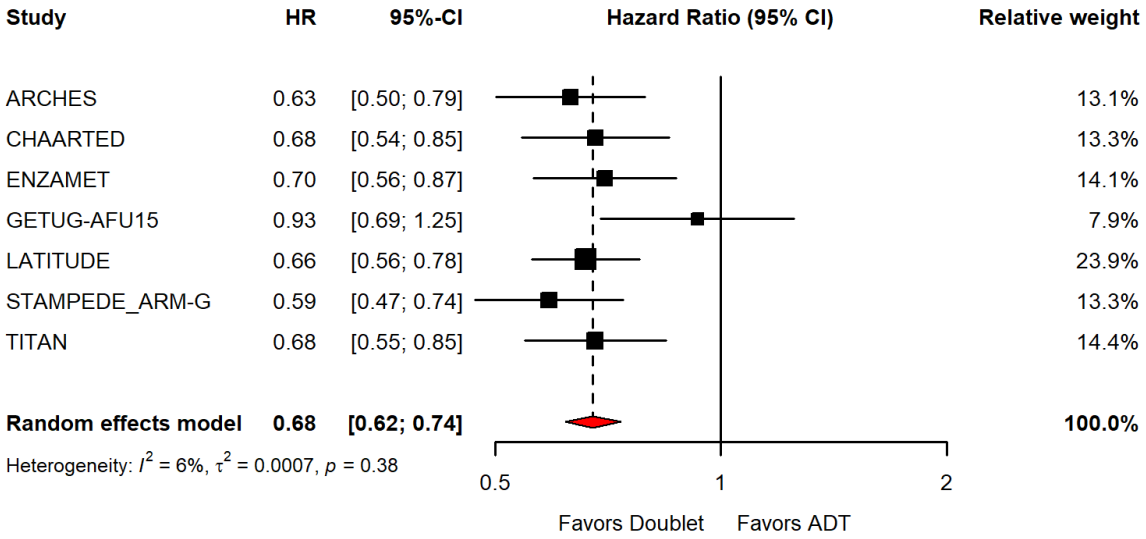
eFigure 10. Forest Plot Showing Progression-Free Survival in Low-Volume Disease



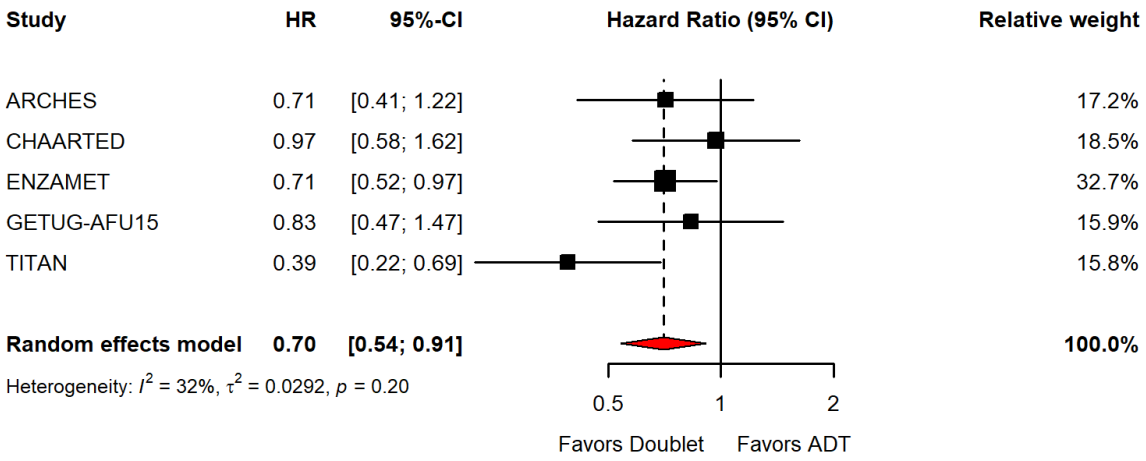
eFigure 11. Forest Plot Showing Progression-Free Survival in High-Volume Disease



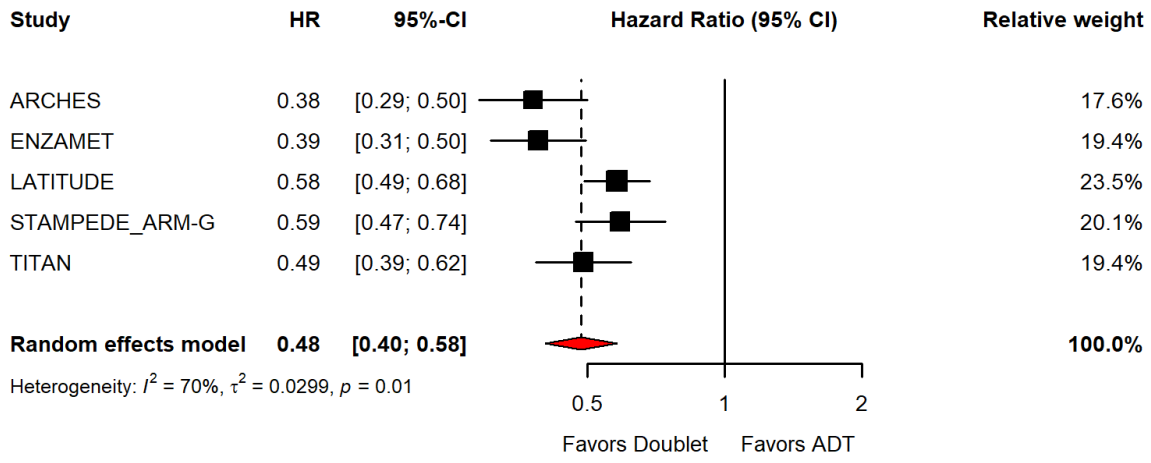
eFigure 12. Forest Plot Showing Overall Survival in Synchronous Disease



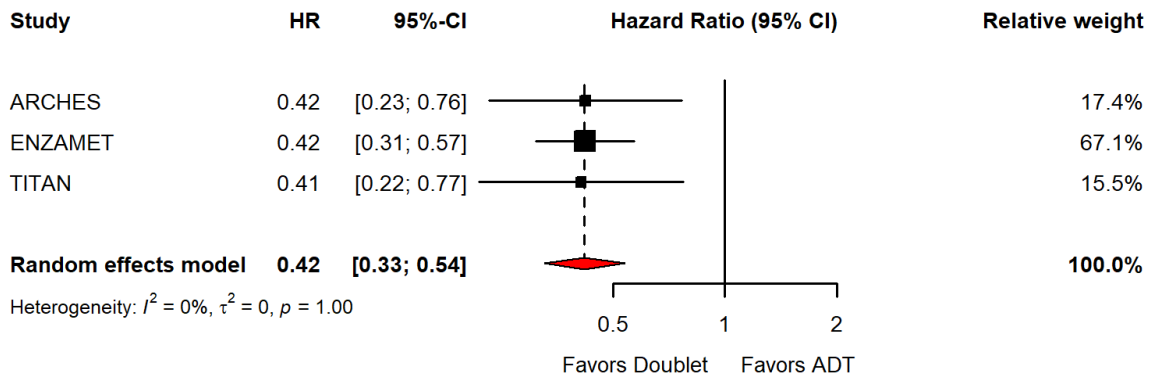
eFigure 13. Forest Plot Showing Overall Survival in Metachronous Disease



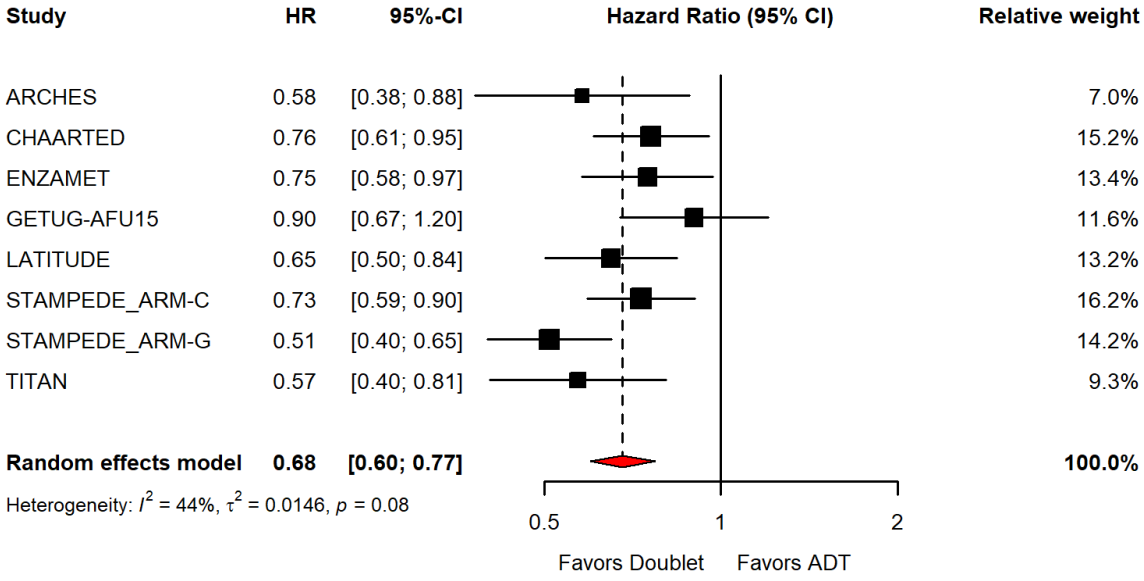
eFigure 14. Forest Plot Showing Progression-Free Survival in Synchronous Disease



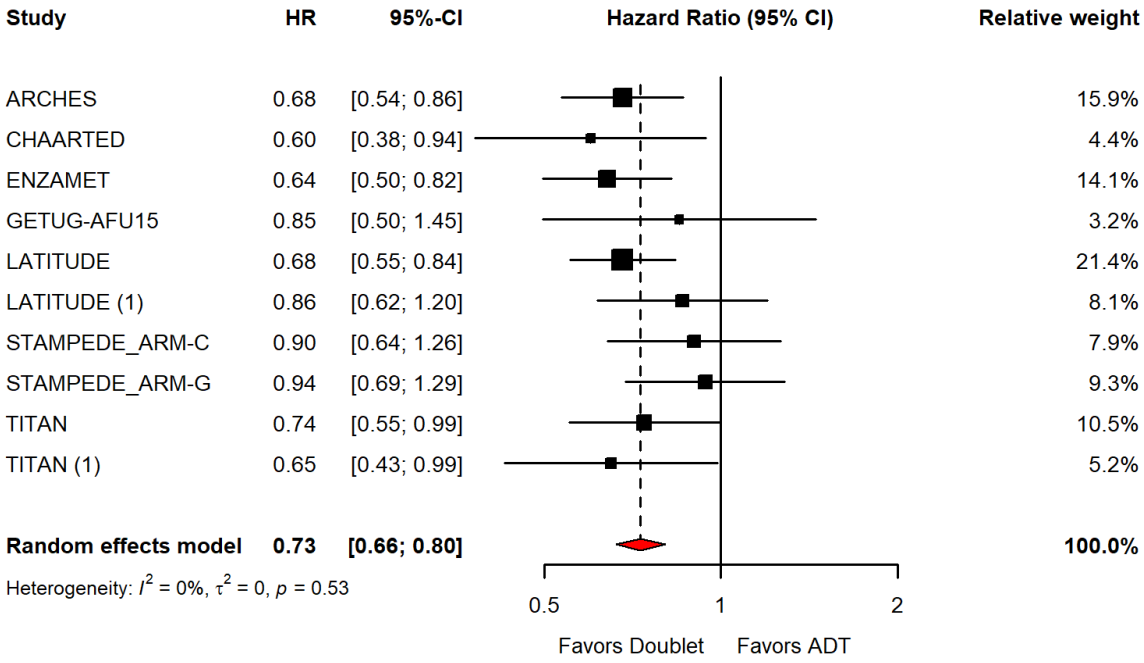
eFigure 15. Forest Plot Showing Progression-Free Survival in Metachronous Disease



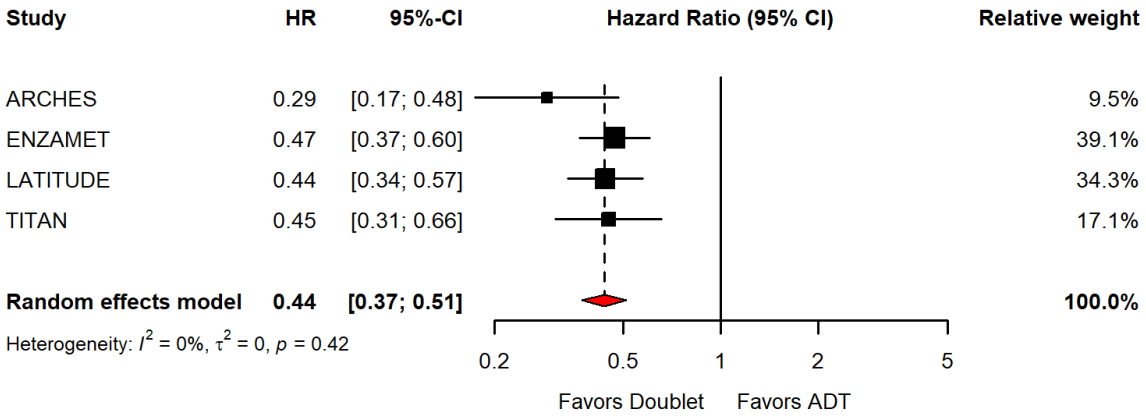
eFigure 16. Forest Plot Showing Overall Survival in Younger Patients



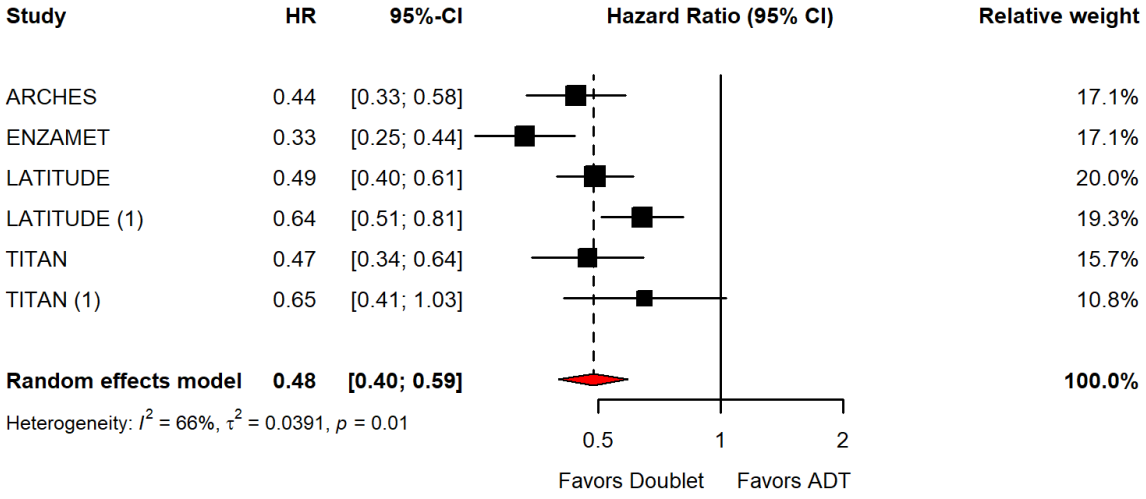
eFigure 17. Forest Plot Showing Overall Survival in Older Patients



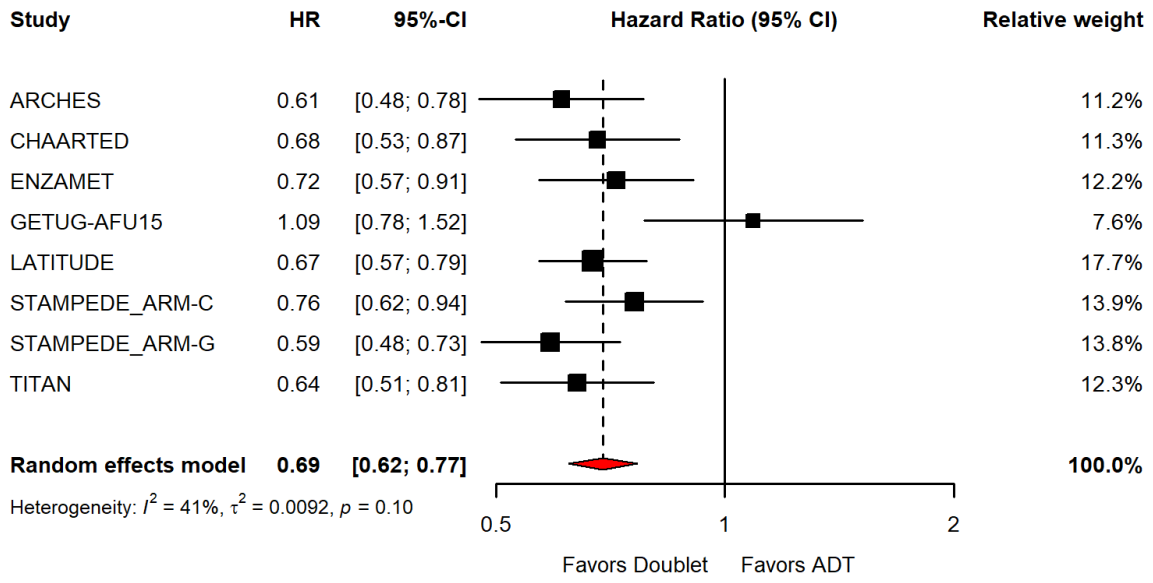
eFigure 18. Forest Plot Showing Progression-Free Survival in Younger Patients



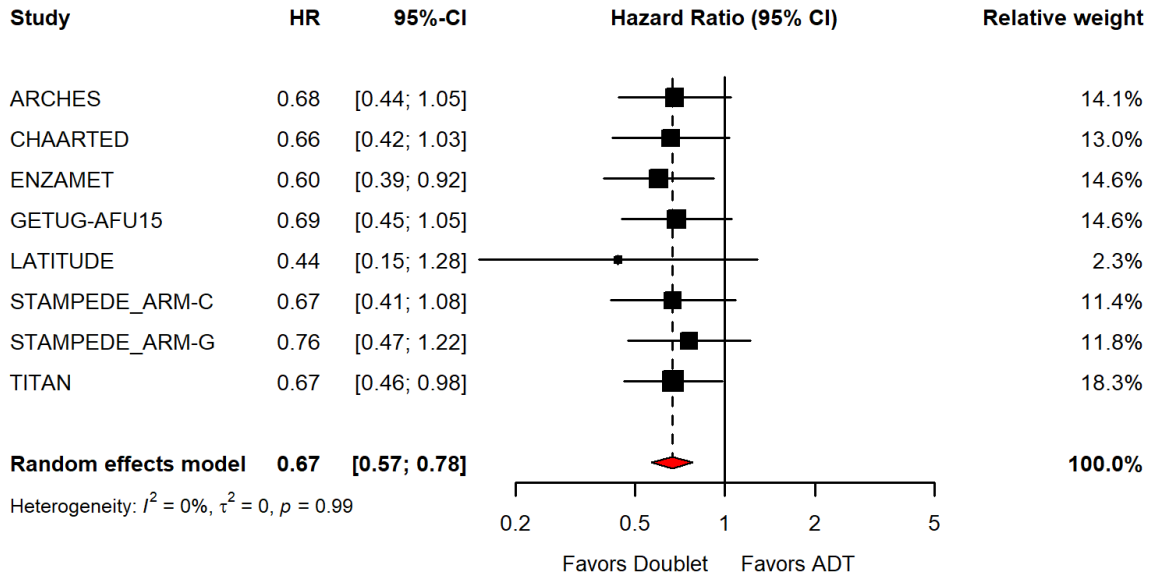
eFigure 19. Forest Plot Showing Progression-Free Survival in Older Patients



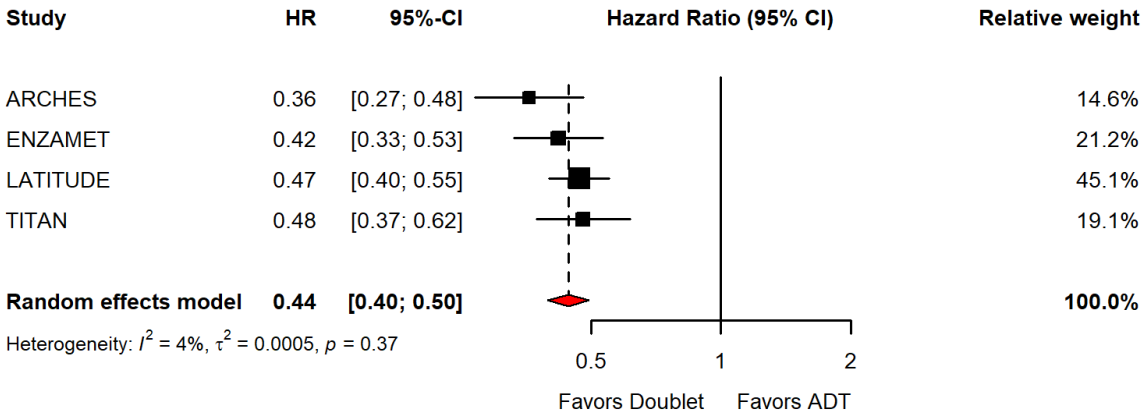
eFigure 20. Forest Plot Showing Overall Survival With Gleason Score 8 or Higher



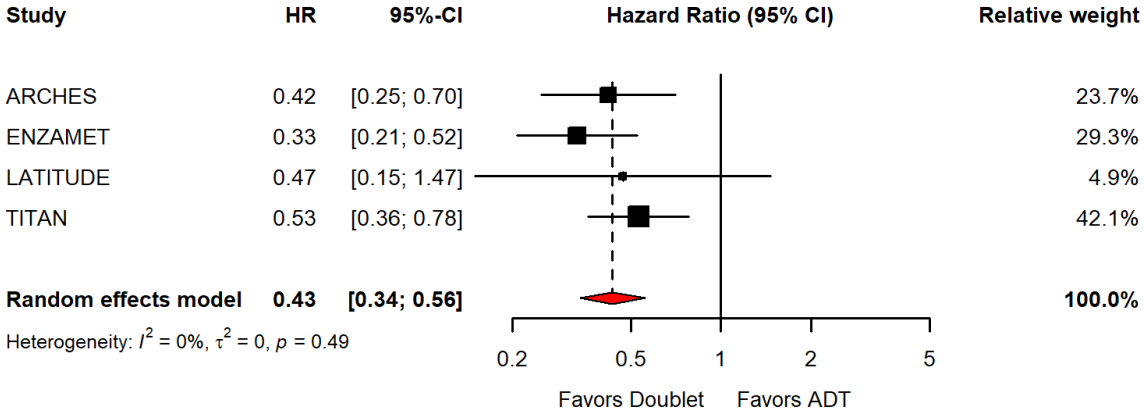
eFigure 21. Forest Plot Showing Overall Survival With Gleason Score 8 or Lower



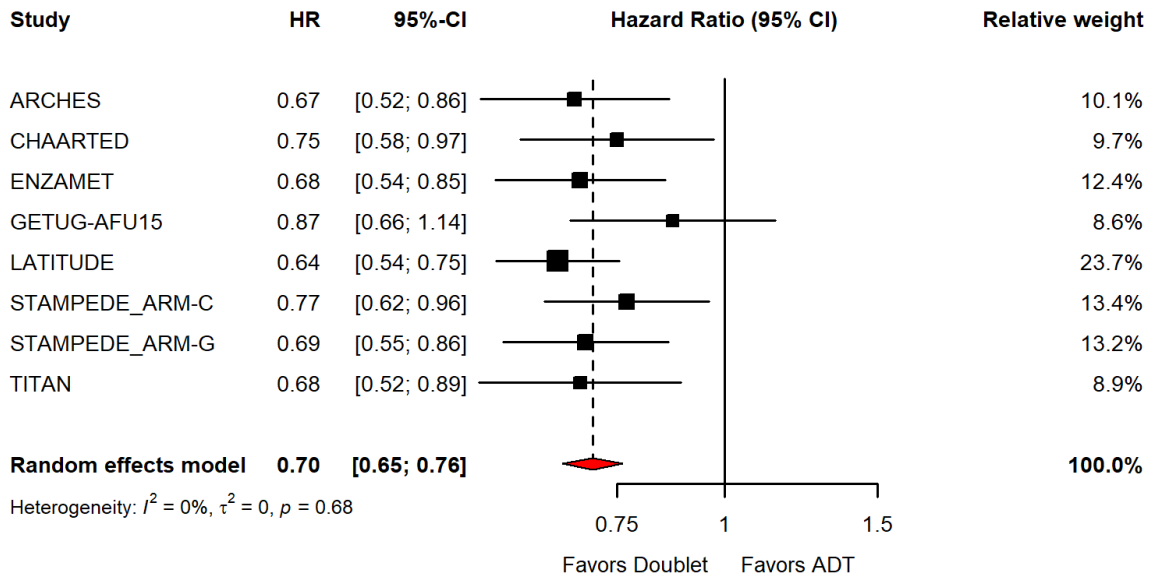
eFigure 22. Forest Plot Showing Progression-Free Survival With Gleason Score 8 or Higher



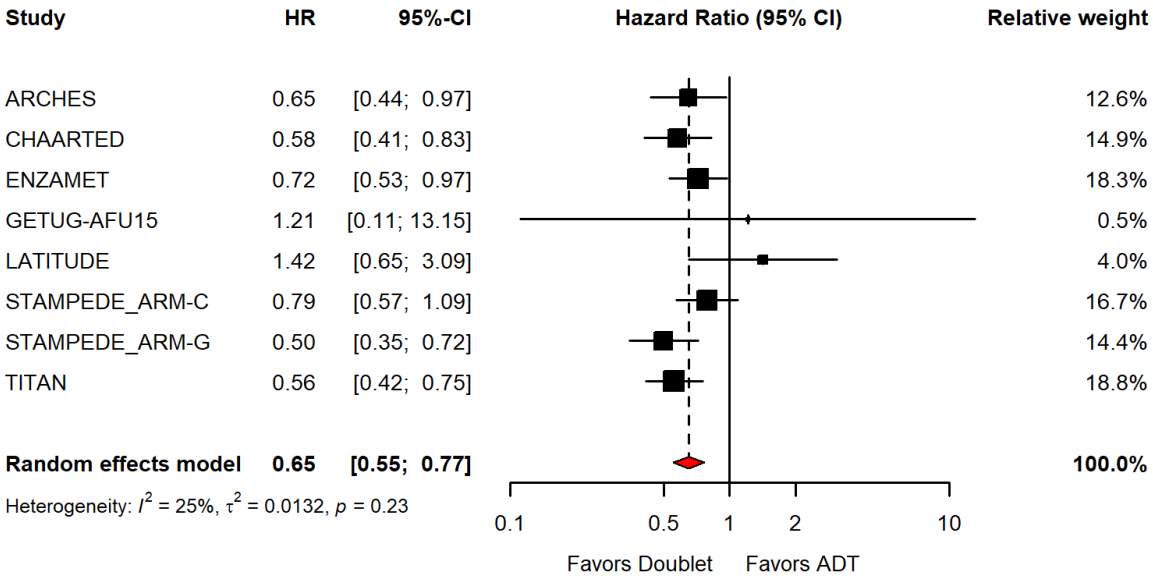
eFigure 23. Forest Plot Showing Progression-Free Survival With Gleason Score 8 or Lower



