SIZE MATTERS: INTEGRATING TUMOUR VOLUME WITH TRANSCRIPTOME SIGNATURES BETTER PREDICTS RESPONSE TO COMBINATION IMMUNE CHECKPOINT INHIBITORS

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1 Background

There has been an urgent and ongoing need to identify biomarkers predictive of immune checkpoint inhibitors (ICIs, e.g. anti-PD1, anti-CTLA4) response to optimise patient selection and improve outcomes[1]. Preclinical and clinical studies have demonstrated that a lower tumour volume burden is associated with better response to ICIs[2]. However, tumour volume is not commonly considered when evaluating predictive transcriptomic signatures of ICI response.

AIM: Assess the performance of tumour volume-normalised transcriptomic signatures in predicting ICI response.

2 Study design

RNA sequencing was performed on 32 pre-treatment (PRE) and 16 early during treatment (EDT) biopsies derived from metastatic melanoma patients treated with combination anti-PD1+CTLA4. Tumour volume was assessed at PRE and at first CT imaging.

At PRE, 24 patients were categorized as responders (irRECIST complete response (CR, n=3), partial response (PR, n=20), and stable disease (SD, n=1) of > 6 months) and 8 were considered non-responders (irRECIST progressive disease (PD, n=6) and PR but with progression free survival (PFS) of < 6 months, n=2).

	PRE (n=32)	EDT (n=16)
Age[a], median (range)	56 (23-80)	55 (25-73)
Sex, n (%)		
Male	18 (56%)	7 (44%)
Female	14 (44%)	9 (56%)
irRECIST response, n (%)		
CR	3 (9%)	1 (6%)
PR	22 (69%)	9 (56%)
SD	1 (3%)	1 (6%)
PD	6 (19%)	5 (31%)
Response, n (%)		
Responders[b]	24 (75%)	9 (56%)
Non-responders[c]	8 (25%)	7 (44%)
Tumour volume, median (range)	91.5 (10-766)	68.5 (0-1000)
LDH (U/L), n (%)		
Normal	23 (72%)	6 (38%)
Elevated	7 (22%)	8 (50%)
Unknown	2 (6%)	2 (13%)

[a]Age at start of treatment

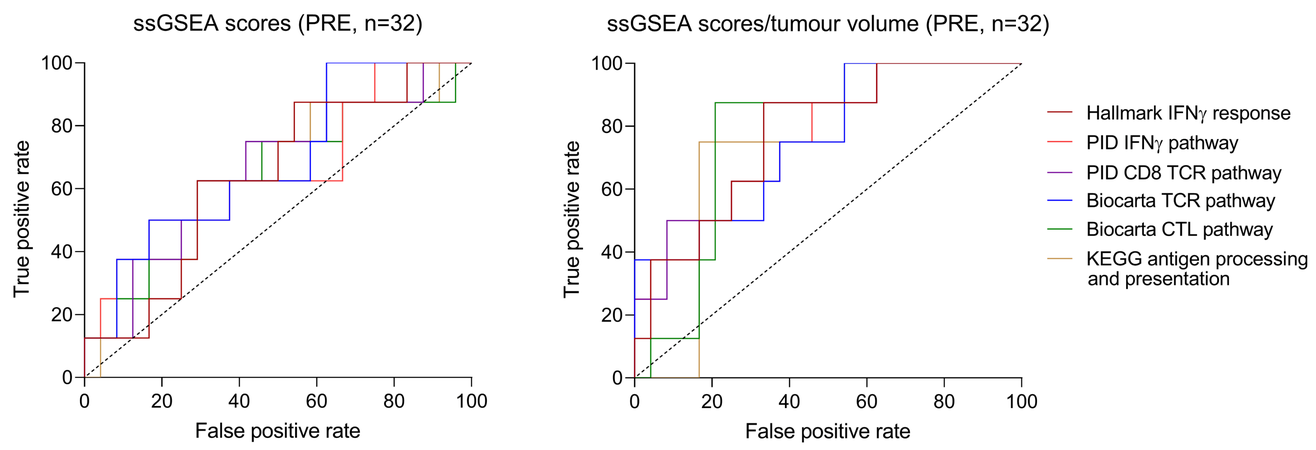
[b]Responders - irRECIST complete response, partial response, and stable disease >6 months

[c]Non-responders - progressive disease and PR with progression free survival (PFS) of < 6 months

