Supplementary Methods

Cell culture

Human AML cell lines MV4-11, OCI-AML-2, and OCI-AML-3 were obtained from Meisen Cell (Zhejiang, China). MOLM-13, KG1α, THP-1, and HEK293T cells were recovered from laboratory stocks originally sourced from the American Type Culture Collection (ATCC). AML cell lines (MV4-11, OCI-AML-2, OCI-AML-3, MOLM-13, KG1α, and THP-1) were cultured in RPMI-1640 medium (Gibco, 11875119) supplemented with 10% fetal bovine serum (FBS; Gibco, 10099141C). HEK293T cells were maintained in high-glucose Dulbecco's modified Eagle medium (DMEM; Gibco, 11965092) supplemented with 10% FBS. All cells were cultured at 37°C in a humidified atmosphere containing 5% CO_2 and were routinely tested for Mycoplasma contamination.

Establishment of venetoclax-resistant cells

VEN-resistant subclones of OCI-AML-2, MV4-11, and MOLM-13 cells were generated through continuous exposure to stepwise increasing concentrations of ABT-199 (Selleck, S8048). Parental cells were initially treated at the half-maximal inhibitory concentration (IC_{50}), as determined by preliminary cytotoxicity assays, until surviving cells resumed logarithmic growth. Drug concentrations were subsequently escalated by 1.5–2-fold per selection cycle. Cells were maintained at each concentration until stable proliferation was achieved before further escalation. Resistant populations were considered established when cells proliferated stably at concentrations up to 10-fold higher than the initial IC_{50}. Resistant cells were thereafter maintained in medium containing ABT-199 at the corresponding final concentration. All cell lines were authenticated by short tandem repeat (STR) profiling before and after resistance induction.

Patient samples

Peripheral blood or bone marrow samples were obtained from patients with AML treated at Guangdong General Hospital. AML was diagnosed according to the World Health Organization (WHO) Classification of Tumours of Haematopoietic and Lymphoid Tissues (revised 4th edition, 2017). Risk stratification was performed according to the European LeukemiaNet (ELN) 2022 recommendations. Mononuclear cells were isolated by Ficoll density gradient centrifugation and

cryopreserved in fetal bovine serum containing 10% dimethyl sulfoxide (DMSO) until use.

For analyses of venetoclax response, patient samples were classified into two groups: a VEN-remission group, consisting of diagnostic samples from patients who achieved complete remission (CR) or complete remission with incomplete hematologic recovery (CRi) following venetoclax-based therapy, and a VEN-refractory/relapsed group, consisting of either diagnostic samples from patients who failed to achieve CR/CRi or samples collected at first relapse after an initial response to VEN-based therapy. Response assessment was performed according to the ELN 2022 criteria. Clinical characteristics of the study cohort are summarized in Supplementary Table S2.

Cell viability assays

Cell viability was assessed using the Cell Counting Kit-8 (CCK-8) assay (Dojindo Molecular Technologies, CK04). Cells (5×10^3 per well) were seeded into 96-well plates and incubated at 37°C in a humidified atmosphere containing 5% CO_2 for 24 h. Cells were subsequently treated with increasing concentrations of ABT-199 or vehicle control (DMSO; final concentration $\leqslant 0.1\%$) for 48 h. Thereafter, 10 μL of CCK-8 reagent was added to each well, followed by incubation at 37°C for 4 h in the dark. Absorbance was measured at 450 nm using a microplate reader (BioTek, USA). All experiments were performed with at least three independent biological replicates, each measured in technical triplicate. Cell viability was calculated as:

$$(A_sample - A_blank) / (A_control - A_blank) \times 100\%$$

Migration and invasion assays

Cell migration and invasion were assessed using 24-well Transwell inserts (8.0 μm pore size; 353097, Corning) coated with or without Matrigel (356234, Corning). For invasion assays, Matrigel was thawed overnight at 4°C, diluted to 200 μg/mL, and used to coat inserts prior to incubation at 37°C for 2 hours. The lower chambers were filled with 650 μL complete medium containing 20% FBS as a chemoattractant. Cells (8×10^4 per well), resuspended in serum-free RPMI-1640, were seeded into the upper chambers and incubated at 37°C in a humidified atmosphere with 5% CO_2 for 24 hours. Following incubation, migrated or invaded cells were harvested and quantified by flow cytometry.