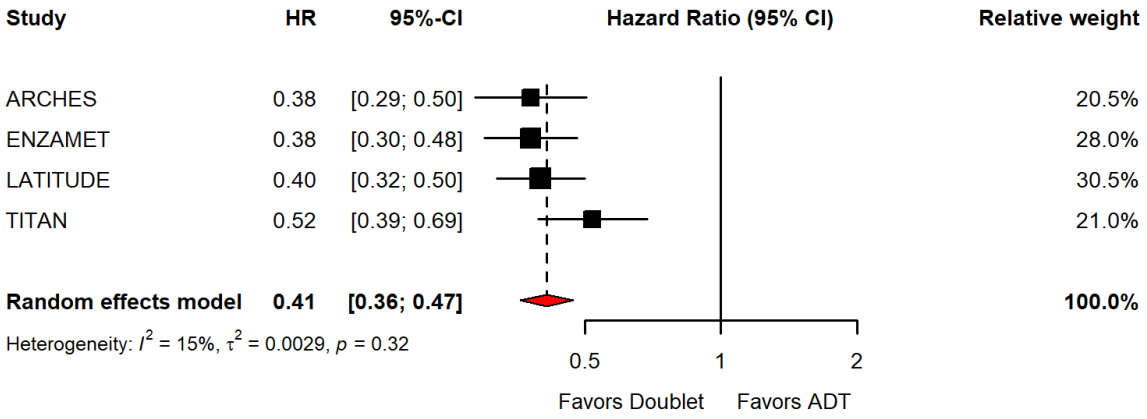
eFigure 24. Forest Plot Showing Overall Survival With Performance Status Score 0



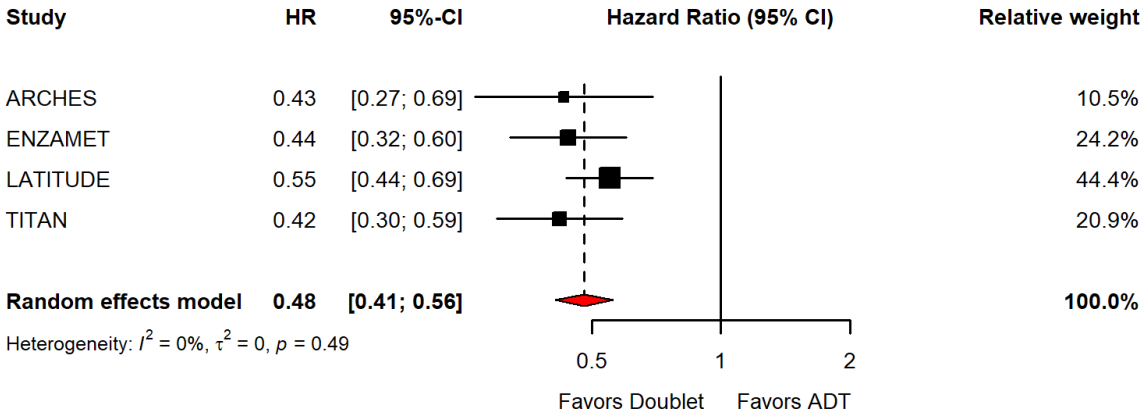
eFigure 25. Forest Plot Showing Overall Survival With Performance Status Score ½



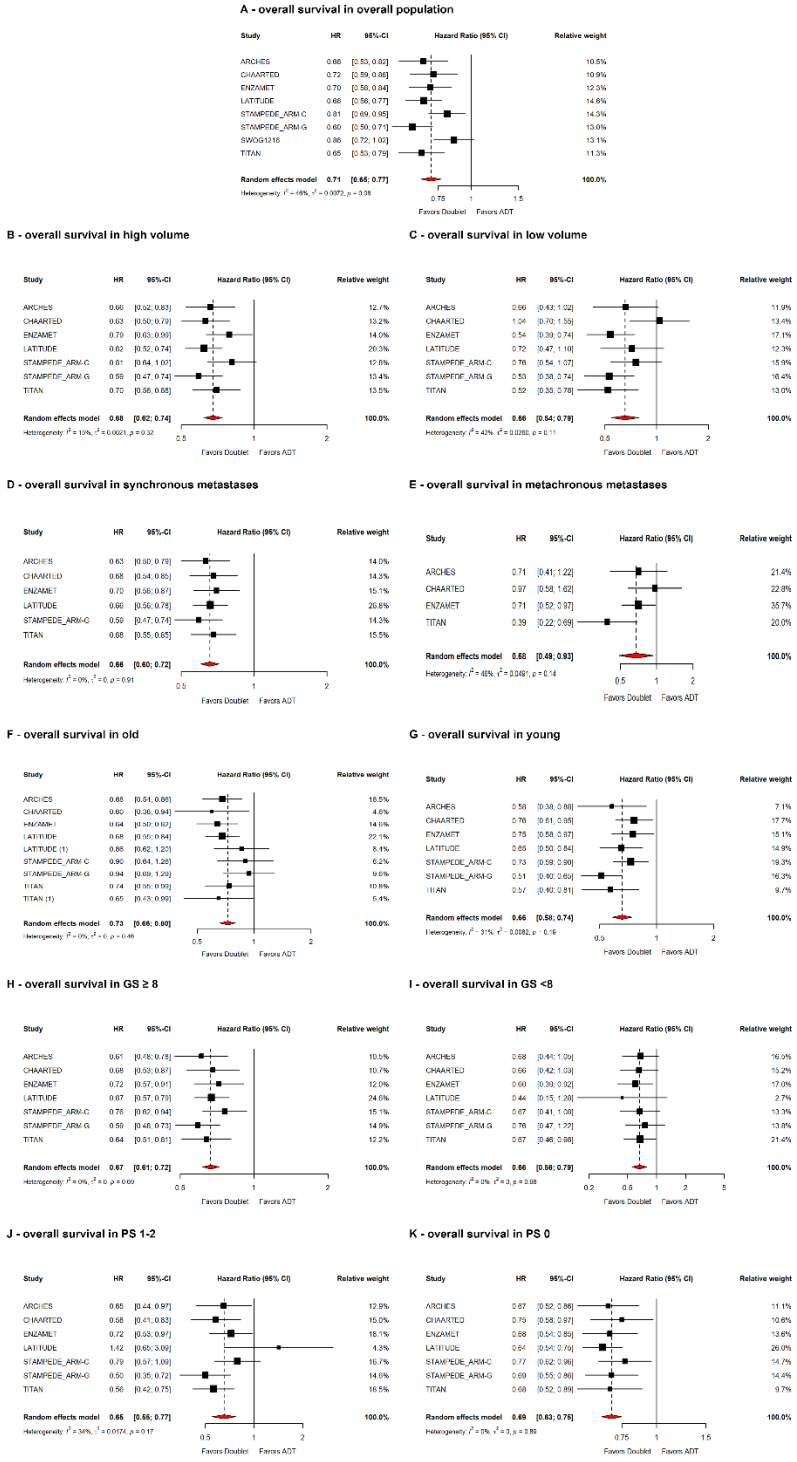
eFigure 26. Forest Plot Showing Progression-Free Survival With Performance Status Score 0



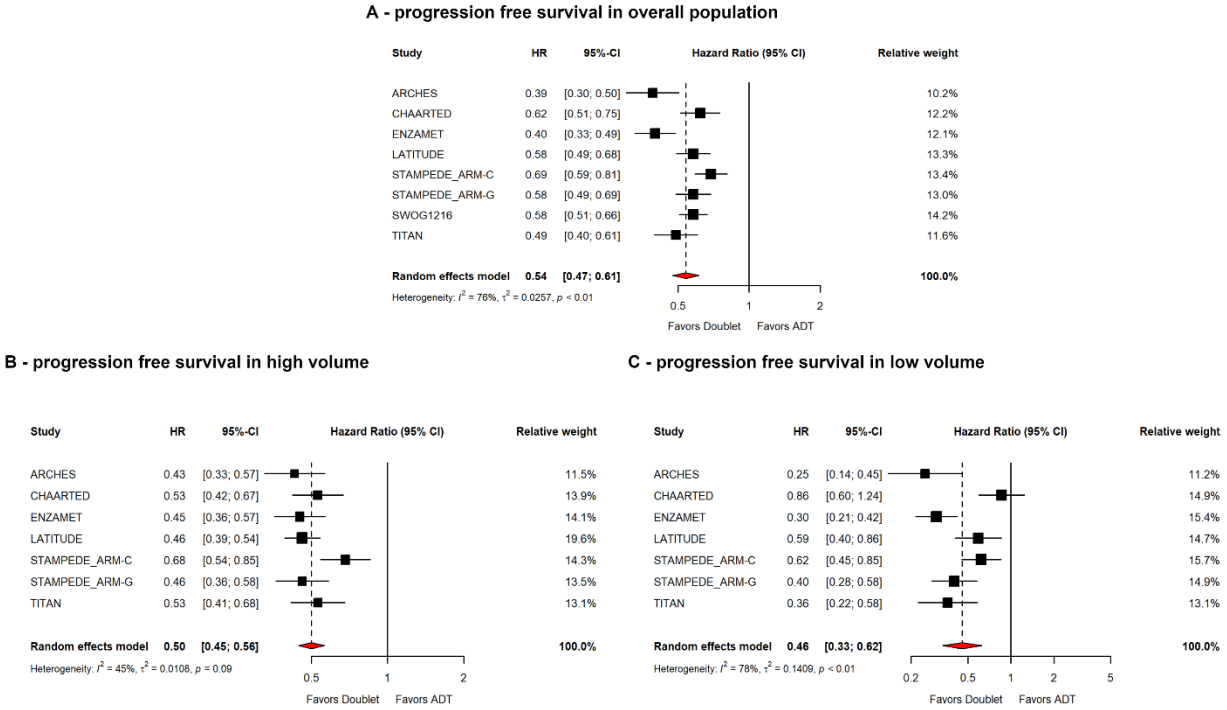
eFigure 27. Forest Plot Showing Progression-Free Survival With Performance Status Score ½



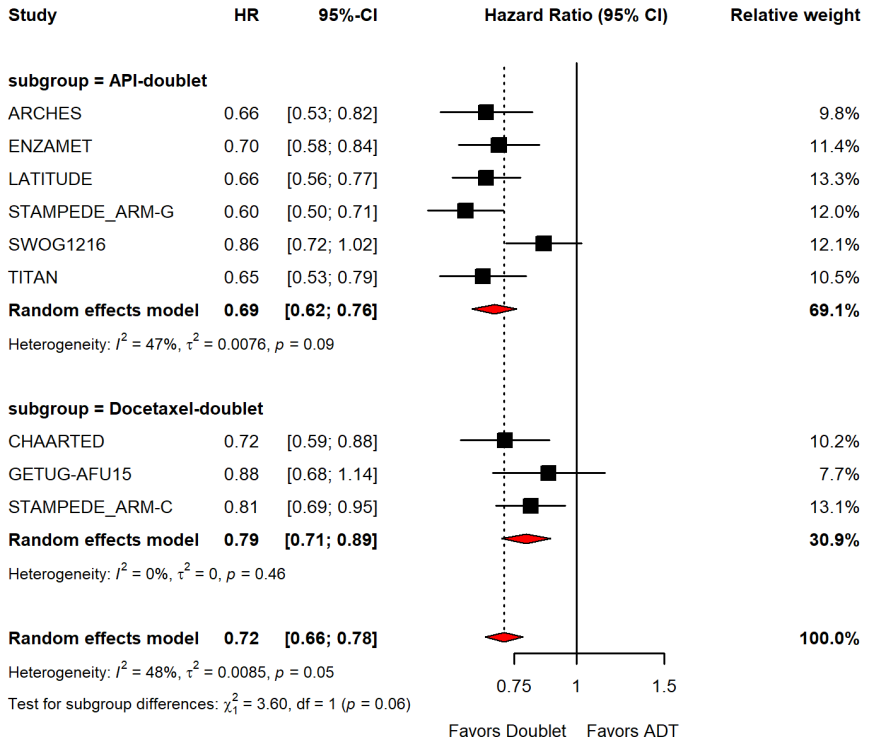
eFigure 28. Forest Plot Showing Sensitivity Analysis for Overall Survival Excluding GETUG Trial



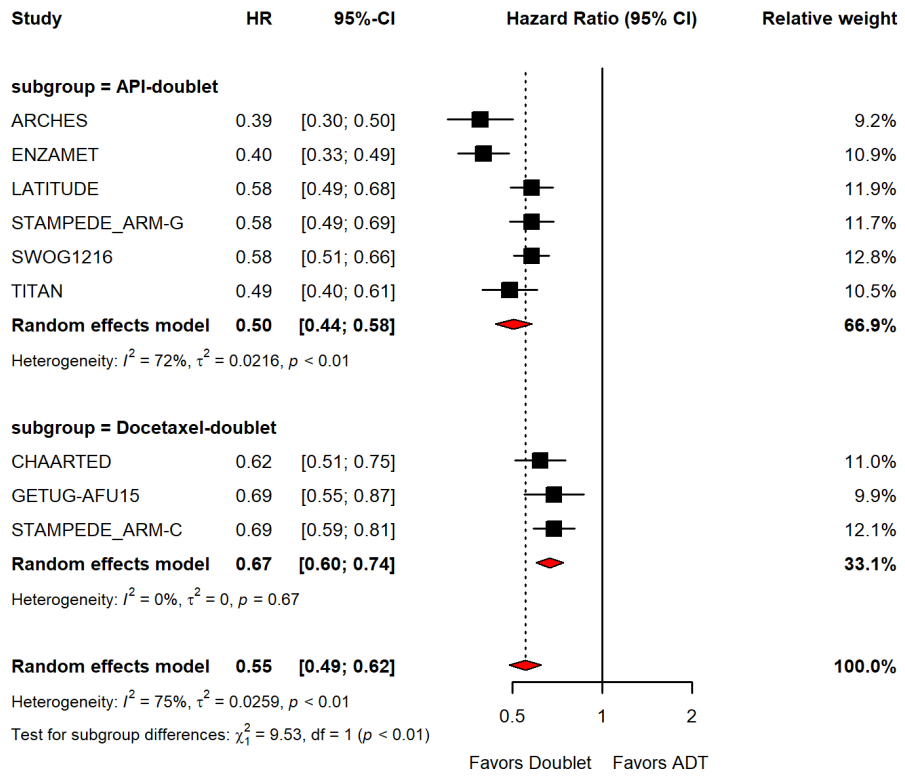
eFigure 29. Forest Plot Showing Sensitivity Analysis for Progression-Free Survival Excluding GETUG Trial



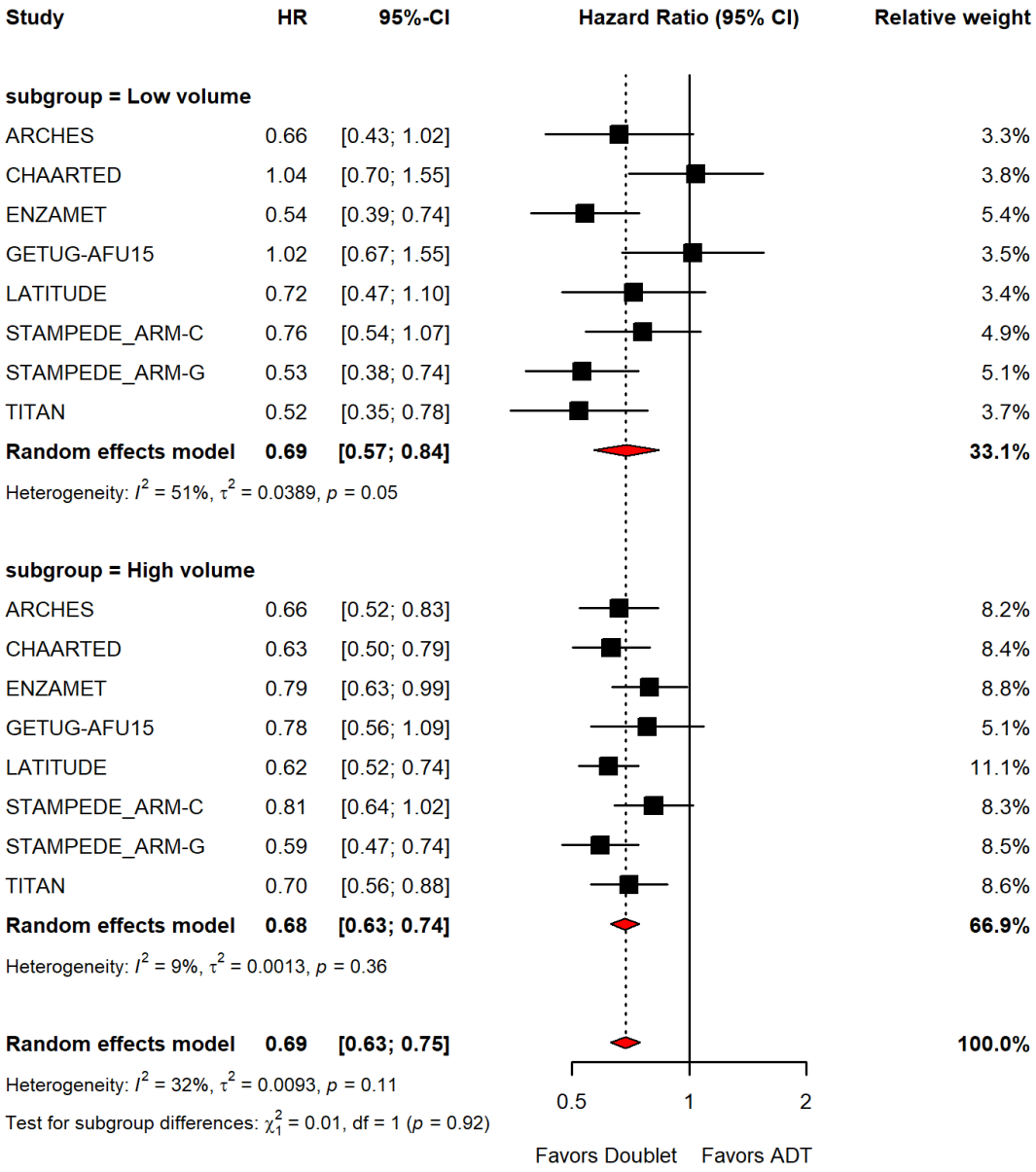
eFigure 30. Subgroup Analysis for Overall Survival by Choice of Doublet Therapy



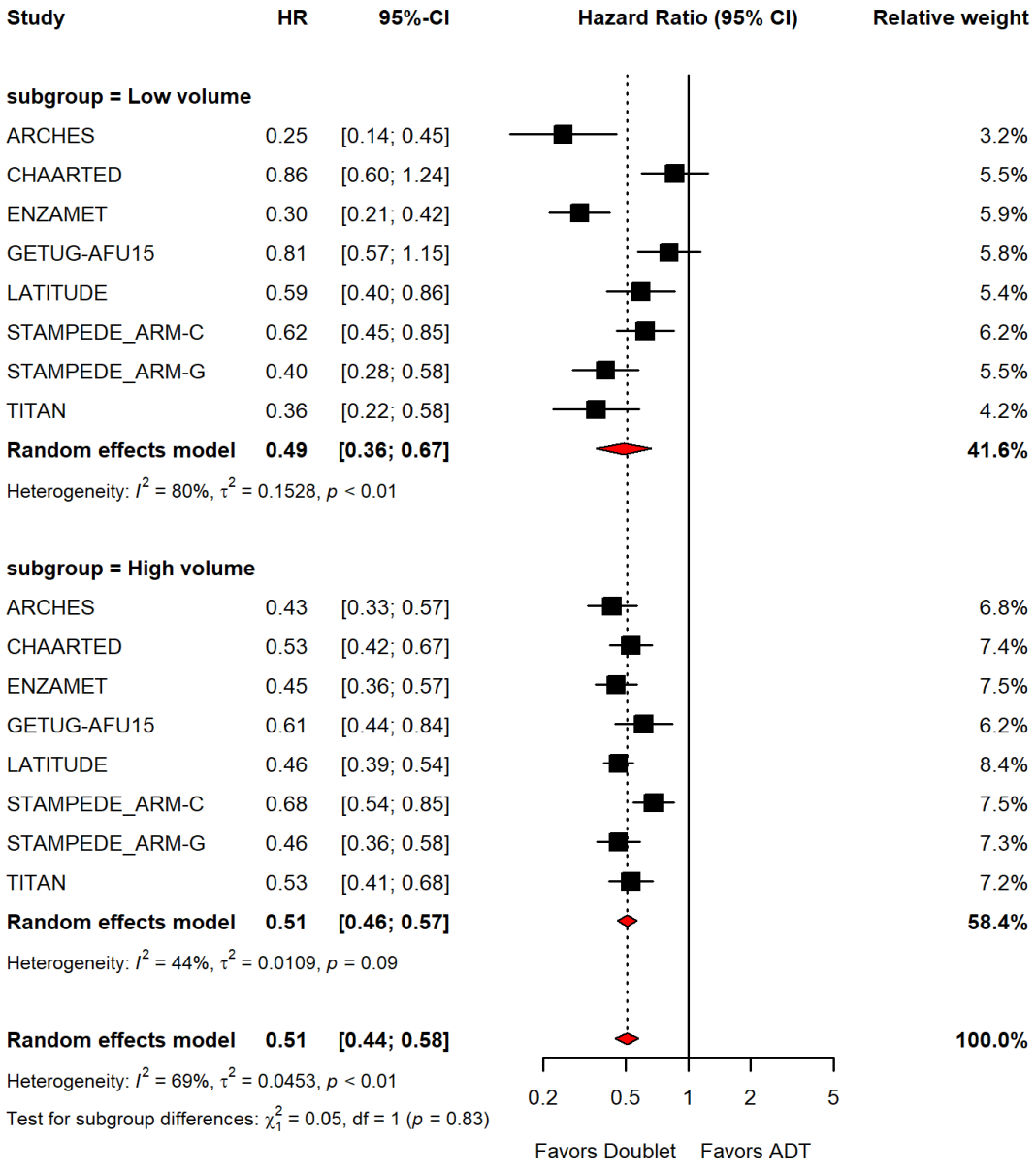
eFigure 31. Subgroup Analysis for Progression-Free Survival by Choice of Doublet Therapy



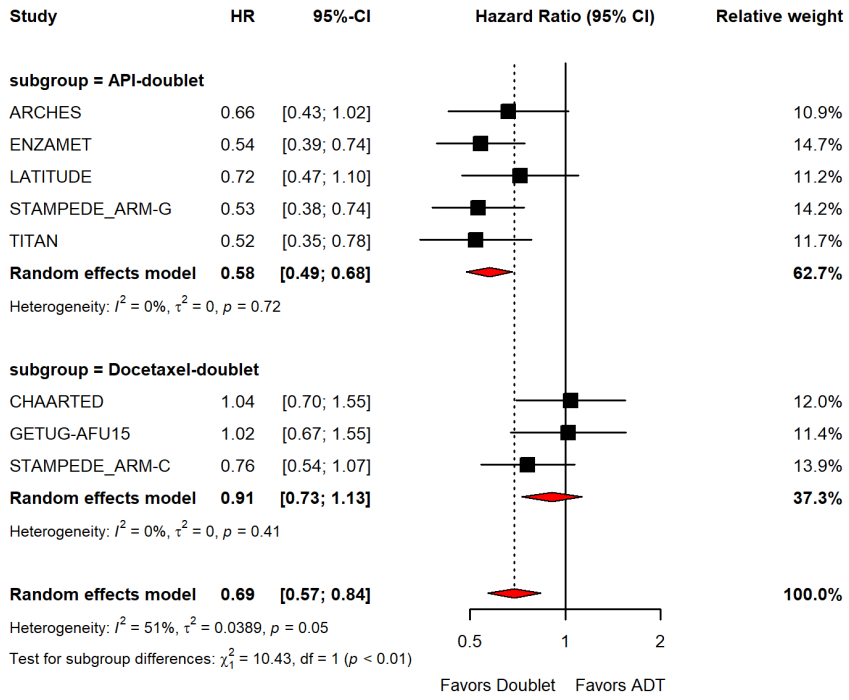
eFigure 32. Subgroup Analysis for Overall Survival by Volume of Disease



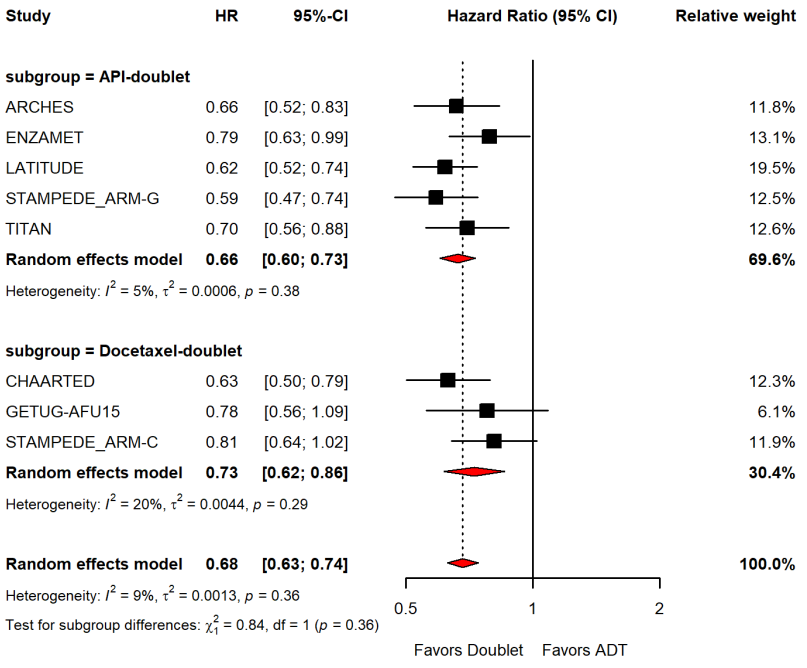
eFigure 33. Subgroup Analysis for Progression-Free Survival by Volume of Disease



