Glycoproteomics-Based Liquid Biopsy Identifies Checkpoint-Inhibitor Responders and Informs Optimal Drug Choice

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Introduction

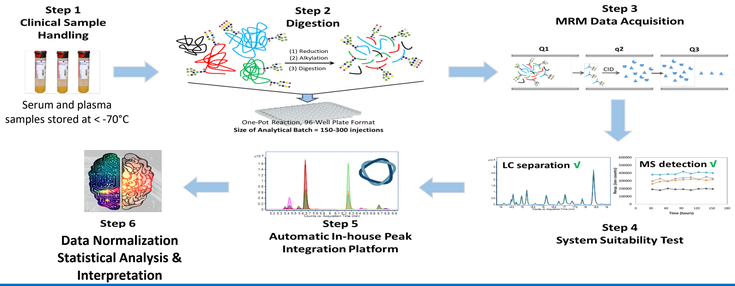
While immune checkpoint inhibitor (ICI) therapy has added a powerful new arsenal of highly effective drugs for the subset of cancer patients who respond to these agents, their use remains burdened by the fact that we lack reliable biomarkers to identify likely responders, to avoid the adverse event incidence and cost of treating likely non-responders. Likewise, we currently have no tools which would help identify the optimal choice of agents; current prescribing practice is not guided by any objective criteria.

We have recently demonstrated that interrogating the serum glycoproteome, using a proprietary platform that couples artificial intelligence to targeted liquid chromatography-mass spectrometry yields highly informative biomarkers for a range of use cases, including prediction of response to ICI treatment. We recently demonstrated this for metastatic malignant melanoma (MM). In the current study, we examined if we could also predict preferential response to individual ICIs.

Methods

We carried out glycoproteomic analysis of pretreatment blood samples in advanced MM patients treated with pembrolizumab (P; n=24) or nivolumab-ipilimumab (N; n=11). Individual glycopeptide (GP) signatures derived from 67 serum proteins were analyzed and correlated with treatment, and progression-free survival (PFS).

Two response groups were defined based on PFS: early failures (EF; PFS event within 6 months) and sustained control (SC; no events for ≥ 12 months). Differential relative abundances for 498 serum GPs were calculated between SC and EF patients to determine GPs more abundant in SC vs. EF by treatment group. A score was developed for each treatment group based on the 20 GPs within each treatment group identified as most statistically significant (one-sided Wilcoxon test). For any patient, the score is the proportion of GPs with relative abundance exceeding their median abundance. A low score is associated with high risk for EF.



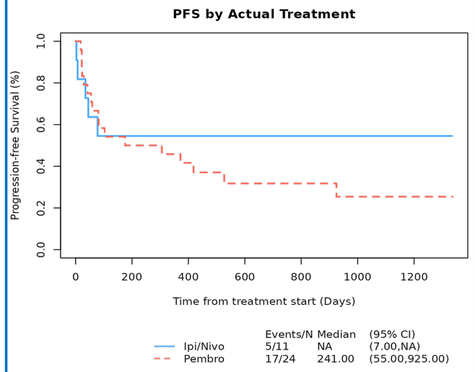
Patient Characteristics

Characteristic	
Age	70 (61, 76)
Sex	
F	11 (31%)
M	25 (69%)
Primary Tumor Type	
Cutaneous	25 (69%)
Acral	2 (5.6%)
Mucosal	2 (5.6%)
Uveal	1 (2.8%)
Unclassified	6 (17%)

Characteristic	
Molecular Subtype	
RAS	11 (31%)
BRAF	8 (22%)
RAS, NF1	3 (8.3%)
RAS, NF1 or triple WT	3 (8.3%)
Triple WT	3 (8.3%)
NF1	2 (5.6%)
Triple WT or NF1	2 (5.6%)
RAS, BRAF	1 (2.8%)
BRAF, RAS, NF1	1 (2.8%)
Unclassified	2 (5.6%)
Treatment	
Pembro	24 (67%)
Ipi/Nivo	12 (33%)