Flow cytometry

Flow cytometry — Apoptosis assays

Cells were treated with indicated concentrations of ABT-199 for 24 hours at 37°C in a humidified 5% CO_2 atmosphere. Cells were then harvested and assessed using the FITC Annexin V Apoptosis Detection Kit I (BD Biosciences, 556547) according to the manufacturer's instructions. Cells were stained with FITC Annexin V and propidium iodide (PI), resuspended in binding buffer, and immediately analyzed using a Cytek Aurora Evo flow cytometer. At least 50,000 events were collected per sample. Cell populations were defined as viable (Annexin V^-/PI^-), early apoptotic (Annexin V^+/PI^-), late apoptotic/necrotic (Annexin V^+/PI^+), and necrotic (Annexin V^-/PI^+), and were quantified using FlowJo software (v10.8.1).

Flow cytometry — Cell cycle analysis

Cells were treated with either 10 μM ABT-199 or vehicle control (DMSO) for 24 hours at 37°C in a humidified 5% CO_2 atmosphere. Cell cycle distribution was analyzed using a PI/RNase Staining Kit (Dojindo, C543) according to the manufacturer's instructions. Cells were harvested, washed once with PBS, and incubated with staining solution at 4°C for 30 minutes followed by 37°C for 30 minutes, protected from light. Cells were then filtered through a 70 μm nylon mesh and immediately analyzed on a Cytek Aurora Evo flow cytometer. At least 50,000 single, intact events were acquired per sample. Cell cycle distribution was modeled using ModFit LT (v5.0). G_0/G_1 arrest was quantified as the fold change in the G_0/G_1 fraction relative to vehicle-treated controls. Only fits with a coefficient of variation (CV) of the G_0/G_1 peak $<8\%$ and reduced chi-square (RCS) values between 1.0 and 3.0 were considered acceptable.

Flow cytometry — Human cell engraftment and tissue infiltration

Following erythrocyte lysis and mouse Fc receptor blocking (as described in Tissue processing and flow cytometry sample preparation), cells were resuspended in FACS buffer (PBS supplemented with 2% FBS and 2 mM EDTA) and stained with fluorochrome-conjugated antibodies against human CD45 and mouse CD45 for 30 minutes at 4°C, protected from light. After washing, cells were resuspended in PBS containing 2% FBS and analyzed on a Cytek Aurora Evo flow cytometer, with at least 100,000 events acquired per sample. Data were analyzed using FlowJo (v10.8.1). Human cell engraftment in peripheral blood and leukemic infiltration in the liver and

spleen were quantified as the percentage of $hCD45^{+}mCD45^{-}$ cells among total viable $CD45^{+}$ leukocytes. OCI-AML-2 cells spiked into non-engrafted mouse blood at 1% served as a positive control.

Lentiviral packaging and transduction

Lentiviral packaging

Lentiviral vectors for both gene knockdown and overexpression were synthesized by GeneChem (Shanghai, China). The shRNA sequences targeting ADAM15 and a non-targeting scramble control are detailed in Supplementary Table S1. All target sequences were confirmed by Sanger sequencing prior to use.

Lentiviral transduction and selection

For lentiviral transduction, AML cells were seeded at a density of 2×10^5 cells/mL in 6-well plates overnight. ADAM15 overexpression vectors were transduced into parental cell lines (OCI-AML-2, MV4-11, and MOLM-13), whereas ADAM15 shRNA knockdown vectors were introduced into the corresponding venetoclax-resistant cell lines (OCI-AML-2/R, MV4-11/R, and MOLM-13/R). Lentiviral particles were added at a multiplicity of infection (MOI) of 6–8. Twelve hours post-transduction, the culture volume was doubled by adding fresh complete medium. Selection was initiated 48 hours post-transduction using 4 μg/mL puromycin (A1113803; Gibco), followed by maintenance in 2 μg/mL puromycin. Knockdown and overexpression efficiencies were verified by quantitative RT-PCR and immunoblotting 72 hours after selection.

BH3 profiling

BH3 peptides (BIM, BID, HRK, NOXA, BAD, PUMA) were synthesized by GL Biochem (Shanghai, China), and their sequences are provided in Supplementary Table S1. Peptides were dissolved in DMSO at a stock concentration of 10 mM and diluted in DTEB to final concentrations of 2, 20, and 100 μM immediately prior to use. Small-molecule inhibitors, including ABT-199, S63845 (Selleck, S8383), WHI-539 (Selleck, S7801), and CCCP (Selleck, S6494), were prepared similarly in DTEB; CCCP was used at 50 μM as a positive control for complete mitochondrial depolarization.