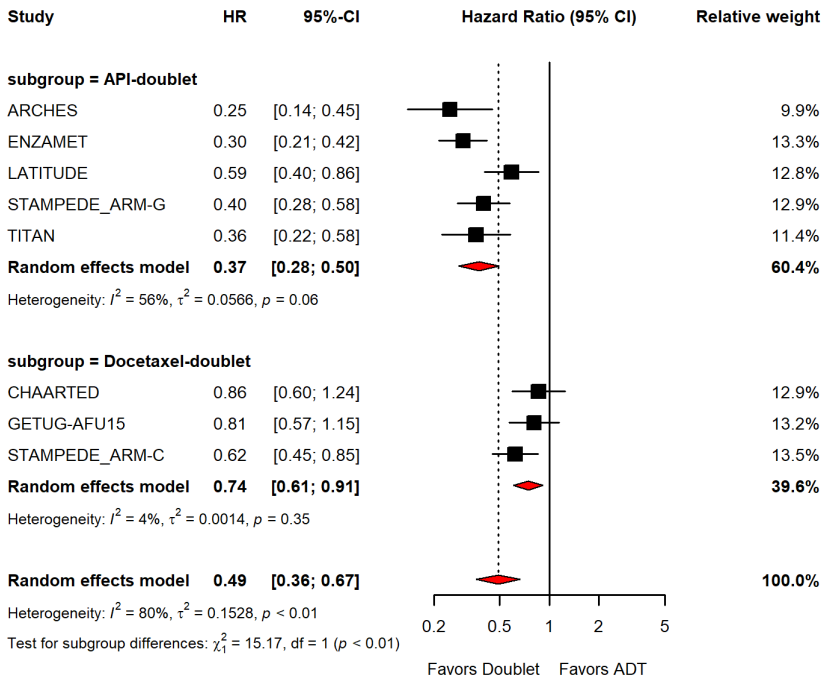
eFigure 34. Subgroup Analysis for Overall Survival in Low Volume by Choice of Doublet Therapy



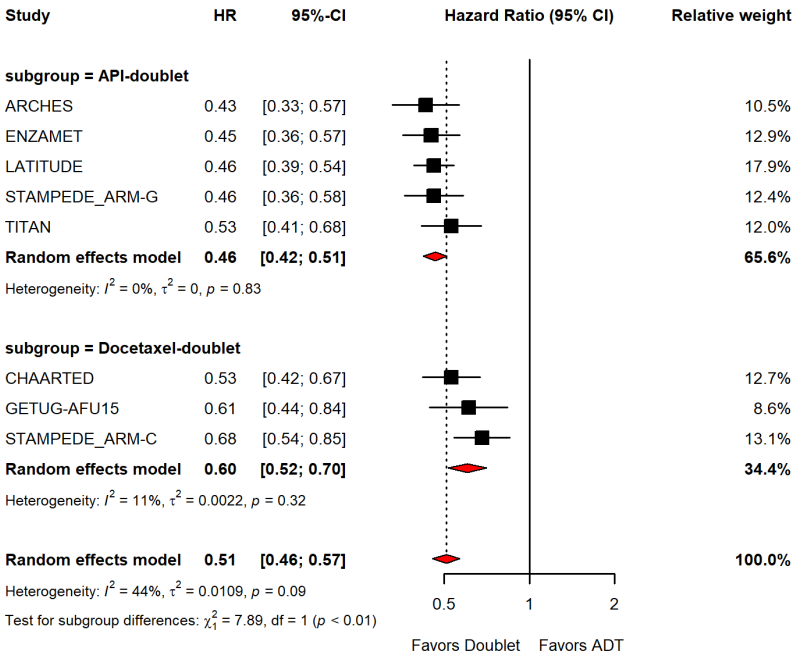
eFigure 35. Subgroup Analysis for Overall Survival in High Volume by Choice of Doublet Therapy



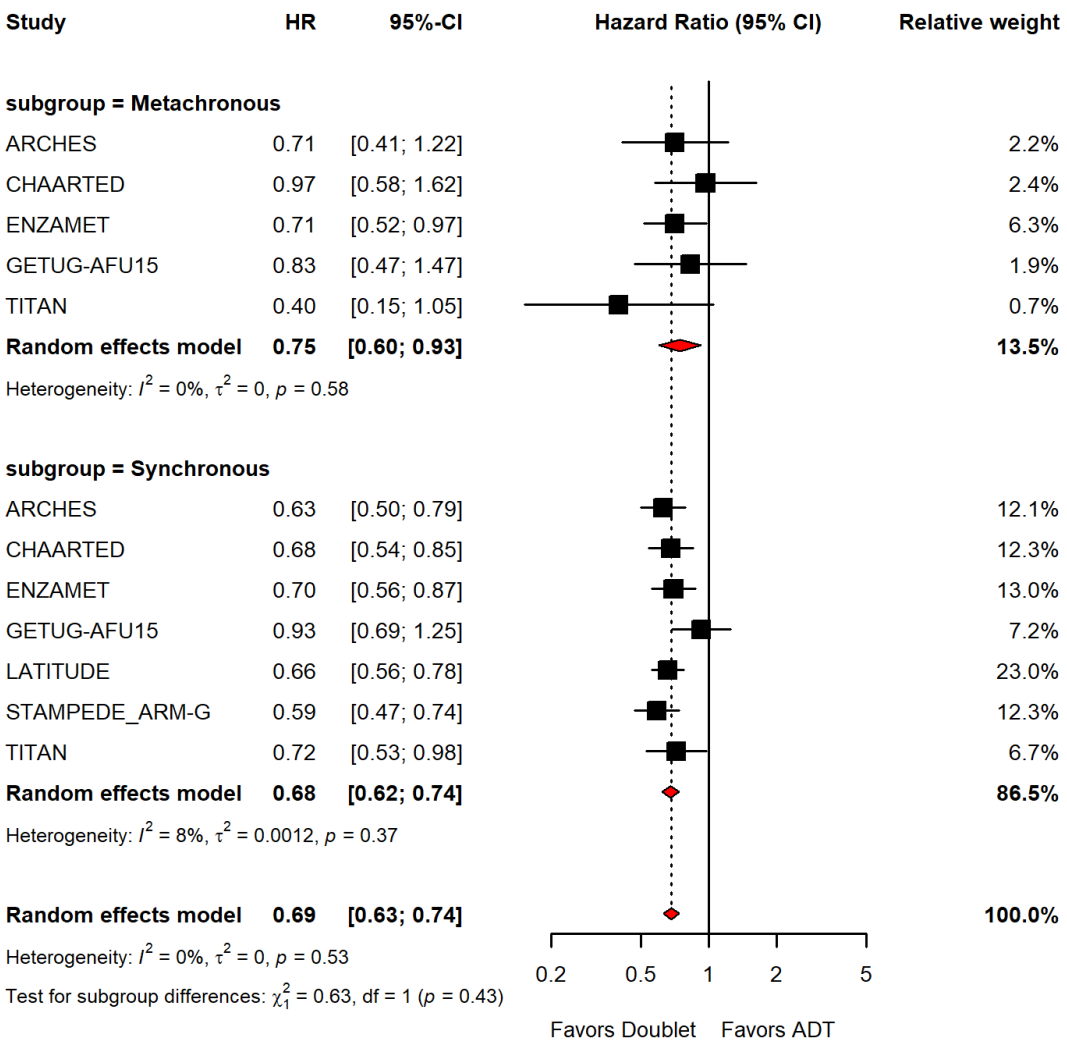
eFigure 36. Subgroup Analysis for Progression-Free Survival in Low Volume by Choice of Doublet Therapy



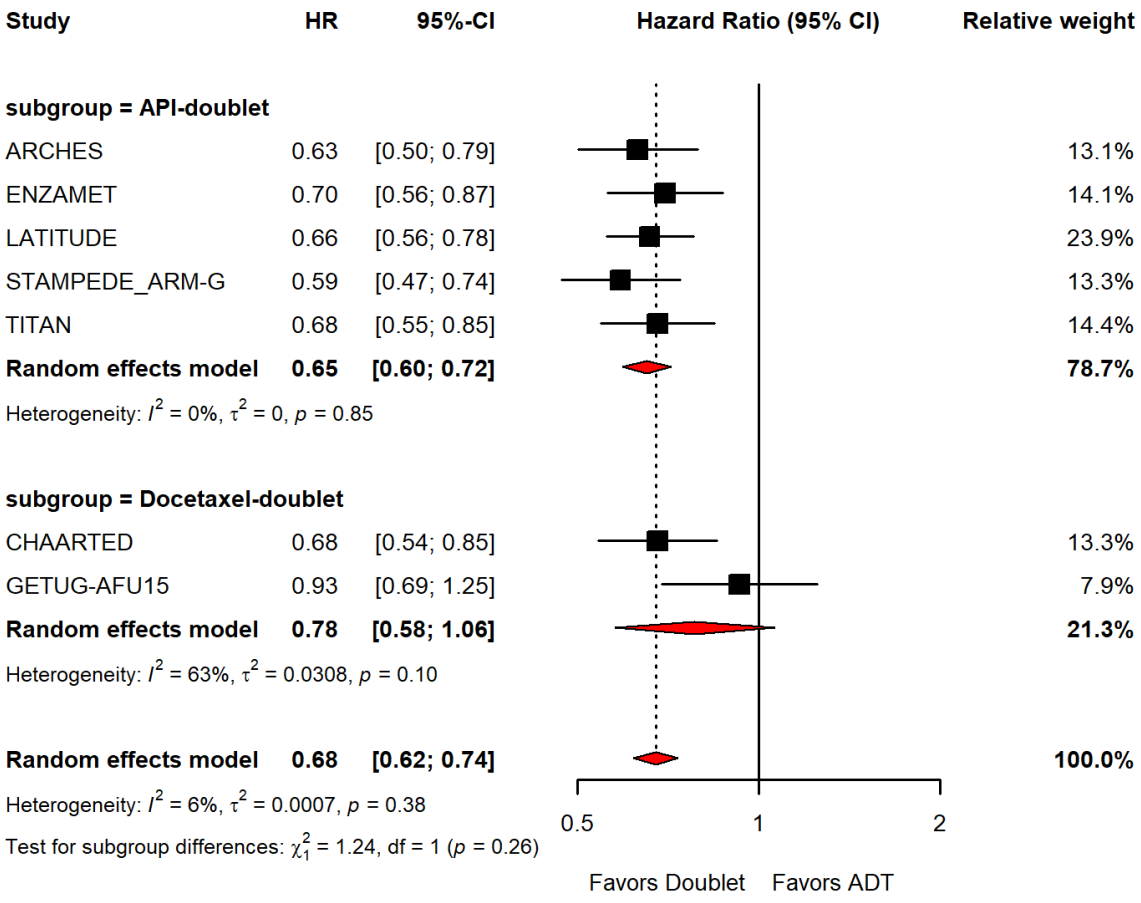
eFigure 37. Subgroup Analysis for Progression-Free Survival in High Volume by Choice of Doublet Therapy



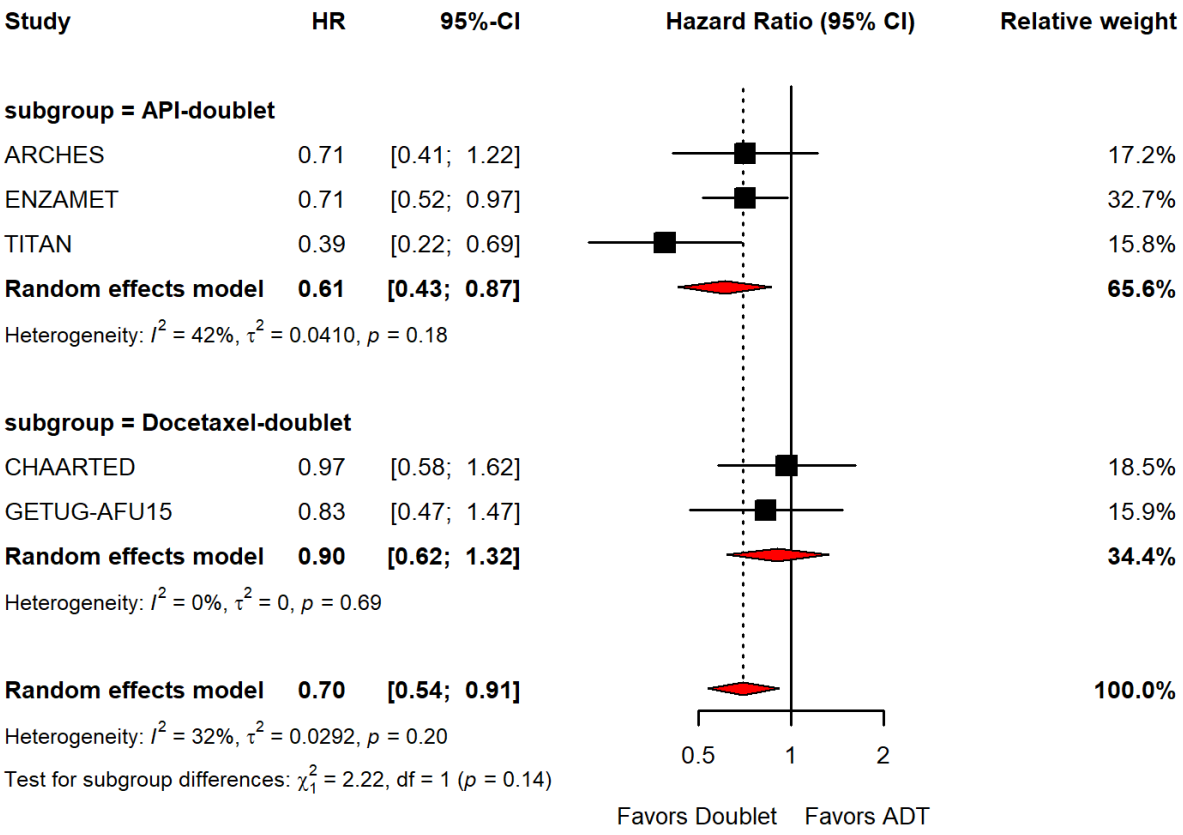
eFigure 38. Subgroup Analysis for Overall Survival by Mode of Metastatic Presentation



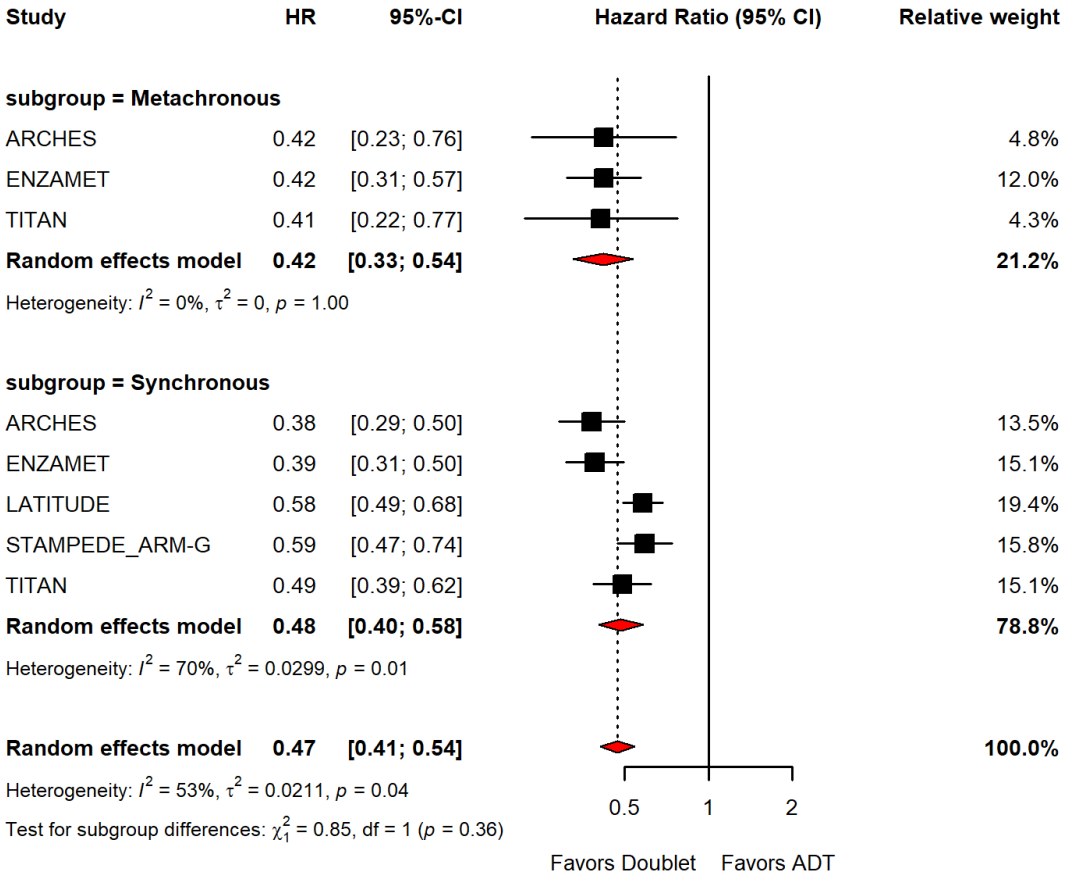
eFigure 39. Subgroup Analysis for Overall Survival in Synchronous Metastases by Choice of Doublet Therapy



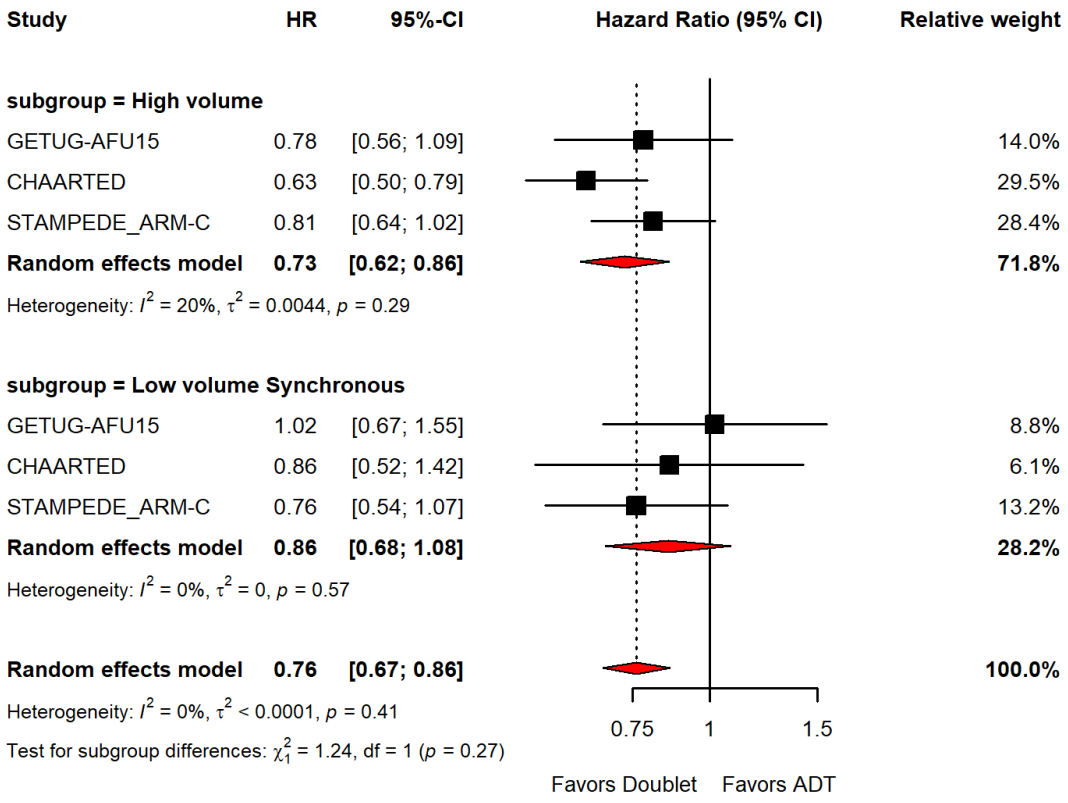
eFigure 40. Subgroup Analysis for Overall Survival in Metachronous Metastases by Choice of Doublet Therapy



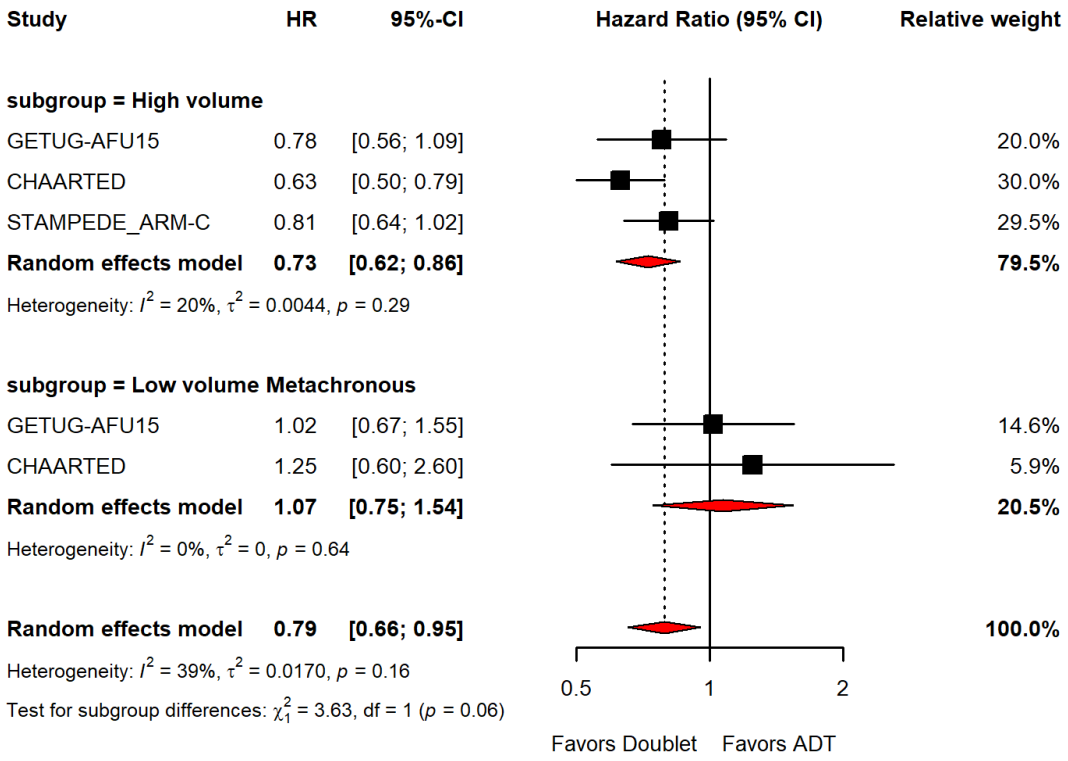
eFigure 41. Subgroup Analysis for Progression-Free Survival by Mode of Metastatic Presentation



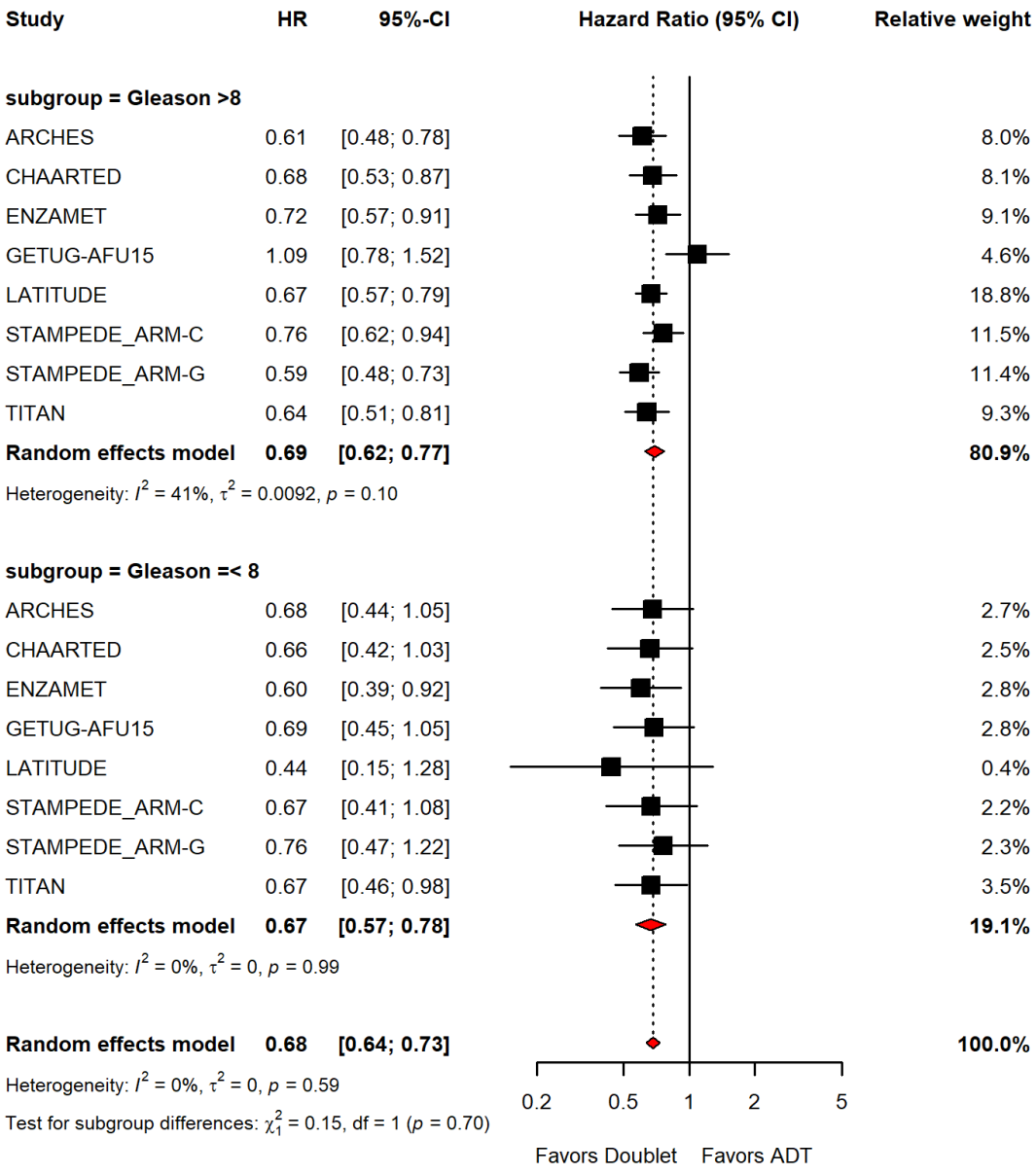
eFigure 42. Subgroup Analysis for Overall Survival With Docetaxel Doublet Between High-Volume and Low-Volume Synchronous Disease



