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Updated overall survival outcomes in ENZAMET (ANZUP 1304), an international, cooperative group trial of enzalutamide in metastatic hormone-sensitive prostate cancer (mHSPC)

Davis ID, Martin AJ, Zielinski RR, Thomson A, Tan TH, Sandhu SK, Reaume MN, Pook DW, Parnis F, North SA, Marx GM, McCaffrey J, McDermott R, Lawrence NJ, Horvath L, Frydenberg M, Chowdhury S, Chi KN, Stockler MR, Sweeney CJ, on behalf of the **ENZAMET Investigators**

Current mHSPC clinical knowledge

Prognostic variables associated with better outcomes with TS alone

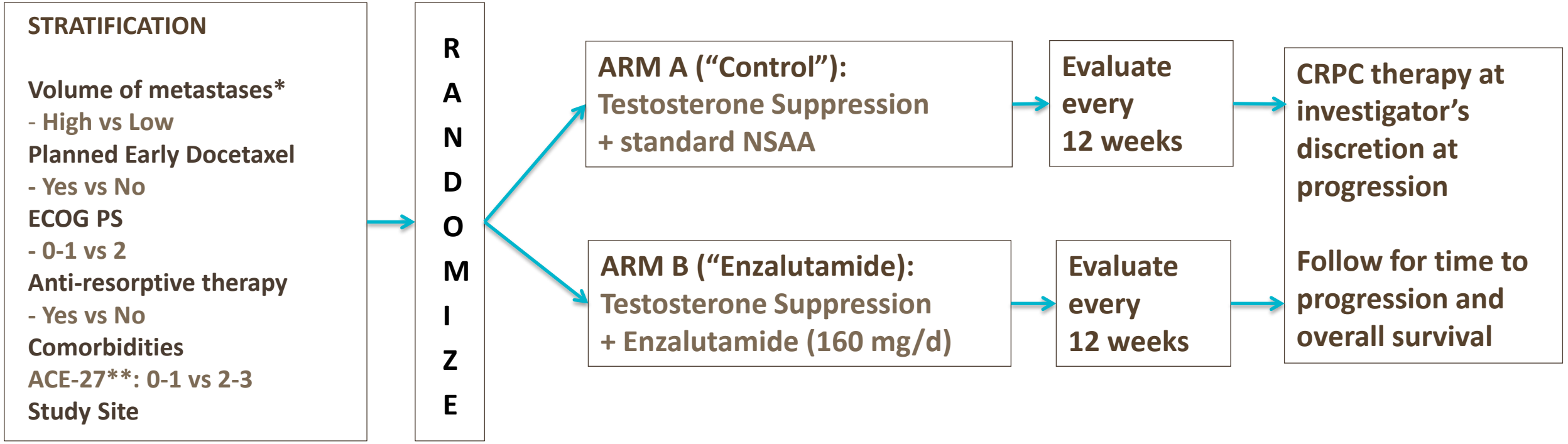
- Low volume better than high volume
- Metachronous metastatic presentation better than synchronous

OS benefit of combination treatment by prognostic groups

- Docetaxel + TS > TS alone: synchronous and metachronous high volume*
- “Strong” ADT (TS + abi / enza / apa) > TS alone: all prognostic groups
- Radiation to primary + TS > TS alone: synchronous low volume disease
- Abiraterone or darolutamide + docetaxel + TS > docetaxel + TS: when docetaxel is thought to be appropriate