Cells were harvested, washed with ice-cold PBS, and resuspended in DTEB (digitonin–trehalose experimental buffer: 10 mM HEPES, 50 mM KCl, 4 mM EGTA, 2 mM EDTA, 0.1% BSA, 135 mM trehalose, and 5 mM succinate, pH 7.5 adjusted with KOH) supplemented with 0.01% digitonin (APExBIO, C3758), 0.01 mg/mL oligomycin (MCE, HY-N6782), and 0.01 mM β-mercaptoethanol (MCE, HY-Y0326). Cells were permeabilized on ice for 10 minutes, then aliquoted into black, clear-bottom 96-well plates (Corning, 3603) at 1×10^5 cells per well and treated with BH3 peptides or small-molecule inhibitors.

Immediately after treatment, JC-1 dye was added to each well at a final concentration of 1 μM. Fluorescence was measured kinetically using a Synergy H1 microplate reader (BioTek, Winooski, VT, USA), with excitation at 485 nm and dual emission detection at 530 nm (JC-1 monomers) and 590 nm (JC-1 aggregates). Plates were maintained at 37°C, and measurements were recorded every 5 minutes for 2 hours. The 590/530 nm fluorescence ratio was calculated at each time point to assess mitochondrial membrane potential ($\Delta\Psi m$).

Mitochondrial priming was calculated as:

$$\text{Priming (\%)} = (R_control - R_peptide) / (R_control - R_CCCP) \times 100\%$$

where R_control is the 590/530 ratio of DMSO-treated cells, R_peptide is the ratio after BH3 peptide treatment, and R_CCCP represents the ratio after complete depolarization (positive control). EC_{50} values were determined by nonlinear regression using GraphPad Prism (v9.5)

RNA extraction and quantitative RT-PCR

Total RNA was extracted from at least 1×10^6 cells using TRIzol Reagent (Invitrogen, 15596026) according to the manufacturer's instructions. Cells were lysed in TRIzol, and RNA was isolated by chloroform phase separation (Accurate Biology, AG21303) followed by isopropanol precipitation (Aladdin, I112021). RNA concentration and purity were assessed by spectrophotometry (A260/A280 = 1.8–2.1; A260/A230 > 2.0). First-strand cDNA was synthesized using the PrimeScript 1st Strand cDNA Synthesis Kit (Takara, 6110A) following the manufacturer's protocol. Quantitative PCR was performed on an ABI 7500 Real-Time PCR System (Applied

Biosystems) using SYBR Green Premix Pro Taq HS qPCR Kit II (Accurate Biology, AG11702). Primer sequences are listed in Supplementary Table S1. Melting curve analysis was conducted to confirm amplification specificity. Relative mRNA expression levels were normalized to GAPDH and calculated using the $2^{-\Delta\Delta Ct}$ method. Each biological replicate was measured in technical triplicate where indicated.

RNA sequencing

RNA sequencing — Library preparation

Total RNA was extracted from $\geq 1 \times 10^6$ cells, and RNA integrity was assessed prior to mRNA purification. Poly(A)$^+$ mRNA was isolated using poly-T oligo-attached magnetic beads (NEB, E7490). Following fragmentation, non-stranded libraries were constructed using the NEBNext Ultra II RNA Library Prep Kit for Illumina (NEB, E7770) with 8 cycles of PCR amplification. Strand-specific libraries were constructed using the NEBNext Ultra II Directional RNA Library Prep Kit for Illumina (NEB, E7760) with 12–15 cycles of PCR amplification. Library quality was assessed using an Agilent 2100 Bioanalyzer and quantified by Qubit fluorometry and qPCR.

RNA sequencing — Sequencing

Qualified libraries were pooled, and cluster generation was performed on an Illumina NovaSeq 6000 platform using the NovaSeq 6000 S4 Reagent Kit v1.5 (Illumina, 20028312). Sequencing was conducted in paired-end 150 bp (PE150) mode.