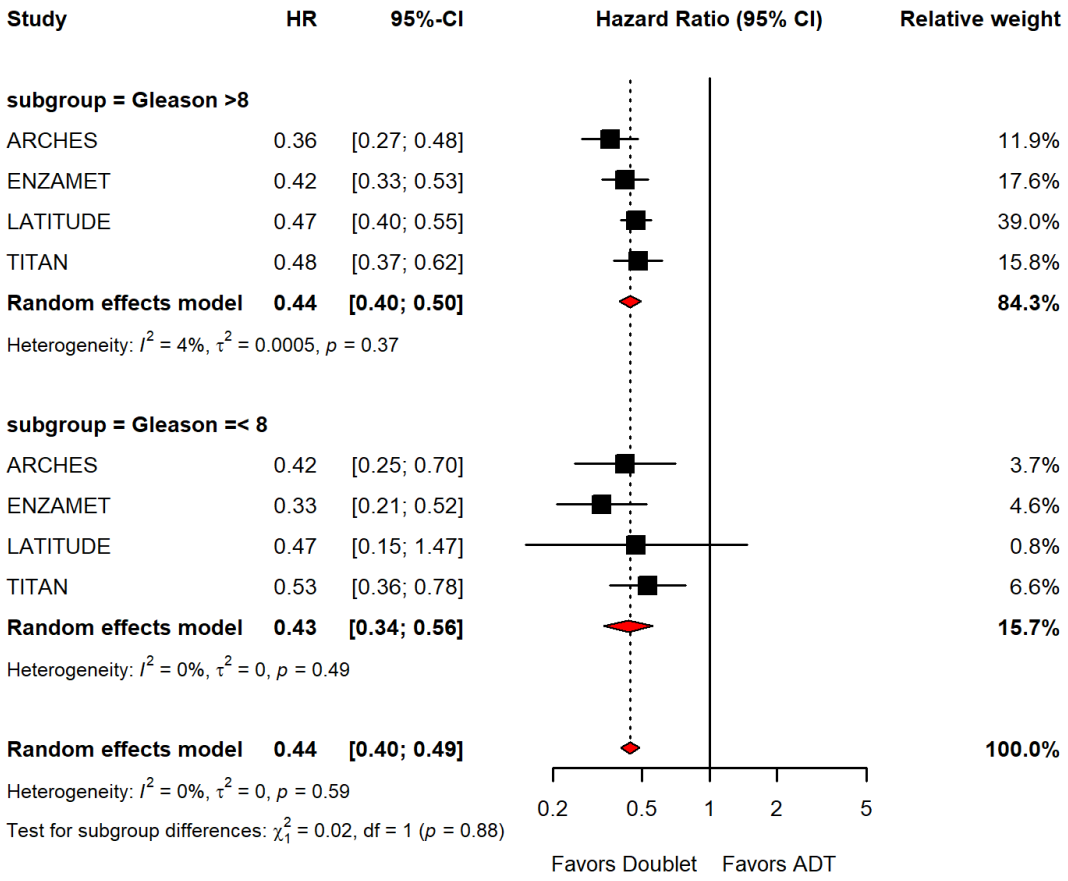
eFigure 43. Subgroup Analysis for Overall Survival With Docetaxel Doublet Between High-Volume and Low-Volume Metachronous Disease



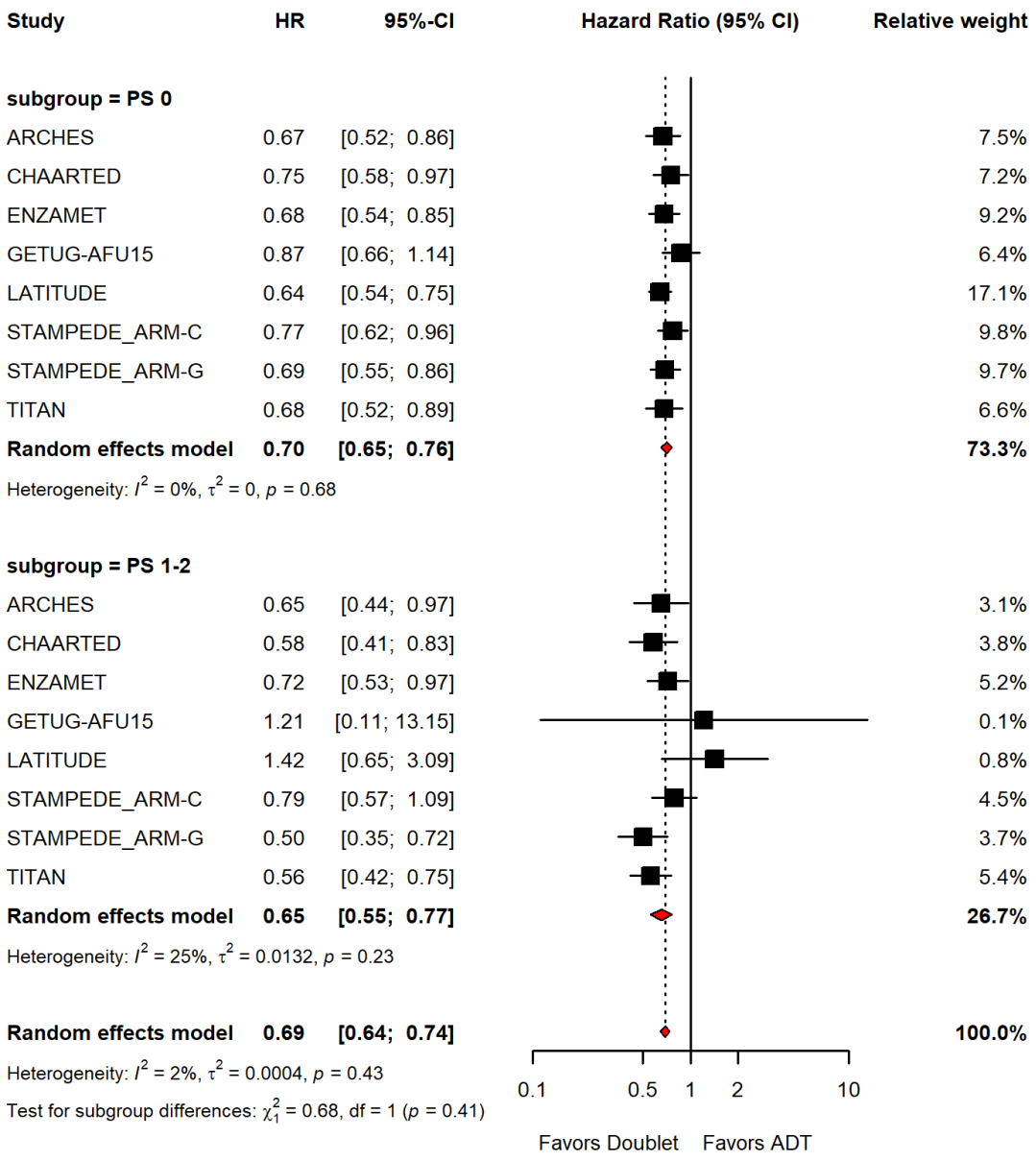
eFigure 44. Subgroup Analysis for Overall Survival by Gleason Score



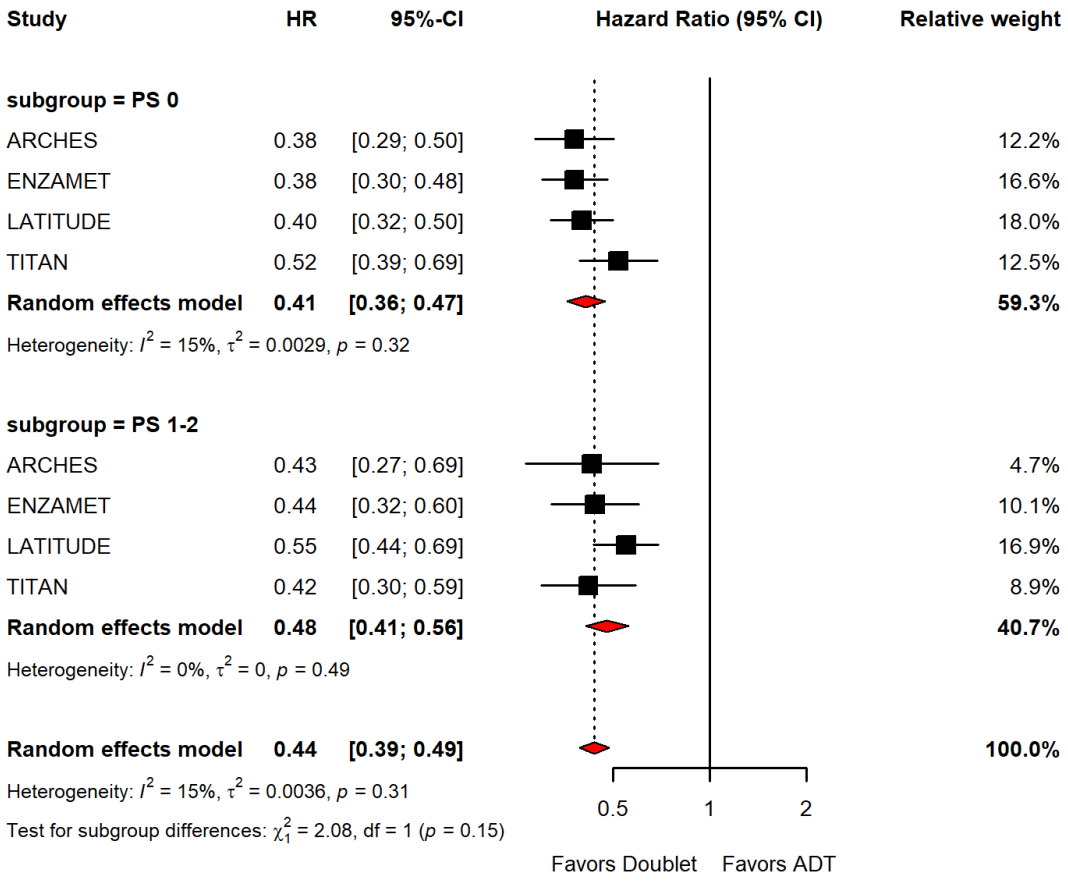
eFigure 45. Subgroup Analysis for Progression-Free Survival by Gleason Score



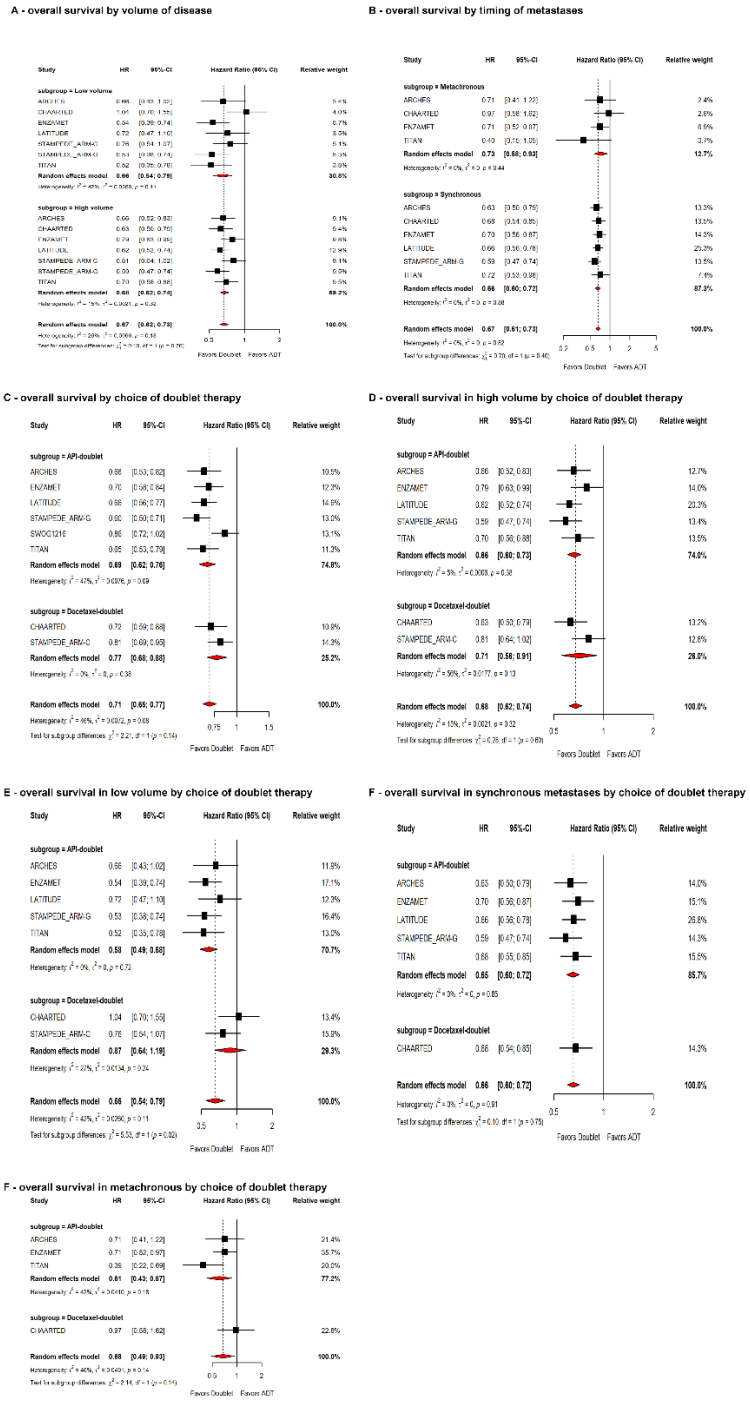
eFigure 46. Subgroup Analysis for Overall Survival by Performance Status Score



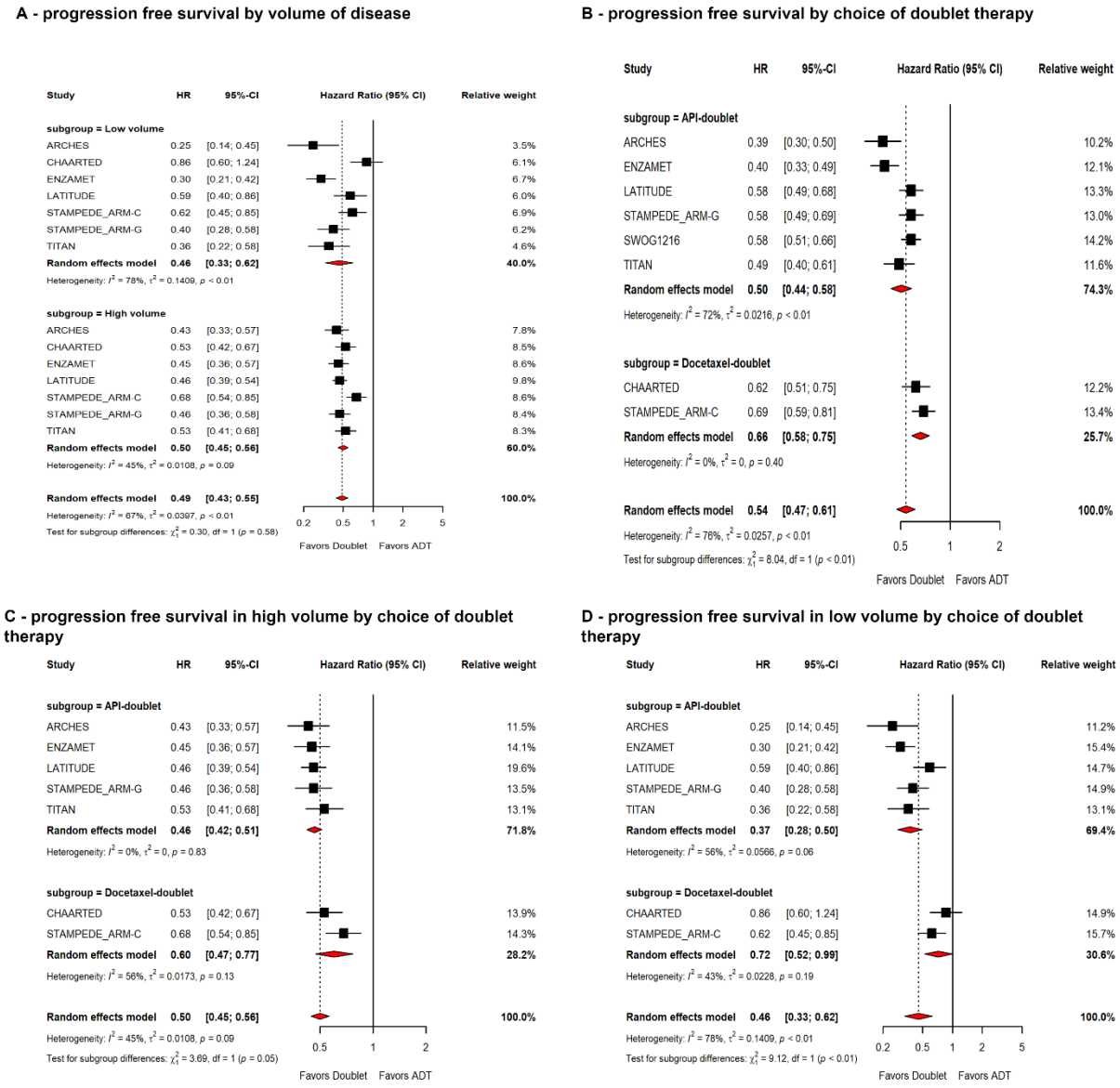
eFigure 47. Subgroup Analysis for Progression-Free Survival by Performance Status Score



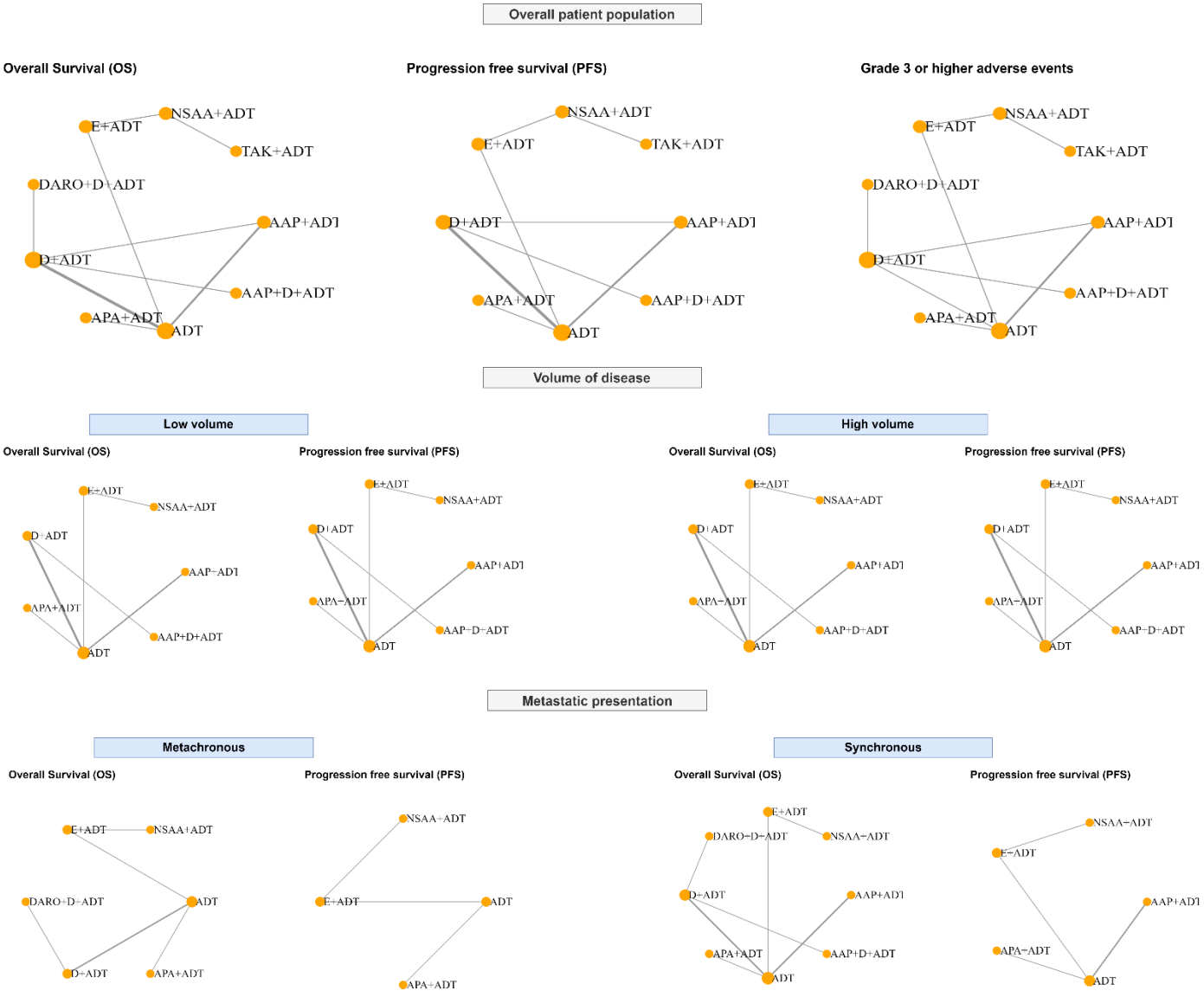
eFigure 48. Subgroup Analyses for Overall Survival Excluding GETUG Trial



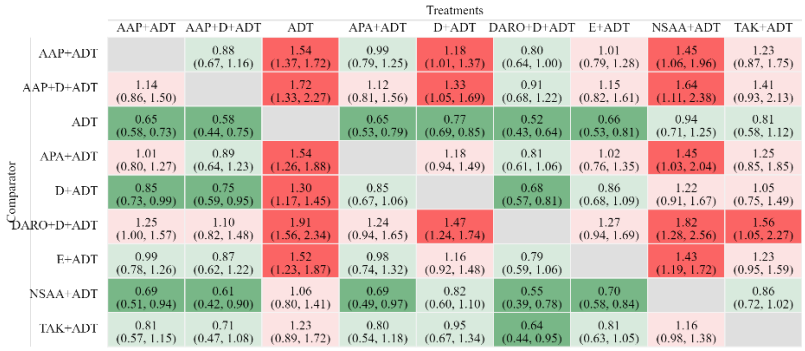
eFigure 49. Subgroup Analyses for Progression-Free Survival Excluding GETUG Trial



eFigure 50. Network Plots for Patient-Important Outcomes in Overall Population and Contemporary Subgroups

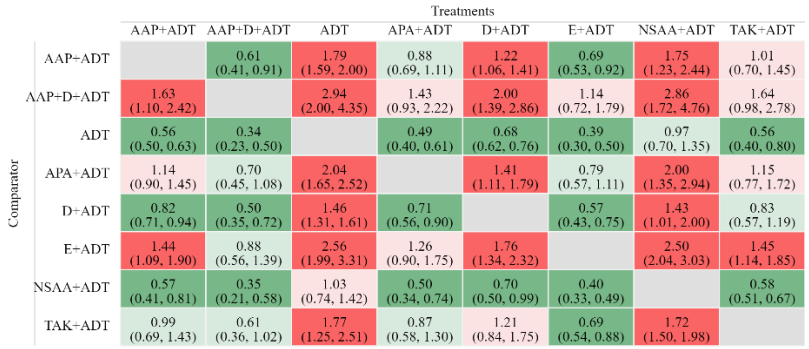


eFigure 51. Mixed Treatment Comparisons for Overall Survival in the Overall Patient Population



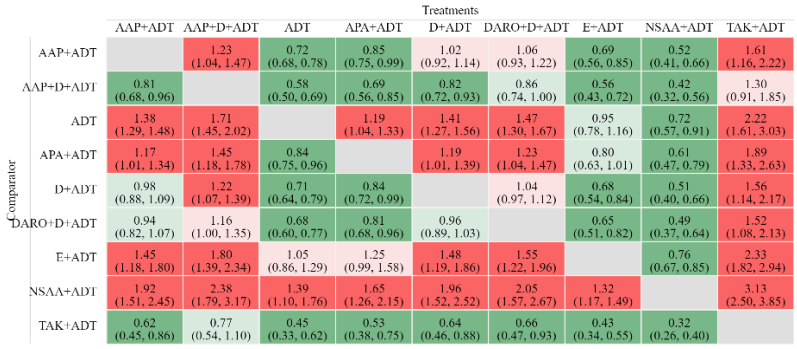
Treatment	P-Score	Rank
DARO+D+ADT	0.9476	1
AAP+D+ADT	0.8179	2
APA+ADT	0.6432	3
AAP+ADT	0.6343	4
E+ADT	0.6307	5
D+ADT	0.3414	6
TAK+ADT	0.3253	7
NSAA+ADT	0.1037	8
ADT	0.0561	9

eFigure 52. Mixed Treatment Comparisons for Progression-Free Survival in the Overall Patient Population



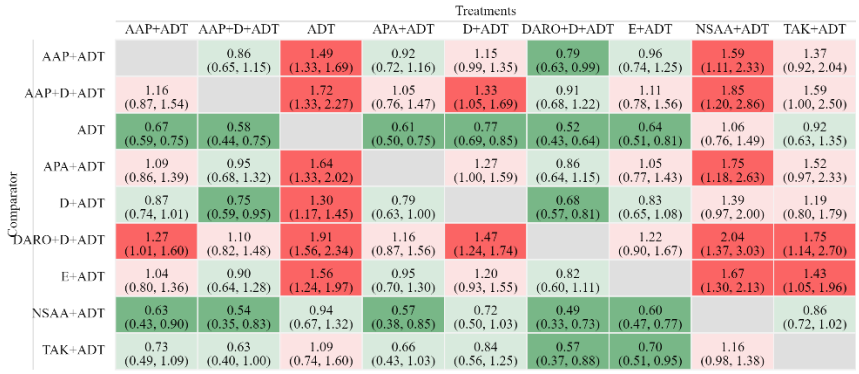
Treatment	P-Score	Rank
AAP+D+ADT	0.9448	1
E+ADT	0.8855	2
APA+ADT	0.6799	3
AAP+ADT	0.5236	4
TAK+ADT	0.5154	5
D+ADT	0.3046	6
NSAA+ADT	0.0833	7
ADT	0.0628	8

eFigure 53. Mixed Treatment Comparisons for Adverse Events (Grade 3 or Higher) in the Overall Patient Population



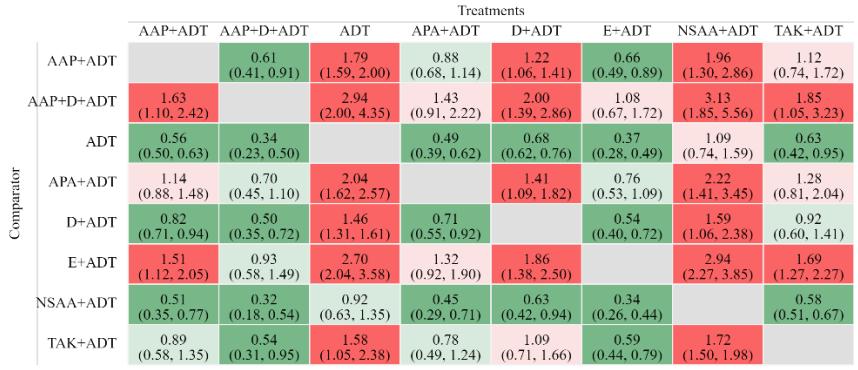
Treatment	P-Score	Rank
NSAA+ADT	0.9996	1
E+ADT	0.8327	2
ADT	0.7879	3
APA+ADT	0.6244	4
AAP+ADT	0.4339	5
D+ADT	0.4069	6
DARO+D+ADT	0.2837	7
AAP+D+ADT	0.1194	8
TAK+ADT	0.0115	9

eFigure 54. Mixed Treatment Comparisons for Overall Survival in the Overall Patient Population (Excluding Patients Who Received Docetaxel in 3 Trials)