* Vale et al .STOPCaP-docetaxel IPD. ASCO 2022 Abstract 5070

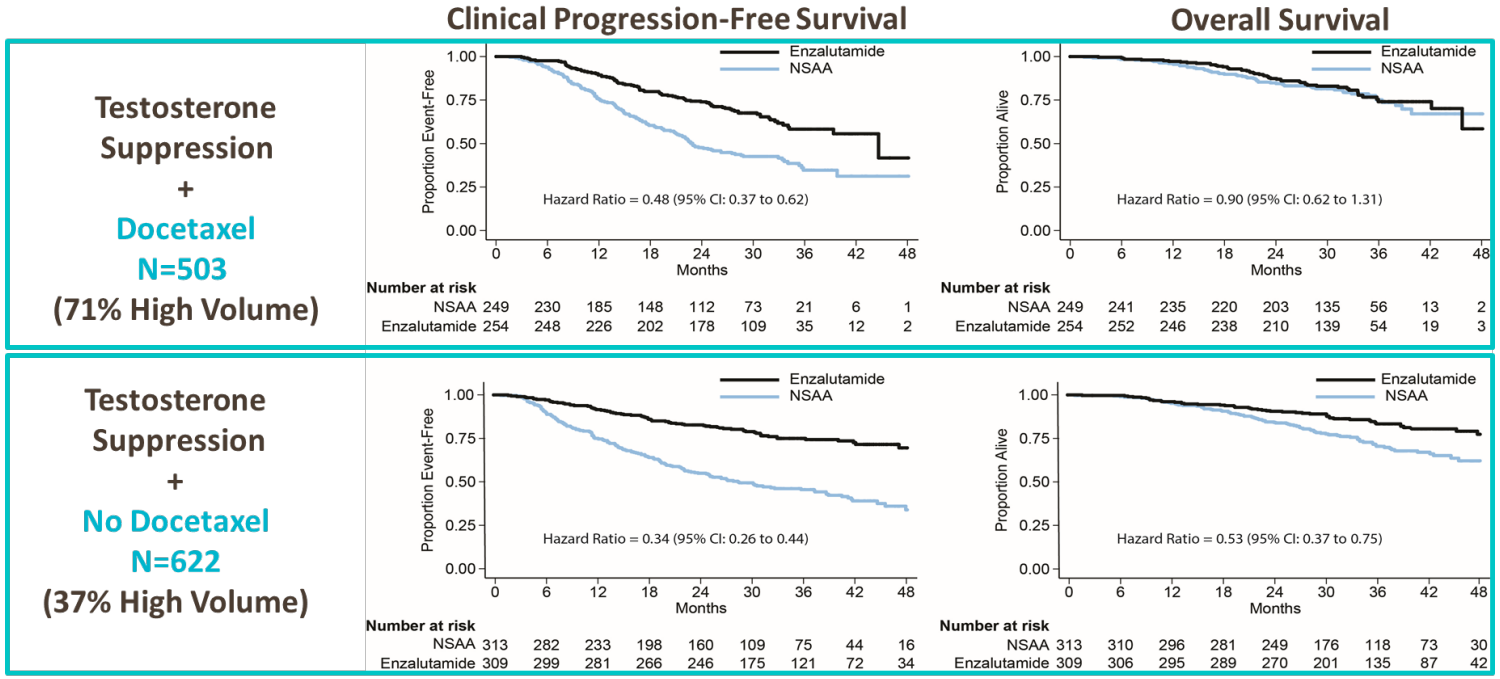
ENZAMET Treatment



- Prior to randomization testosterone suppression up to 12 weeks and 2 cycles of docetaxel was allowed.
- Intermittent ADT and cyproterone were not allowed
- NSAA: bicalutamide; nilutamide; flutamide
- *High volume: visceral metastases and/or 4 or more bone metastases (at least 1 beyond pelvis and vertebral column)
- **Adult Co-morbidity Evaluation-27

Interim analysis (235 deaths; data cutoff 28 Feb 2019) [1]

- Primary endpoint met: Improved OS for the combined overall cohort (HR 0.67)
- No evidence of additional benefit for enzalutamide in patients planned to receive early docetaxel
- Strong signal in favor of triplet (enzalutamide + TS + docetaxel) for secondary endpoints of PSA PFS and clinical PFS
- Some additional toxicity, particularly early; outweighed by clinical benefit [2]



[1] Davis ID et al. NEJM 381: 121-131, 2019; Sweeney CJ et al, ASCO Plenary 2019. [2] Stockler MR et al. J Clin Oncol 40: 837-846, 2022.

