(PS1538) TRANSCRIPTIONAL REWIRING TO A MONOCYTIC STATE REVEALS THERAPEUTIC VULNERABILITIES IN MENIN INHIBITOR RESISTANCE AML

Topic: 03. Acute myeloid leukemia - Biology & translational research

Lanpeng Chen*[1], Bart Van Lith[1], Siyu Liu[2], Pearl Lee[1], Alwin Schuller[3], Lisa Drew[3]

[1]Acerta Pharma, AstraZeneca, Haematology R&D Small Molecule Discovery, Oss, The Netherlands; [2]AstraZeneca, Oncology Data Sciences, Waltham, United States of America; [3]AstraZeneca, Haematology R&D Small Molecule Discovery, Waltham, United States of America;

Background

In clinical trials, Menin inhibitors (MENi) produce robust pharmacodynamic effects in relapsed/refractory acute myeloid leukemia (AML), notably downregulating the *HOXA/MEIS1* axis and inducing myeloid differentiation. However, clinical resistance to MENi has been observed by acquired *MEN1* mutations as well as other mechanisms. Together, these findings suggest that alternative, Menin-independent oncogenic pathways can emerge to bypass Menin-dependency.

Aims

To characterize the molecular drivers of acquired MENi resistance and identify targetable therapeutic vulnerabilities in leukemic cells that have evaded Menin suppression.

Methods

We generated three MOLM-13 acute myeloid leukemia (*KMT2A*-rearranged AML) cell line models with acquired resistance to clinical-stage MENi (Revumenib, Bleximenib, and Ziftomenib) via stepwise dose escalation. Transcriptomic profiling was performed by RNASeq to identify a conserved MENi-resistance signature using weighted gene co-expression network analysis (WGCNA) (Langfelder & Horvath, 2008) and GeneAgent, an LLM-based gene-set analysis tool (Wang et al., 2025). These findings were integrated with large-scale patient multi-omic datasets (BeatAML) to assess how resistance-associated genes correlate with specific genetic backgrounds and transcriptional AML phenotypes.

Results

MENi-resistant (MENi-r) MOLM-13 cell lines mirrored on-target clinical effects, maintaining suppressed *HOX* gene expression and increased myeloid differentiation. Notably, no mutations were found in the *MEN1* gene, while the resistant cells exhibited a shift in cell viability to MENi, consistent with reduced drug sensitivity.
Transcriptomic analysis of overlapping changes revealed a complex resistance program. MENi-r cells underwent transcriptional rewiring characterized by myeloid differentiation, activation of MAPK and stress regulation pathways, and remodeling of cell-cycle control, while maintaining suppression of *HOXA/MEIS1* axis. Altogether, resistance appears to arise via adaptive lineage plasticity, shifting cells toward an inflammatory monocytic phenotype. This reprogrammed state likely bypasses the Menin blockade by activating compensatory PI3K/AKT and MAPK signaling.
Using WGCNA and GeneAgent, a MENi resistance gene signature was developed from genes robustly upregulated in the resistant lines. When integrated with BeatAML patient data, this MENi-r gene signature was significantly enriched in a subset of *NPM1c* and *KMT2A*-rearranged AML patients who exhibited a "differentiation-shifted" phenotype, defined by elevated myeloid gene signature expression (van Galen et al., 2019) . This subgroup of patients exhibited a high frequency of *RAS* mutations, MAPK pathway activation and dependency, and resistance to venetoclax. Of note, several immune receptors (e.g. CSF1R) were prominent within the MENi resistance signature and highly expressed in both the MENi-r models and the patient subgroup, highlighting potential targetable vulnerabilities in combination with MENi.

Summary/Conclusion

MENi resistance in AML is context-dependent and aligns with the AML hierarchical state; it can be defined as a differentiation-shifted, RAS/MAPK-driven state supported by inflammatory and metabolic adaptation. The overlap identifies rational combination strategies, potentially the use of MEK inhibitors, to overcome resistance. Future studies will focus on validating transcriptomic RAS activity and cell-state signatures as actionable biomarkers and evaluate these combinations in vitro and in vivo.