Backgrounder

BMF-219 in Oncology

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BMF-219 Preclinical and Clinical Results in Liquid Tumors

BMF-219: Enrolling Patients In Multiple Liquid Tumors – AML (COVALENT-101)

Development Stage: Phase I Clinical Trial (COVALENT-101) enrolling patients with relapsed/refractory acute leukemia

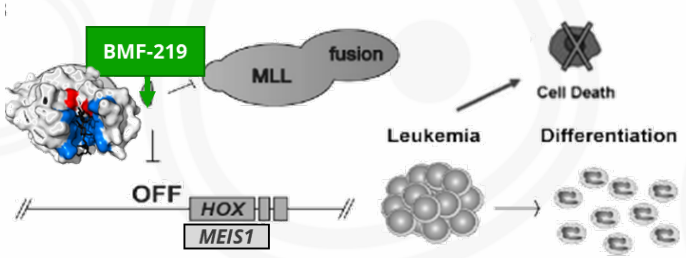
Key Facts

Estimated Target Population

Acute Leukemia (Mutation)	Estimated US Patient Population (Annual Incidence)
MLL-r	~2,500
NPM1 mutant	~7,500
Ras Driven	~6,500

MOA

BMF-219 covalently blocks menin / MLL interaction



- BMF-219 directly inhibits MLL-menin interaction and was optimized to cause cell killing, rather than cell differentiation.
- In preclinical studies, BMF-219 shows robust cell killing and reduction of expression of key genes (including MYC, MEIS1, HOXA9, and BCL2)

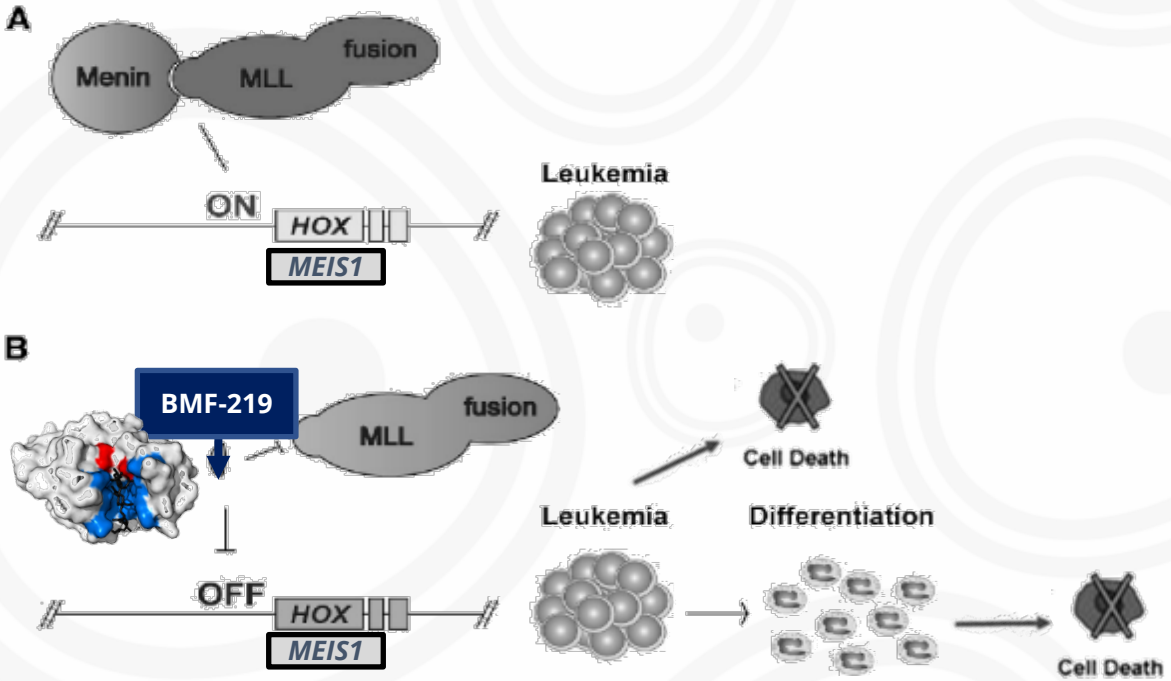
Relevant Pathway

Menin / MLL interaction can modify chromatin, activating key leukemic genes

Menin / MLL complex forms and modifies chromatin at histone H3, activating *HOXA9* and *MEIS1*

BMF-219 Shown to Inhibit a Complex Interaction Independent of the MLL Fusion Partner

Role of Menin-MLL Complex



Modified after Uckelmann (Scott Armstrong Lab) , ASH 2018, Abstract # 546

BMF-219 : a covalent inhibitor at the Menin-MLL interface

Menin-MLL Fusions

Different fusions result in different binding affinities between MLL fusion proteins and Menin

MLL Fusions (AML/ALL)	Prevalence (%)
AF4	**36%**
AF9	**19%**
ENL	**13%**
AF10	**8%**
ELL	**4%**
PTD	**4%**
…80+ additional fusions	**16%**