Planned 470 event analysis (data cutoff 19 Jan 2022)

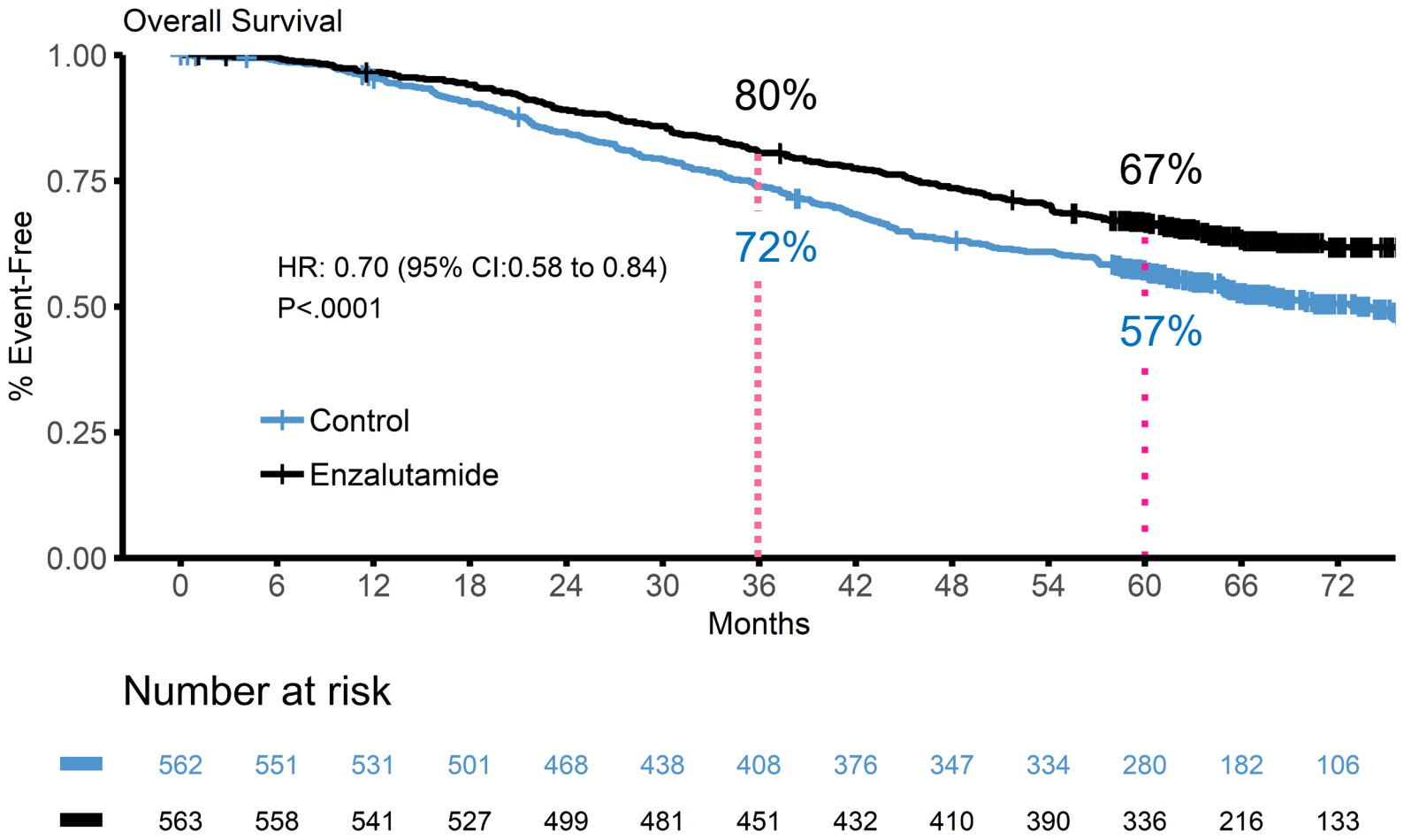
- Longer term data - median followup 68 months
- Adjusted prespecified Statistical Analysis Plan:
  - 470 deaths (no additional interim analyses)
  - Identify synchronous vs metachronous M1: “M0 at primary diagnosis (Y/N)”

<u>Exploratory subgroup analysis</u>:

Is the effect of enzalutamide modified by prognostic grouping and docetaxel use?

