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A Biomarker Signature to Predict Complete Response to Itacitinib and Corticosteroids in Acute Graft-Versus-Host Disease

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Introduction

- Acute graft-versus-host disease (aGVHD) represents a potentially life-threatening condition associated with patients undergoing allogeneic hematopoietic stem cell transplantation
- aGVHD is characterized by increased levels of inflammatory mediators and activated T cells in circulation, leading to tissue and organ damage
- Corticosteroids are primarily used as first-line treatment for aGVHD; however, this approach does not provide therapeutic benefit for a significant portion of patients with aGVHD
- The combination of itacitinib, a Janus kinase (JAK)1-selective inhibitor, with corticosteroids was evaluated in a parallel-cohort phase 1 trial (NCT02614612) and resulted in improved overall responses for patients with steroid-naive and -refractory aGVHD
- Suppression of tumorigenicity 2 (ST2), regenerating islet-derived 3α (REG3A), and tumor necrosis factor receptor 1 (TNFR1), which have previously been shown to distinguish steroid-treated patients with an increased risk of progressive aGVHD,[1] did not clearly distinguish complete responders and non-responders in the phase 1 trial[2]
- In this study, we utilized broad proteomic analysis to identify and quantitate potentially predictive biomarkers of therapeutic response in order to predict complete response to the combination treatment

Methods

- Plasma samples were collected from 25 patients enrolled in the phase 1 clinical trial prior to and at day 28 following treatment. All patients provided written consent prior to enrollment
- Clinical patients were separated into responders and non-responders based on the Center for International Blood and Marrow Transplant Research response criteria at day 28 and illustrated in the tables below

Responders	
Complete responder (CR)	n = 10
Very good partial responder (VGPR)	n =1
Partial responder (PR)	n = 8

Non-responders	
Progressive disease (PD)/death	n = 6

- Doses of itacitinib were 200 mg once daily (QD; n = 13) and 300 mg QD (n = 12). Because there was no difference in response related to itacitinib dose and owing to the limited sample size, data from both cohorts were combined
- Owing to limited sample size, data from steroid-naive (n = 9) and steroid-refractory (n = 16) patients were combined
- Broad proteomic analysis of over 1000 proteins was conducted by Olink Proteomics Inc. (Watertown, MA) using a proximity extension assay (PEA) as described by the manufacturer. Data are presented as normalized protein expression (NPX) in log2 scale
- Candidate biomarkers were quantitated by PEA using standard curves based on commercially available recombinant proteins developed over a range of concentrations in the same biological matrix of each candidate biomarker, and quantitated by extrapolation from each respective standard curve. Protein Simple (San Jose, CA) Ella detection was performed as described[3]
- Statistical differences were evaluated using unpaired and paired *t* tests, 1-way analysis of variance (ANOVA), and Pearson correlation. Significance was conferred when $P < 0.05$

Prognostic Biomarkers

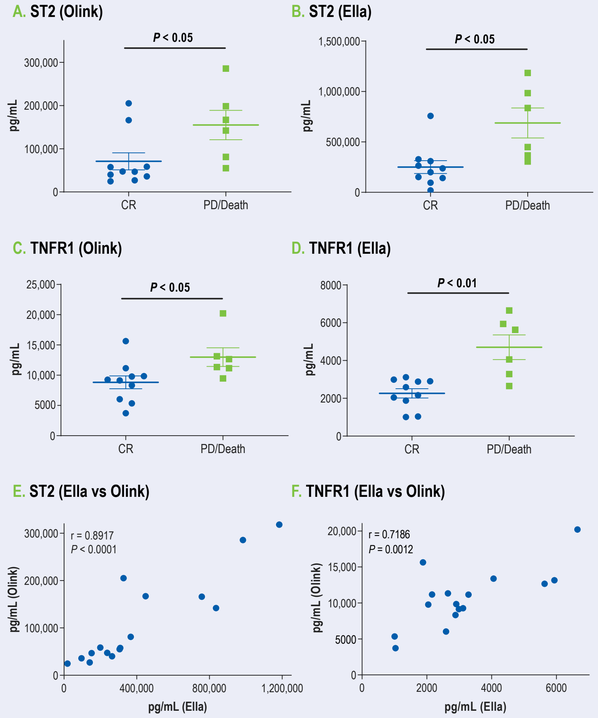
Table 1. Measurement of Previously Identified Biomarkers by Olink

Protein	NPX_CR (n = 10)	NPX_PD (n = 6)	Fold Change	*P* Value
REG3A	1.61	3.26	−3.13	0.0557
ST2	7.38	8.15	−1.71	0.0970
TNFR1	7.45	8.13	−1.61	0.0775
IL-2–RA	4.98	5.37	−1.30	0.5419

Data presented as mean of normalized protein expression (NPX; log2 scale) from complete responder (CR) and progressive disease (PD) cohorts.
Fold change represents ratio of NPX between CR/PD.
IL-2–RA, interleukin-2–receptor alpha.

Validation of Olink Quantitation

Figure 1. Validation of Proximal Extension Assay



Statistical differences were evaluated using unpaired *t* tests, 1-way ANOVA, and Pearson correlation. Significance was conferred when $P < 0.05$. Data are shown as individual values, mean, and standard error of the mean.
Response cohorts: CR, complete responder; PD, progressive disease.