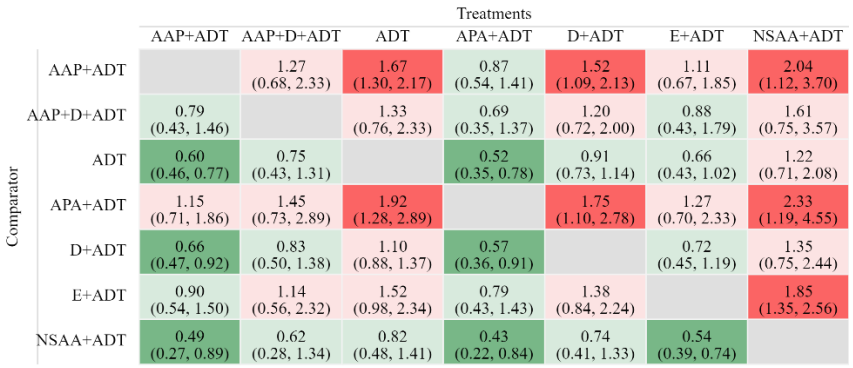
Treatment	P-Score	Rank
DARO+D+ADT	0.9335	1
AAP+D+ADT	0.8002	2
APA+ADT	0.7309	3
E+ADT	0.6622	4
AAP+ADT	0.5860	5
D+ADT	0.3644	6
TAK+ADT	0.2447	7
ADT	0.1218	8
NSAA+ADT	0.0564	9

eFigure 55. Mixed Treatment Comparisons for Progression-Free Survival in the Overall Patient Population (Excluding Patients Who Received Docetaxel in 3 Trials)



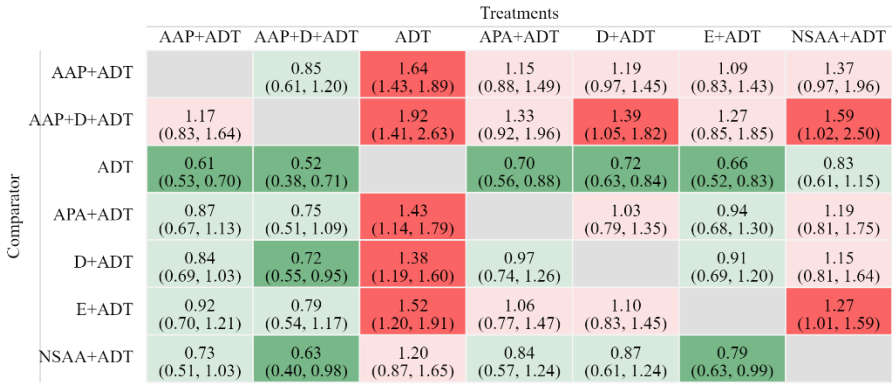
Treatment	P-Score	Rank
AAP+D+ADT	0.934	1
E+ADT	0.9014	2
APA+ADT	0.6887	3
AAP+ADT	0.5531	4
TAK+ADT	0.4416	5
D+ADT	0.3346	6
ADT	0.0972	7
NSAA+ADT	0.0494	8

eFigure 56. Mixed Treatment Comparisons for Overall Survival in Low-Volume Disease



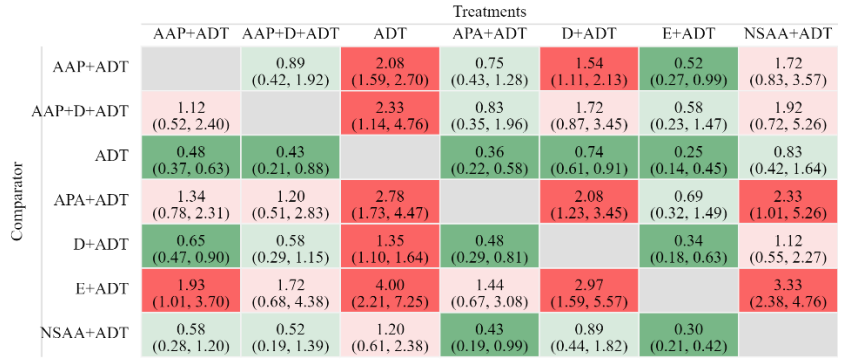
Treatment	P-Score	Rank
APA+ADT	0.8882	1
AAP+ADT	0.7835	2
E+ADT	0.6791	3
AAP+D+ADT	0.5368	4
D+ADT	0.3334	5
ADT	0.1922	6
NSAA+ADT	0.0868	7

eFigure 57. Mixed Treatment Comparisons for Overall Survival in High-Volume Disease



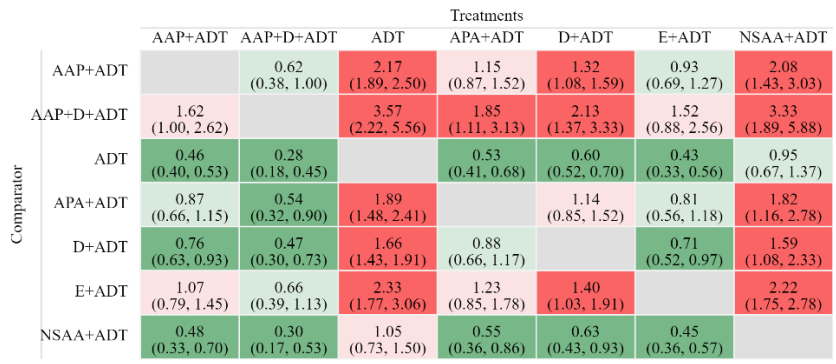
Treatment	P-Score	Rank
AAP+D+ADT	0.9328	1
AAP+ADT	0.7794	2
E+ADT	0.6277	3
APA+ADT	0.4985	4
D+ADT	0.4145	5
NSAA+ADT	0.2241	6
ADT	0.023	7

eFigure 58. Mixed Treatment Comparisons for Progression-Free Survival in Low-Volume Disease



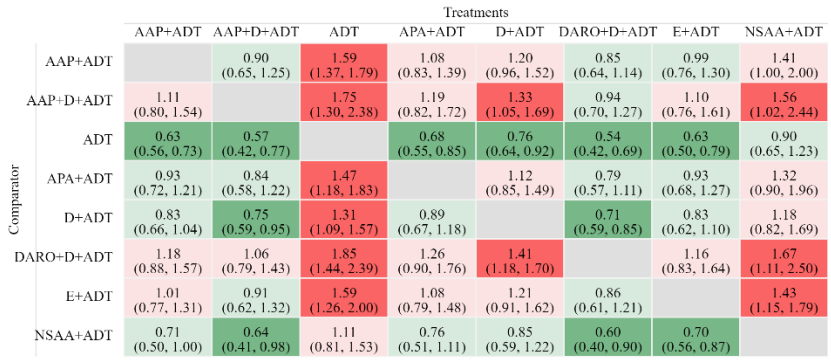
Treatment	P-Score	Rank
E+ADT	0.946	1
APA+ADT	0.7769	2
AAP+D+ADT	0.6521	3
AAP+ADT	0.5798	4
D+ADT	0.2818	5
NSAA+ADT	0.2113	6
ADT	0.0521	7

eFigure 59. Mixed Treatment Comparisons for Progression-Free Survival in High-Volume Disease



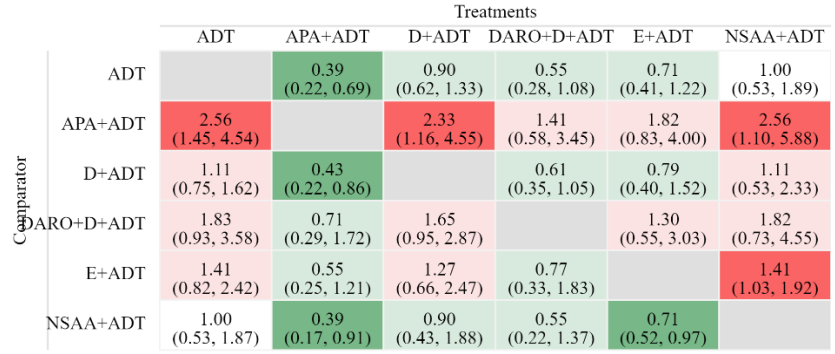
Treatment	P-Score	Rank
AAP+D+ADT	0.9835	1
E+ADT	0.7641	2
AAP+ADT	0.6987	3
APA+ADT	0.5191	4
D+ADT	0.3656	5
NSAA+ADT	0.1021	6
ADT	0.0669	7

eFigure 60. Mixed Treatment Comparisons for Overall Survival in Synchronous Disease



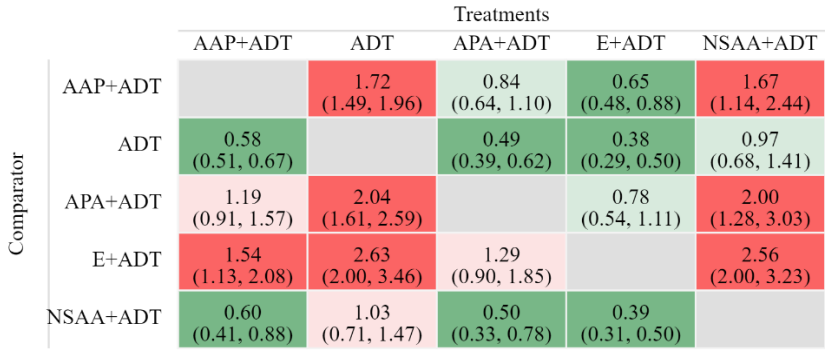
Treatment	P-Score	Rank
DARO+D+ADT	0.8904	1
AAP+D+ADT	0.7948	2
E+ADT	0.6573	3
AAP+ADT	0.6433	4
APA+ADT	0.5137	5
D+ADT	0.3121	6
NSAA+ADT	0.1513	7
ADT	0.0371	8

eFigure 61. Mixed Treatment Comparisons for Overall Survival in Metachronous Disease



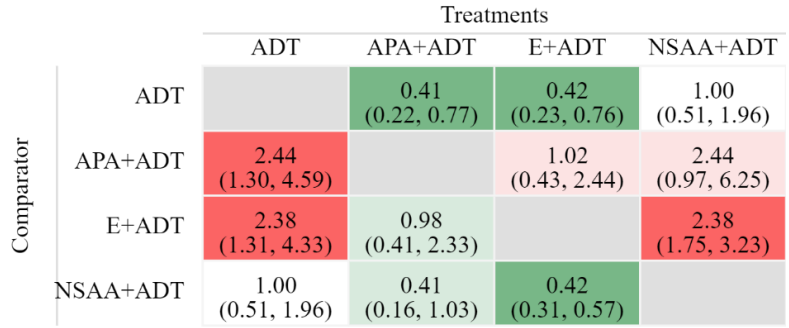
Treatment	P-Score	Rank
APA+ADT	0.9365	1
DARO+D+ADT	0.7545	2
E+ADT	0.5968	3
D+ADT	0.3169	4
NSAA+ADT	0.2051	5
ADT	0.1901	6

eFigure 62. Mixed Treatment Comparisons for Progression-Free Survival in Synchronous Disease



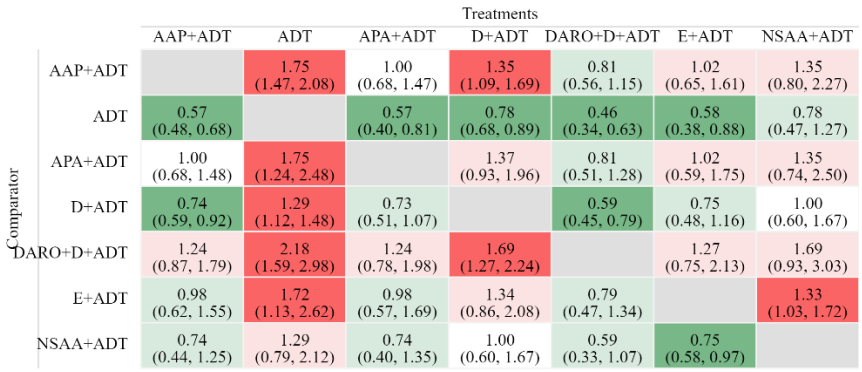
Treatment	P-Score	Rank
E+ADT	0.9781	1
APA+ADT	0.7445	2
AAP+ADT	0.5261	3
NSAA+ADT	0.1404	4
ADT	0.111	5

eFigure 63. Mixed Treatment Comparisons for Progression-Free Survival in Metachronous Disease



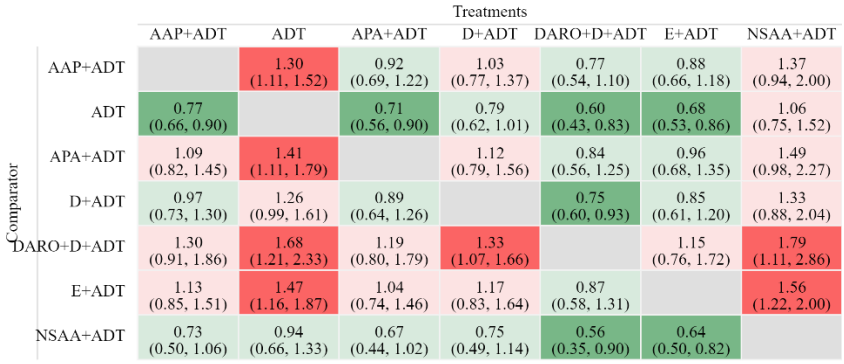
Treatment	P-Score	Rank
APA+ADT	0.8299	1
E+ADT	0.8254	2
NSAA+ADT	0.1763	3
ADT	0.1684	4

eFigure 64. Mixed Treatment Comparisons for Overall Survival in Younger Patients



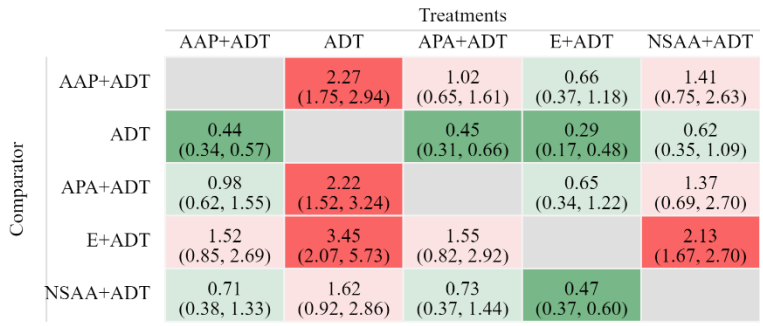
Treatment	P-Score	Rank
DARO+D+ADT	0.9112	**1**
AAP+ADT	0.6703	2
APA+ADT	0.668	3
E+ADT	0.6664	4
NSAA+ADT	0.2824	5
D+ADT	0.2751	6
ADT	0.0266	7

eFigure 65. Mixed Treatment Comparisons for Overall Survival in Older Patients



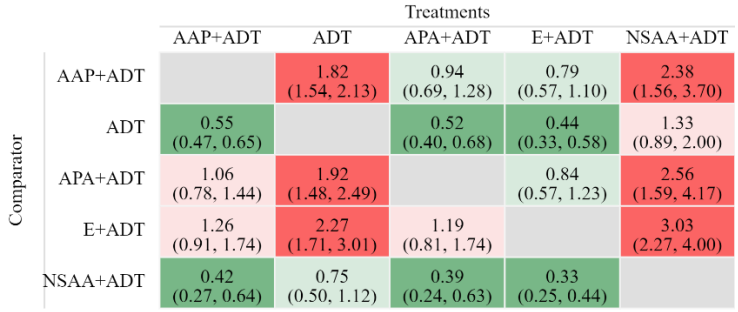
Treatment	P-Score	Rank
DARO+D+ADT	0.9088	1
E+ADT	0.7453	2
APA+ADT	0.6715	3
AAP+ADT	0.5116	4
D+ADT	0.461	5
ADT	0.1113	6
NSAA+ADT	0.0904	7

eFigure 66. Mixed Treatment Comparisons for Progression-Free Survival in Younger Patients



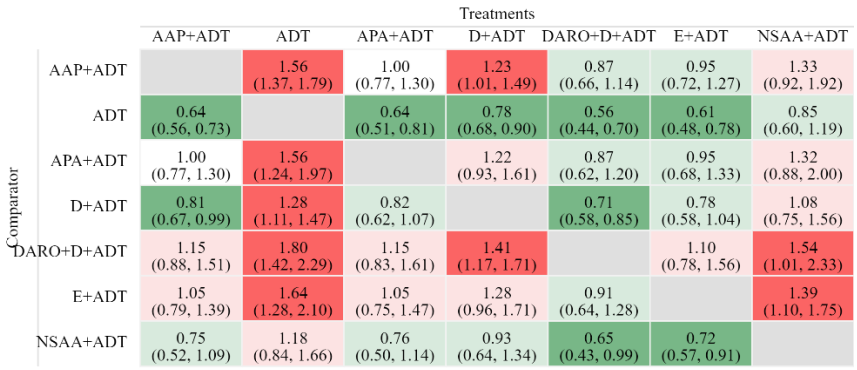
Treatment	P-Score	Rank
E+ADT	0.9589	1
AAP+ADT	0.6176	2
APA+ADT	0.5918	3
NSAA+ADT	0.3198	4
ADT	0.0119	5

eFigure 67. Mixed Treatment Comparisons for Progression-Free Survival in Older Patients



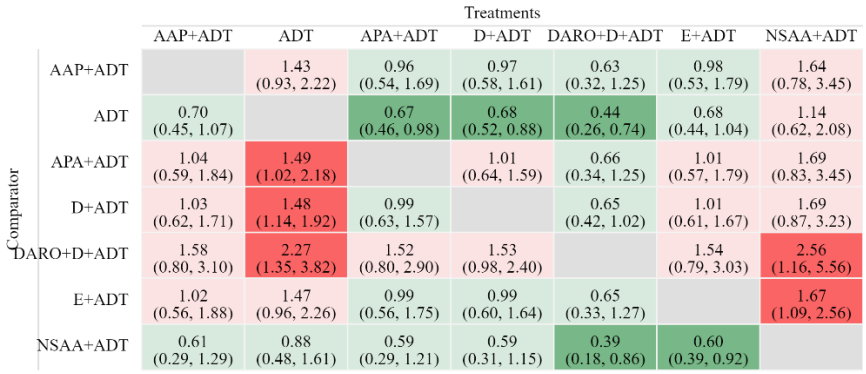
Treatment	P-Score	Rank
E+ADT	0.9316	1
APA+ADT	0.7116	2
AAP+ADT	0.6068	3
ADT	0.2303	4
NSAA+ADT	0.0198	5

eFigure 68. Mixed Treatment Comparisons for Overall Survival With Gleason Score 8 or Higher



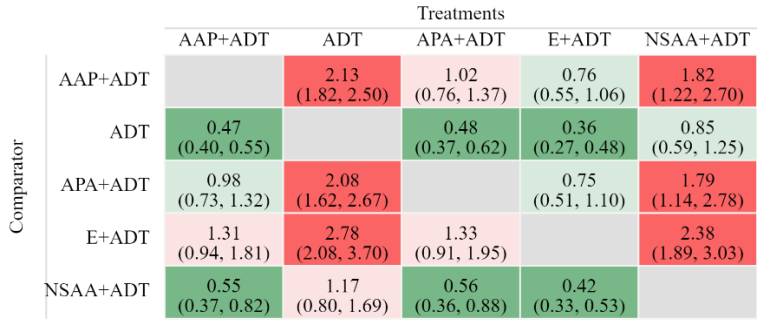
Treatment	P-Score	Rank
DARO+D+ADT	0.888	1
E+ADT	0.7472	2
AAP+ADT	0.6586	3
APA+ADT	0.6534	4
D+ADT	0.299	5
NSAA+ADT	0.2252	6
ADT	0.0286	7

eFigure 69. Mixed Treatment Comparisons for Overall Survival With Gleason Score 8 or Lower



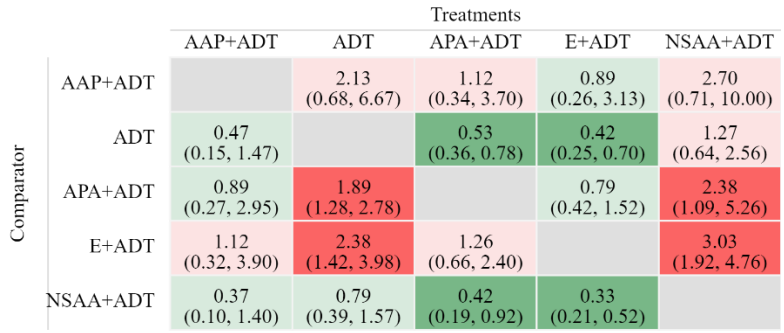
Treatment	P-Score	Rank
DARO+D+ADT	0.9436	1
APA+ADT	0.598	2
E+ADT	0.5916	3
D+ADT	0.587	4
AAP+ADT	0.5528	5
NSAA+ADT	0.1279	6
ADT	0.099	7

eFigure 70. Mixed Treatment Comparisons for Progression-Free Survival With Gleason Score 8 or Higher



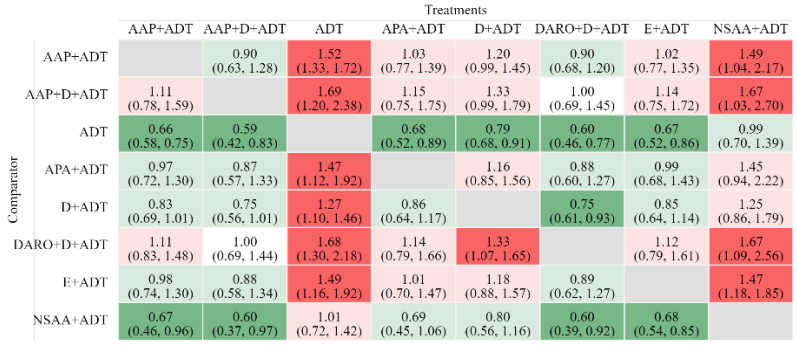
Treatment	P-Score	Rank
E+ADT	0.9686	1
AAP+ADT	0.6524	2
APA+ADT	0.6271	3
NSAA+ADT	0.1997	4
ADT	0.0522	5

eFigure 71. Mixed Treatment Comparisons for Progression-Free Survival With Gleason Score 8 or Lower



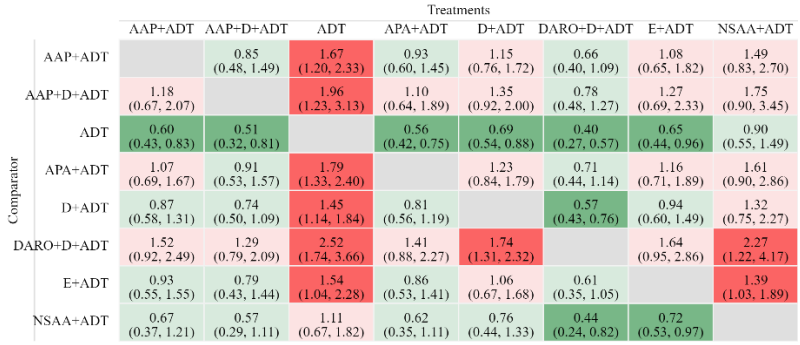
Treatment	P-Score	Rank
E+ADT	0.8325	1
AAP+ADT	0.7099	2
APA+ADT	0.6615	3
ADT	0.2126	4
NSAA+ADT	0.0835	5

eFigure 72. Mixed Treatment Comparisons for Overall Survival With Performance Status Score 0



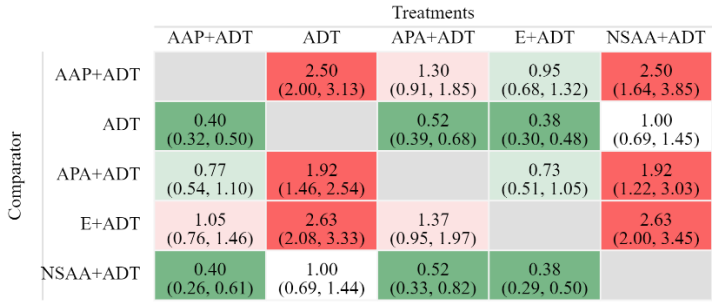
Treatment	P-Score	Rank
DARO+D+ADT	0.8189	1
AAP+D+ADT	0.8048	2
AAP+ADT	0.6605	3
E+ADT	0.6262	4
APA+ADT	0.5952	5
D+ADT	0.3212	6
NSAA+ADT	0.1059	7
ADT	0.0673	8

eFigure 73. Mixed Treatment Comparisons for Overall Survival With Performance Status Score ½



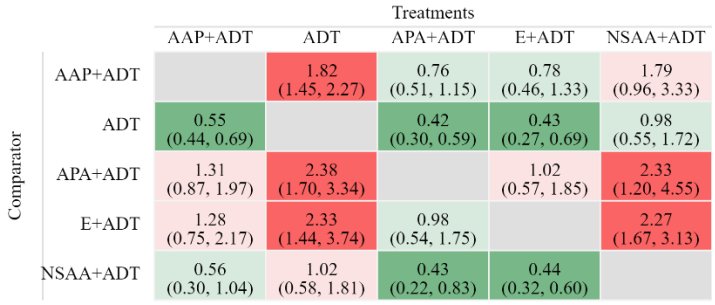
Treatment	P-Score	Rank
DARO+D+ADT	0.9539	1
AAP+D+ADT	0.7385	2
APA+ADT	0.657	3
AAP+ADT	0.5686	4
E+ADT	0.4972	5
D+ADT	0.3844	6
NSAA+ADT	0.1485	7
ADT	0.052	8

eFigure 74. Mixed Treatment Comparisons for Progression-Free Survival With Performance Status Score 0



Treatment	P-Score	Rank
E+ADT	0.8941	1
AAP+ADT	0.8259	2
APA+ADT	0.5294	3
NSAA+ADT	0.1257	4
ADT	0.125	5

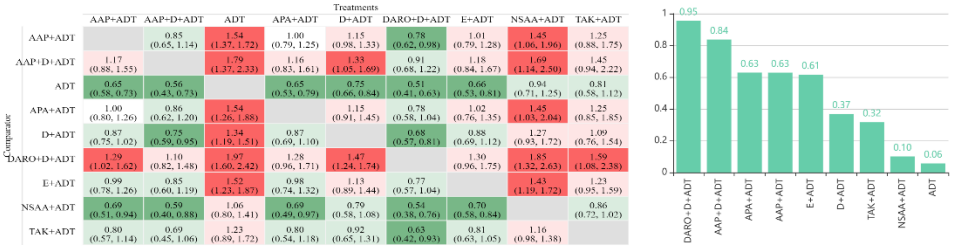
eFigure 75. Mixed Treatment Comparisons for Progression-Free Survival With Performance Status Score ½



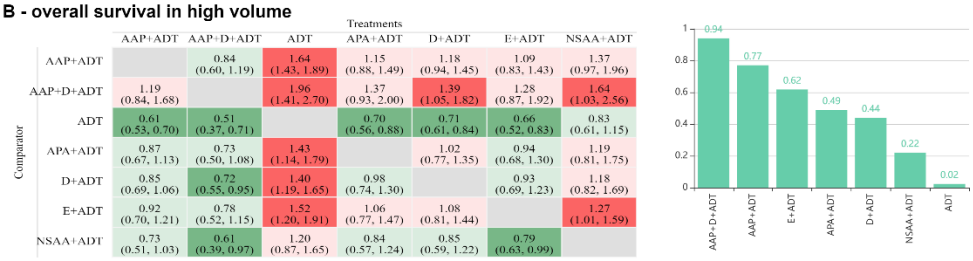
Treatment	P-Score	Rank
APA+ADT	0.8566	1
E+ADT	0.8218	2
AAP+ADT	0.5616	3
NSAA+ADT	0.1429	4
ADT	0.1172	5

eFigure 76. Mixed Treatment Comparisons for Overall Survival in the Overall Population and High and Low Volume of Disease Excluding the GETUG Trial