- Two binary factors for prognosis:
  - M1 at initial diagnosis (synchronous, de novo), or not (ie not M0 or Mx)
  - High volume mHSPC at study entry, or not

Overall survival – combined cohort



Median OS:

Control (NSAA): 73.2 mo (64.7 - NR)
Enzalutamide: NR (NR - NR)

5-year survival:

Control (NSAA): 57%
Enzalutamide: 67%

Median follow-up: 68 months

NR: not reached

Therapy after progression

- Participants continued on enzalutamide for longer
  - Median 22.6mo NSAA
  - Median 57.8mo enza
- Substantial crossover in control arm to enzalutamide or abiraterone for CRPC
- 76% of those on NSAA arm received enzalutamide OR abiraterone after progression; 26% on enzalutamide arm
- 39% of those with cancer progression on enzalutamide had no further treatment recorded

Treatment	NSAA (N=413)		Enzalutamide (N=268)	
	N	%	N	%
Enzalutamide	205	49.6	0	0
Abiraterone	148	35.8	70	26.1
Other NHA	2	0.5	1	0.4
Docetaxel	105	25.4	69	25.7
Cabazitaxel	104	25.2	57	21.3
Other chemo	38	9.2	37	13.8
ICI	11	2.7	11	4.1
PARP inhibitor	21	5.1	7	2.6
^{177}Lu-PSMA	12	2.9	9	3.4
Radium-223	28	6.8	26	9.7
Sipuleucel-T	3	0.7	1	0.4
None	60	14.5	104	38.8

NHA, novel hormonal agent; ICI, immune checkpoint inhibitor

Other key considerations

- ENZAMET was representative, including all combinations of patient subgroups:
  - Synchronous / metachronous; high volume / low volume; use of docetaxel
  - Treated contemporaneously in same trial
- Docetaxel use:
  - At investigator discretion
  - Based on assessment of “chemofitness” or predicted benefit
  - 45% planned for concurrent docetaxel up to 6 cycles (median 6)
  - Before randomization: 108 received 1 cycle, 62 received 2 cycles
- Design allows exploratory description of subgroup outcomes
  - Not formal comparisons due to confounding

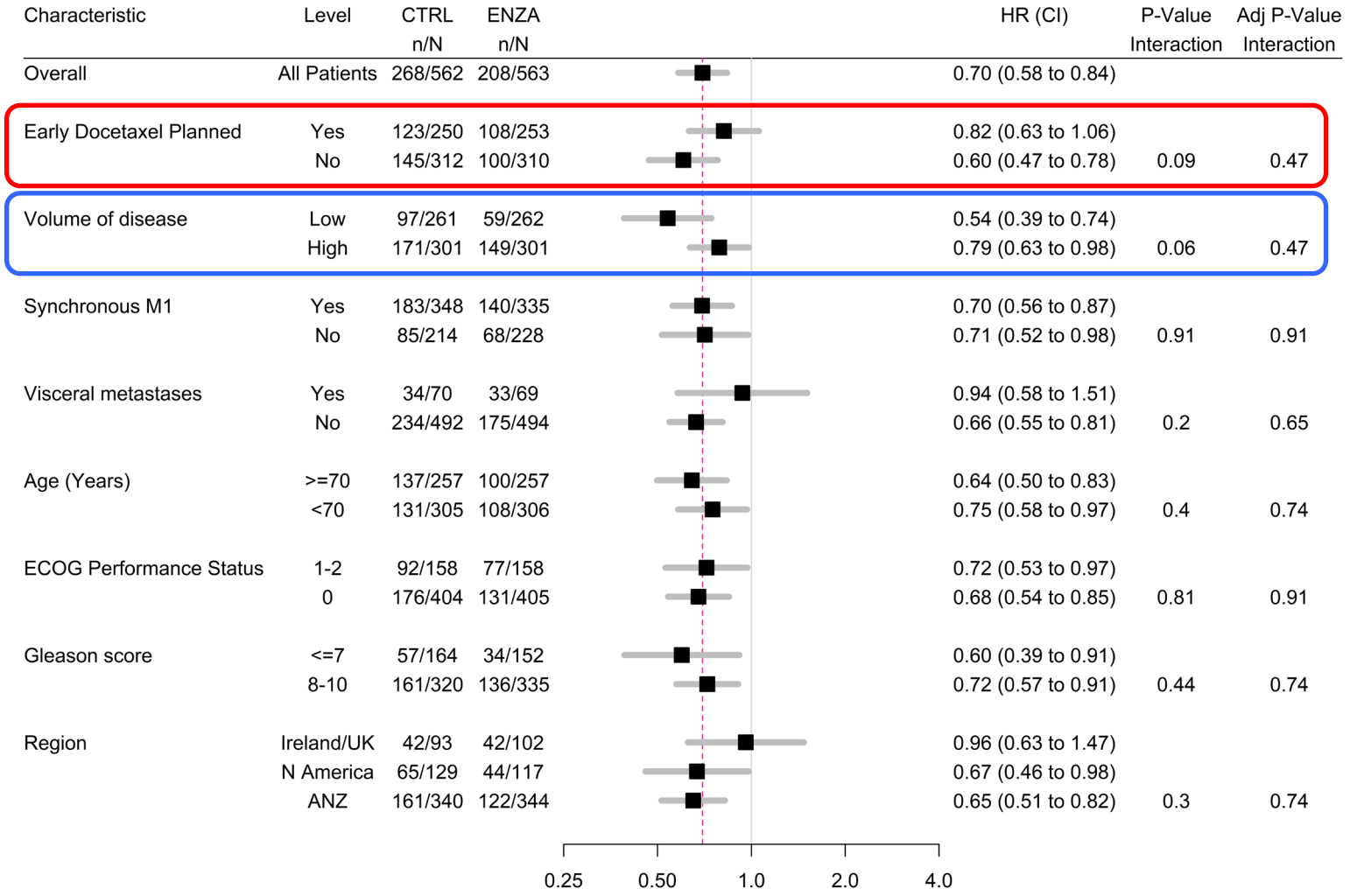
Overall survival: prespecified subgroup analysis