- Plasma from patients with CR and PD was tested for ST2 (A, B) and TNFR1 (C, D) levels by Olink PEA (A, C) and by a validated platform, Protein Simple Ella (B, D); correlation between the 2 assay platforms is shown in E (ST2) and F (TNFR1)

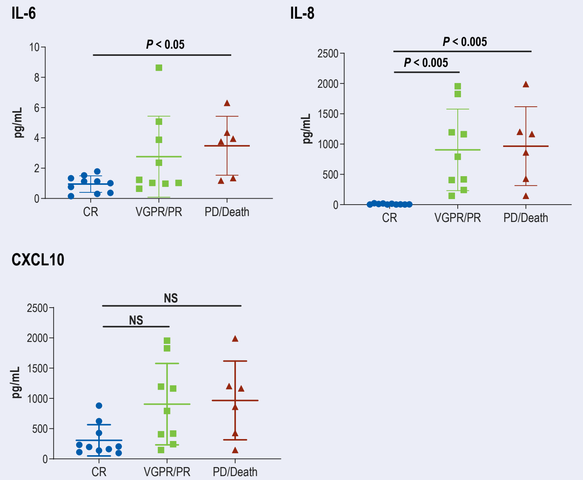
JAK/STAT-Related Biology

Table 2. Proinflammatory Proteins Associated With JAK/STAT Signaling

Protein	NPX_CR (n = 10)	NPX_PD (n = 6)	Fold Change	*P* Value
IL-8 (CXCL8)	7.48	9.89	−5.30	0.001
IL-6	2.01	3.98	−3.92	0.0016
CXCL10 (IP-10)	7.91	9.72	−3.50	0.0308

Data presented as mean of normalized protein expression (NPX; log2 scale) from complete responder (CR) and progressive disease (PD) cohorts.
Fold change represents ratio of NPX between CR/PD.
JAK/STAT, Janus kinas/signal transducer and activator of transcription.

Figure 2. Proinflammatory Biomarker Levels in Circulation



Statistical differences were evaluated using unpaired *t* tests, 1-way ANOVA, and Pearson correlation. Significance was conferred when $P < 0.05$. Data are shown as individual values, mean, and standard error of the mean.
Response cohorts: CR, complete responder; VGPR, very good partial responder; PR, partial responder; PD, progressive disease.
NS, not significant.

Novel Predictive Biomarkers

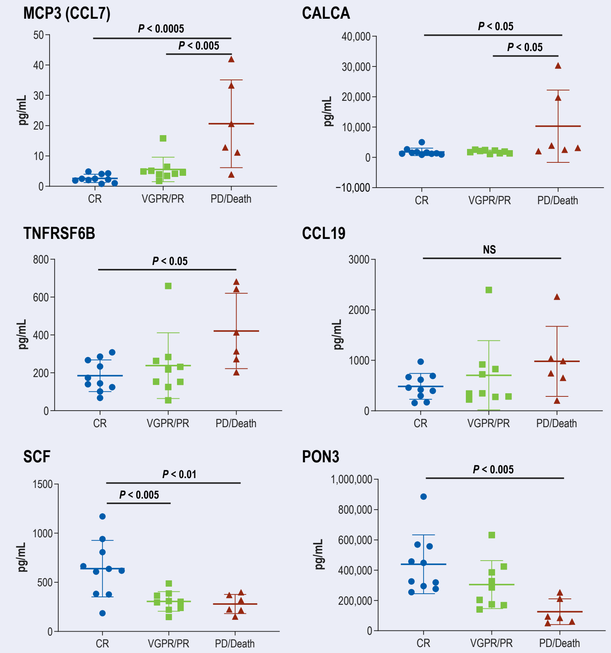
Table 3. Novel Biomarkers Identified by Olink

Protein	NPX_CR (n = 10)	NPX_PD (n = 6)	Fold Change	*P* Value
MCP3 (CCL7)	2.82	5.86	−8.17	3.27E-05
CALCA	6.18	9.17	−7.93	0.0109
TNFRSF6B (DCR3)	4.75	6.14	−2.61	0.0024
CCL19	7.10	8.07	−1.96	0.0553
SCF (KIT-L)	9.46	7.79	3.18	0.0017
PON3	5.35	2.90	5.46	0.0004

Data presented as mean of normalized protein expression (NPX; log2 scale) from complete responder (CR) and progressive disease (PD) cohorts.
Fold change represents ratio of NPX between CR/PD.

Novel Predictive Biomarkers

Figure 3. Quantitation of Predictive Biomarkers



Statistical differences were evaluated using unpaired *t* tests, 1-way ANOVA, and Pearson correlation. Significance was conferred when $P < 0.05$. Data are shown as individual values, mean, and standard error of the mean.
Response cohorts: CR, complete responder; VGPR, very good partial responder; PR, partial responder; PD, progressive disease.
NS, not significant.

Conclusions

- **Proteomic profiling of patients with aGVHD treated with a combination of corticosteroids and itacitinib identified a number of potentially predictive biomarkers**
- **Predictive biomarkers may identify patients with aGVHD with a higher probability of achieving complete response following treatment with the combination of itacitinib and corticosteroids**
- **Algorithms are currently being evaluated for their predictability of complete response**

Disclosures

All authors: Employment and stock ownership – *Incyte Corporation.*

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