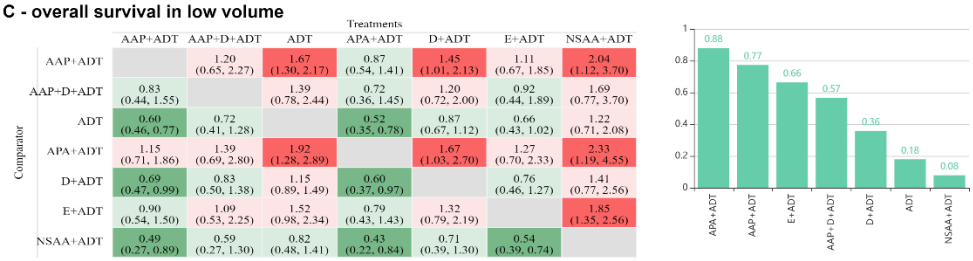
A - overall survival in overall patient population



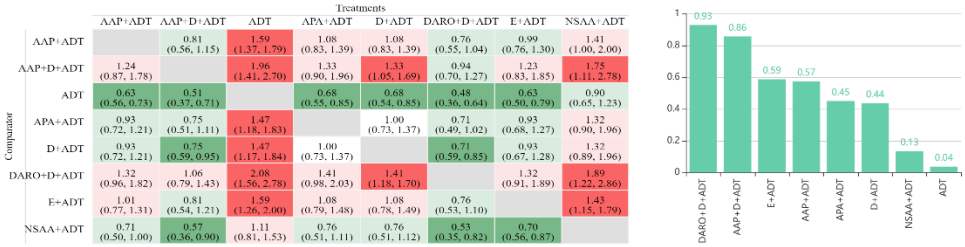
B - overall survival in high volume



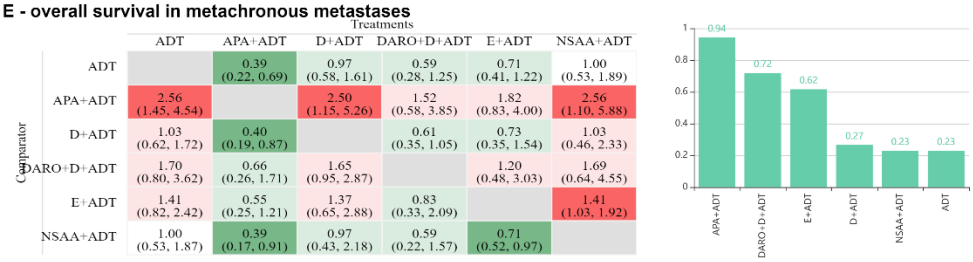
C - overall survival in low volume



D - overall survival in synchronous metastases



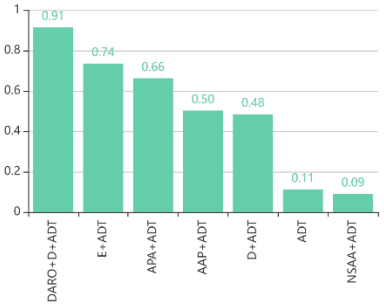
E - overall survival in metachronous metastases



eFigure 77. Mixed Treatment Comparisons for Overall Survival in Older and Younger Patients and Gleason Score 8 or Higher and Lower Than 8 Excluding the GETUG Trial

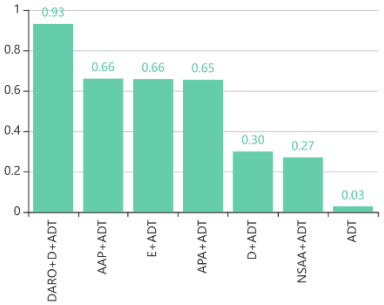
A - overall survival in old

Comparator \ Treatments	AAP+ADT	ADT	APA+ADT	D+ADT	DARO+D+ADT	E+ADT	NSAA+ADT
AAP+ADT		1.30 (1.11, 1.52)	0.92 (0.69, 1.22)	1.01 (0.74, 1.37)	0.76 (0.52, 1.11)	0.88 (0.66, 1.18)	1.37 (0.94, 2.00)
ADT	0.77 (0.66, 0.90)		0.71 (0.56, 0.90)	0.78 (0.59, 1.02)	0.58 (0.41, 0.83)	0.68 (0.53, 0.86)	1.06 (0.75, 1.52)
APA+ADT	1.09 (0.82, 1.45)	1.41 (1.11, 1.79)		1.10 (0.76, 1.59)	0.83 (0.54, 1.25)	0.96 (0.68, 1.35)	1.49 (0.98, 2.27)
D+ADT	0.99 (0.73, 1.35)	1.29 (0.98, 1.69)	0.91 (0.63, 1.31)		0.75 (0.60, 0.93)	0.88 (0.61, 1.25)	1.37 (0.88, 2.13)
DARO+D+ADT	1.32 (0.90, 1.93)	1.71 (1.21, 2.42)	1.21 (0.80, 1.85)	1.33 (1.07, 1.66)		1.16 (0.76, 1.79)	1.82 (1.11, 2.94)
E+ADT	1.13 (0.85, 1.51)	1.47 (1.16, 1.87)	1.04 (0.74, 1.46)	1.14 (0.80, 1.64)	0.86 (0.56, 1.31)		1.56 (1.22, 2.00)
NSAA+ADT	0.73 (0.50, 1.06)	0.94 (0.66, 1.33)	0.67 (0.44, 1.02)	0.73 (0.47, 1.14)	0.55 (0.34, 0.90)	0.64 (0.50, 0.82)	



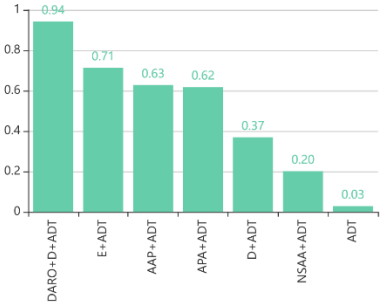
B - overall survival in young

Comparator \ Treatments	AAP+ADT	ADT	APA+ADT	D+ADT	DARO+D+ADT	E+ADT	NSAA+ADT
AAP+ADT		1.75 (1.47, 2.08)	1.00 (0.68, 1.47)	1.30 (1.03, 1.64)	0.77 (0.53, 1.11)	1.02 (0.65, 1.61)	1.35 (0.80, 2.27)
ADT	0.57 (0.48, 0.68)		0.57 (0.40, 0.81)	0.75 (0.64, 0.87)	0.44 (0.32, 0.61)	0.58 (0.38, 0.88)	0.78 (0.47, 1.27)
APA+ADT	1.00 (0.68, 1.48)	1.75 (1.24, 2.48)		1.30 (0.89, 1.92)	0.78 (0.48, 1.23)	1.02 (0.59, 1.75)	1.35 (0.74, 2.50)
D+ADT	0.77 (0.61, 0.97)	1.34 (1.15, 1.57)	0.77 (0.52, 1.12)		0.59 (0.45, 0.79)	0.78 (0.50, 1.22)	1.04 (0.62, 1.75)
DARO+D+ADT	1.30 (0.90, 1.88)	2.27 (1.64, 3.14)	1.29 (0.81, 2.08)	1.69 (1.27, 2.24)		1.32 (0.78, 2.22)	1.75 (0.97, 3.13)
E+ADT	0.98 (0.62, 1.55)	1.72 (1.13, 2.62)	0.98 (0.57, 1.69)	1.28 (0.82, 2.01)	0.76 (0.45, 1.29)		1.33 (1.03, 1.72)
NSAA+ADT	0.74 (0.44, 1.25)	1.29 (0.79, 2.12)	0.74 (0.40, 1.35)	0.96 (0.57, 1.61)	0.57 (0.32, 1.03)	0.75 (0.58, 0.97)	



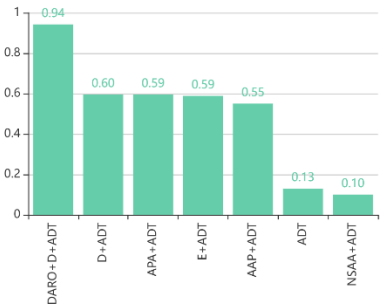
C - overall survival in GS ≥ 8

Comparator \ Treatments	AAP+ADT	ADT	APA+ADT	D+ADT	DARO+D+ADT	E+ADT	NSAA+ADT
AAP+ADT		1.56 (1.37, 1.79)	1.00 (0.77, 1.30)	1.14 (0.93, 1.39)	0.81 (0.61, 1.06)	0.95 (0.72, 1.27)	1.33 (0.92, 1.92)
ADT	0.64 (0.56, 0.73)		0.64 (0.51, 0.81)	0.72 (0.62, 0.85)	0.51 (0.40, 0.66)	0.61 (0.48, 0.78)	0.85 (0.60, 1.19)
APA+ADT	1.00 (0.77, 1.30)	1.56 (1.24, 1.97)		1.14 (0.85, 1.49)	0.80 (0.57, 1.12)	0.95 (0.68, 1.33)	1.32 (0.88, 2.00)
D+ADT	0.88 (0.72, 1.08)	1.38 (1.17, 1.62)	0.88 (0.67, 1.17)		0.71 (0.58, 0.85)	0.84 (0.63, 1.12)	1.16 (0.80, 1.69)
DARO+D+ADT	1.24 (0.94, 1.64)	1.95 (1.52, 2.49)	1.25 (0.89, 1.75)	1.41 (1.17, 1.71)		1.19 (0.83, 1.69)	1.64 (1.09, 2.50)
E+ADT	1.05 (0.79, 1.39)	1.64 (1.28, 2.10)	1.05 (0.75, 1.47)	1.19 (0.89, 1.60)	0.84 (0.59, 1.20)		1.39 (1.10, 1.75)
NSAA+ADT	0.75 (0.52, 1.09)	1.18 (0.84, 1.66)	0.76 (0.50, 1.14)	0.86 (0.59, 1.25)	0.61 (0.40, 0.92)	0.72 (0.57, 0.91)	



D - overall survival in GS < 8

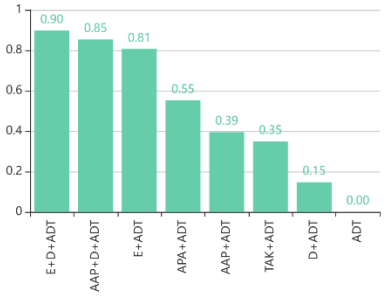
Comparator \ Treatments	AAP+ADT	ADT	APA+ADT	D+ADT	DARO+D+ADT	E+ADT	NSAA+ADT
AAP+ADT		1.43 (0.93, 2.22)	0.96 (0.54, 1.69)	0.95 (0.56, 1.64)	0.63 (0.31, 1.27)	0.98 (0.53, 1.79)	1.64 (0.78, 3.45)
ADT	0.70 (0.45, 1.07)		0.67 (0.46, 0.98)	0.67 (0.48, 0.93)	0.43 (0.25, 0.76)	0.68 (0.44, 1.04)	1.14 (0.62, 2.08)
APA+ADT	1.04 (0.59, 1.84)	1.49 (1.02, 2.18)		0.99 (0.60, 1.64)	0.65 (0.33, 1.27)	1.01 (0.57, 1.79)	1.69 (0.83, 3.45)
D+ADT	1.05 (0.61, 1.80)	1.50 (1.08, 2.09)	1.01 (0.61, 1.66)		0.65 (0.42, 1.02)	1.02 (0.60, 1.75)	1.69 (0.85, 3.33)
DARO+D+ADT	1.60 (0.79, 3.24)	2.30 (1.32, 4.02)	1.54 (0.79, 3.03)	1.53 (0.98, 2.40)		1.56 (0.78, 3.13)	2.63 (1.15, 5.88)
E+ADT	1.02 (0.56, 1.88)	1.47 (0.96, 2.26)	0.99 (0.56, 1.75)	0.98 (0.57, 1.68)	0.64 (0.32, 1.29)		1.67 (1.09, 2.56)
NSAA+ADT	0.61 (0.29, 1.29)	0.88 (0.48, 1.61)	0.59 (0.29, 1.21)	0.59 (0.30, 1.17)	0.38 (0.17, 0.87)	0.60 (0.39, 0.92)	



eFigure 78. Mixed Treatment Comparisons for Progression-Free Survival in the Overall Population and High and Low Volume of Disease Excluding the GETUG Trial

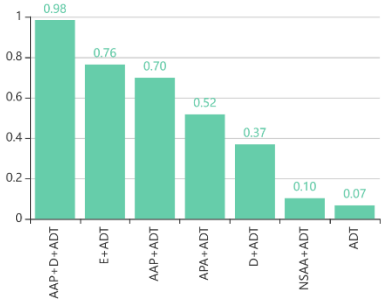
A - progression free survival in overall patient population

Comparator \ Treatments	AAP+ADT	AAP+D+ADT	ADT	APA+ADT	D+ADT	E+ADT	E+D+ADT	TAK+ADT
AAP+ADT		0.61 (0.41, 0.90)	1.79 (1.59, 1.96)	0.87 (0.68, 1.10)	1.22 (1.06, 1.41)	0.65 (0.52, 0.80)	0.58 (0.44, 0.79)	1.03 (0.87, 1.22)
AAP+D+ADT	1.64 (1.11, 2.41)		2.94 (2.00, 4.17)	1.43 (0.93, 2.17)	2.00 (1.39, 2.86)	1.06 (0.70, 1.61)	0.96 (0.62, 1.49)	1.69 (1.14, 2.50)
ADT	0.56 (0.51, 0.63)	0.34 (0.24, 0.50)		0.49 (0.40, 0.61)	0.68 (0.62, 0.76)	0.36 (0.30, 0.44)	0.33 (0.25, 0.43)	0.58 (0.51, 0.67)
APA+ADT	1.15 (0.91, 1.46)	0.70 (0.46, 1.08)	2.04 (1.65, 2.52)		1.41 (1.11, 1.79)	0.75 (0.56, 0.98)	0.67 (0.47, 0.95)	1.19 (0.92, 1.52)
D+ADT	0.82 (0.71, 0.94)	0.50 (0.35, 0.72)	1.46 (1.31, 1.61)	0.71 (0.56, 0.90)		0.53 (0.43, 0.65)	0.48 (0.37, 0.62)	0.85 (0.71, 1.00)
E+ADT	1.54 (1.25, 1.91)	0.94 (0.62, 1.43)	2.74 (2.28, 3.29)	1.34 (1.02, 1.78)	1.88 (1.53, 2.32)		0.90 (0.65, 1.27)	1.59 (1.27, 2.00)
E+D+ADT	1.71 (1.27, 2.29)	1.04 (0.67, 1.62)	3.03 (2.30, 4.00)	1.49 (1.05, 2.11)	2.08 (1.61, 2.70)	1.11 (0.79, 1.54)		1.75 (1.30, 2.38)
TAK+ADT	0.97 (0.82, 1.15)	0.59 (0.40, 0.88)	1.72 (1.50, 1.98)	0.84 (0.66, 1.09)	1.18 (1.00, 1.41)	0.63 (0.50, 0.79)	0.57 (0.42, 0.77)	



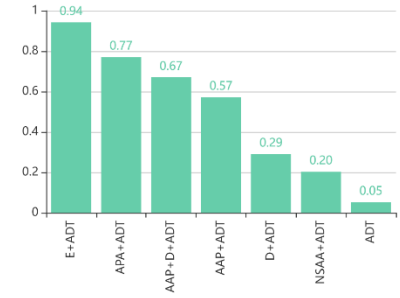
B - progression free survival in high volume

Comparator \ Treatments	AAP+ADT	AAP+D+ADT	ADT	APA+ADT	D+ADT	E+ADT	E+D+ADT
AAP+ADT		0.62 (0.38, 1.00)	2.17 (1.89, 2.50)	1.15 (0.87, 1.52)	1.32 (1.08, 1.59)	0.89 (0.69, 1.15)	0.67 (0.47, 0.96)
AAP+D+ADT	1.62 (1.00, 2.62)		3.57 (2.22, 5.56)	1.85 (1.11, 3.13)	2.13 (1.37, 3.33)	1.45 (0.87, 2.38)	1.09 (0.64, 1.85)
ADT	0.46 (0.40, 0.53)	0.28 (0.18, 0.45)		0.53 (0.41, 0.68)	0.60 (0.52, 0.70)	0.41 (0.33, 0.51)	0.31 (0.22, 0.43)
APA+ADT	0.87 (0.66, 1.15)	0.54 (0.32, 0.90)	1.89 (1.48, 2.41)		1.14 (0.85, 1.52)	0.78 (0.56, 1.08)	0.58 (0.38, 0.88)
D+ADT	0.76 (0.63, 0.93)	0.47 (0.30, 0.73)	1.66 (1.43, 1.91)	0.88 (0.66, 1.17)		0.68 (0.52, 0.88)	0.51 (0.38, 0.68)
E+ADT	1.12 (0.87, 1.45)	0.69 (0.42, 1.15)	2.43 (1.96, 3.02)	1.29 (0.93, 1.79)	1.47 (1.13, 1.91)		0.75 (0.51, 1.11)
E+D+ADT	1.49 (1.04, 2.14)	0.92 (0.54, 1.57)	3.25 (2.33, 4.52)	1.72 (1.14, 2.60)	1.96 (1.46, 2.64)	1.33 (0.90, 1.98)	

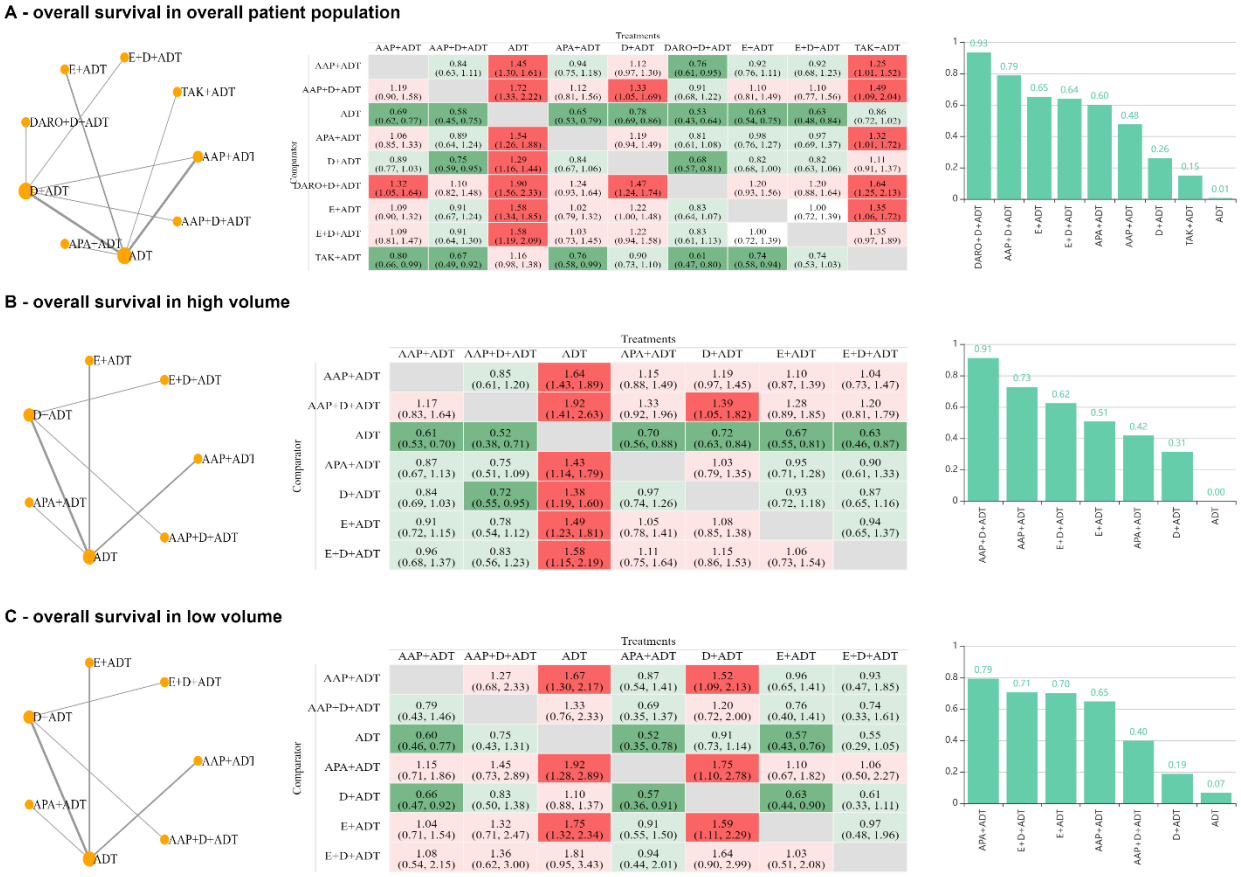


C - progression free survival in low volume

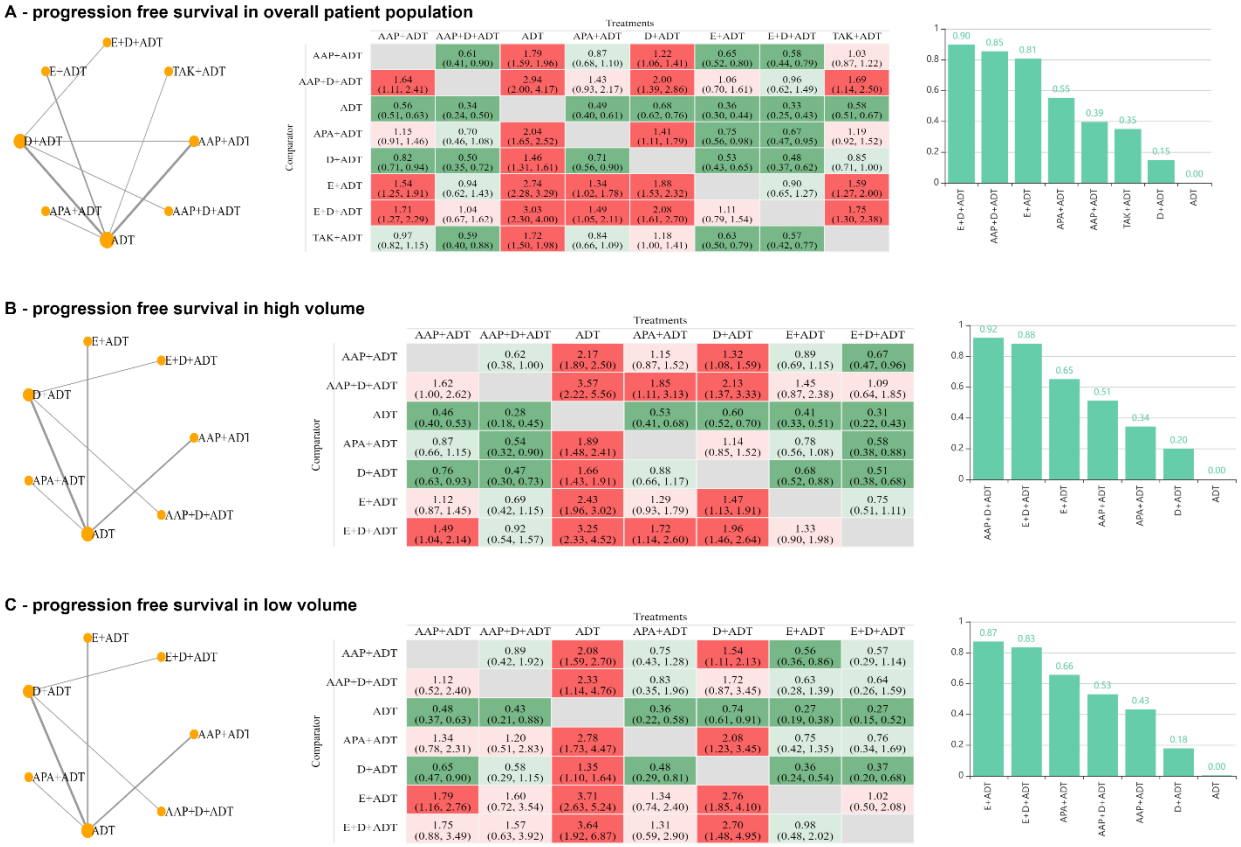
Comparator \ Treatments	AAP+ADT	AAP+D+ADT	ADT	APA+ADT	D+ADT	E+ADT	NSAA+ADT
AAP+ADT		0.85 (0.40, 1.85)	2.08 (1.59, 2.70)	0.75 (0.43, 1.28)	1.47 (1.03, 2.13)	0.52 (0.27, 0.99)	1.72 (0.83, 3.57)
AAP+D+ADT	1.17 (0.54, 2.53)		2.44 (1.16, 5.00)	0.87 (0.36, 2.08)	1.72 (0.87, 3.45)	0.60 (0.24, 1.54)	2.00 (0.74, 5.56)
ADT	0.48 (0.37, 0.63)	0.41 (0.20, 0.86)		0.36 (0.22, 0.58)	0.71 (0.56, 0.91)	0.25 (0.14, 0.45)	0.83 (0.42, 1.64)
APA+ADT	1.34 (0.78, 2.31)	1.15 (0.48, 2.75)	2.78 (1.73, 4.47)		2.00 (1.16, 3.33)	0.69 (0.32, 1.49)	2.33 (1.01, 5.26)
D+ADT	0.68 (0.47, 0.97)	0.58 (0.29, 1.15)	1.40 (1.10, 1.78)	0.50 (0.30, 0.86)		0.35 (0.18, 0.67)	1.16 (0.56, 2.38)
E+ADT	1.93 (1.01, 3.70)	1.66 (0.65, 4.24)	4.00 (2.21, 7.25)	1.44 (0.67, 3.08)	2.85 (1.50, 5.42)		3.33 (2.38, 4.76)
NSAA+ADT	0.58 (0.28, 1.20)	0.50 (0.18, 1.35)	1.20 (0.61, 2.38)	0.43 (0.19, 0.99)	0.86 (0.42, 1.77)	0.30 (0.21, 0.42)	



eFigure 79. Mixed Treatment Comparisons for Overall Survival Using Subgroup Data (Docetaxel and Nondocetaxel) From the PEACE-1 and ENZAMET Trials



eFigure 80. Mixed Treatment Comparisons for Progression-Free Survival Using Subgroup Data (Docetaxel and Nondocetaxel) From the PEACE-1 and ENZAMET Trials



eTable 1. Outcome Definitions in Included Clinical Trials

PEACE-1	Radiographic progression-free survival	The time from randomization to the appearance of first radiological evidence of progressive disease or death; progressively increasing soft-tissue lesions; or new bone lesions according to PCWG 2.
	Overall survival	The time between randomization and death from any cause. Patients without events were censored at the date of last follow-up.
	Castration resistance free survival	Outcome definition not reported
	Biochemical progression free survival	Progression free survival including PSA progression as an event
	Time to chemotherapy for CRPC	Outcome definition not reported
	Clinical progression free survival	Outcome definition not reported
	Toxicity	NCI-CTCAE v4.0 scale was used for adverse events
STAMPEDE	Progression-free survival	Defined as Failure free survival excluding patients with biochemical (PSA progression) failure.
	Failure-free survival	Time from randomization to first evidence of at least one of: biochemical failure; progression either locally, in lymph nodes, or in distant metastases; or death from prostate cancer.
	Metastatic progression-free survival	Time from randomization to progression or death from any cause.
	Time to treatment after progression	Time to first of any treatment after a Failure -free survival event and time to first life-extending therapy (defined as available agents with proven survival gain in castrate-refractory prostate cancer: docetaxel, abiraterone, cabazitaxel, enzalutamide, and radium-223).
	Overall survival	The time from randomization to death from any cause.
	Prostate cancer-specific survival	The time from randomization to PSA progression or death due to prostate cancer.
	Skeletal related event	Outcome definition not reported
	Toxicity	NCI-CTCAE (initially, v3.0; later, v4.0). scale was used for adverse events
	Quality of Life (QoL)	QoL was assessed with the self-administered EORTC QLQ-C 30.
TITAN	Radiographic progression-free survival	The time from randomization to the appearance of first radiological evidence of progressive disease or death; progressively increasing soft-tissue lesions; or new bone lesions according to PCWG 2.

