Predictive Biomarkers of Response to the IRAK4/FLT3 Inhibitor Emavusertib in Hematological Malignancies

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BACKGROUND

- hrMDS and AML present with a dynamic and diverse mutational landscape
- Splicing mutations drive overexpression of a highly active IRAK4 isoform triggering inflammation, oncogenesis and survival of cancer cells through the activation of NFκB and other pathways (Fig 1)
- Emavusertib is a potent inhibitor of IRAK4 and FLT3 with efficacy in pre-clinical (3) and clinical studies
- **Goal**: to present our findings from RNAseq and proteomics analyses describing potential biomarkers of response to emavusertib in clinical samples from the ongoing TakeAim Leukemia trial CA-4948-102 (NCT04278768)

Fig 1

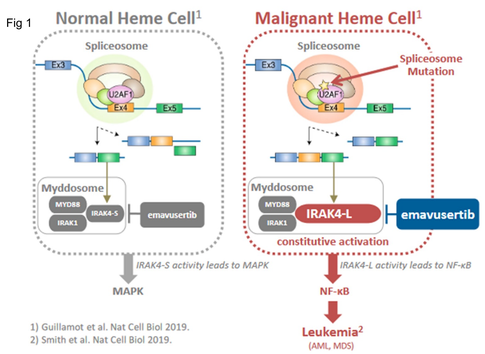

Fig 1. Spliceosome mutations (*SF3B1*, *U2AF1*) drive IRAK4-L isoform leading to overactivity of NFκB pathway

METHODS

- Baseline and on treatment samples from patients that received emavusertib monotherapy treatment were collected from 26 AML, and 16 hrMDS (TakeAim Leukemia Phase I/II Study CA-4948-102, NCT04278768)
- Bulk RNA sequencing was performed on PBMCs and bone marrow samples (Tempus Inc, Chicago IL)
- QC was performed with FASTQC V0.11.8. Low quality reads were removed using Trimgalore V0.6.3
- Raw counts were normalized to total number of reads by calculating log2 Counts Per Million (CPM)
- Cytokines/chemokines were quantified in 51 paired plasma samples by the Luminex platform (ThermoFisher, Vienna, Austria)

Abbreviations

MDS: Myelodysplastic neoplasms, AML: Acute Myeloid Leukemia, PBMCs: peripheral blood mononuclear cells, On-Tx: on treatment, IL1β: Interleukin 1 beta, VEGF-A: vascular endothelial growth factor A, CXCL12 (SDF1α): C-X-C motif chemokine 12, IL2: interleukin 2, sPD1: soluble PD1, sCD47: soluble CD47

RESULTS

- IL1β plasma levels show higher levels in AML non-responders than in responders (P≤0.05). No significative differences in IL1β are observed in hrMDS patients (Fig 2A)
- RNAseq data indicates that *IL1β* (a known positive regulator of IRAK4 pathway) shows higher levels of expression in aML and hrMDS non-responder patients (P≤0.05) (Fig 2B)
- IL1β protein levels in plasma correlates with RNAseq gene expression data (Person's correlation test, P≤0.05) (Fig 2C)
- In AML samples, responders to emavusertib have higher VEGF-A protein levels at baseline than non-responders, while in hrMDS, responders have significantly lower VEFG-A levels at baseline (P≤0.05) indicating potential differences in proliferation and cell migration in both pathologies (Fig 3A)
- *VEGF-A* mRNA levels show no differences between responders and non-responders, but hrMDS samples present similar pattern than VEGF-A protein levels in plasma (Fig 3B)
- SDF1α (CXCL12) plasma levels in hrMDS responders seem to be significantly lower (P≤0.05) at baseline when compared to non-responders indicating a potential decrease in cell migration and proliferation of heme cells. No differences were observed in AML samples. Data shows potential role of CXCL12 plasma levels as a predictive biomarker of response in hrMDS patients (Fig 4)
- In hrMDS, on-Tx samples have higher (P≤0.05) sPD1 plasma protein levels compared to baseline samples independently of the responses to emavusertib monotherapy treatment (Fig 5)