Total N = 1125

Docetaxel: 503

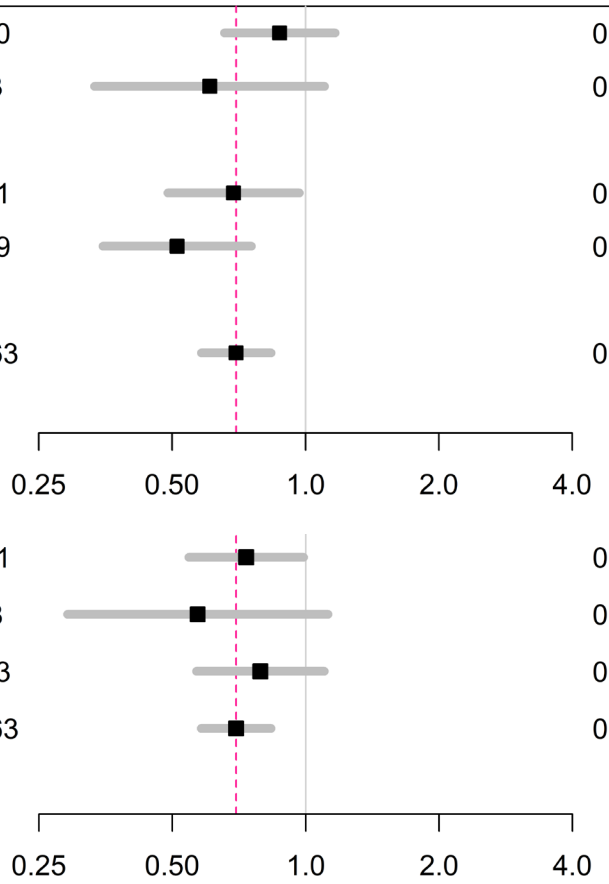
High volume: 602

Synchronous M1: 683



Overall survival: volume, M1 timing, docetaxel

Characteristic (Patient Subset)	Level	CTRL n/N	ENZA n/N	HR (CI)	CTRL 5-yr OS (%)	ENZA 5-yr OS (%)
Volume of Disease (Docetaxel=Yes)	High	96/179	90/180	0.87 (0.66 to 1.17)	51	54
	Low	27/71	18/73	0.61 (0.33 to 1.10)	67	78
Volume of Disease (Docetaxel=No)	High	75/122	59/121	0.69 (0.49 to 0.97)	47	57
	Low	70/190	41/189	0.51 (0.35 to 0.75)	66	81
Overall	All Patients	268/562	208/563	0.70 (0.58 to 0.84)	57	67
M1 Synchronous, Docetaxel	All	96/181	79/181	0.73 (0.55 to 0.99)	52	60
M1 Synchronous, Docetaxel	Low Vol	21/44	14/48	0.57 (0.29 to 1.12)	57	73
M1 Synchronous, Docetaxel	High Vol	75/137	65/133	0.79 (0.57 to 1.10)	51	55
Overall	All Patients	268/562	208/563	0.70 (0.58 to 0.84)	57	67