	Second progression-free survival	The time from randomization to the first appearance of investigator-determined disease progression; death due to its progression; clinical progression); the patient was on prostate cancer therapy, or death caused by any non-specific event.
	Overall survival	The time from randomization to death resulting from any cause.
	Time to symptomatic local progression	The time from randomization to the appearance of symptomatic local progression.
	Time to Castration resistance	
	Time to pain progression	The time from randomization to pain progression (increase in 2 points from baseline in BPI-SF)
	Time to PSA progression	The time from randomization to the rising PSA levels based on PCWG 2 criteria.
	Time to cytotoxic chemotherapy	The time from randomization to initiation of cytotoxic chemotherapy.
	Time to skeletal-related event	The occurrence of symptomatic pathologic fracture, spinal cord compression, radiation to bone, or surgery to bone
	Time to chronic opioid use	Time form randomization to chronic opioid use (≥3 weeks for oral and ≥7 days for non-oral formulations)
	Toxicity	NCI-CTCAE v4.0.3 scale was used for adverse events
	Quality of Life (QoL)	QoL was assessed with the self-administered FACT-P total score, EQ-5D-5L, BPI-SF, and BFI
ARCHES	Radiographic progression-free survival	The time from randomization to the appearance of first radiological evidence of progressive disease assessed by ICR or death from any cause within 24 weeks of drug discontinuation. Radiographic disease progression is defined as progressive disease by RECIST (version 1.1).
	Overall survival	The time from randomization to death resulting from any cause.
	Objective response rate	The percentage of patients with measurable disease at baseline who achieved a complete or partial response in their soft tissue disease using the RECIST (version 1.1).
	Time to PSA progression	The time from randomization to a ≥25% increase and an absolute increase of ≥2 ng/ml above the normal range of PSA, which is confirmed by a second consecutive value at least 3 weeks interval.

	Time to initiation of new antineoplastic therapy	Time from randomization to the initiation of antineoplastic therapy (including cytotoxic and hormonal therapies) subsequent to the study treatments
	PSA undetectable rate	The percentage of patients with detectable (≥ 0.2 ng/mL) PSA at baseline, which becomes undetectable (< 0.2 ng/mL) during study treatment. Only PSA assessments taken prior to the initiation of new antineoplastic therapy were evaluated
	Time to deterioration in urinary symptoms	Increase in urinary symptoms subscale scores by ≥ 50% of the standard deviation observed in urinary symptoms subscale score at baseline EORTC QLQ-PR25 (Q31–Q33).
	Time to first symptomatic skeletal event	The time from randomization to the occurrence of the first symptomatic skeletal event, defined as clinically apparent spinal cord damage or pathologic bone fracture; radiation or surgery to bone.
	Time to castration resistance	The time from randomization to the first castration-resistant event (radiographic disease progression, PSA progression, or SSE with castrate levels of testosterone [< 50 ng/dL]), whichever occurs first.
	Time to pain progression	The time from randomization to pain progression, defined as an increase of ≥30% in pain severity score from baseline using BPI-SF criteria.
	Toxicity	NCI-CTCAE v4.0.3 scale was used for adverse events
	Time to deterioration Quality of Life (QoL)	The time from randomization to a 10-point reduction of the FACT-P total score
LATITUDE	Radiographic progression-free survival	The time from randomization to the appearance of first radiological evidence of progressive disease or death; Soft-tissue lesions were evaluated by either CT or MRI on the basis of RECIST (version 1.1); new bone lesions were evaluated according to PCWG 2.
	Secondary progression-free survival	Time from randomization to progression on subsequent treatment or death
	Overall survival	The time from randomization to death resulting from any cause.

	Time to PSA progression	The time from randomization to a ≥25% increase and an absolute increase of ≥2 ng/ml above the normal range of PSA, which is confirmed by a second consecutive value at least 3 weeks interval.
	Time to initiation of chemotherapy	The time from randomization to initiation of chemotherapy for prostate cancer
	Time to subsequent prostate cancer therapy	The time from randomization to initiation of any subsequent therapy for prostate cancer, including hormonal therapy
	Time to pain progression	The time from randomization to pain progression, defined as an increase of ≥30% in pain severity score from baseline using BPI-SF criteria observed at two consecutive evaluations performed at 4 weeks interval at least.
	Time to next symptomatic skeletal event/Skeletal related event	The time from randomization to any one of the following skeletal-related events: clinical or pathological fracture, spinal cord compression, palliative radiotherapy to bone, or surgery to bone.
	Toxicity	NCI-CTCAE v4.0 scale was used for adverse events
	Quality of Life (QoL)	QoL was assessed with the self-administered FACT-P total score and BPI-SF
	PSA response	A decrease in PSA response, at least 50% from the baseline value.
ENZAMET	Overall survival	The time from randomization to death resulting from any cause or to the date at which the patient was last known to be alive.
	PSA progression-free survival	The time from randomization to the earliest event of PSA progression per PCWG2 criteria; clinical progression; death due to any cause or the last known date of follow-up without PSA progression.
	Clinical progression-free survival	Time to earliest sign of radiographic progression according to the criteria of the PCWG2 for bone lesions and the RECIST (version 1.1) for soft-tissue lesions; the development of symptoms attributable to cancer progression; or the initiation of another anticancer treatment for prostate cancer.
	Quality of Life (QoL)	QoL was assessed with the self-administered EORTC QLQ-C 30.
	Toxicity	NCI-CTCAE v4.0.2 scale was used for adverse events
CHAARTED	Overall survival	The time from randomization to death resulting from any cause.

	Clinical progression free survival	The time to the appearance of symptomatic bone metastases, progression according to RECIST (version 1.0), clinical deterioration due to cancer per investigator's opinion.
	Time to castration-resistant prostate cancer	The time until documented clinical or serologic progression with a testosterone level of less than 50 ng per deciliter (or source documentation of medical castration or surgical castration)
	Quality of Life (QoL)	QoL was assessed with the self-administered FACT-P, FACT-Taxane, FACIT-Fatigue.
GETUG-AFU15	Overall survival	The time from randomization to death resulting from any cause.
	Clinical progression free survival	Progression of pre-existing lesions with Response Evaluation Criteria in Solid Tumors (RECIST; version 1.0)12 or the occurrence of (new) bone lesions, whichever happened first.
	Biochemical progression free survival	The progressive rise in PSA according to "PSA Working Group'' definition; Confirmed PSA decrease of 50% and an increase of at least 50% above nadir (minimum increase of 5 ng/ml).
	Toxicity	NCI-CTCAE v3.0. scale was used for adverse events
	Quality of Life (QoL)	QoL was assessed with the self-administered EORTC QLQ-C 30.
ARASENS	Overall survival	The time from randomization to death resulting from any cause.
	Time to castration resistant prostate cancer	The time from randomization to occurrence of the following events, whichever occurred first: PSA progression with serum testosterone at a castrate level (<0.5 ng/mL) or radiological progression of soft-tissue, visceral, or bone lesions; radiological progression by soft tissue/visceral lesions was determined according to RECIST (version 1.1). Bone lesions were recorded separately from soft tissue/visceral lesions and determined according to PCWG3
	Time to pain progression	the time from randomization to the first date when a patient experienced pain progression assessed by BPI-SF.
	Symptomatic skeletal event–free survival	The time from randomization to the first occurrence of an SSE or death from any cause, whichever occurred first. An SSE is defined as external-beam radiation therapy to relieve skeletal symptoms, new symptomatic pathologic bone fracture, or occurrence of spinal cord compression or tumor related orthopedic surgical intervention, whichever occurred first.
	Time to a first symptomatic skeletal event	The time from randomization to the first occurrence of an SSE
	Time to initiation of subsequent systemic antineoplastic therapy	The time from randomization to initiation of first subsequent systemic antineoplastic therapy
	Time to worsening of disease-related physical symptoms	The time from randomization to the first date when a patient experienced an increase in disease-related physical symptoms according to the NCCN–FACT FPSI–17

	Time to initiation of opioid treatment	The time from randomization to the start of first opioid use for ≥7 consecutive days
	Toxicity	NCI-CTCAE v4.0.3. scale was used for adverse events
SWOG1216	Overall survival	The time from randomization to death resulting from any cause.
	Progression-free survival	From the date of randomization to first occurrence of PSA or radiographic progression, symptomatic deterioration or death due to any cause.
	PSA response	Outcome definition not reported
	Toxicity	Outcome definition not reported

Abbreviations: CRPC: Castration resistant prostate cancer; PCWG2: Prostate cancer working group 2; RECIST: Response Evaluation Criteria in Solid Tumors; EORTC QLQ-C 30: European Organization for Research and Treatment of Cancer quality-of-life questionnaire C30; EORTC QLQ-PR25: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Prostate 25; BPI-SF: Brief Pain Inventory Short Form; FACT-P = Functional Assessment of Cancer Therapy- Prostate; PSA: Prostate specific analysis; SSE: Symptomatic skeletal event; NCCN–FACT FPSI–17: National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy prostate cancer symptom index 17-item questionnaire. NCI-CTCAE v4.0: National Cancer Institute-Common Terminology Criteria for Adverse Events version.

eTable 2. Overall Survival and Progression-Free Survival by Receipt of Docetaxel in the ENZAMET, ARCHES, and TITAN Trials

Overall Survival			
ENZAMET			
	E + ADT ± D	**ADT ± D**	**Hazard Ratio**
Overall population	102/563	143/562	0.67 (0.52–0.86)
Docetaxel given (API + ADT + D)	108/253	123/250	0.82 (0.63-1.06)
Docetaxel not given (API + ADT)	50/309	88/313	0.60 (0.47-0.78)
ARCHES			
	E + ADT ± D	**ADT ± D**	**Hazard Ratio**
Overall population	154/574	202/576	0.66 (0.53-0.81)
Docetaxel given (API + ADT + D)	30/103	37/102	0.74 (0.46-1.20)
Docetaxel not given (API + ADT)	124/471	165/474	0.64 (0.51-0.81)
TITAN			
	APA + ADT ± D	**ADT ± D**	**Hazard Ratio**
Overall population	170/525	235/527	0.65 (0.53-0.79)
Docetaxel given (API + ADT + D)	21/58	17/55	1.12 (0.59-2.12)
Docetaxel not given (API + ADT)	149/467	218/472	0.61 (0.50-0.76)
Progression free survival			
ENZAMET			
	E + ADT ± D	**ADT ± D**	**Hazard Ratio**
Overall population	167/563	320/562	0.40 (0.33–0.49)
Docetaxel given (API + ADT + D)	91/254	146/249	0.48 (0.37–0.62)
Docetaxel not given (API + ADT)	76/309	174/313	0.34 (0.26–0.44)
ARCHES			
	E + ADT ± D	**ADT ± D**	**Hazard Ratio**
Overall population	91/574	201/576	0.39 (0.30-0.50)
Docetaxel given (API + ADT + D)	21/103	35/102	0.52 (0.30-0.89)
Docetaxel not given (API + ADT)	70/471	166/474	0.37 (0.28-0.49)
TITAN			
	APA + ADT ± D	**ADT ± D**	**Hazard Ratio**
Overall population	134/525	231/527	0.49 (0.40–0.61)
Docetaxel given (API + ADT + D)	10/58	19/55	0.47 (0.22–1.01)
Docetaxel not given (API + ADT)	124/467	212/472	0.49 (0.39–0.62)

Abbreviations: E: enzalutamide; D: docetaxel; APA: apalutamide; API: androgen pathway inhibitors; ADT: androgen deprivation

eTable 3. Proportions of Patients by Volume of Disease and Timing of Metastatic Presentation in Included Trials

Proportion of different prognostic groups across included trials										
Studies	**Arms**	**Volume - N (%)**		**Timing of metastases - N (%)**		**Prognostic groups - N (%)**				**Source of information**
		High	**Low**	**Synchronous**	**Metachronous**	**Synchronous HV**	**Synchronous LV**	**Metachronous HV**	**Metachronous LV**	
GETUG-AFU	Docetaxel + ADT	92(48)	100(52)	128(67)	62(33)	73(38.0)	55(28.6)	18(9.4)	44(22.9)	PMID: 29475737; Follow-up publication
	ADT	91(47)	102(53)	144(76)	46(24)	80(41.5)	64(33.2)	11(5.7)	35(18.1)	
CHAARTED	Docetaxel + ADT	263(66.2)	134(33.8)	289(72.8)	108(27.2)	214(53.9)	75(18.9)	49(12.3)	59(14.9)	PMID: 29384722; Follow-up publication
	ADT	250(63.6)	143(36.4)	286(72.8)	106(27.0)	207(52.7)	79(20.1)	42(10.7)	64(16.3)	
STAMPEDE Arm C	Docetaxel + ADT	148(41)	124(34)	~345(95)	~17(5)	~141(39)	~118(32.6)	~7(1.9)	~6(1.7)	PMID: 31560068; Follow-up publication
	ADT	320(44)	238(34)	~688(95)	~54(5)	~304(42)	~226(31.2)	~16(2.2)	~12(1.7)	
STAMPEDE Arm G	Abiraterone + ADT	243(54.1)	206(45.9)	428(95.3)	21(4.7)	237(55.3)	191(42.5)	NA	NA	PMID: 31447077; Follow-up publication
	ADT	256(56.6)	196(43.4)	431(98.1)	8(1.8)	249(57.8)	182(42.2)	NA	NA	
LATITUDE	Abiraterone + ADT	487(81.6)	110(18.4)	597(100)	0(0)	487(81.6)	110(18.4)	0(0)	0(0)	PMID: 30987939; Follow-up publication
	ADT	468(77.7)	133(22.1)	602(100)	0(0)	468(77.7)	133(22.1)	0(0)	0(0)	
ENZAMET	Enzalutamide + ADT	291(52)	272(48)	325(57.7)	238(42.3)	NA	NA	NA	NA	PMID: 31157964; Original publication
	NSAA + ADT	297(53)	265(47)	327(58.2)	235(41.8)	NA	NA	NA	NA	
ARCHES	Enzalutamide + ADT	354(61.7)	220(38.3)	402(70)	83(14.5)	297(51.7)	151(26.3)	54(9.4)	63(11.1)	10.1200/JCO.2022.40.6_suppl.115;
	ADT	373(64.8)	203(35.2)	365(63.4)	86(14.9)	309(53.6)	133(23.1)	62(10.8)	67(11.6)	
TITAN	Apalutamide + ADT	325(61.9)	200(38.1)	411(78.3)	85(16.2)	NA	NA	NA	NA	PMID: 31150574; Original publication
	ADT	335(63.6)	192(36.4)	441(83.7)	59(11.2)	NA	NA	NA	NA	
PEACE1	Abiraterone + Docetaxel + ADT	224(63)	131(37)	355(100)	0(0)	224(63)	131(37)	0(0)	0(0)	PMID: 35405085 Original publication
	Docetaxel + ADT	232(65)	123(35)	355(100)	0(0)	232(65)	123(35)	0(0)	0(0)	
ARASENS	Abiraterone + Docetaxel + ADT	NA	NA	558(85.7)	86(13.2)	NA	NA	NA	NA	PMID: 35179323; Original publication
	Docetaxel + ADT	NA	NA	566(86.5)	82(12.5)	NA	NA	NA	NA	
SWOG 1216	TAK + ADT	NA	NA	NA	NA	NA	NA	NA	NA	10.1200/JCO.2021.39.15_suppl.5001
	NSAA + ADT	NA	NA	NA	NA	NA	NA	NA	NA	

eTable 4. Overall Survival Rate by Volume of Disease and Timing of Metastatic Presentation in Included Trials

Percent of patients surviving in different prognostic groups across included trials										
Studies	Arms	Follow up (months)	Volume (%)		Timing of metastases (%)		Prognostic groups (%)			
			High	Low	Synchronous	Metachronous	Synchronous HV	Synchronous LV	Metachronous HV	Metachronous LV
GETUG-AFU	Docetaxel + ADT	83.2	NA	NA	NA	NA	NA	NA	NA	NA
	ADT		NA	NA	NA	NA	NA	NA	NA	NA
CHAARTED	Docetaxel + ADT	54	47.9	61.9	NA	NA	47.7	56	49	69.5
	ADT		35.2	65.7	NA	NA	31.9	57	50	76.6
STAMPEDE Arm C	Docetaxel + ADT	79	33.8	71.8	NA	NA	NA	NA	NA	NA
	ADT		24.1	57.1	NA	NA	NA	NA	NA	NA
STAMPEDE Arm G	Abiraterone + ADT	42	60.5	81.1	69.6	NA	60.3	79.6	NA	NA
	ADT		44.5	73	55.5	NA	43.8	71.4	NA	NA
LATITUDE	Abiraterone + ADT	51.8	50.5	69.1	53.9	NA	50.5	69.1	NA	NA
	ADT		38.2	59.4	43	NA	38.2	59.4	NA	NA
ENZAMET	Enzalutamide + ADT	34	72.5	91.9	80.6	83.6	NA	NA	NA	NA
	ADT + NSAA		67.3	82.6	71.3	79.1	NA	NA	NA	NA
ARCHES	Enzalutamide + ADT	45	66.4	84.1	71.7	79.5	66	82.8	70.4	87.3
	ADT		58.2	77.3	61.5	76	56	74.4	69.4	82.1
TITAN	Apalutamide + ADT	44	78.8	93	82.7	91.8	NA	NA	NA	NA
	ADT		71	89.6	77.1	81.4	NA	NA	NA	NA
PEACE1	Abiraterone + Docetaxel + ADT	46	58.9	77.9	65.9	NA	58.9	77.9	NA	NA
	Docetaxel + ADT		48.3	74.8	57.5	NA	48.3	74.8	NA	NA
ARASENS	Darolutamide + Docetaxel + ADT	~43	NA	NA	63.1	74.4	NA	NA	NA	NA
	Docetaxel + ADT		NA	NA	52.1	63.4	NA	NA	NA	NA
SWOG 1216	TAK + ADT	59	NA	NA	NA	NA	NA	NA	NA	NA
	NSAA + ADT		NA	NA	NA	NA	NA	NA	NA	NA

eTable 5. Summary of Additional Trial and Population Characteristics

Summary of additional trial and population characteristics							
Studies	**Arms**	**Performance status/WHO score**		**Gleason score**		**Region of recruitment**	**Source of information**
		0	**1/2**	**<8**	**≥8**		
GETUG-AFU	Docetaxel + ADT	181 (99)	2(1)	84 (45)	103 (55)	Europe	PMID: 29475737; Follow-up publication
	ADT	176 (96)	7 (4)	78 (41)	113 (59)		
CHAARTED	Docetaxel + ADT	277 (69.8)	120 (30.2)	117 (30)	241 (60.7	North America	PMID: 29384722; Follow-up publication
	ADT	272 (69.2)	121 (30.8)	104 (26)	243 (61.8)		
STAMPEDE Arm C	Docetaxel + ADT	270 (75)	203 (28)	110 (19)	436 (74)	Europe	PMID: 26719232; 31560068 Original/Follow-up publication
	ADT	520 (72)	92 (25)	282 (24)	810 (68)		
STAMPEDE Arm G	Abiraterone + ADT	745 (78)	215 (22)	221 (23)	715 (74)		PMID: 28578639; Original publication
	ADT	744 (78)	213 (22)	223 (23)	721 (75)		
LATITUDE	Abiraterone + ADT	NA	NA	13 (2)	584 (98)	North America, South America, Europe, South Africa, Asia, Oceania	PMID: 30987939; Follow-up publication
	ADT	NA	NA	16 (3)	586 (97)		
ENZAMET	Enzalutamide + ADT	404 (71.9)	158(28)	152 (27)	335(59.5)	North America, Europe, Asia, Oceania	PMID: 31157964; Original publication
	NSAA + ADT	405 (72.1)	157 (28)	163 (29)	321 (57.1)		
ARCHES	Enzalutamide + ADT	448 (78)	125 (21.8)	171 (29.8)	386 (67.2	North America, South America, Europe, Asia, Oceania	PMID: 31329516; Original publication
	ADT	443 (76.9)	133 (23.1)	187 (32.5)	373 (64.8)		
TITAN	Apalutamide + ADT	328 (62.5)	197 (37.5	174 (33.1)	351 (66.9)	North America, South America, Europe, Asia, Oceania	PMID: 31150574; Original publication
	ADT	348 (66)	179 (34.0)	169 (32)	358 (67.9)		
PEACE1	Abiraterone + Docetaxel + ADT	250 (70%)	105 (30%)	145 (25)	429 (75)	Europe	10.1016/S0140-6736(22)00367-1
	Docetaxel + ADT	246 (69%)	109 (31%)	132 (23)	441 (77)		
ARASENS	Darolutamide + Docetaxel + ADT	466 (71.6)	185 (28.4)	110 (22.4)	505 (77.6)	North America, South America, Europe, Asia, Oceania	PMID: 35179323; Original publication
	Docetaxel + ADT	462 (70.6)	190 (29.1)	138 (21.1)	516 (78.9)		
SWOG 1216	TAK + ADT	NA	NA	211 (32.9)	372 (58.3)	North America	PMID: 35446628; Original publication
	NSAA + ADT	NA	NA	207 (32.3)	382 (59.8)		

eTable 6. Summary of Subsequent Therapy Across the Included Trials

Proportion of subsequent therapy administered across trials				
Studies	**Arms**	**Any subsequent therapy**	**Hormonal**	**Source of information**
GETUG-AFU	Docetaxel + ADT	NA	Enzalutamide: 9(5); Abiraterone: 19(10); Other novel anti-androgen: 2(1)	PMID: 23306100; Follow-up publication
	ADT	NA	Enzalutamide: 7(4); Abiraterone 21(11); Other novel anti-androgen 1(<1)	
CHAARTED	Docetaxel + ADT	NA	Enzalutamide/Abiraterone: 105(26.4); Antiandrogen/ketoconazole: 80 (20.2)	PMID: 26244877; Follow-up publication
	ADT	NA	Enzalutamide/Abiraterone: 104(26.5); Antiandrogen/ketoconazole: 91 (23.2)	
STAMPEDE Arm C	Docetaxel + ADT	139(44)	Enzalutamide: 25(8)*; Abiraterone: 89(28)	PMID: 26719232; Follow-up publication
	ADT	383(50)	Enzalutamide: 66(9)*; Abiraterone: 177(23)	
STAMPEDE Arm G	Abiraterone + ADT	131(53)	Enzalutamide: 25(10)*; Abiraterone: 8(3)	PMID: 28578639; Follow-up publication
	ADT	310(58)	Enzalutamide: 138(26)*; Abiraterone: 120(22)	
LATITUDE	Abiraterone + ADT	125(21)	Enzalutamide: 30(10)*; Abiraterone: 10(3)	PMID: 28578607; Follow-up publication
	ADT	246(41)	Enzalutamide: 76(16)*: Abiraterone: 53(11)	
ENZAMET	Enzalutamide + ADT	112(67)	Enzalutamide: 0(0)*; Abiraterone: 46(27.5); Other novel anti-androgen: 1(0.6)	PMID: 31157964; Follow-up publication
	NSAA + ADT	271(85)	Enzalutamide: 141(44.1)*; Abiraterone: 113(35.3); Other novel anti-androgen: 2(0.6)	
ARCHES	Enzalutamide + ADT	131(22.8)	Enzalutamide: 7(1.2)*; Abiraterone 26(4.5); Other novel anti-androgen: 8(1.4)	PMID: 35420921; Follow-up publication
	ADT	221(38.4)	Enzalutamide: 61(10.6)*; Abiraterone 42(7.3); Other novel anti-androgen: 23(4)	
TITAN	Apalutamide + ADT	87(51.2)	Enzalutamide: 3(1.8); Bicalutamide: 16(9.4)	PMID: 31150574; Follow-up publication
	ADT	190(70.1)	Enzalutamide: 17(6.3); Bicalutamide: 31(11.4)	
PEACE1	Abiraterone + Docetaxel + ADT	104(74)	Enzalutamide: 57(40); Abiraterone: 22(16)	PMID: 35405085; Follow-up publication
	Docetaxel + ADT	221(84)	Enzalutamide: 119(45); Abiraterone: 153(58)	
ARASENS	Darolutamide + Docetaxel + ADT	179(56.8)	Enzalutamide: 48(15.2)*; Abiraterone: 112(35.6)	PMID: 35179323; Follow-up publication
	Docetaxel + ADT	374(75.6)	Enzalutamide: 136(27.5)*; Abiraterone: 232(46.9)	
SWOG 1216	TAK + ADT	203(61.3)	NA	PMID: 35446628; Follow-up publication
	NSAA + ADT	311(77.4)	NA	

eTable 7. Overall Survival in Patients Receiving Doublet Therapy (API or Docetaxel) Stratified by Volume of Disease and Timing of Metastatic Presentation

Population	Hazard ratio (95% CI)[a]	P-value of interaction	Interpretation
Overall patient population[a]			
High volume disease	0.68 (0.63-0.74)	0.36	Doublet therapy is associated with consistent OS benefit across high and low volume. There is no effect modification by volume of disease in overall population
Low volume disease	0.69 (0.57-0.84)		
Synchronous metastases	0.68 (0.62-0.74)	0.43	Doublet therapy is associated with consistent OS benefit across synchronous and metachronous presentation. There is no effect modification by the timing of metastases presentation in overall population
Metachronous metastases	0.75 (0.60-0.93)		
Synchronous metastases			
API doublet	0.65 (0.60-0.72)	0.26	In patients with synchronous metastases, API doublet therapy derives significantly greater OS benefit than docetaxel doublet therapy when compared to ADT alone. However, there is no effect modification by choice of doublet therapy in patients with synchronous presentation
Docetaxel doublet	0.78 (0.58-1.06)		
Metachronous metastases			
API doublet	0.61 (0.43-0.87)	0.14	In patients with metachronous metastases, API doublet therapy derives significantly greater OS benefit than docetaxel doublet therapy when compared to ADT alone. However, there is no effect modification by choice of doublet therapy in patients with metachronous presentation
Docetaxel doublet	0.90 (0.62-1.32)		

