(PS1524) GB3226, A FIRST-IN-CLASS DUAL ENL-YEATS/FLT3 INHIBITOR, SUPPRESSES SEC-DRIVEN TRANSCRIPTION AND ONCOGENIC SIGNALING IN PRECLINICAL AML MODELS

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

Louis Renzetti*[1], Stacia Kargman[1], Joseph Vacca[2], Mayumi Sugita[3], Sebastien Degorce[4], Tammy Ladduwahetty[4], Bradley Sherborne[4], Simon Taylor[4], Gillian Watt[4], Bhupinder Singh[1], Susan Tantawi[1], Monica Guzman[3], Brian Jacoby[1]

[1]Galecto Inc., Copenhagen, Denmark; [2]Bridge Medicines, New York, United States of America; [3]Weill Cornell Medicine, New York, United States of America; [4]Pharmaron, Hertfordshire, United Kingdom;

Background

Relapsed/refractory (R/R) acute myeloid leukaemia (AML) remains associated with poor outcomes, particularly in molecular subtypes characterised by persistent SEC-dependent transcriptional programs and activating FLT3 mutations (~30% of adult AML). The YEATS domain of ENL (MLLT1) sustains oncogenic transcription of HOXA9, MEIS1 and MYC, while FLT3 mutations drive leukaemic proliferation and relapse. We hypothesised that concurrent inhibition of ENL-YEATS-mediated transcription and FLT3 signalling may provide a superior therapeutic strategy capable of constraining both leukaemic stemness and proliferative signalling.

Aims

Here, we describe the preclinical pharmacology and activity of GB3226, a first-in-class, orally bioavailable, small molecule, dual inhibitor targeting the ENL-YEATS domain and FLT3.

Methods

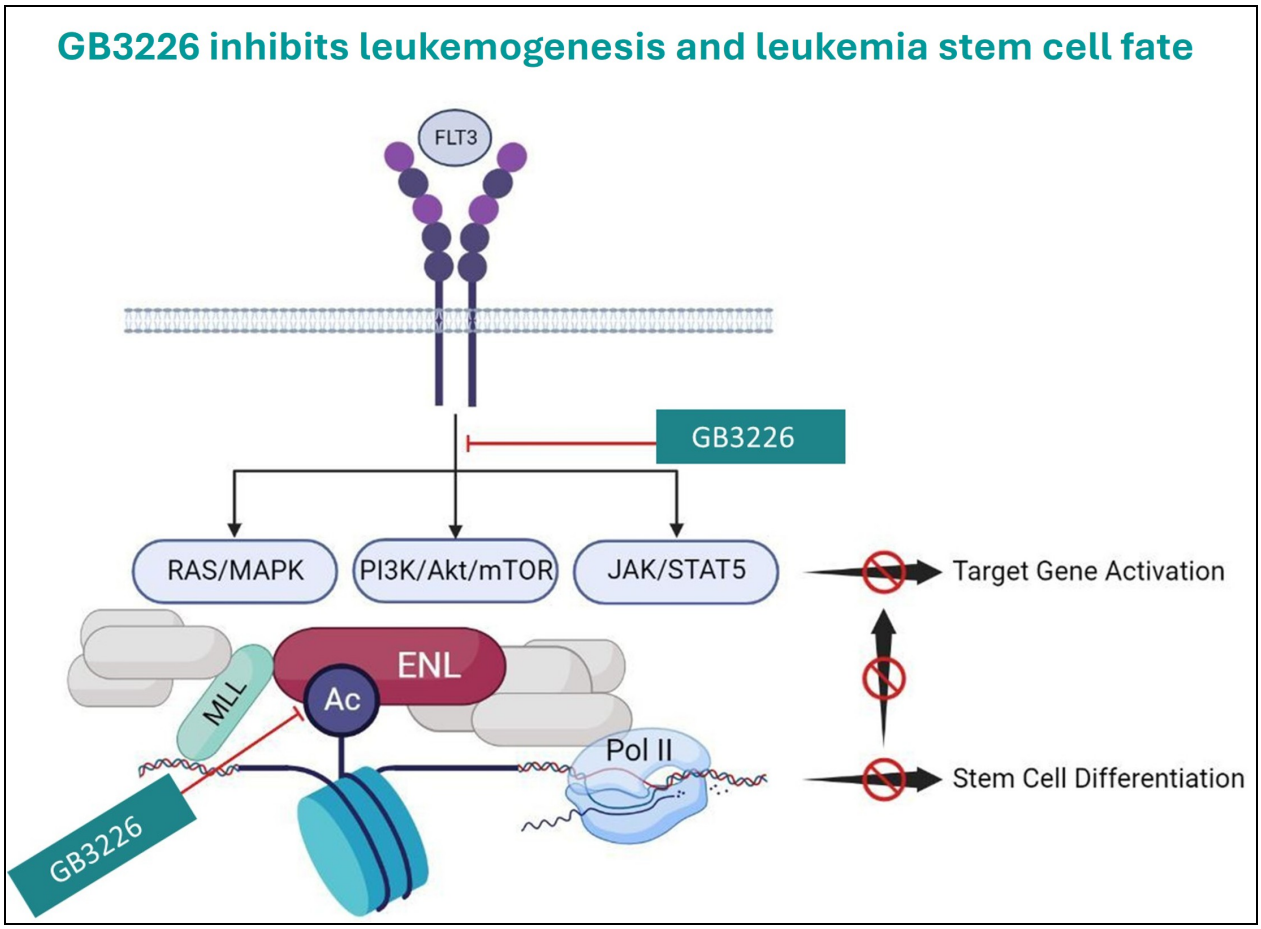
GB3226 was developed through structure-based drug design as an optimized analog of a selective ENL-YEATS tool compound (TDI-11055). Biochemical binding assays assessed ENL-YEATS and FLT3 inhibition. Kinase selectivity was evaluated across 370 kinases. Anti-proliferative activity was assessed in AML cell lines and primary AML samples. Transcriptomic analyses evaluated suppression of SEC target genes. In vivo efficacy was evaluated in subcutaneous and disseminated MV4;11 xenograft models. Pharmacokinetics and safety were assessed in multi-species nonclinical studies.

Results

GB3226 potently inhibited ENL-YEATS (IC50=185 nM) and FLT3 WT (Kd=3nM) and clinically relevant mutant variants, including FLT3-ITD and D835 substitutions (Kd=3–27 nM), with high selectivity across epigenetic and kinase panels. GB3226 was inactive in a bromodomain panel. In a kinase panel of 370 kinases, GB3226 was active (IC50=40-60 nM) vs c-KIT, CLK1, CLK4, MELK and TRKC and was inactive vs the remaining kinases. In AML cell lines (MV4;11, MOLM13), GB3226 potently inhibited the proliferation (IC50=18-32 nM) and demonstrated additive to synergistic activity with cytarabine, venetoclax, gilteritinib, and revumenib. In primary AML patient samples, GB3226 exhibited anti-proliferative activity across multiple genotypes, including FLT3+, ASXL1+, NPM1c+ and TET2+. In vivo, oral administration of GB3226 (25, 50 and 100 mg/kg, BID or QD) induced rapid tumour regression in subcutaneous models and significantly reduced leukaemia burden and prolonged survival in disseminated models. The efficacy was statistically superior to gilteritinib and revumenib. Anti-leukaemic activity correlated with suppression of SEC target genes (HOXA9, MEIS1, MYC) in tumour tissue. GB3226 demonstrated favourable pharmacokinetics supporting once-daily administration, no hERG inhibition (IC50>30 µM), no QTc prolongation in canine studies, and an acceptable safety profile in 28-day repeat-dose GLP toxicology studies.

Summary/Conclusion

GB3226 is a first-in-class dual inhibitor of ENL-YEATS and FLT3 that simultaneously suppresses SEC-driven oncogenic transcription and FLT3-mediated signalling. Preclinical studies demonstrate that GB3226 exhibits potent anti-leukaemic activity and has the potential for combination with multiple therapeutic agents across diverse AML genotypes. These findings support clinical evaluation of GB3226 as a differentiated therapeutic strategy in AML.



GB3226 is a potent, dual inhibitor of ENL-YEATS and FLT3