RNA sequencing — Bioinformatics pipeline

Raw reads were processed using Illumina RTA3 for base calling and bcl2fastq (v2.20) for demultiplexing and FASTQ conversion. Read quality was evaluated using FastQC (v0.11.9) and MultiQC (v1.12). Clean reads were aligned to the reference genome using HISAT2 (v2.2.1) with default parameters. Gene expression levels were quantified as FPKM using StringTie (v2.1.4). Differential expression analysis was performed using DESeq2 (v1.30.1) with $|\log_2 \text{fold change}| \geq 1$ and adjusted $P < 0.05$ as significance thresholds.

Untargeted metabolomics

Cells prepared for RNA-seq were aliquoted in parallel for metabolomics analysis (MOLM-13, MOLM-13/R, OCI-AML-2, OCI-AML-2/R, MV4-11, MV4-11/R). Briefly, 1×10^6 cells were

rapidly quenched in liquid nitrogen (−196°C) to immediately arrest metabolic activity. Samples were then subjected to metabolomic profiling by Metware Biotechnology Co., Ltd. (Wuhan, China).

Metabolites were identified based on accurate mass (mass error < 5–10 ppm), retention time, and MS/MS fragmentation patterns by comparison with in-house spectral libraries (Metware database) and public databases, including HMDB, KEGG, METLIN, and MassBank. Differentially abundant metabolites were defined as those with variable importance in projection (VIP) scores > 1.0.

Co-immunoprecipitation

After treatment with 10 μM ABT-199 for 12 h, cells were harvested and subjected to immunoprecipitation using the Pierce Crosslink Immunoprecipitation Kit (Thermo Fisher Scientific, 26147) according to the manufacturer's instructions. Approximately 1×10^7 cells (~50 mg wet pellet) were lysed in 500 μL ice-cold IP lysis buffer (kit component) supplemented with protease inhibitor cocktail (Roche, 11697498001) and phosphatase inhibitor cocktail (Roche, 04906837001). Two percent of the total lysate was reserved as input prior to pre-clearing.

For ADAM15 immunoprecipitation, 2.5 μg of goat anti-ADAM15 antibody or goat IgG isotype control was diluted in 100 μL coupling buffer and incubated with Protein A/G Plus agarose for antibody immobilization. For HCK immunoprecipitation, 2.5 μg of rabbit anti-HCK antibody or rabbit IgG isotype control was processed in parallel. Antibody-crosslinked resin was incubated with pre-cleared lysates overnight at 4°C with end-over-end rotation. Bound proteins were eluted, resolved by SDS-PAGE, and analyzed by immunoblotting with the indicated antibodies. Input lysates were included as loading controls.

Immunoblotting

Immunoblotting — Protein extraction and quantification

For ABT-199 treatment, cells were exposed to 10 μM ABT-199 or vehicle control (DMSO) for 12 h. For HCK inhibition studies, cells were pretreated with 10 μM PP2 (Src/HCK inhibitor, MedChemExpress, HY-13805) or DMSO for 30 min prior to ABT-199 exposure. Patient-derived mononuclear cells were isolated by Ficoll density gradient centrifugation before lysis.

Cells in logarithmic growth phase were harvested, washed with PBS, and lysed on ice in RIPA lysis buffer (Thermo Fisher Scientific, 89901) supplemented with protease and phosphatase inhibitor cocktails. Protein concentrations were determined using the BCA Protein Assay Kit (Thermo Fisher Scientific, 23225). Lysates were mixed with loading buffer (Epizyme, LT101) and denatured at 95°C for 10 min.

Immunoblotting — Subcellular fractionation

Subcellular fractions were isolated from 2×10^6 cells using the Nuclear and Cytoplasmic Protein Extraction Kit (Epizyme, LT101) according to the manufacturer's instructions, with protease and phosphatase inhibitor cocktails added during lysis.

Immunoblotting — Western blotting

Equal amounts of protein (20 µg) were separated by SDS-PAGE and transferred onto PVDF membranes using a wet transfer system. Membranes were blocked for 10 min at room temperature in Protein Free Rapid Blocking Buffer (Epizyme, PS108), followed by overnight incubation at 4°C with primary antibodies diluted in Antibody Dilution Buffer (Epizyme, PS119).

After washing with TBST, membranes were incubated with HRP-conjugated secondary antibodies for 1 h at room temperature. Protein signals were detected using the Omni-ECL Pico Light Chemiluminescence Kit (Epizyme, QS202) and imaged on a MiniChemi system (Sinsage, Beijing, China). Membranes were stripped using Western Blot Fast Stripping Buffer (Epizyme, PS107) when reprobing was required.