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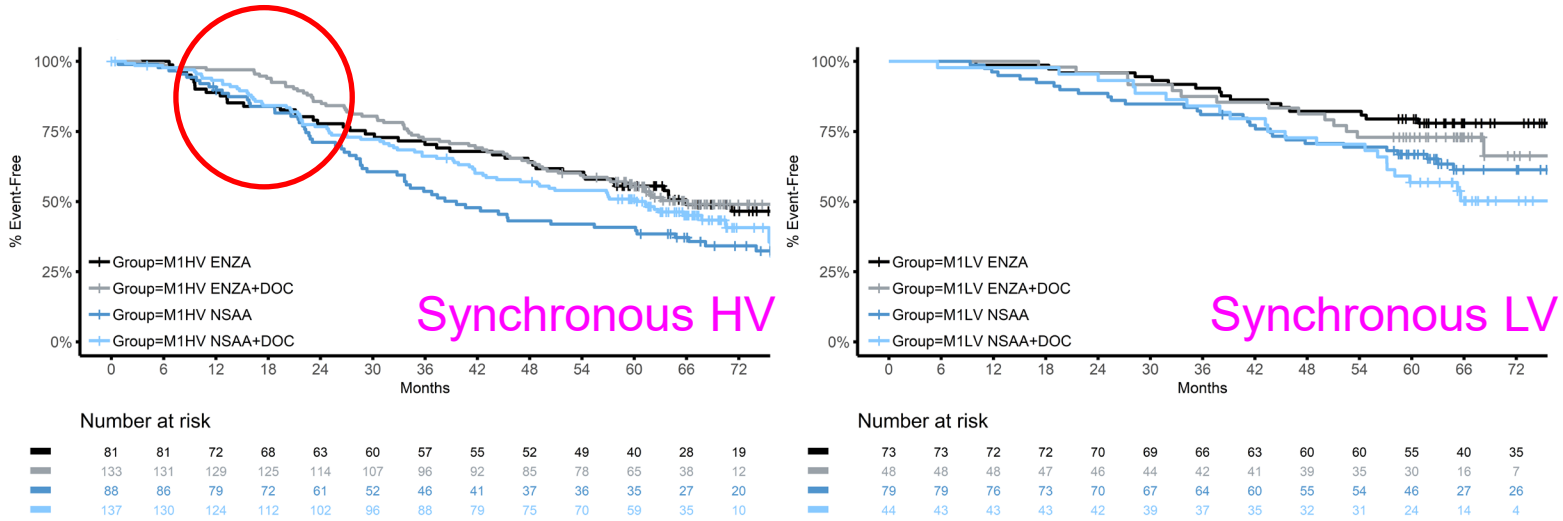