[1]n (%); Median (IQR)

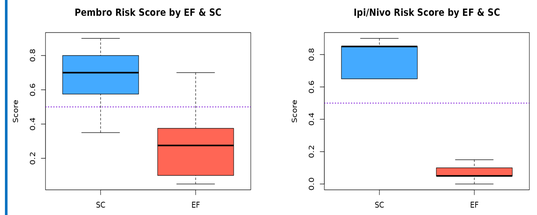
Baseline PFS



	Early Failure (EF)	
Treatment	PFS < 6 Months	PFS < 9 Months
Ipi/Nivo	5	5
Pembro	12	12
	Sustained Control (SC)	
	PFS > 12 months	PFS > 18 months
Ipi/Nivo	6	6
Pembro	11	6

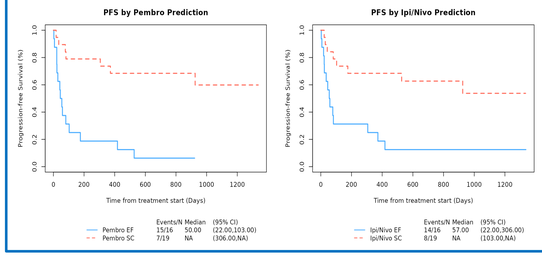
Comparison of Risk Scores by Survival Group

Glycoproteomic risk scores based on the markers most significantly associated with early failure show clear separation between the EF and SC groups. Dichotomizing the scores at 0.5 would provide a clear way to predict response to either Pembro or Ipi/Nivo. However, additional detail regarding the optimal treatment could be extracted by comparing the subject-level scores.



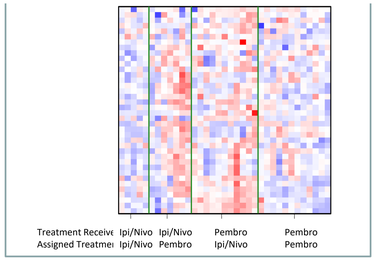
PFS by Response Prediction (All Patients)

Our data suggest approximately half of the patients examined might have had improved PFS had they received the alternate therapy. When examined for all patients in the cohort, the EF/SC response predictions seem to separate the patients extremely well.



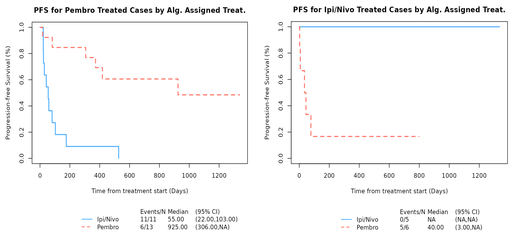
Heatmap for Pembro & Ipi/Nivo Prediction Markers by Actual Treatment and Optimal Treatment Assignment

The heatmap for the selected glycopeptides, grouped by subject-treatment subgroups, shows different levels of relative abundance for subjects with a mismatch between the treatment received and the optimal treatment assignment.



PFS by Assigned/Predicted Best Treatment Group

We examined the predicted best treatment assignment for our data within subgroups treated with Pembro or Ipi/Nivo. We saw strong agreement with our algorithm, where subjects treated with the best (i.e., optimal) treatment choice significantly outperformed subjects treated with the alternative. Log-rank p-values comparing PFS by assigned treatment within Pembro- and Ipi/Nivo-treated cases were 0.009 and 0.0004, respectively.



Conclusions

Our data show that serum glycoproteomic analysis can be used for targeted treatment assignment for checkpoint inhibitors in general and for specific agents. Additional analyses must be done to validate specific glycoproteomic markers across multiple datasets. However, this analysis establishes a proof of principle for the future of glycoproteomics. The addition of glycoproteomic-based assays to the precision medicine landscape is fundamental to improving patient outcomes.