β-actin (Boster, BA0412) and GAPDH (Boster, BM1623) were used as loading controls. HRP-conjugated goat anti-rabbit IgG (Proteintech, SA00001-2) and goat anti-mouse IgG (Proteintech, SA00001-1) secondary antibodies were used at a dilution of 1:5000.

Band intensities were quantified using ImageJ (v1.54p, NIH).

Immunofluorescence staining and confocal microscopy

Digitonin was selected as the permeabilization agent in place of the conventional Triton X-100 because digitonin selectively permeabilizes the cholesterol-rich plasma membrane at low

concentrations while preserving the integrity of intracellular organellar membranes. This approach enables accurate subcellular localization of the transmembrane protein ADAM15 without disrupting its native membrane context.

For pre-treatment, cells were exposed to 10 μM ABT-199 or vehicle control (DMSO) for 2 h at 37°C prior to fixation. Cells were then washed with PBS and fixed in 4% paraformaldehyde at room temperature for 30 min. Cells were permeabilized with PBS containing 0.005% digitonin (permeabilization buffer) for 5 min and blocked with 2% BSA (Merck, V900933) in permeabilization buffer for 30 min at room temperature.

Cells were then incubated overnight at 4°C in a humidified chamber with primary antibodies diluted in PBS containing 2% BSA, 0.005% digitonin, and 0.01% Tween-20 (Beyotime, ST825). After washes with permeabilization buffer, cells were incubated with Alexa Fluor-conjugated secondary antibodies for 1 h at room temperature in the dark. Nuclei were counterstained with DAPI. Coverslips were mounted using mounting medium (Servicebio, G1401) and imaged using a confocal microscope.

Colocalization was quantified using ImageJ (v1.54p, NIH).

In vivo xenograft assays

In vivo xenograft assays — Animals and cell transplantation

Female NOD.CB17-Prkdc^scid/NcrCrl (NOD/SCID) mice (6 weeks old) were obtained from Cyagen Biosciences (Suzhou, China) and maintained under specific pathogen-free (SPF) conditions. All animal procedures were approved by the Institutional Animal Care and Use Committee (IACUC; approval no. G2025074) and conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals. Each mouse was intravenously injected via the lateral tail vein with 4×10^6 cells suspended in 200 μL PBS. The following experimental groups were established:

(i) OCI-AML-2 (parental);

(ii) OCI-AML-2/R (venetoclax-resistant);

(iii) OCI-AML-2/R-shADAM15 (venetoclax-resistant, ADAM15 knockdown);

(iv) OCI-AML-2/R-scramble (venetoclax-resistant, non-targeting shRNA control);

(v) Cell-free control (200 μL PBS only).

In vivo xenograft assays — Engraftment assessment

At day 7 post-transplantation, peripheral blood was collected via submandibular vein puncture into EDTA-coated tubes. Engraftment was evaluated by: (i) flow cytometric analysis of human CD45 (hCD45) and mouse CD45 (mCD45); and (ii) morphological assessment of leukemic blasts on Wright-Giemsa-stained blood smears by a certified hematopathologist. Successful engraftment was defined as ≥1% $hCD45^+$ cells in peripheral blood.

In vivo xenograft assays — Treatment protocol

Engrafted mice were randomly assigned to treatment groups ($n \geq 6$ per group) and treated with venetoclax (ABT-199, 50 mg/kg) or vehicle control by oral gavage once daily (QD), starting on day 7 post-transplantation until study endpoint. Body weight was monitored weekly. Disease progression was assessed weekly by flow cytometric analysis of peripheral blood hCD45/mCD45 chimerism.

In vivo xenograft assays — Endpoint criteria and tissue collection

Mice were euthanized by CO_2 asphyxiation upon reaching predefined humane endpoints, including: (i) $hCD45^+$ cells >60% of peripheral blood leukocytes; (ii) body weight loss >20%; (iii) hematocrit <20%; (iv) severe lethargy or impaired mobility; or (v) tumor diameter >1.5 cm. Survival was defined as the interval from treatment initiation to euthanasia.

At endpoint, peripheral blood was collected via cardiac puncture for complete blood count and flow cytometry. Bone marrow cells were harvested from femurs and tibias by flushing with FACS buffer. Major organs (liver, spleen, and visible tumor or infiltrated tissues) were collected, weighed, and processed for downstream analyses, including formalin fixation for histology and immunohistochemistry, snap-freezing for molecular assays, and preparation of single-cell suspensions for flow cytometry.

