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POSTER ABSTRACTS

617.ACUTE MYELOID LEUKEMIAS: BIOMARKERS, MOLECULAR MARKERS AND MINIMAL RESIDUAL DISEASE IN DIAGNOSIS AND PROGNOSIS

Clinico-Genomic Characterization of AML Patients Based on *IL2RA* (CD25) Expression Uncovers an Association with Stem Cell Signatures and FLT3-ITD Status and Informs Drug Combinations

Habib Hamidi, MPH,PhD[1], *Diana Dunshee*[1], *Brian Higgins*[2], *Monique Dail*[3], *Michael Boyiadzis, MD*[3]

[1] Genentech, Inc., South San Francisco, CA
[2] Roche Innovation Center, New York, NY
[3] Genentech, South San Francisco, CA

Background

Acute myeloid leukemia (AML) is a heterogeneous disease with poor outcomes, thus there remains a need to integrate molecular information to identify patients most likely to respond to drugs and combinations. Disease segmentation based on transcriptomics has provided valuable insight into disease risk and the likelihood of response to targeted compounds. IL2RA(CD25) is a receptor expressed on both AML leukemic and immune cells, and has shown initial promise as a potential dual target of leukemic blasts and regulatory T (Treg) cells in pre-clinical models (Pousse et al. Front. Oncol. 2023). We used a systems approach based on a recently described transcriptomic classifier for AML (Hamidi et al. ASH 2021) and other molecular tools to characterize the association between *IL2RA* expression levels and AML genomic markers, clinical features and patient outcomes. In addition, we evaluated *IL2RA* in relation to *ex vivo* drug sensitivity, to identify patient segments who are most likely to benefit from CD25-targeting drugs.

Methods

BEAT-AML (NCT01728402) RNAseq data from patient samples, associated *ex vivo* drug sensitivity data (N=283), was VOOM normalized. Patients were binned into quartiles based on *IL2RA* expression. Gene signature scoring was performed using xCell cell type enrichment algorithm and GSVA for Hallmark pathways and scRNAseq signature based on Van Galen et al. Cell 2019. Associations were performed with clinical outcome (log-rank test), gene signatures (Spearman correlation), mutations (Wilcoxon test) and *ex vivo* drug sensitivity (Kruskal Wallis test).

Results

We characterized the BeatAML dataset and found that elevated *IL2RA* expression associates with inferior overall survival (p=0.014) and high-risk features. In addition, we identified a strong association between *IL2RA* expression and FLT3-ITD status (Figure), as well as other genetic alterations. Using correlation analyses, we established an association between *IL2RA* expression levels and "primitive" AML signatures (leukemic stem cell (LSC), R=0.4, p=6.8x10-12, hematopoietic stem cell (HSC)-like, R=0.43, p=6.8x10-14) and Tregs (R=0.47, p=1.7x10-15), and an anti-correlation with promonocytic signatures (R=-0.23, p=1.1x10-4). Interestingly, HSC-like and Treg signatures were also correlated (R=0.19, p=0.00087), consistent with an association between stem cell abundance and a repressive immune microenvironment. Finally, using a multivariate model adjusting for the effect of Tregs and LSCs, the prognostic value of *IL2RA* remained significant (p=0.029).

We previously used unsupervised machine learning clustering based on consensus non-negative factorization (cNMF) to discover novel transcription-based classification (Hamidi ASH 2021). Using this methodology, we identified a strong correlation between *IL2RA* expression in cNMF subtypes (p=1.6x10-10). Moreover, this method uncovered patient subtypes in which *IL2RA* correlates with LSC (cNMF 6.3), Treg (6.4, 6.6) or both signatures (6.1, 6.2). This differential association was independent of prognostic category, maturation state or venetoclax sensitivity (Table).

