A Phase 1/1b Open-Label, Dose Escalation, First-in-Human Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Preliminary Anti-leukemic Activity of the Orally Available CLK Inhibitor, BH-30236, in Adults with R/R AML or HR-MDS

Eytan Stein MD[1], Alice S Mims MD[2], Zhuoer Xie MD[3], Gabriel Mannis MD[4] ,Justin Watts MD[5], Farhad Ravandi MD[6], Gary Schiller MD[7], Brian Ball MD[8], Hongtao Liu MD PhD[9] , Jessica Altman MD[10], Eunice Wang MD[11], J Jean Cui PhD[12], Jihao Zhou MD PhD[12], Zachary Zimmerman MD PhD[12], Stephen A Strickland MD[13]

[1]Memorial Sloan Kettering Cancer Center, New York,NY; [2]Ohio State University Cancer Center, Columbus, OH; [3]Moffitt Cancer Center, Tampa, FL; [4]Stanford Cancer Institute, Palo Alto, CA; [5]University of Miami Sylvester Comprehensive Cancer Center, Miami, FL; [6]MD Anderson Cancer Center ,Houston,TX; [7]University of California Los Angeles, Los Angeles, CA; [8]City of Hope, Duarte, CA; [9]University of Wisconsin, Madison, WI; [10]Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL; [11]Roswell Park Comprehensive Cancer Center, Buffalo,NY; [12]Blossom Hill Therapeutics, San Diego, CA; [13]SCRI at TriStar Centennial, Nashville, TN.

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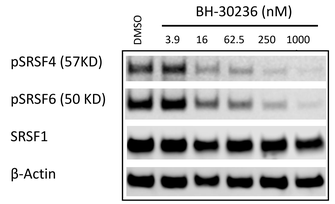
Background

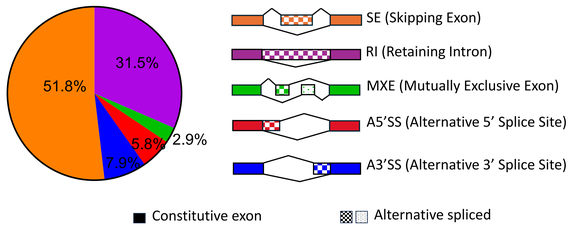
- Dysregulated RNA splicing is a hallmark of cancers and regulates proliferation, apoptosis, immune surveillance, and therapeutic resistance.[1]
- Spliceosome mutations occur in 40–85% of MDS and 10–25% of AML cases, while aberrant splicing is observed in myeloid malignancies even in the absence of mutations.[2]
- Genetic screens have shown that the loss of splicing factors sensitizes AML to the BCL2 inhibitor venetoclax.[3]
- BH-30236 is a first-in-class, orally bioavailable, ATP-competitive, macrocyclic CDC-like kinase 1, 2 and 4 (CLK 1, 2 and 4) inhibitor that also inhibits FLT3, PIM3, and DYRK1/2.[4]

- BH-30236 effectively modulates phosphorylation of CLK substrate SRSFs in Kasumi-1 cells.

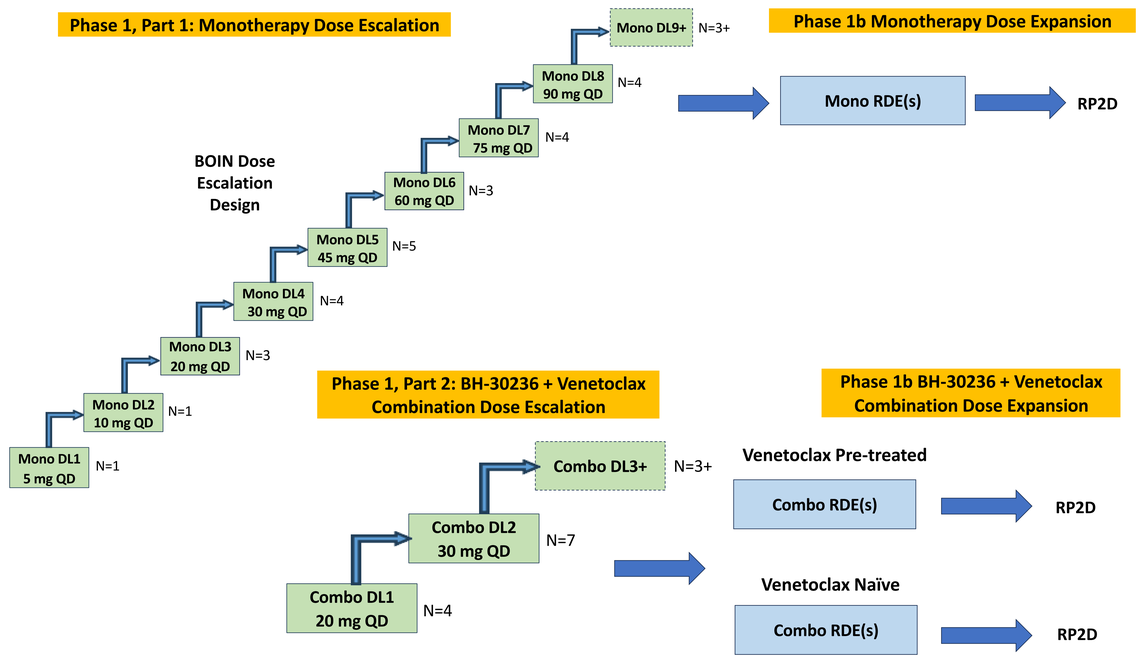


- RNAseq analyses on 6 patient-derived AML cells after treatment with BH-30236 indicate BH-30236 alters splicing of genes associated with mRNA splicing, DNA damage, and chromosome remodeling

Common Alternative Splicing Events following BH-30236 treatment



Study Schema



Study Population

Key Inclusion Criteria

Pathologically confirmed diagnosis of AML or HR-MDS which is treatment refractory or relapsed following prior systemic therapy per ELN 2022 for AML or IWG 2023 for HR-MDS; Adults ≥18 years; ≤5 prior systemic therapies; bone marrow blasts ≥5%; ECOG ≤2.