Fig 2A

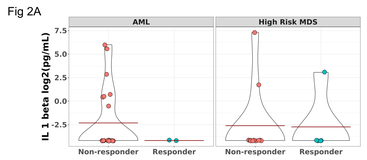

Fig 2B

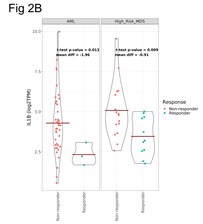

Fig 2C

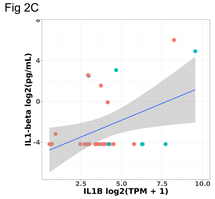

Fig 2. IL1β protein levels (Fig 2A) and gene expression (Fig 2B) between hrMDS and AML responders and non-responders may serve as predictive biomarker of response. Fig 2C. Pearson's positive correlation between IL1β protein and *IL1β* RNA levels

Fig 3A

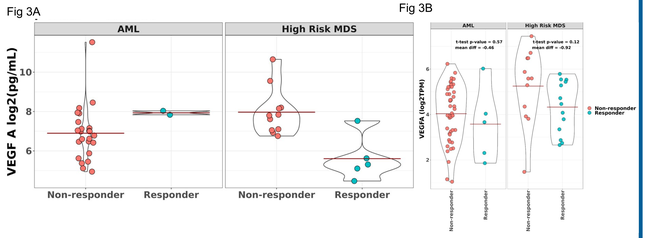

Fig 3B

Fig 3A. VEGF-A protein plasma levels in responders and non-responders (AML and hrMDS). Data indicates a potential role for VEGF-A as a predictive biomarker of responses in hrMDS patients. . Fig 3B.*VEGF-A* RNA levels in hrMDS/AML responders and non-responders showing similar pattern when compared to protein levels in hrMDS plasma samples

Fig 4

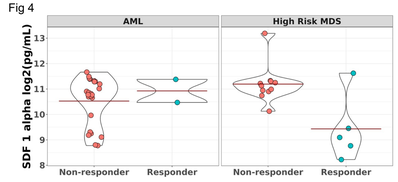

Fig 4. SDF1α (CXCL12) protein levels in plasma samples of AML/hrMDS patients. Data indicates potential role of CXCL12 as a predictive biomarker of response

Fig 5

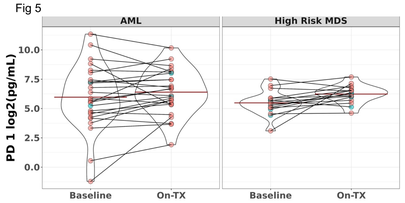

Fig 5. Soluble PD1 plasma levels in hrMDS/AML paired patient samples indicates and increase on sPD1 levels on-Tx samples from hrMDS patients

- AML and hrMDS show differential baseline plasma markers with hrMDS presenting lower IL2 and higher sCD47 at baseline when compared to AML, indicating potential differences in proliferation and immunological function status in both diseases (P≤0.05) (Fig 6)

Fig 6

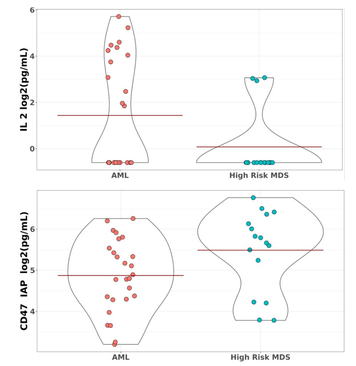

Fig 6. IL2 and sCD47 baseline plasma levels in hrMDS/AML patients show different concentrations in AML when compared to hrMDS samples suggesting differential biomarkers for each pathology

CONCLUSIONS

- We were able to identify several predictive biomarkers of response to emavusertib monotherapy in hematological malignancies
- Markers, such as, *IL1β* show significant lower mRNA levels in hrMDS responders (baseline and on-Tx). IL1β protein levels are significantly lower in hrMDS/AML responders to emavusertib monotherapy indicating a potential decreased levels of the IL1β/TLR associated pathway potentially decreasing IRAK4 activation status
- VEGF and CXCL12, levels appear to be lower in hrMDS responders when compared to non-responders, showing potential as predictive biomarkers of response to emavusertib indicating decreased proliferation, survival and migration oh heme cells (4)
- Immune checkpoint protein, PD1 show increased levels in plasma during emavusertib treatment regardless of the response. AML samples show higher levels of IL2 indicating a potential aberrant expression of IL2 by leukemic cells (5), while sCD47 levels are higher in hrMDS suggesting differential proliferation and phagocytic signaling between the two pathologies (6)
- AML and hrMDS have shown different predictive biomarkers to emavusertib clinical responses
- Our data suggest that inflammatory, migration and angiogenesis related mediators hold potential as predictive biomarkers of response to emavusertib monotherapy Tx in heme malignancies

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