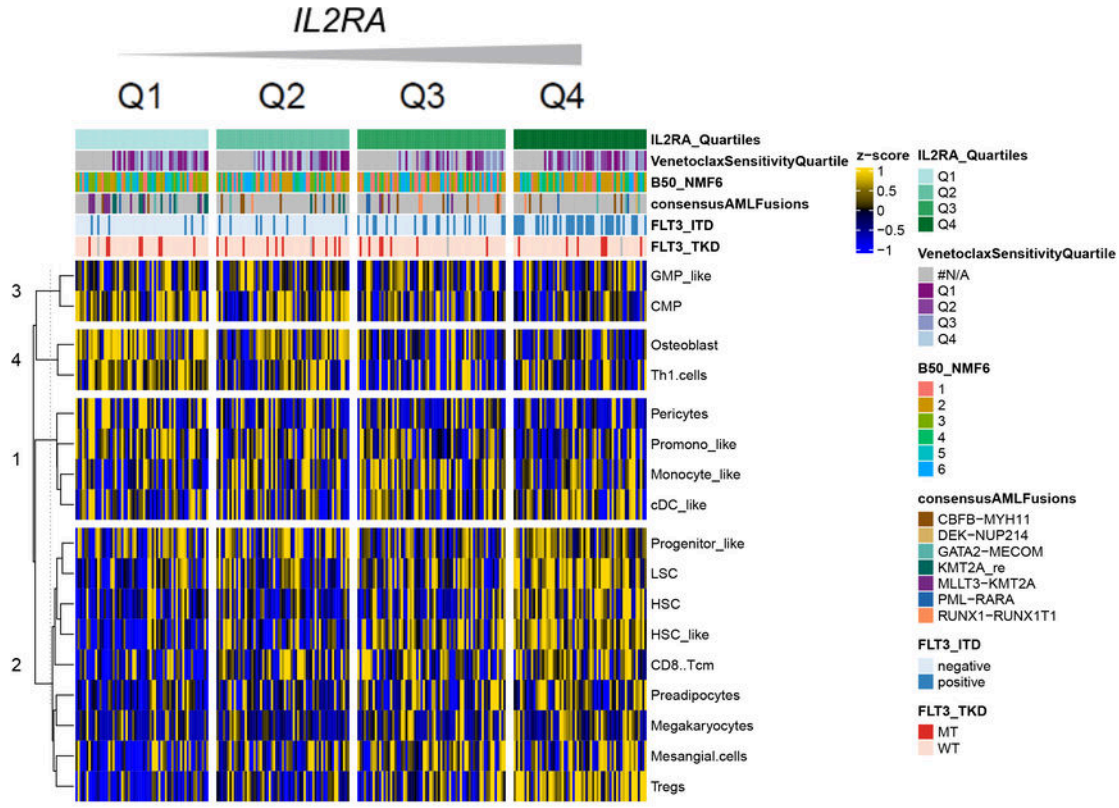
Transcription-based classifiers have been shown to be highly predictive of *ex vivo* drug sensitivity. Consistent with an association between *IL2RA* expression and FLT3-ITD status, we identified strong correlations between *IL2RA* and sensitivity to FLT-3 and other tyrosine kinase inhibitors, providing a rationale for combining these compounds with CD25-targeting therapeutics. In contrast, there was no correlation between *IL2RA* levels and venetoclax AUC (p=0.25), while the cNMF classification system similarly revealed that patient segments with increased *IL2RA* expression had heterogeneous venetoclax sensitivity (Table), supporting CD25 targeting in patients who may not respond to venetoclax.

Conclusion

AML patients with elevated *IL2RA* expression have inferior prognosis, enrichment of stem-like and Treg signatures and FLT3-ITD alterations. Transcriptomics-based clustering could be used to guide combination therapies based on potential impact of CD25 targeting on Tregs, leukemic cells, or both populations. *Ex vivo* drug sensitivity analyses support combinations of CD25-targeting agents with FLT3 inhibitors, as well as venetoclax. Additional work to evaluate these and other combinations using functional assays is warranted.

Disclosures Hamidi: *Genentech:* Current Employment, Current equity holder in publicly-traded company. **Dunshee:** *Genentech, Inc.:* Current Employment; *F. Hoffmann-La Roche Ltd:* Current equity holder in publicly-traded company. **Higgins:** *Genentech:* Current Employment, Current equity holder in publicly-traded company; *F. Hoffmann-La Roche:* Current Employment, Current equity holder in publicly-traded company. **Dail:** *Genentech:* Current Employment. **Boyiadzis:** *Genentech:* Current Employment.

Figure



Table

	IL2RA VOOM normalized (interquartile range)	*IL2RA*-LSC signature correlation R (p-value)	*IL2RA*-Treg signature correlation R (p-value)	ELN Risk	Maturation	Venetoclax sensitivity
cNMF6.1	2.39 (0.73 - 3.19)	0.47 (0.001)	0.42 (0.0036)	Favorable/ Intermed. II	Mature	Resistant
cNMF6.2	2.67 (0.70 - 4.99)	0.5 (4.4e-6)	0.47 (1.9e-5)	Favorable/ Intermed. I	HSC-Progenitor	Highly sensitive
cNMF6.3	-0.236 (-1.64 - 0.22)	0.43 (0.041)	0.12 (0.58)	Adverse/ Intermed. II	Mature	Intermed. sensitive
cNMF6.4	2.25 (1.60 - 4.49)	-0.24 (0.13)	0.56 (0.00021)	Adverse	HSC-Progenitor	Intermed. sensitive
cNMF6.5	1.2 (-0.18 - 2.85)	-0.87 (0.62)	0.30 (0.075)	Favorable	Progenitor	Highly sensitive
cNMF6.6	1.95 (0.49 - 3.58)	-0.18 (0.37)	0.59 (0.001)	Favorable/ Intermed. I	Mixed	Resistant

Figure 1

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