Key Exclusion Criteria

Diagnosis of acute promyelocytic leukemia or chronic myeloid leukemia with blast crisis; Active or known CNS leukemia; Prior treatment with a CLK inhibitor; QTc > 470 milliseconds; LVEF < 40% by ECHO or MUGA scan; allogeneic HSCT within 3 months or donor lymphocyte infusion within 30 days of protocol specified therapy.

Study Objectives

Primary Objectives

Dose Escalation:
- To evaluate the safety/ tolerability of BH-30236 as a monotherapy or in combination in adult subjects with R/R AML or HR-MDS and determine the MTD.
- To identify the RDEs for BH-30236 as a monotherapy or in combination.

Dose Expansion:
- To evaluate the safety, tolerability, and preliminary anti-leukemic activity of BH-30236 as a monotherapy or in combination at selected RDEs to determine the RP2D.

Secondary Objectives

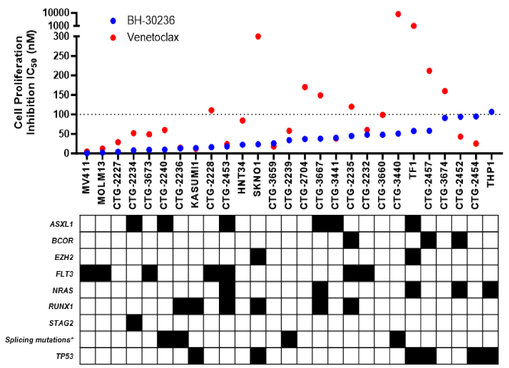
- To characterize PK properties of BH-30236 as a monotherapy or in combination.
- To characterize the preliminary anti-leukemic activity of BH-30236 as a monotherapy or in combination in terms of ORR, CR/CRh rate for AML, and CR/PR rate in HR-MDS.

Exploratory Objectives

- To evaluate BH-30236 effect as a monotherapy or in combination on overall survival (dose expansion only).
- To evaluate prognostic markers and predictors of anti-leukemic activity and/or resistance to BH-30236.
- To characterize target engagement and pharmacodynamic effects of BH-30236.
- To analyze preliminary exposure-toxicity/response relationships.

BH-30236 Demonstrated Marked Anti-leukemic Activity in Preclinical Models

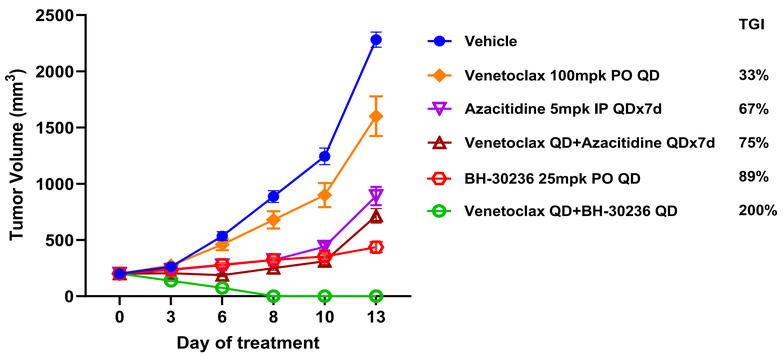
BH-30236 exhibits stronger anti-leukemic activity than venetoclax in a majority of patient-derived AML cells and human AML cell lines across diverse molecular subtypes.



* Mutations include SF3B1, SRSF2, and U2AF1

BH-30236 displayed profound synergy with venetoclax, and the combination of BH-30236 with venetoclax demonstrated substantially better efficacy than standard of care azacytidine + venetoclax in MOLM-13, a venetoclax resistant CDX AML model.

MOLM-13 model in SCID/Beige mice



Study Design

Study Identifier
- NCT06501196 (BH-30236-01)

Design
- Multi-center, Bayesian Optimal Interval (BOIN) dose escalation with parallel monotherapy and combination therapy arms.
- Expansion at selected doses in monotherapy and venetoclax combination to establish a Recommended Phase 2 Dose (RP2D).

Treatment
- Monotherapy: BH-30236 PO QD, continuous dosing in 28-day cycles.
- Combination: BH-30236 PO QD (starting 20 mg), 28-day cycle + venetoclax target dose of 400 mg PO QD, 28-day cycle.

Assessments
- Dose-limiting toxicities (DLTs) are evaluated over the first 28 days of treatment.
- Disease response assessment is performed according to European Leukemia Network 2022 or International Working Group 2023 guidelines for AML and MDS, respectively.
- Exploratory analyses include assessment of measurable residual disease, longitudinal profiling of genomic alterations and characterization of gene expression and alternative splicing modulation in the bone marrow and/or peripheral blood.

Study Status

Phase 1
- Study (NCT06501196) ongoing at 13 US centers with active dose escalation in both monotherapy and combination therapy arms.
- Sponsor: BlossomHill Therapeutics, Inc., San Diego, CA.
- Contact: clinicaltrials@bhtherapeutics.com

References

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