Association of circulating immune and metabolic markers with clinical outcomes in the ENZAMET trial (ANZUP 1304)

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1. Background

Androgen deprivation therapy (ADT) + enzalutamide (ENZ)

- ENZAMET trial: 1125 participants with metastatic hormone sensitive prostate cancer (mHSPC) were randomized to ADT + ENZ or ADT + NSAA (conventional non-steroidal anti-androgen).[1]
- ADT + ENZA improved overall survival (OS) compared to ADT + NSAA (HR 0.70, 95% CI 0.58-0.84; p<0.0001).
- 5 year OS: ENZ arm 67%, NSAA arm 57%.[1]
- ENZ resistance: 11% of mHSPC patients on ADT + ENZ die within 2 years of commencing therapy.[1]

ADT + docetaxel (DCX)

- CHAARTED trial: ADT + DCX improved OS compared to ADT alone (HR 0.61, 95% CI 0.47-0.80; p<0.001).[2]

Circulating immune & metabolic markers in prostate cancer

- Serum IL8, IGFBP1 and IGF1:IGFPB1 ratio were prognostic for OS in CHAARTED.[3,4]
- Plasma IL8, IL6, YKL40, MIC1, IL17E, IL28A and IL33 were prognostic in metastatic castration-resistant prostate cancer.[5]

2. Aims

Perform post-hoc analysis of ENZAMET trial to:

- **Validate the prognostic association of circulating IL8, IGFBP1 and IGF1:IGFBP1 ratio in mHSPC.**
- **Assess the association of a panel of inflammation markers and cytokines with clinical outcomes in mHSPC.**

3. Methods & study cohort

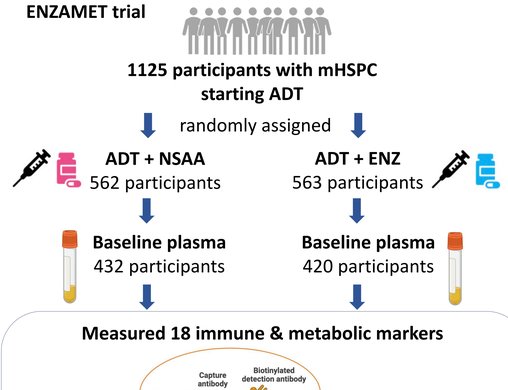

Table 1. Baseline characteristics of

Baseline characteristic	n (%) NSAA, N = 432	ENZ, N = 420	p-value[1]
Volume of disease			>0.9
Low	201 (47%)	196 (47%)	
High	231 (53%)	224 (53%)	
Concurrent docetaxel	188 (44%)	189 (45%)	0.7
ACE-27 score			0.7
0-1	321 (74%)	317 (75%)	
2-3	111 (26%)	103 (25%)	
Anti-resorptive therapy	32 (7.4%)	32 (7.6%)	>0.9
Region			0.10
Australia/New Zealand	277 (64%)	292 (70%)	
Ireland/UK	43 (10.0%)	45 (11%)	
North America	112 (26%)	83 (20%)	
Gleason grade			0.3
≤ 7	125 (34%)	111 (30%)	
8-10	245 (66%)	253 (70%)	
Unknown	62	56	
ECOG performance status			0.7
0	316 (73%)	303 (72%)	
1-2	116 (27%)	117 (28%)	
Age			0.4
< 70	241 (56%)	223 (53%)	
≥ 70	191 (44%)	197 (47%)	
Visceral metastases	52 (12%)	48 (11%)	0.8
Metastatic status			0.2
M0 (metachronous)	157 (36%)	171 (41%)	
M1 (synchronous)	275 (64%)	249 (59%)	

[1]Pearson's Chi-squared test

4. Results

- IL8, IGFBP1 and IGF/IGFBP1 were confirmed to be independent prognostic biomarkers in mHSPC treated with ADT + ENZ or ADT + NSAA (Fig 1).
- Some of the exploratory circulating immune markers were also independent prognostic markers (Fig 2).
- None of the markers were predictive of ENZ response (interaction p>0.05).

