Abstract ID: 11546
Contact: daniel@venn.bio

Serum glycoproteomic signatures predict overall survival in bone and soft tissue sarcoma patients treated with immune checkpoint inhibitor therapy

Daniel Serie[1], Chad Pickering[1], Rachel Rice[1], Maurice Wong[1], Hector Huang[1], Maya Kansara[2], Subotheni Thavaneswaran[2,3,4], Mandy Ballinger[2,3,5], Lucille Sebastian[4], David M Thomas[2], Klaus Lindpaintner[1]

[1]InterVenn Biosciences, 2 Tower Place, South San Francisco, CA; [2] Garvan Institute, Darlinghurst NSW, Australia; [3]St Vincent's Clinical School, University of New South Wales, Sydney, NSW, Australia; [4] NHMRC Clinical Trials Centre, University of Sydney, Sydney, NSW, Australia; [5] Omico, Sydney, NSW, Australia

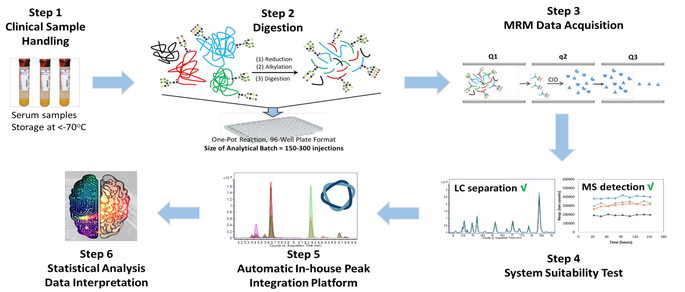
Introduction

Glycosylation is one of the most ubiquitous and functionally important forms of post-translational modification. InterVenn has built a novel platform that combines LC/MS with a proprietary, artificial-intelligence-based data processing engine, allowing for highly scalable and reproducible quantification of glycoproteins with site- and glycan-specificity.

Using this platform, we interrogated pre-treatment samples from a cohort of 103 individuals presenting with one of 20 solid cancer types, including 43 patients with bone and soft tissue sarcoma. All patients were treated with combination durvalumab and tremelimumab immune checkpoint inhibitor (ICI) therapy.

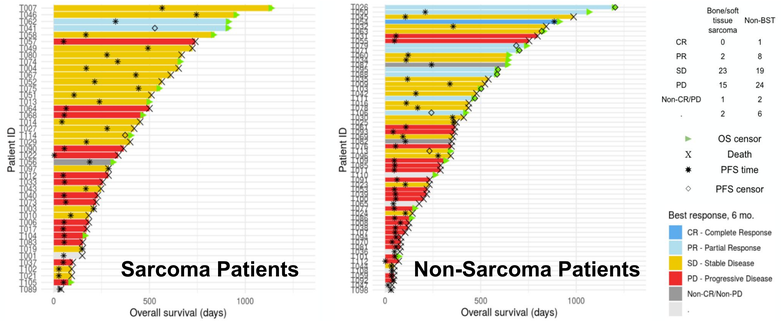
Demographics and Methods

- Assessed 519 glycopeptide (GP) biomarkers derived from 70 serum proteins
- Cohort: 56 females, 47 males; median age 53 (18 – 84) years
- Follow-up for overall survival (OS) ranged from 1 to 40 months (median = 11.4 months, with 70 OS and 90 PFS events)
- OS was assessed for individual GPs via age-adjusted Cox regression models
- Leave-one-out-cross-validation (LOOCV) was employed to generate penalized multivariable prediction scores
- Stratified sub-group analyses were carried out in the sarcoma population
- Analytical Workflow:



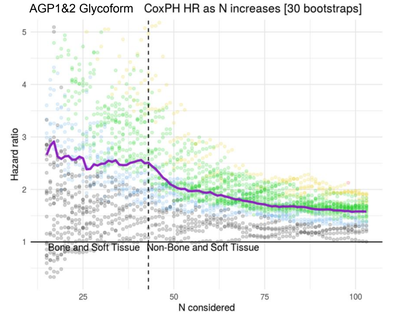
Results

Clinical Response and Survival



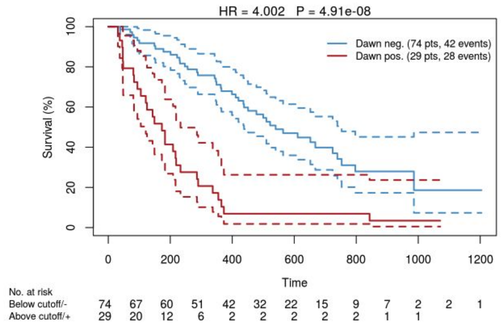
Swimmer plots demonstrate clinical response and long term survival.

Sarcoma-Specific Signal



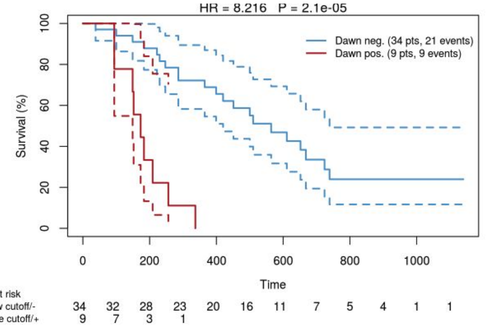
Bootstrapped signal with increasing N indicates specificity for sarcomas.

All-Tumors Model (4 GPs)



154 of 519 biomarkers significantly associate with OS in the full cohort (FDR < 0.05). LOOCV modeling results in held-out scores that distinguish patients likely vs. unlikely to exhibit long-term benefit, post-ICI therapy.

Sarcoma-only Model (2 GPs)



LOOCV models in the sarcoma subset demonstrate even stronger prognostic capabilities. All 9 sarcoma patients with an unfavorable GP-classifier score experienced quick progression, highlighting the potential of a GP-based approach to predict benefit from ICI therapy.

Discussion

The GPs most strongly associated with benefit from ICI-treatment in sarcoma patients (11 of the 154 significant GPs in the full cohort) were derived from six secreted proteins, with functions potentially relevant to ICI response:

- Promoting endocytosis and opsonization
- Binding heme and transporting to the liver
- Activation of innate immunity through the C1 complex
- Inflammatory responses to trauma
- Antibodies playing an important role in primary defense mechanisms
- Transporting iron across cellular membranes

The degradation of the signal when including non-sarcoma patients (left) indicates a level of disease-specificity to the GPs investigated. Further investigations into functional mechanisms of progression are required.

Conclusion

Our results indicate that, by stratifying patients using glycoproteomics-based liquid biopsy profiling, ICI treatment - currently not approved in sarcoma - may become clinically viable in a subgroup of patients thus identified as likely to respond, providing important clinical benefit.

Site- and glycan-specific characterization of protein glycosylation holds strong promise as a new source for useful clinical biomarkers.