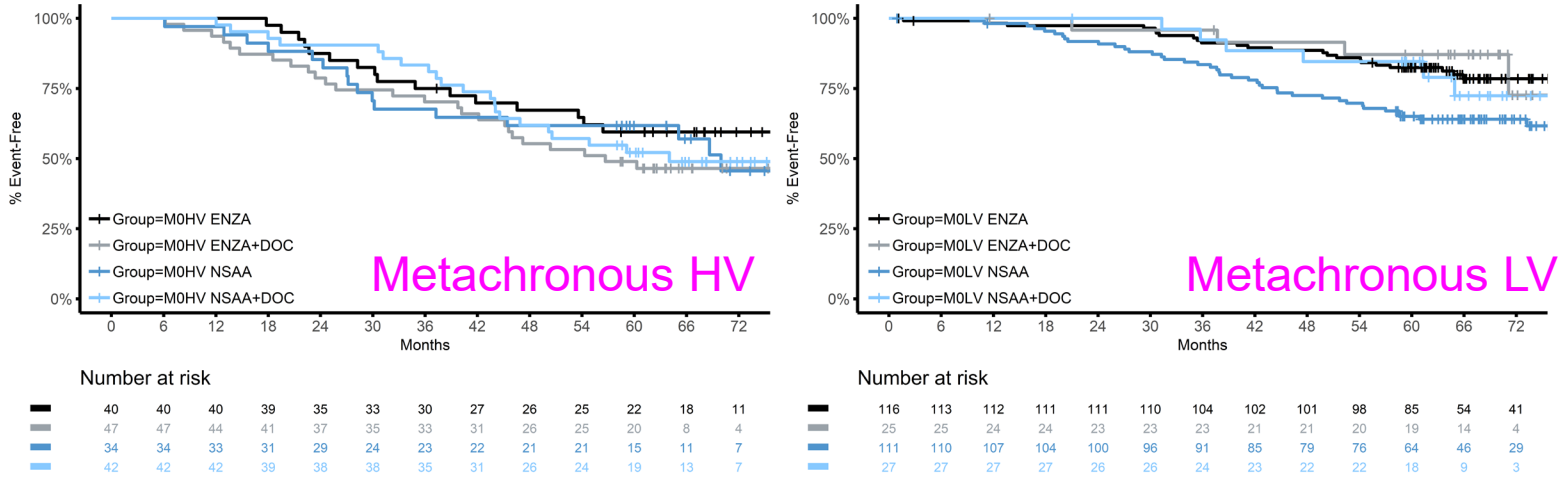
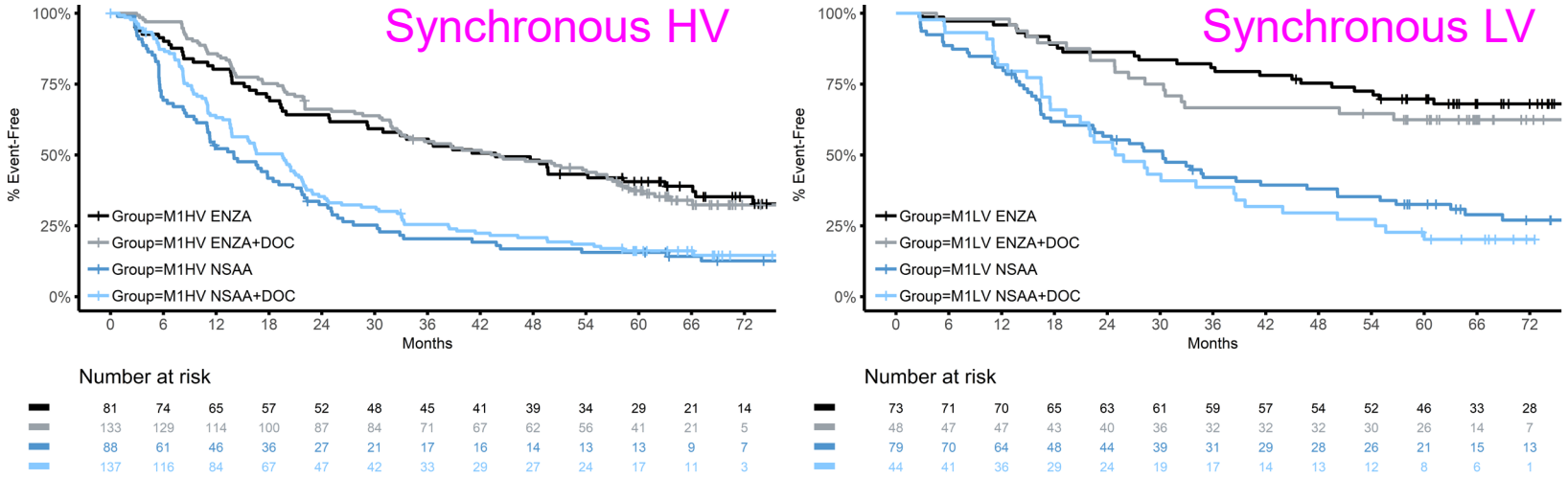