Fig 1. Validation. Hazard ratios of baseline IL8, IGFBP1 & ratio of IGF1/IGFBP1 in ENZAMET, in univariable analysis (a-c) and multivariable analysis with clinical variables (d).

a.

IL8 (Interleukin-8)

Univariable analysis		Overall survival (OS)			Clinical progression-free survival (cPFS)		
log2 of pg/ml	**N**	**n**	**OS HR (95% CI)**	**P–value**	**n**	**cPFS HR (95% CI)**	**P–value**
All participants	840	381	1.1 (1.01–1.19)	**0.029**	528	1.08 (1.01–1.16)	**0.022**
ADT + NSAA	426	221	1.14 (1.02–1.28)	**0.020**	328	1.14 (1.04–1.25)	**0.006**
ADT + Enza	414	160	1.05 (0.92–1.19)	0.5	200	1.04 (0.93–1.16)	0.5
ADT + NSAA, no DCX	241	121	1.11 (0.93–1.32)	0.2	181	1.07 (0.93–1.23)	0.3
ADT + NSAA, with DCX	185	100	1.18 (1.02–1.37)	**0.029**	147	1.21 (1.07–1.37)	**0.003**

0.5 1 2 — High levels better / High levels worse

b.

IGFBP1 (Insulin growth factor binding protein-1)

Univariable analysis		Overall survival (OS)			Clinical progression-free survival (cPFS)		
log2 of ng/ml	**N**	**n**	**OS HR (95% CI)**	**P–value**	**n**	**cPFS HR (95% CI)**	**P–value**
All participants	845	382	1.12 (1.04–1.21)	**0.004**	529	1.09 (1.02–1.16)	**0.011**
ADT + NSAA	427	221	1.1 (0.99–1.21)	0.084	328	1.05 (0.97–1.15)	0.2
ADT + Enza	418	161	1.14 (1.02–1.27)	**0.025**	201	1.12 (1.02–1.24)	**0.022**
ADT + NSAA, no DCX	241	121	1.15 (1–1.33)	0.052	180	1.06 (0.94–1.19)	0.3
ADT + NSAA, with DCX	186	100	1.04 (0.9–1.2)	0.6	148	1.05 (0.93–1.19)	0.4

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c.

IGF1:IGFBP1 ratio

Univariable analysis		Overall survival (OS)			Clinical progression-free survival (cPFS)		
log2 of ratio	**N**	**n**	**OS HR (95% CI)**	**P–value**	**n**	**cPFS HR (95% CI)**	**P–value**
All participants	845	382	0.94 (0.9–0.98)	**0.008**	529	0.96 (0.92–0.99)	**0.015**
ADT + NSAA	427	221	0.95 (0.9–1.01)	0.081	328	0.97 (0.93–1.02)	0.3
ADT + Enza	418	161	0.93 (0.88–1)	**0.042**	201	0.93 (0.87–0.98)	**0.011**
ADT + NSAA, no DCX	241	121	0.94 (0.87–1.02)	0.14	180	0.97 (0.91–1.04)	0.4
ADT + NSAA, with DCX	186	100	0.95 (0.87–1.04)	0.3	148	0.96 (0.9–1.03)	0.3

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d.

		OS model		cPFS model	
	Variables in model[1]	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
1	IL8	1.09 (1.00 - 1.18)	**0.047**	1.09 (1.02 - 1.17)	**0.013**
	Treatment arm	0.65 (0.53 - 0.80)	**<0.001**	0.41 (0.34 - 0.48)	**<0.001**
	Docetaxel	0.96 (0.77 - 1.19)	0.7	0.99 (0.83 - 1.19)	>0.9
	Volume of disease	2.42 (1.90 - 3.06)	**<0.001**	2.3 (1.88 - 2.81)	**<0.001**
	Visceral metastases	0.87 (0.64 - 1.18)	0.4	0.85 (0.65 - 1.10)	0.2
2	IGFBP1	1.1 (1.02 - 1.18)	**0.018**	1.07 (1.00 - 1.14)	**0.044**
	Treatment arm	0.65 (0.53 - 0.80)	**<0.001**	0.41 (0.34 - 0.49)	**<0.001**
	Docetaxel	0.95 (0.77 - 1.18)	0.6	0.98 (0.82 - 1.18)	0.9
	Volume of disease	2.48 (1.95 - 3.15)	**<0.001**	2.32 (1.90 - 2.83)	**<0.001**
	Visceral metastases	0.92 (0.68 - 1.24)	0.6	0.9 (0.69 - 1.17)	0.4
3	IGF1:IGFBP1 ratio	0.94 (0.90 - 0.98)	**0.004**	0.95 (0.91 - 0.98)	**0.005**
	Treatment arm	0.65 (0.53 - 0.79)	**<0.001**	0.41 (0.34 - 0.49)	**<0.001**
	Docetaxel	0.96 (0.77 - 1.19)	0.7	0.99 (0.82 - 1.19)	>0.9
	Volume of disease	2.53 (1.99 - 3.20)	**<0.001**	2.36 (1.93 - 2.88)	**<0.001**
	Visceral metastases	0.91 (0.67 - 1.23)	0.6	0.9 (0.69 - 1.17)	0.4

[1] Immune/metabolic markers in log2 units

Fig 2. Exploratory analysis. Hazard ratios of immune markers at baseline in multivariable analysis with treatment arm, volume of disease, docetaxel & visceral metastases.

Multivariable analysis with clinical variables		Overall survival (OS)			Clinical progression-free survival (cPFS)		
log2	**N**	**n**	**OS HR (95% CI)**	**P–value**	**n**	**cPFS HR (95% CI)**	**P–value**
CRP	838	380	1.08 (1.03–1.14)	**0.002**	526	1.07 (1.03–1.12)	**0.001**
CXCL12	844	383	0.94 (0.85–1.03)	0.2	530	0.94 (0.86–1.02)	0.2
CXCL16	843	381	1.31 (1.04–1.65)	**0.020**	530	1.03 (0.9–1.19)	0.7
IFNg	840	381	0.98 (0.94–1.03)	0.4	528	0.97 (0.93–1.01)	0.15
IL17E	840	381	0.98 (0.92–1.05)	0.6	528	0.96 (0.91–1.02)	0.2
IL1b	840	381	0.98 (0.93–1.05)	0.6	528	0.98 (0.93–1.04)	0.6
IL2	840	381	0.98 (0.92–1.05)	0.6	528	0.99 (0.94–1.04)	0.6
IL28A	839	381	0.91 (0.86–0.97)	**0.002**	527	0.93 (0.89–0.98)	**0.004**
IL33	839	381	0.95 (0.88–1.02)	0.13	527	0.98 (0.92–1.04)	0.5
IL6	840	381	1.1 (1.04–1.17)	**0.001**	528	1.06 (1.01–1.11)	**0.027**
MCP1	840	381	1.01 (0.89–1.15)	0.9	528	0.97 (0.87–1.08)	0.6
MIC1	831	375	1.23 (1.08–1.4)	**0.002**	522	1.17 (1.05–1.3)	**0.004**
MIP3a	840	382	1.01 (0.9–1.14)	0.9	528	1.02 (0.93–1.13)	0.6
MPIF1	843	381	1.1 (1–1.2)	**0.041**	530	1.05 (0.97–1.13)	0.2
YKL40	843	381	1.17 (1.06–1.29)	**0.001**	530	1.06 (0.99–1.15)	0.11

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5. Conclusions

- **IL8, IGFBP1 and IGF1:IGFBP1 ratio were validated as prognostic biomarkers in mHSPC,**
  - **higher IL8 and higher IGFBP1 levels were associated with worse OS.**
  - **higher IGF1:IGFBP1 ratio was associated with better OS.**
- **Several pro-inflammatory (CRP, CXCL16, IL6, MPIF1), anti-tumour (IL28A) and macrophage-associated (MIC1, YKL40) proteins/cytokines were associated with poorer clinical outcomes in mHSPC.**
- **None of the markers were predictive of response to enzalutamide.**

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Acknowledgements: *We thank our funders (NHMRC, Cancer Australia, Astellas Pharma Inc., Noel Castan Fellowship), study staff and trial participants.*

Abstract # 1607P