Abbreviations: API: androgen pathway inhibitors (including abiraterone acetate, apalutamide and enzalutamide); CI: confidence interval

a. All effect estimates (hazard ratios) outlined here, are for doublet regimens as compared to standard ADT. These comparisons only include trials which assessed the efficacy of addition of API or docetaxel to standard ADT relative to ADT only. We assumed the relative efficacy of ADT to be similar to ADT+NSAA (nonsteroidal antiandrogen) which was the comparator in ENZAMET trial for the purpose of pooling studies together for direct comparisons. These comparisons do not include evidence from trials assessing triplet therapy relative to docetaxel and ADT (ARASENS and PEACE-1)

eTable 8. Overall Survival With Docetaxel Doublet Therapy in Patients With High-Volume Disease and Low-Volume Synchronous and Metachronous Presentation

Population	Hazard ratio (95% CI)[a]	P-value of interaction	Interpretation
Patients receiving docetaxel[a]			
High volume disease	0.73 (0.62-0.86)	0.27	Patients receiving docetaxel doublet therapy and having high volume disease may derive greater benefit than patients with low volume disease and synchronous presentation as compared to those receiving ADT alone However, there is no statistically significant effect modification between high volume disease and low volume synchronous presentation with regards to OS improvement in patients receiving docetaxel doublet therapy
Low volume - Synchronous	0.86 (0.68-1.08)		
High volume disease	0.73 (0.62-0.86)	0.06	Patients receiving docetaxel doublet therapy and having high volume disease may derive greater benefit than patients with low volume disease and metachronous presentation as compared to those receiving ADT alone However, there is statistically significant effect modification between high volume disease and low volume metachronous presentation with regards to OS improvement in patients receiving docetaxel doublet therapy
Low volume - Metachronous	1.07 (0.75-1.54)		

Abbreviations: CI: confidence interval

a. All effect estimates (hazard ratios) outlined here, are for docetaxel doublet therapy as compared to standard ADT. These comparisons only include trials that assessed the efficacy of the addition of docetaxel to standard ADT relative to ADT only. These comparisons do not include evidence from trials assessing triplet therapy relative to docetaxel and ADT (ARASENS and PEACE-1)

eTable 9. Progression-Free Survival With Doublet Therapy (API or Docetaxel) Compared With ADT by Clinically Relevant Subgroups

Population	Hazard ratio (95% CI)[a]	P-value of interaction
Overall patient population		
High volume disease	0.51 (0.46-0.57)	0.83
Low volume disease	0.49 (0.36-0.67)	
Synchronous metastases	0.48 (0.40-0.58)	0.36
Metachronous metastases	0.42 (0.33-0.54)	
API doublet [b]	0.50 (0.44-0.58)	<0.01
Docetaxel doublet [b]	0.67 (0.60-0.74)	
High volume		
API doublet [b]	0.46 (0.42-0.51)	<0.01
Docetaxel doublet [b]	0.60 (0.52-0.70)	
Low volume		
API doublet [b]	0.37 (0.28-0.50)	<0.01
Docetaxel doublet [b]	0.74 (0.61-0.91)	
Synchronous metastases		
API doublet	0.48 (0.40-0.58)	Not applicable
Docetaxel doublet	Not available	
Metachronous metastases		
API doublet	0.42 (0.33-0.54)	Not applicable
Docetaxel doublet	Not available	

Abbreviations: API: androgen pathway inhibitors (including abiraterone acetate, apalutamide and enzalutamide); CI: confidence interval

a. All effect estimates (hazard ratios) outlined here, are for doublet regimens as compared to standard ADT. These comparisons only include trials which assessed the efficacy of addition of API or docetaxel to standard ADT relative to ADT only. We assumed the relative efficacy of ADT to be similar to ADT+NSAA (nonsteroidal antiandrogen) which was the comparator in ENZAMET trial for the purpose of pooling studies together for direct comparisons. These comparisons do not include evidence from trials assessing triplet therapy relative to docetaxel and ADT (ARASENS and PEACE-1)
b. It should be noted that the definition of progression free survival varied across trials and progression free survival may be an advantageous endpoint for API due to fixed dosing schedule of docetaxel when compared to most androgen pathway inhibitors trials which used an indefinite dosing till disease progression

eTable 10. Survival Outcomes With Doublet Therapy (API or Docetaxel) Compared With ADT by Additional Subgroups of Interest

Population	Hazard ratio (95% CI)[a]	P-value of interaction	Interpretation
Outcome: Overall Survival (OS)			
Gleason score (GS)			
GS >8	0.69 (0.62-0.77)	0.7	Doublet therapy is associated with consistent OS benefit across GS >8 and ≤8 subgroups. There is no effect modification by GS
GS ≤8	0.67 (0.57-0.78)		
Performance status (PS)			
PS 0	0.70 (0.65-0.76)	0.41	Doublet therapy is associated with consistent OS benefit across PS 0 and 1-2 subgroups. There is no effect modification by PS
PS 1-2	0.65 (0.55-0.77)		
Age (years)			
>65 or 70 years	0.73 (0.66-0.80)	Not applicable	Doublet therapy is associated with consistent OS benefit across older and younger men. Age categories were inconsistent across trials and hence effect modification was not evaluated
<65 or 70 years	0.68 (0.60-0.77)		
Outcome: Progression free Survival (PFS)[b]			
Gleason score (GS)			
GS >8	0.44 (0.40-0.50)	0.88	Doublet therapy is associated with consistent PFS benefit across GS >8 and ≤8 subgroup There is no effect modification by GS
GS ≤8	0.43 (0.34-0.56)		
Performance status (PS)			
PS 0	0.41 (0.36-0.47)	0.15	Doublet therapy is associated with consistent PFS benefit across PS 0 and 1-2 subgroups. There is no effect modification by PS
PS 1-2	0.48 (0.41-0.56)		
Age (years)			
>65 or 70 years	0.48 (0.40-0.59)	Not applicable	Doublet therapy is associated with consistent PFS benefit across older and younger men. Age categories were inconsistent across trials and hence effect modification was not evaluated
<65 or 70 years	0.44 (0.37-0.51)		

Abbreviations: API: androgen pathway inhibitors (including abiraterone acetate, apalutamide and enzalutamide); CI: confidence interval

a. All effect estimates (hazard ratios) outlined here, are for doublet regimens as compared to standard ADT. These comparisons only include trials which assessed the efficacy of addition of API or docetaxel to standard ADT relative to ADT only. We assumed the relative efficacy of ADT to be similar to ADT+NSAA (nonsteroidal antiandrogen) which was the comparator in ENZAMET trial for the purpose of pooling studies together for direct comparisons. These comparisons do not include evidence from trials assessing triplet therapy relative to docetaxel and ADT (ARASENS and PEACE-1)

b. It should be noted that the definition of progression free survival varied across trials and progression free survival may be an advantageous endpoint for API due to fixed dosing schedule of docetaxel when compared to most androgen pathway inhibitors trials which used an indefinite dosing till disease progression

eTable 11. GRADE Summary of Findings Table Outlining Certainty of Evidence and Absolute Risks With Doublet Therapy Compared With ADT Alone in the Overall Patient Population

Outcome	Number of participants (studies)	Relative effect [a]	Anticipated absolute effects		Certainty
			Risk with ADT (per 1000)	Risk difference with doublet therapy (per 1000)	
Overall survival	9069 (8 RCTs)	HR 0.72 (0.66-0.78)	433	98 fewer (121 fewer to 75 fewer)	
Progression free survival [b]	9069 (8 RCTs)	HR 0.55 (0.49-0.62)	485	179 fewer (207 fewer to 148 fewer)	
Grade ≥3 adverse events	9480 (6 RCTs)	RR 1.42 (1.19-1.69)	345	145 more (66 more to 238 more)	

High Certainty Benefit	High Certainty Harm
Moderate Certainty Benefit	Moderate Certainty Harm
Low Certainty Benefit	Low Certainty Harm
Very Low Certainty Effect	

a. All effect estimates (hazard ratios) outlined here, are for doublet regimens as compared to standard ADT. These comparisons only include trials which assessed the efficacy of addition of API or docetaxel to standard ADT relative to ADT only. We assumed the relative efficacy of ADT to be similar to ADT+NSAA (nonsteroidal antiandrogen) which was the comparator in ENZAMET trial for the purpose of pooling studies together for direct comparisons. These comparisons do not include evidence from trials assessing triplet therapy relative to docetaxel and ADT (ARASENS and PEACE-1)

b. It should be noted that the definition of progression free survival varied across trials and progression free survival may be an advantageous endpoint for API due to fixed dosing schedule of docetaxel when compared to most androgen pathway inhibitors trials which used an indefinite dosing till disease progression

eTable 12. GRADE Summary of Findings Table Outlining Certainty of Evidence and Absolute Risks With Doublet Therapy Compared With ADT Alone in Clinically Relevant Prognostic Subgroups

Outcome	Number of participants (studies)	Relative effect [a]	Anticipated absolute effects		Certainty
			Risk with ADT (per 1000)	Risk difference with doublet therapy (per 1000)	
Overall Survival					
High volume	3793 (7 RCTs)	HR: 0.68 (0.63-0.74)	550	131 fewer (155 fewer to 104 fewer)	
Low volume	2280 (7 RCTs)	HR: 0.69 (0.57-0.84)	383	100 fewer (142 fewer to 50 fewer)	
Synchronous	4579 (7 RCTs)	HR: 0.68 (0.62-0.74)	464	118 fewer (143 fewer to 94 fewer)	
Metachronous	1077 (5 RCTs)	HR: 0.70 (0.54-0.91)	274	73 fewer (115 fewer to 21 fewer)	
Progression free survival [b]					
High volume	4772 (7 RCTs)	HR: 0.51 (0.46-0.57)	662	237 fewer (269 fewer to 201 fewer)	
Low volume	3103 (7 RCTs)	HR: 0.49 (0.36-0.67)	460	199 fewer (261 fewer to 122 fewer)	
Synchronous	4422 (5 RCTs)	HR: 0.48 (0.40-0.58)	522	224 fewer (266 fewer to 174 fewer)	
Metachronous	863 (3 RCTs)	HR: 0.42 (0.33-0.54)	418	215 fewer (255 fewer to 165 fewer)	

High Certainty Benefit	High Certainty Harm
Moderate Certainty Benefit	Moderate Certainty Harm
Low Certainty Benefit	Low Certainty Harm
Very Low Certainty Effect	

a. All effect estimates (hazard ratios) outlined here, are for doublet regimens as compared to standard ADT. These comparisons only include trials which assessed the efficacy of addition of API or docetaxel to standard ADT relative to ADT only. We assumed the relative efficacy of ADT to be similar to ADT+NSAA (nonsteroidal antiandrogen) which was the comparator in ENZAMET trial for the purpose of pooling studies together for direct comparisons. These comparisons do not include evidence from trials assessing triplet therapy relative to docetaxel and ADT (ARASENS and PEACE-1)

b. It should be noted that the definition of progression free survival varied across trials and progression free survival may be an advantageous endpoint for API due to fixed dosing schedule of docetaxel when compared to most androgen pathway inhibitors trials which used an indefinite dosing till disease progression

eTable 13. GRADE Summary of Findings Table Outlining Certainty of Evidence and Absolute Risks With Triplet Therapy Compared With Other Treatments by Timing of Metastatic Presentation

Comparators	Abiraterone acetate + Docetaxel + ADT	Darolutamide + Docetaxel + ADT	
	Synchronous		Metachronous
Abiraterone acetate + Docetaxel + ADT **Synchronous** 341 per 1000	NA	**17 fewer per 1000** (from 88 fewer to 70 more) HR: 0.94 (0.70-1.27) 913 patients (2 RCTs) Rank 2	NA
Darolutamide + Docetaxel + ADT **Synchronous** 369 per 1000 **Metachronous** 255 per 1000	**17 more per 1000** (from 64 fewer to 113 more) HR: 1.06 (0.79-1.43) 913 patients (2 RCTs) Rank 1	Rank 1	Rank 2
Apalutamide + ADT **Synchronous** 341 per 1000 **Metachronous** 235 per 1000	**45 fewer per 1000** (from 126 fewer to 58 more) HR: 0.84 (0.58-1.22) 766 patients (2 RCTs) Rank 5	**60 fewer per 1000** (from 129 fewer to 30 more) HR: 0.79 (0.57-1.11) 969 patients (2 RCTs)	**80 more per 1000** (from 91 fewer to 368 more) HR: 1.41 (0.58-3.45) 171 patients (2 RCTs) Rank 1
Enzalutamide + ADT **Synchronous** 341 per 1000 **Metachronous** 266 per 1000	**28 fewer per 1000** (from 104 fewer to 82 more) HR: 0.90 (0.65-1.32) 1128 patients (3 RCTs) Rank 3	**40 fewer per 1000** (from 116 fewer to 55 more) HR: 0.86 (0.61-1.21) 1331 patients (3 RCTs)	**54 fewer per 1000** (from 169 fewer to 166 more) HR: 0.77 (0.33-1.83) 441 patients (3 RCTs) Rank 3
Abiraterone acetate + ADT **Synchronous** 395 per 1000	**31 fewer per 1000** (from 116 fewer to 71 more) HR: 0.90 (0.65-1.25) 1380 patients (3 RCTs) Rank 4	**47 fewer per 1000** (from 120 fewer to 41 more) HR: 0.85 (0.64-1.14) 1583 patients (3 RCTs) Rank 4	NA
Docetaxel + ADT **Synchronous** 469 per 1000 **Metachronous** 384 per 1000	**91 fewer per 1000** (from 157 fewer to 17 fewer) HR: 0.75 (0.59-0.95) 1565 patients (4 RCTs) Rank 6	**107 fewer per 1000** (from 157 fewer to 53 more) HR: 0.71 (0.59-0.85) 1768 patients (4 RCTs)	**128 fewer per 1000** (from 228 fewer to 15 more) HR: 0.61 (0.35-1.05) 276 patients (3 RCTs) Rank 4
NSAA+ADT **Synchronous** 287 per 1000 **Metachronous** 209 per 1000	**92 fewer per 1000** (from 157 fewer to 5 fewer) HR: 0.64 (0.41-0.98) 682 patients (2 RCTs) Rank 7	**103 fewer per 1000** (from 160 fewer to 25 fewer) HR: 0.60 (0.40-0.90) 885 patients (2 RCTs)	**88 fewer per 1000** (from 159 fewer to 66 more) HR: 0.55 (0.22-1.37) 321 patients (2 RCTs) Rank 5
ADT **Synchronous** 490 per 1000 **Metachronous** 327 per 1000	**171 fewer per 1000** (from 244 fewer to 85 fewer) HR: 0.57 (0.42-0.77) 2557 patients (6 RCTs) Rank 8	**185 fewer per 1000** (from 244 fewer to 118 more) HR: 0.54 (0.42-0.69) 2760 patients (6 RCTs)	**131 fewer per 1000** (from 222 fewer to 21 more) HR: 0.55 (0.28-1.08) 380 patients (4 RCTs) Rank 6
High Certainty Benefit	**Moderate Certainty Benefit**	**Low Certainty Benefit**	**Very Low Certainty Effect**
High Certainty Harm	**Moderate Certainty Harm**	**Low Certainty Harm**	

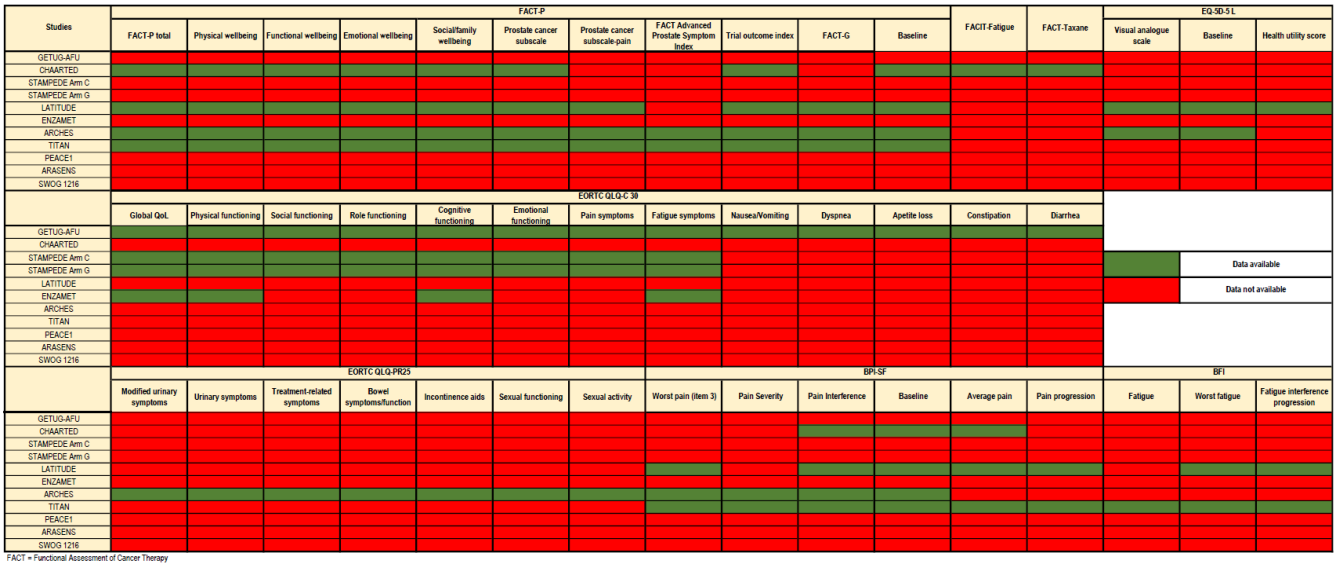
Abbreviations: GRADE: grading of recommendations, assessment, development, and evaluation; ADT: androgen deprivation therapy; NSAA: non-steroidal antiandrogen; HR: hazard ratio; RR: relative risks

This table provides a summary of relative and absolute risks for mixed treatment comparisons derived from frequentist network meta-analysis using four levels of certainty: high (further research is very unlikely to change our confidence in the estimate of effect), moderate (further research is likely to have an important impact on our confidence in estimate of effect and may change the estimate), low (further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate), and very low (very uncertain about the estimate

eTable 14. Adverse Events and Patient-Level Considerations for Androgen Pathway Inhibitors (API) in Patients With mCSPC

Adverse events and patient level considerations
Abiraterone
1. Requires steroid administration 2. May be associated with an increased risk of hepatoxicity, and hypokalemia and should be avoided diabetic patients
Enzalutamide
1. May be associated with an increased risk of neurotoxicity including cognitive impairment, seizures, and cardiovascular disease
Apalutamide
1. May be associated with an increased risk of neurotoxicity including cognitive impairment, seizures, and cardiovascular disease, and rash
Darolutamide
1. May be associated with an increased risk of hypertension

eTable 15. Reporting Matrix Outlining the Heterogeneity in Health-Related Quality-of-Life Assessment in Included Trials



FACT = Functional Assessment of Cancer Therapy
FACT-P = FACT-Prostate
FACT-G= FACT-General
FACT-T = FACT-Taxane
EORTC QLQ-PR25 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Prostate 25
BPI-SF = Brief Pain Inventory Short Form
EQ-5D-5 L = EuroQoL 5-Dimensions, 5-Levels
PRO = Patient reported outcome
BFI = Brief Fatigue Inventory
Brief Pain Inventory (BPI) pain subscale;
HRQL = Health-related quality of life (EORTC QLQ-PR25 + EORTC QLQ-C 30)
FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue

eTable 16. Summary of the Quality of Life With Contemporary Systemic Therapies in Patients With mCSPC

Studies	Arms	Quality of life interpretation
GETUG-AFU	Docetaxel + ADT	The addition of docetaxel to ADT results in impaired QoL. However global scores at 12 months were similar to ADT alone
	ADT	
CHAARTED	Docetaxel + ADT	The addition of docetaxel to ADT had worse QoL outcomes than men treated with ADT alone at 3 months - as observed in the CHAARTED trial - which improved by 12 months
	ADT	
STAMPEDE	Docetaxel + ADT	Comparative QoL analysis of STAMPEDE data demonstrated better QoL outcomes in patients who received abiraterone as compared to those who received docetaxel in addition to ADT
	Abiraterone + ADT	
LATITUDE	Abiraterone + ADT	Patient-reported outcomes in the LATITUDE trial showed that the addition of abiraterone to ADT in patients with mCSPC improved overall progression of pain, prostate cancer symptoms, fatigue, functional decline, and overall QoL
	ADT	
ENZAMET	Enzalutamide + ADT	The addition of enzalutamide to ADT in patients with mCSPC improves QoL and deterioration free survival
	ADT + NSAA	
ARCHES	Enzalutamide + ADT	The addition of enzalutamide to ADT in patients with mCSPC maintains high functioning QoL and low symptom burden
	ADT	
TITAN	Apalutamide + ADT	The addition of apalutamide to ADT in patients with mCSPC was well tolerated and did not diminish QoL in patients
	ADT	
PEACE1	Abiraterone + Docetaxel + ADT	Not available
	Docetaxel + ADT	
ARASENS	Darolutamide + Docetaxel + ADT	Not available
	Docetaxel + ADT	
SWOG 1216	TAK + ADT	Not available
	NSAA + ADT	

eTable 17. Reporting Matrix for Outcomes Assessed in Included Trials

	Studies									
Outcomes	**GETUG-AFU**	**CHAARTED**	**STAMPEDE**	**LATITUDE**	**ENZAMET**	**ARCHES**	**TITAN**	**PEACE-1**	**ARASENS**	**SWOG-1216**
Overall survival	■	■	■	■	■	■	■	■	■	■
Progression-free survival	■	■	■	■	■	■	■	■	■	■
Secondary/secondary progression-free survival	■	■	■	■	■	■	■	■	■	■
Radiographic progression-free survival	■	■	■	■	■	■	■	■	■	■
Clinical progression free survival	■	■	■	■	■	■	■	■	■	■
Biochemical progression free survival	■	■	■	■	■	■	■	■	■	■
PSA progression-free survival	■	■	■	■	■	■	■	■	■	■
Failure-free survival	■	■	■	■	■	■	■	■	■	■
Metastatic progression-free survival	■	■	■	■	■	■	■	■	■	■
Prostate cancer-specific survival	■	■	■	■	■	■	■	■	■	■
Castration resistance free survival	■	■	■	■	■	■	■	■	■	■
Time to castration resistance	■	■	■	■	■	■	■	■	■	■
Time to PSA progression	■	■	■	■	■	■	■	■	■	■
PSA undetectable rate	■	■	■	■	■	■	■	■	■	■
PSA Response	■	■	■	■	■	■	■	■	■	■
Objective response rate	■	■	■	■	■	■	■	■	■	■
Time to treatment after progression	■	■	■	■	■	■	■	■	■	■
Time to chemotherapy (initiation of new or cytotoxic or for CRPC)	■	■	■	■	■	■	■	■	■	■
Time to initiation of subsequent systemic therapy	■	■	■	■	■	■	■	■	■	■
Time to pain progression	■	■	■	■	■	■	■	■	■	■
Time to symptomatic local progression	■	■	■	■	■	■	■	■	■	■
Time to skeletal-related event (including first event or first symptomatic event)	■	■	■	■	■	■	■	■	■	■
Symptomatic skeletal event–free survival	■	■	■	■	■	■	■	■	■	■
Time to worsening of disease-related physical symptoms	■	■	■	■	■	■	■	■	■	■
Time to deterioration in urinary symptoms	■	■	■	■	■	■	■	■	■	■
Time to chronic opioid use	■	■	■	■	■	■	■	■	■	■
Time to initiation of opioid treatment	■	■	■	■	■	■	■	■	■	■
Quality of Life	■	■	■	■	■	■	■	■	■	■
Toxicity	■	■	■	■	■	■	■	■	■	■
Outcomes reported or reporting anticipated in updated reports	■									
Outcomes not available or reported	■									

eTable 18. Strengths

Strengths
1. To our knowledge, this the first living systematic review which evaluates the comparative effectiveness of first-line treatment options in patients diagnosed with metastatic castration sensitive prostate cancer (mCSPC)
2. We have conducted detailed secondary and subgroup analyses stratified by disease volume, timing of metastatic presentation, choice of doublet therapy, age, Gleason scores, and performance status/WHO scores. Furthermore, we have conducted sensitivity analyses and found consistent pattern of results which suggested robustness of our analyses
3. We have assessed the certainty of evidence using the GRADE approach and provided balanced presentations of benefit and harm in terms of relative and absolute measures of treatment effect.
4. The living interactive platform enables dynamic visualization of data from contemporary trials which has the potential to improve clinical decision-making. The data are presented in a way that emphasize relevant variables such as volume of disease and timing of metastatic presentation. We acknowledge the uncertainties associated with process of publishing future updates from this living review. However, we are committed to maintain this living review until optimal information size is met.

eTable 19. Limitations

Limitations	Discussion
Outcomes such as prostate-specific antigen (PSA) progression, time to subsequent therapy, time to skeletal-related event, and time to castration resistance were not analyzed. These outcomes might have a competing role in choosing the optimal therapy and could potentially alter treatment selection in some patients	These outcomes were not analyzed in this report owing to sparse reporting across trials which limited meaningful analyses (**eTable 11**). However, we are monitoring data in this regard and the analyses will be updated as soon data for new outcomes emerges.
The definition of progression free survival (PFS) varied across different trials.	Most trials reported radiographic PFS (**eTable 1**). Therefore, our results might be more representative of radiographic PFS if not of other PFS variants. Our PFS results are unlikely to overestimate the treatment effect as it has been assumed in prior studies that progression on radiographic scans occurs earlier than a symptomatic progression, initiation of new anticancer treatment, and death from other causes. Nevertheless, we downgraded the certainty in evidence for PFS outcome to reflect this indirectness across trials
PFS assessed for fixed number of cycles in docetaxel vs. indefinite dosing of androgen pathway inhibitors	PFS may be advantageous endpoint for androgen pathway inhibitors considering that docetaxel was administered for a fixed number of cycles in the trials while androgen pathway inhibitors were administered indefinitely till disease progression. However, we have also assessed overall survival which is a more robust endpoint and found consistent pattern of results.
None of these trials were originally designed to capture treatment efficacy by volume of disease/timing of metastatic presentation	Only some trials stratified patients by volume of disease. Most trials reported these subgroups as post hoc analyses without stratification and adjustment for potential confounding relationships. However, trial-level data did not allow us to adjust for potential covariates. An individual patient data meta-analysis may offer more insights.
The follow-up durations for different treatment options varied across the included trials.	With the living evidence approach, the results will be updated when long-term results from relevant trials as well as when the data regarding efficacy by volume of disease from the ARASENS trial, and mature data for low volume patients from the PEACE-1 trial are published.
Only PEACE-1 data by volume of disease was used in the analysis for triplet therapy. Comparative efficacy of triplet therapy in high-volume patients is based on the findings from the PEACE-1 trial which only included patients with synchronous (de novo) metastases. While results from ARASENS suggest that differences in treatment effect may not exist by the timing of metastatic presentation, the results by volume of disease are not yet available.	