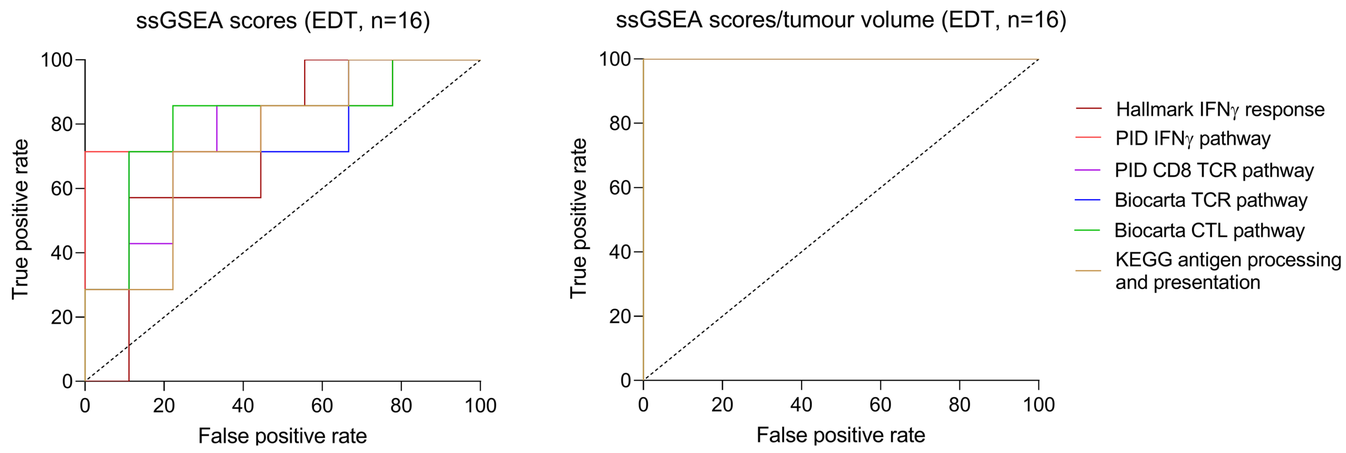
CR, complete response; PR partial response; SD, stable disease; PD, progressive disease, LDH, lactate dehydrogenase, normal range 120-250 U/L.

3 Results

Analysis of immune-associated transcriptome gene sets at PRE (n=32) did not differentiate responders from non-responders. However, when immune-associated signatures were considered with tumour volume (ssGSEA score divided by tumour volume), a significant distinction was observed between responders and non-responders. ROC curve analysis of EDT samples (n=16) also confirmed superior predictive performance when tumour volume was integrated with immune-associated transcriptomic signatures.



Transcriptome gene sets	ssGSEA scores		ssGSEA scores/tumour volume	
	AUC	P value	AUC	P value
Hallmark IFNγ response	0.6406	0.2400	0.7760	0.0211
PID IFNγ pathway	0.6563	0.1917	0.7604	0.0296
PID CD8 TCR pathway	0.6615	0.1773	0.7865	0.0167
Biocarta TCR pathway	0.6823	0.1277	0.7552	0.0330
Biocarta CTL pathway	0.6354	0.2578	0.7813	0.0188
KEGG antigen processing and presentation	0.6563	0.1917	0.7396	0.0453



Transcriptome gene sets	ssGSEA scores		ssGSEA scores/tumour volume	
	AUC	P value	AUC	P value
Hallmark IFNγ response	0.7302	0.1248	1	0.0009
PID IFNγ pathway	0.8254	0.0300	1	0.0009
PID CD8 TCR pathway	0.7619	0.0807	1	0.0009
Biocarta TCR pathway	0.7619	0.0807	1	0.0009
Biocarta CTL pathway	0.8095	0.0390	1	0.0009
KEGG antigen processing and presentation	0.7460	0.1009	1	0.0009

4 Conclusion

Integrating tumour volume with transcriptomic immune signatures provides a more accurate approach to predict ICI response in advanced melanoma. Accurate prediction early during treatment is particularly valuable in the neoadjuvant ICI setting, where definitive response prediction can guide surgical decisions and determine the need for adjuvant treatment versus surveillance. These findings underscore the value of re-examining new and existing biomarkers to refine predictive accuracy.

Acknowledgements

We thank all patients and their families. This work was supported by the Precision Cancer Therapy Group, Sydney Precision Bioinformatics Group, Melanoma Pathology Translational Research Group, Melanoma Institute Australia and funding from the National Health and Medical Research Council.

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