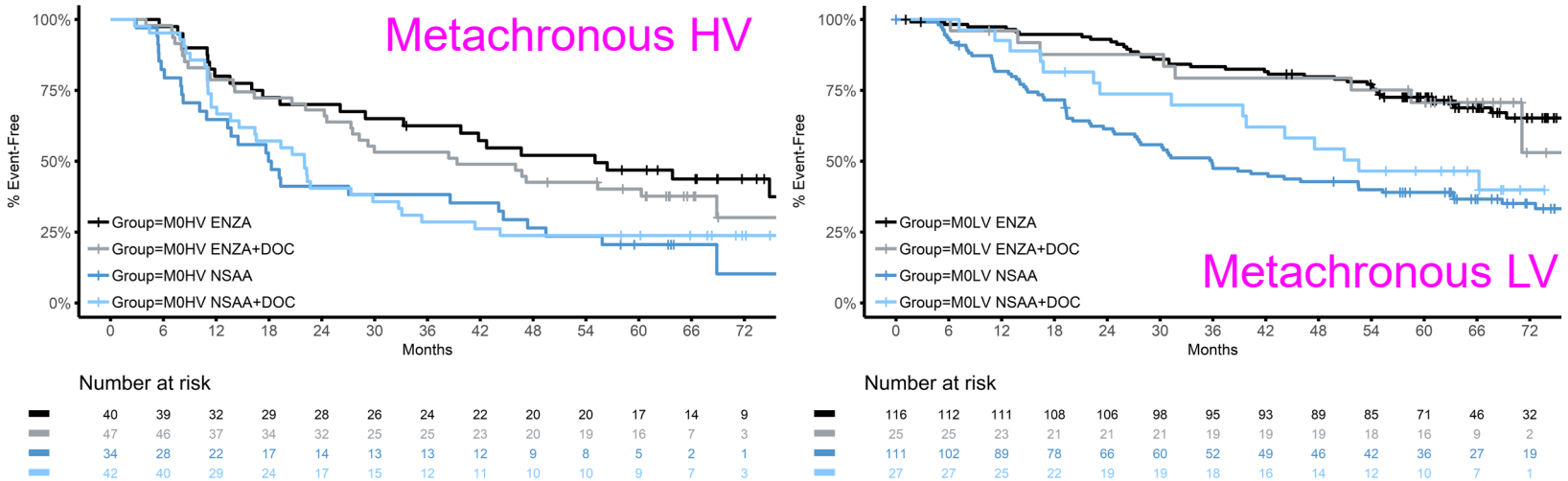


- Enzalutamide
- Enzalutamide + docetaxel
- NSAA
- NSAA + docetaxel

HV: high volume. LV: low volume

PSA progression-free survival





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Discussion

Strengths

- Active control arm; outcomes comparable to contemporary trials
- Concurrent use of docetaxel allowed as a standard of care
- Mix of synchronous / metachronous; and HV / LV
- "Hard" primary endpoint of overall survival

Limitations

- Docetaxel use not randomized
- Study not powered for exploratory subset analyses
- Do not confuse treatment effects with different prognostic groups

Clinical Impressions

- No major differences found in enzalutamide efficacy across subgroups
- Confirms benefit of enzalutamide in mHSPC, especially in low volume
- Exploratory analyses suggest additional benefit when added to TS + docetaxel

Conclusions

- Enzalutamide added to testosterone suppression for mHSPC, and compared to an active comparator (NSAA ± docetaxel)
  - *Provided clinically meaningful improvements in OS for the combined study cohort*
- Study is ongoing
- Benefits were :
  - Most apparent for low volume mHSPC in those for whom docetaxel was not deemed necessary
  - Still apparent with synchronous high volume mHSPC where docetaxel was deemed necessary (*despite median overall survival >60 months with TS + docetaxel + NSAA)*

Hypotheses from exploratory subgroup analyses:

Greatest benefit of triplet may be in those with poorest prognosis disease (synchronous, high-volume), and able to receive docetaxel

Other subgroups: TS + enzalutamide provides substantial increases in OS that are not augmented by concurrent docetaxel

Acknowledgements

- We acknowledge and thank the 1125 patients and their support network for their participation in the ENZAMET study; the principal investigators, co-investigators, study coordinators, clinical research associates, nurses and data managers at the 83 centres in Australia, New Zealand, Canada, Ireland, United Kingdom and USA for their dedication and enthusiasm
- We thank Astellas for their financial support and study drug
- ANZUP receives valuable infrastructure support from the Australian Government through Cancer Australia

ENZAMET was designed and conducted by the Australian and New Zealand Urogenital and Prostate Cancer Trials Group - ANZUP

In collaboration with: