

GB3226, a Novel, Orally Active, First-in-Class, Small Molecule Dual Inhibitor of ENL-YEATS and FLT3 Kinase for the Treatment of Relapsed/Refractory Acute Myeloid Leukemia

Poster no: 6106

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Background

- Acute myeloid leukemia (AML) remains a formidable challenge in hematology, particularly for patients with relapsed or refractory (R/R) disease, where treatment options are limited and outcomes remain poor¹. Outcomes are dismal in patients with HOXA9/MEIS1 upregulated biology with co-mutations in FLT3²
- ENL (MLLT1), a chromatin reader protein, binds to acetylated histones through the YEATS domain and is crucial for sustaining oncogenic gene expression in leukemia³
- Genetic or pharmacological disruption of ENL-YEATS reduces leukemia burden^{3,4}
- FLT3, a receptor tyrosine kinase overexpressed in most AML blasts. Roughly 30% of newly diagnosed adult AML patients exhibit FLT3 mutations⁵
- Dual inhibition of ENL-YEATS and FLT3 may offer superior efficacy
- GB3226 is a first-in-class, orally bioavailable dual inhibitor targeting the ENL-YEATS domain and FLT3 kinase, two key drivers of leukemogenesis
- Here we report the pre-clinical characterization of GB3226 and its therapeutic application in AML

Figure 1. GB3226 is designed to disrupt key oncogenic/leukemogenic pathways in AML

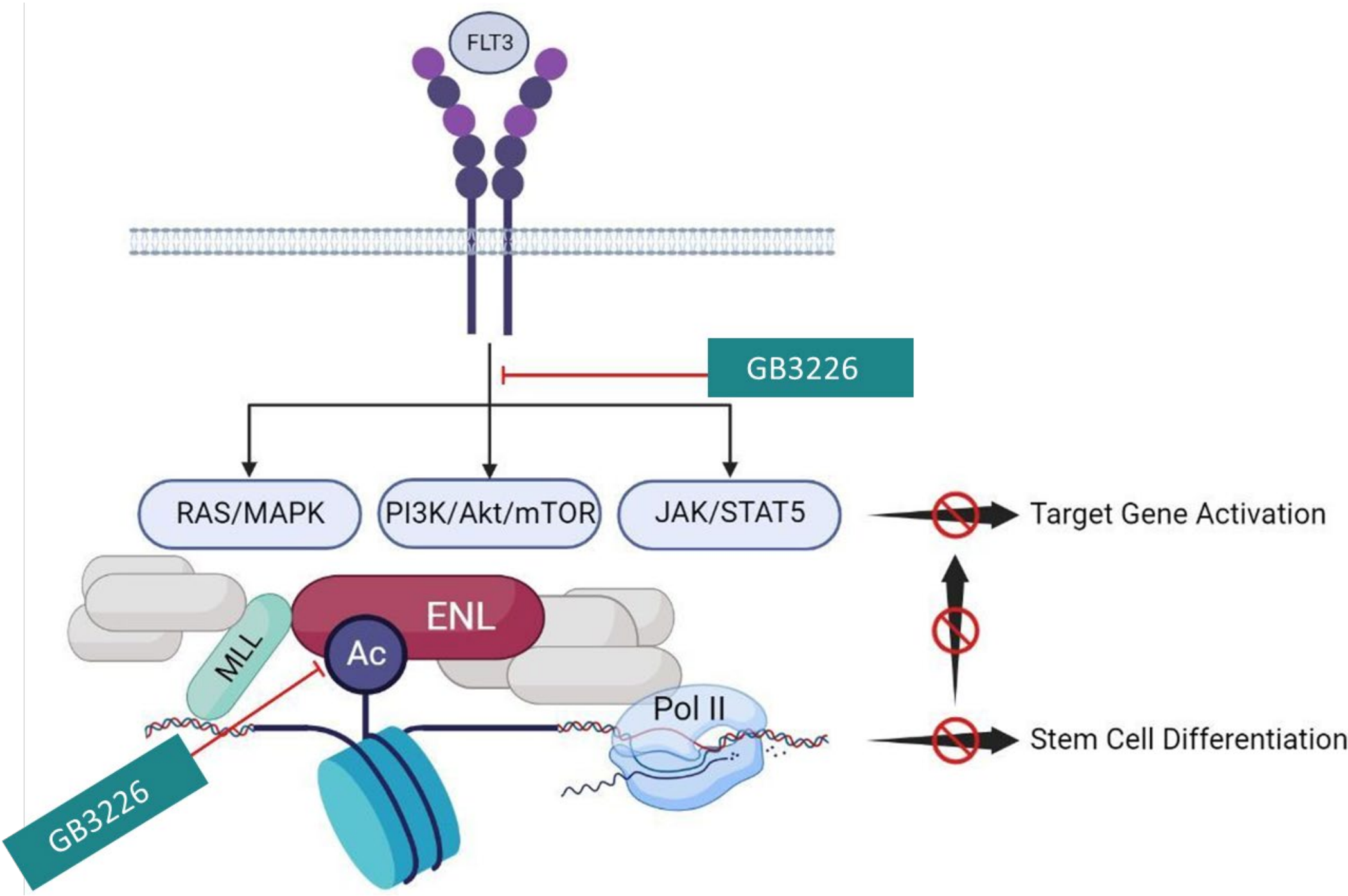


Figure 2. GB3226 is a potent dual inhibitor of ENL-YEATS and FLT3

ASSAY	GB3226 (μM)	TARGET	GB3226
ENL TR-FRET IC50	0.185		Kd (nM)
ITC Kd	0.271	FLT3	2.9
CETSA IP (MV4;11 Cells)	2.1	FLT3 (D835H)	21
FLT3 IC50	0.007	FLT3 (D835V)	3.9
MV4;11 Cells IC50	0.018	FLT3 (D835Y)	12
MOLM13 Cells IC50	0.032	FLT3 (ITD)	27
OCI-AML3 Cells IC50	0.60	FLT3 (ITD, D835V)	3.6
K562 Cells IC50	1.31	FLT3 (ITD,F691L)	>100

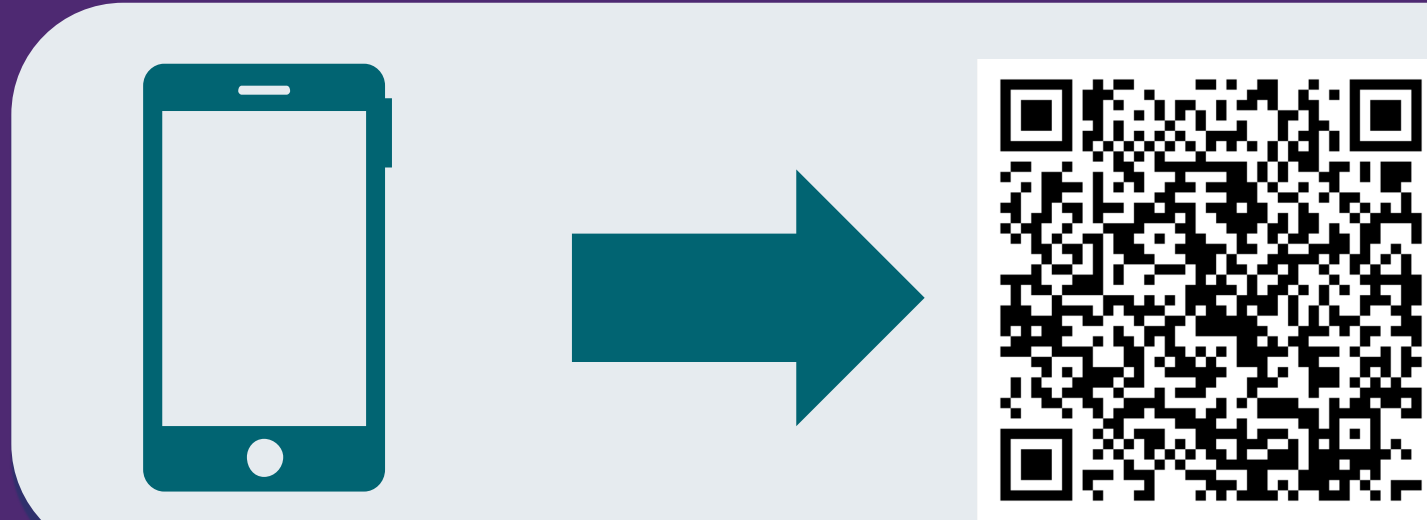
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Summary

- GB3226 is a novel, first-in-class, orally active, dual ENL-YEATS/FLT3 inhibitor
- Preclinical data presented here support the clinical development of GB3226 either as monotherapy or in combination with SoC and/or targeted therapies in AML
 - GB3226 had no effect on hERG channel activity (IC50>50 μM), exhibited no QTc prolongation in dog cardiovascular safety studies, and was well tolerated in pilot 14-day repeat-dose toxicology studies in rats and dogs (data not shown)
- Dual-targeting of ENL-YEATS and FLT3 has the potential to overcome resistance mechanisms seen with single-pathway agents (menin or FLT3 inhibitors) and enhance suppression of leukemic stemness
- A Phase I/Ib clinical study (ENLIGHT-AML, NCT07084584) is planned for 2026 with an IND filing in Q1, 2026. Please see poster # 1652 presented at this meeting



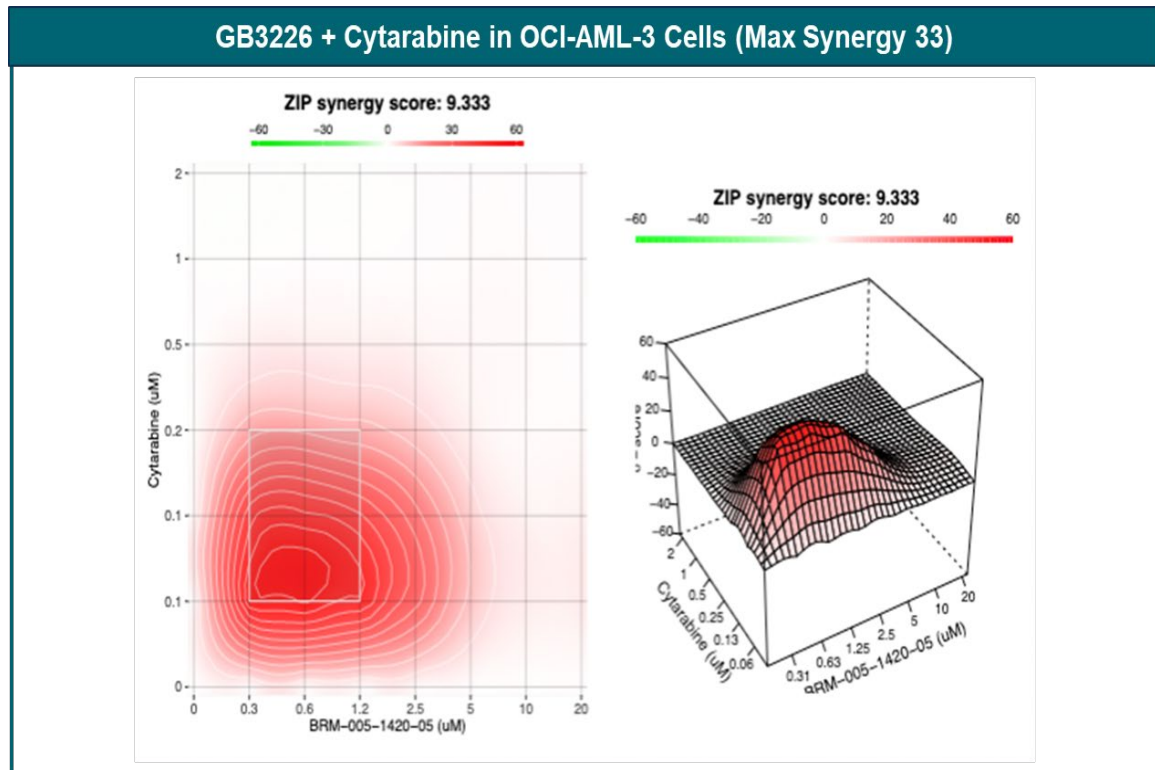
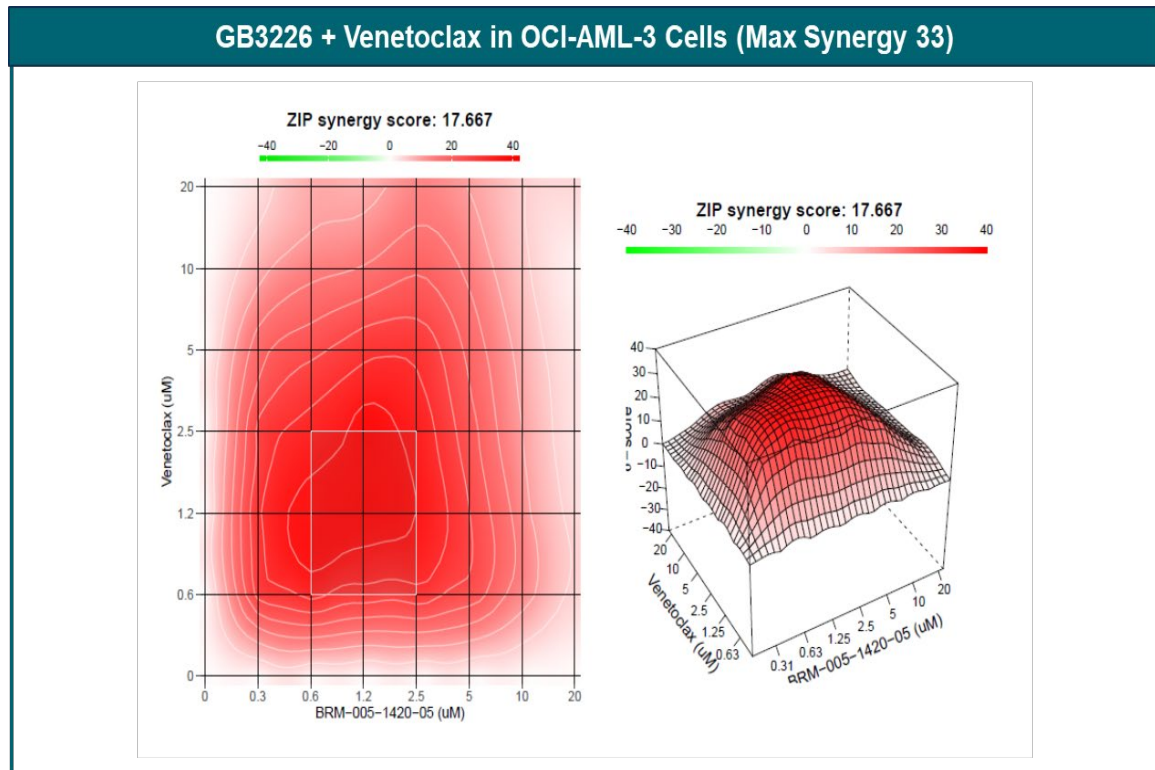
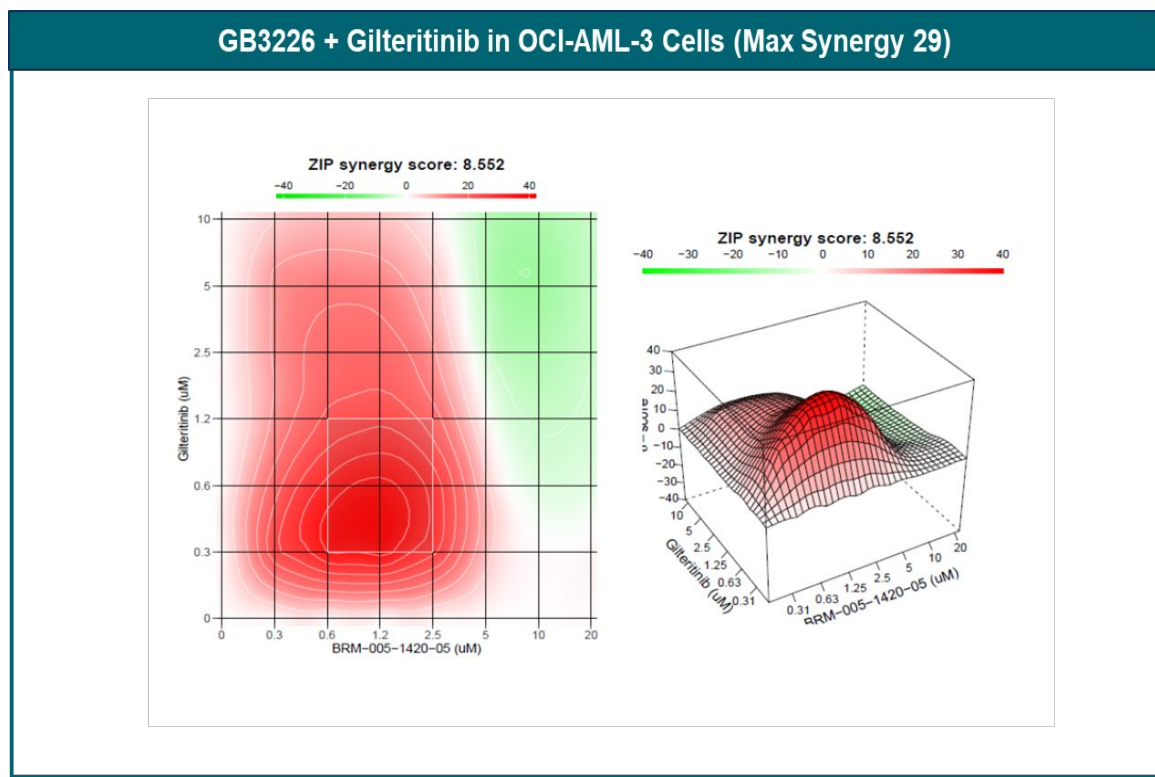
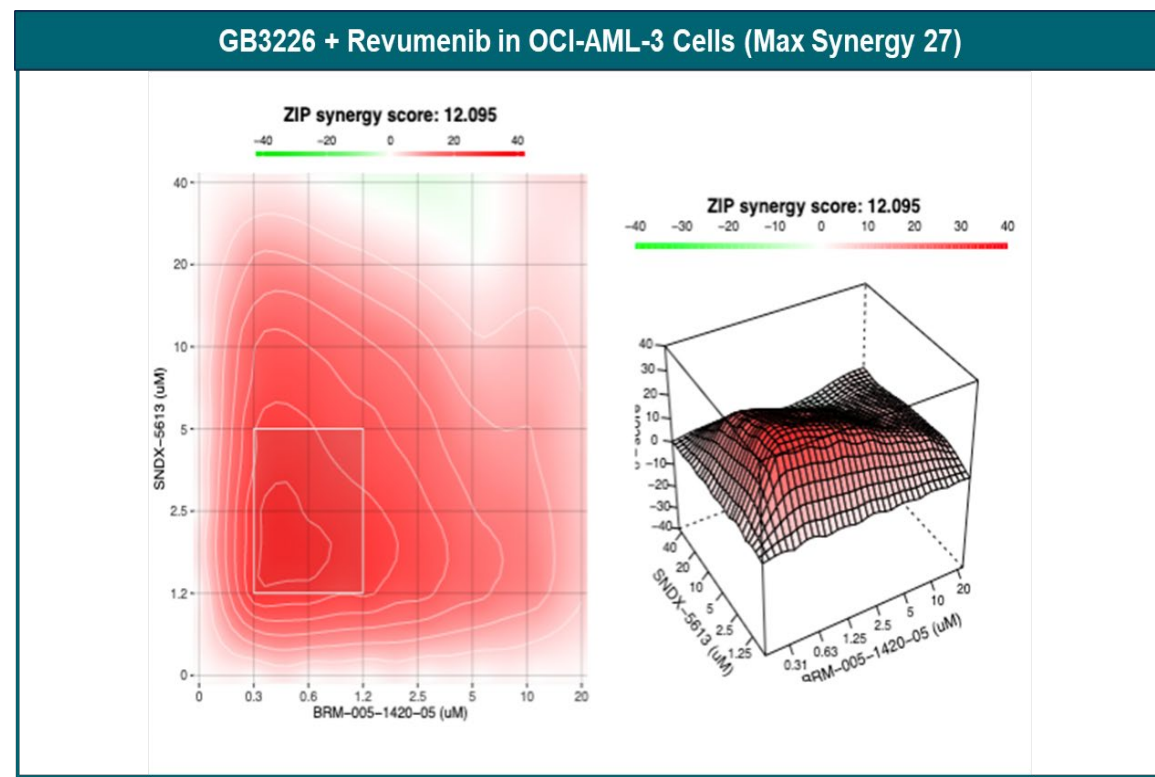
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Figure 3. GB3226 exhibits a good selectivity profile vs epigenetic and kinase targets

ASSAY	IC50 (μM)
Bromodomain Panel 36 bromodomains (10 μM final)	None
Kinase Panel (~370 Kinases)	52 > 70% Inh @ 10 μM
FLT3 IC50	0.007
FLT3 D835Y IC50	<.002
FLT3 D835Y / F691L IC50	13
CLK-1	0.05
CLK-4	0.08
IRAK	1.9
ARK5	1.0
c-Kit	0.04
MELK	0.06
TRKC	0.04

Figure 4. GB3226 is additive to synergistic in combination studies in AML cell lines

- Illustrative GB3226 synergy topography in OCI-AML-3 cells in 2D and 3D view. BRM-005-1420-05 = GB3226; SNDX-5613 = revumenib



- Summary of day 4-16 synergy values (ZIP score) of GB3226 in combination with cytarabine, gilteritinib, revumenib, and venetoclax in AML cell lines. ZIP score > 10, is indicative of **synergy**; -10 to 10, indicates additive activity; <-10, antagonistic

Cell Line	Combination	Synergy Value Day 4, 8, 12, 16	Max Synergy Day 4, 8, 12, 16
HL60	Cytarabine	9.5, 11.6, 7.3, 5.3	14.8, 24.50, 15.5
HL60	Gilteritinib	-6, 18.3, 7.7, 9.3	1.1, 39, 13.2, 1803
HL60	Revumenib	9.0, 9.0, 5.2, 4.5	13.9, 16.9, 14.8, 12.2
HL60	Venetoclax	-3.2, 4.6, 1.0, 1.9	-0.7, 7.6, 2, 4.0
MOLM-13	Gilteritinib	1.9, 3.8, 4.6, 3.6	4.3, 9.4, 9.0, 7.5
MOLM-13	Revumenib	2.4, 6.2, 6.7, 6.6	6.6, 12.9, 17.2, 19.0
MOLM-13	Venetoclax	2.7, 6.8, 5.4, 5.1	6.7, 13.3, 10.8, 15.1
MV4;11	Gilteritinib	7.0, 3.2, 3.4, 2.5	13.1, 6.2, 8.2, 10.1
MV4;11	Revunemib	6.4, 4.7, 9.6, 8.7	8.2, 13.3, 20, 23
MV4;11	Venetoclax	8.5, 8.1, 8.0, 7.0	17.3, 19.0, 19.2, 16.1
OCI-AML-3	Cytarabine	1.6, 8.4, 9.3, 2.5	5.5, 19.4, 33, 7.5
OCI-AML-3	Gilteritinib	0.6, 2.9, 8.9, 7.0	5.0, 10.4, 29, 23
OCI-AML-3	Revumenib	4.3, 19.5, 12.1, 6	6.5, 24.1, 27, 17
OCI-AML-3	Venetoclax	9.1, 9.2, 17.7, 10.2	20.3, 16.4, 33.5, 18

Figure 5. GB3226 inhibits proliferation of primary AML patient samples

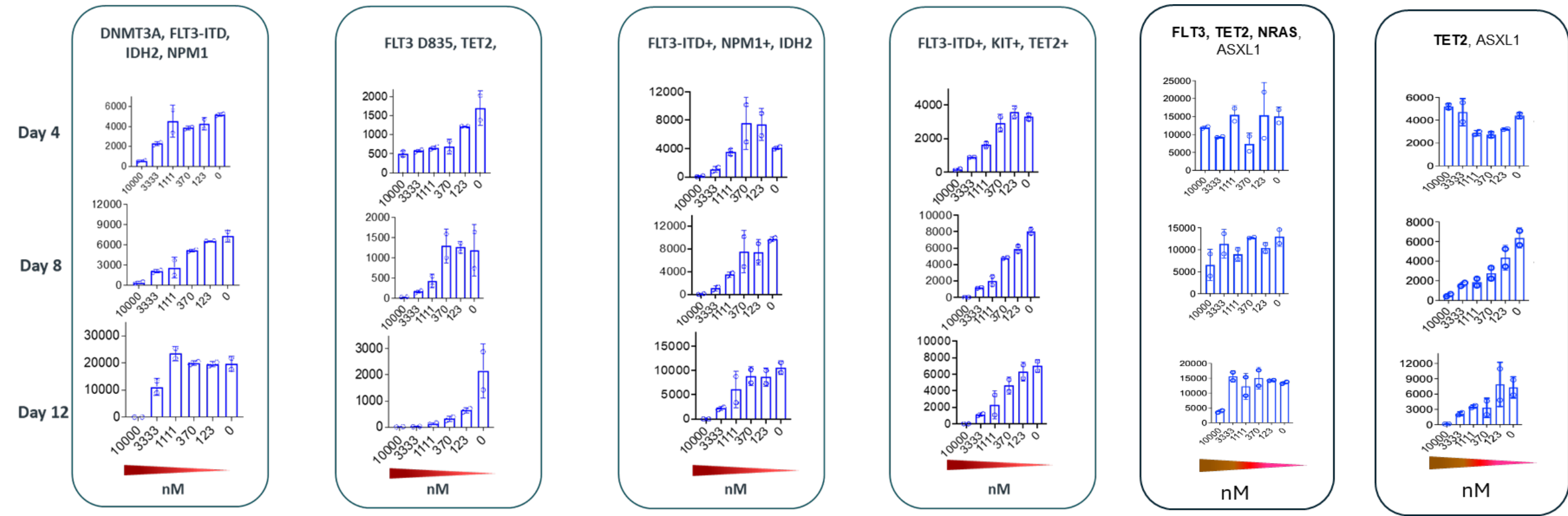
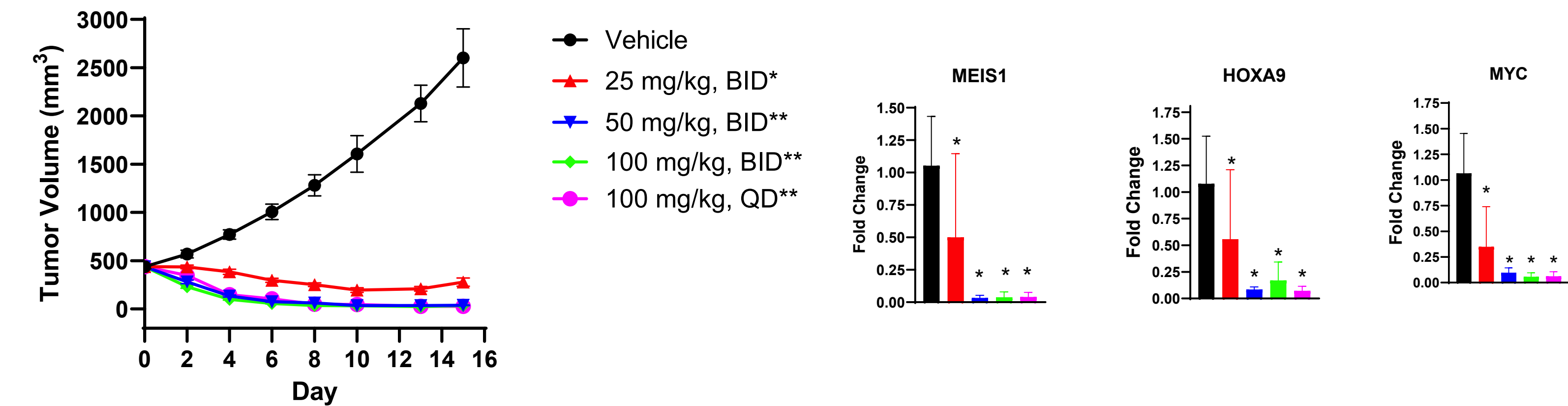
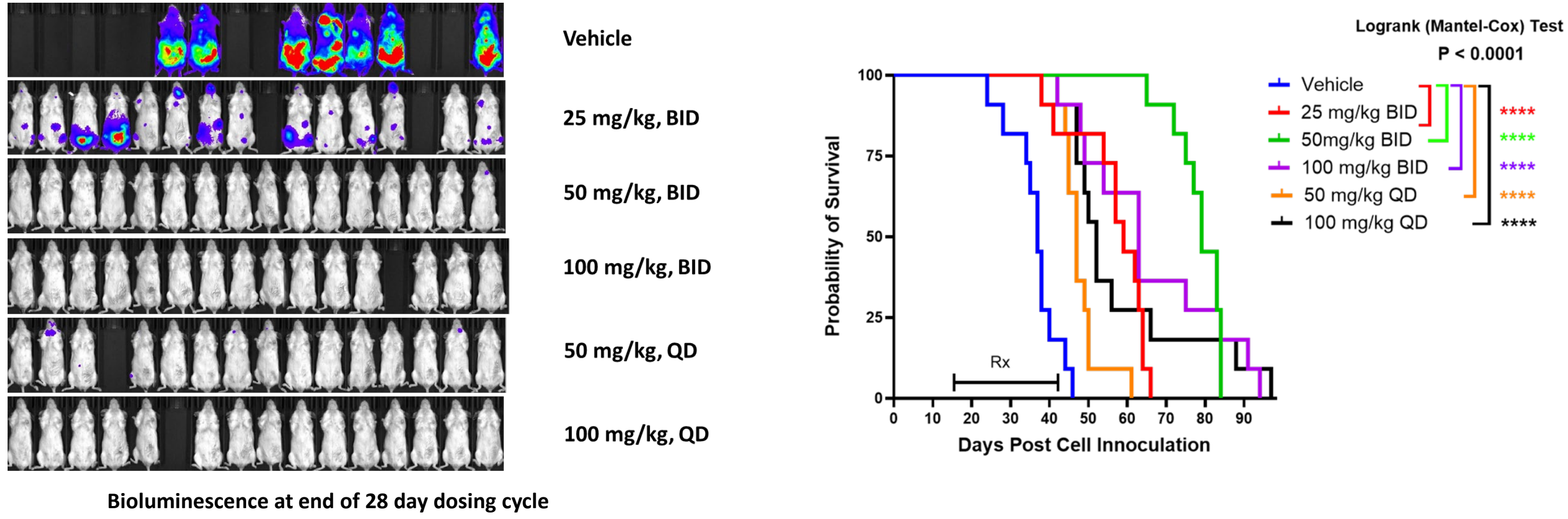


Figure 6. GB3226 suppresses tumor growth and MEIS1, HOXA9 and MYC in vivo



MV4;11 cells were implanted subcutaneously into the flank of Balb/c nude mice. Tumors were allowed to grow to ~500 mm³, mice were randomized into groups and then the groups dosed po, daily, for 14 days with either vehicle or GB3226. Mice were sacrificed on day 15 and biomarkers measured in tumor samples. *P < 0.05; **P < 0.01

Figure 7. GB3226 inhibits leukemia burden and prolongs survival in vivo



MV4;11-luc cells were injected, iv, into the tale vein of female NCG mice. After 14 days, the mice were randomized into groups and then the groups were dosed po, daily, for 28 days with either vehicle or GB3226. Tumor burden was assessed by bioluminescence signal (left) measured 1x week for 4 weeks. Survival (right) was monitored until the end of the study.

Acknowledgements

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