In vivo xenograft assays — Tissue processing and flow cytometry sample preparation

Peripheral blood and bone marrow were collected into EDTA-coated tubes. Solid tissues (liver, spleen, tumors, and infiltrated organs) were mechanically dissociated and passed through a 70-μm cell strainer (Biosharp, BS-70-XBS) to obtain single-cell suspensions. Red blood cells were lysed using RBC Lysis Buffer (Leagene, CS0003) for 5 min at room temperature, followed by washing with FACS buffer. Cells were resuspended in FACS buffer and incubated with mouse Fc Block (BD Biosciences, 553141; 1:100) for 5 min at 4°C prior to antibody staining.

In vivo xenograft assays — Wright-Giemsa staining

Peripheral blood smears were fixed in methanol, stained with Wright-Giemsa solution (Solarbio, G1020) for 10 min, rinsed with distilled water, and air-dried prior to microscopic evaluation. Leukemic burden was assessed by quantifying blast morphology in conjunction with total nucleated cell counts.

In vivo xenograft assays — Histology and immunohistochemistry

Tissue samples were fixed in 10% neutral-buffered formalin, paraffin-embedded, and sectioned at 4 μm. Sections were subjected to hematoxylin and eosin (H&E) staining or immunohistochemical analysis using standard protocols. For IHC, sections were incubated with primary antibodies overnight at 4°C, followed by HRP-conjugated secondary antibodies and visualization with DAB substrate. Nuclei were counterstained with hematoxylin.

Bioinformatics analysis

Bioinformatics analysis — RNA-seq differential expression

All statistical analyses were performed using R (v4.3.1). For RNA-seq data, normalization and differential expression analysis were conducted using the DESeq2 package (v1.40.2). Differentially expressed genes (DEGs) were identified using the Wald test with Benjamini-Hochberg false discovery rate (FDR) correction. Genes with $|\log_2$ fold change (FC)$| > 1$ and adjusted $P < 0.05$ were considered significant.

Bioinformatics analysis — Metabolomic differential analysis

For metabolomic data, normalization was performed using probabilistic quotient normalization

(PQN) followed by $\log_2$ transformation. Differential metabolite analysis was conducted using the limma package (v3.56.2) with moderated t-statistics and FDR correction. Metabolites with $|\log_2 FC| > 0.5$ and adjusted $P < 0.05$ were considered significantly altered.

Bioinformatics analysis — Pathway enrichment and GSEA

KEGG pathway enrichment analysis was performed for both DEGs and differentially abundant metabolites using the clusterProfiler package (v4.8.1). Gene set enrichment analysis (GSEA) was additionally conducted for transcriptomic data with 1,000 permutations. Enrichment results were visualized using ggplot2 (v3.4.2) and enrichplot (v1.20.0).

Bioinformatics analysis — Multi-omics integration

Integration of transcriptomic and metabolomic datasets was performed using the mixOmics package (v6.24.0). Pearson correlation coefficients were calculated between DEGs and differential metabolites, with $|r| > 0.7$ and $P < 0.01$ considered significant.

Bioinformatics analysis — Protein-protein interaction network

Protein-protein interaction (PPI) networks were constructed for DEGs using the STRING database (v12.0) with a minimum interaction score of 0.4 and visualized in Cytoscape (v3.10.0). Hub genes were identified based on degree and betweenness centrality using the CytoHubba plugin.

BeatAML cohort analysis

Clinical data, drug sensitivity profiles, and transcriptomic data from the BeatAML cohort were obtained from a publicly available database (https://www.vizome.org/). Patients were stratified into venetoclax-sensitive (Q1) and venetoclax-resistant (Q4) groups based on venetoclax area under the curve (AUC) values using a quartile-based approach.

Differential expression of ADAM15 between groups was assessed using an unpaired two-tailed Student's t-test. Correlations between ADAM15 expression and venetoclax AUC were evaluated using Pearson or Spearman correlation, as appropriate.

Patients were further dichotomized into ADAM15-high and ADAM15-low groups using the optimal cutoff. Overall survival was analyzed using the Kaplan-Meier method with log-rank testing.

All analyses were performed in R (v4.3.1) using the survival (v3.5-5) and survminer (v0.4.9) packages.