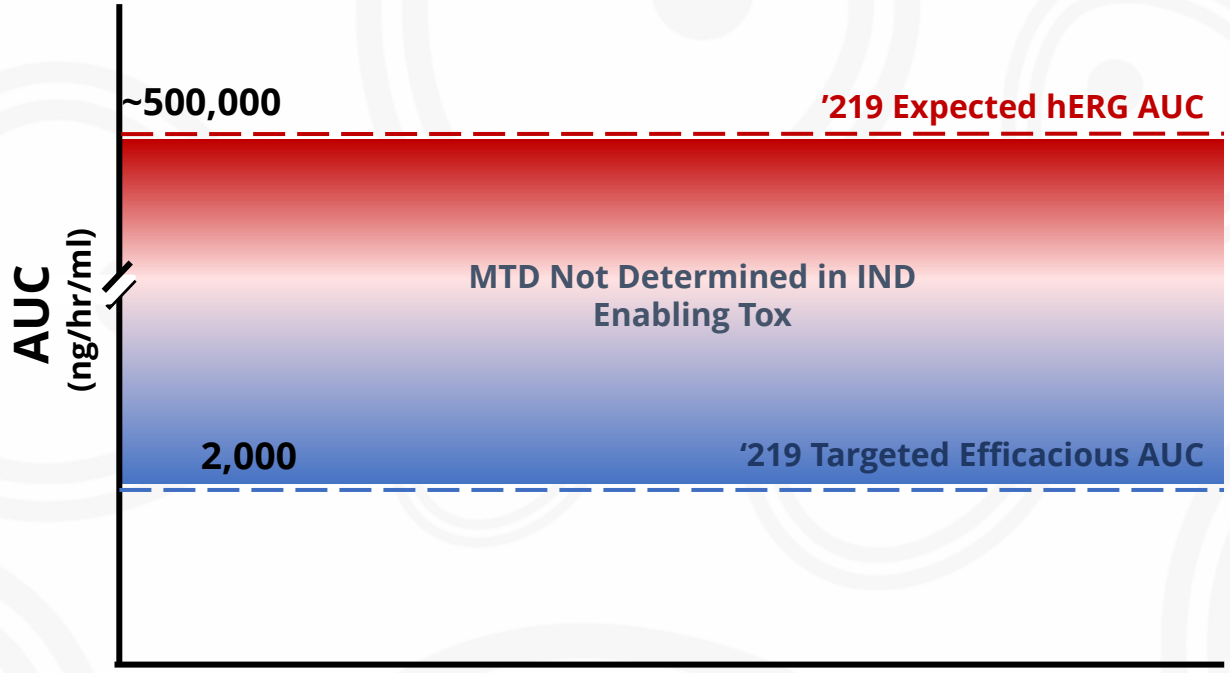
Source: Meyer, C. et al. (2017). The MLL recombinome of acute leukemias in 2017. Leukemia, 32(2), 273–284.

BMF-219- A Next Generation Covalent Targeted Agent in Oncology

BMF-219: A Molecule That Really Grabs You and Won't Let Go

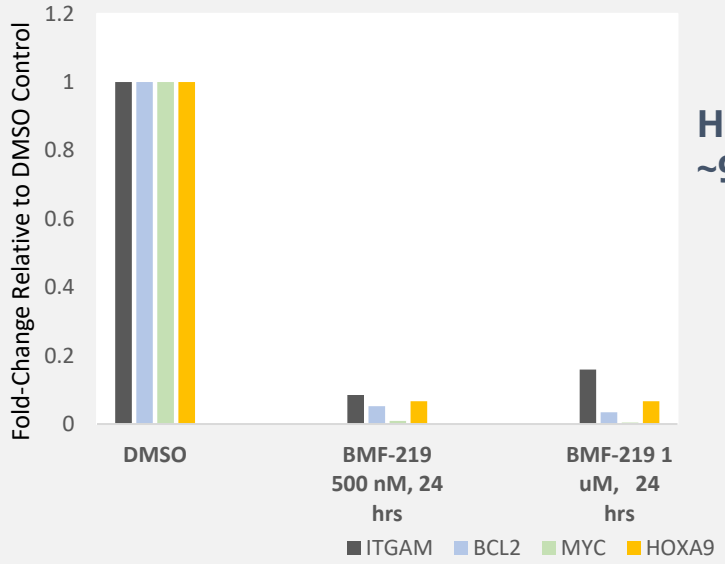
BMF-219 Properties	
Molecular Weight Approximately 500 kD	✓
Nanomolar Potency in Key Targeted Cell Lines:	
MLL-r	✓
NPM1 FLT3-ITD	✓
DLBCL MYC Driven Tumors	✓
MM	✓
KRAS Mutants (pan mutation)	✓
hERG inhibition ~5% at 10 µM	✓
Significant Downregulation of HOXA9, MEN1, and MYC	✓
No Histopath Findings in IND Enabling Tox Studies	

Predicted Efficacious Human AUC for BMF-219



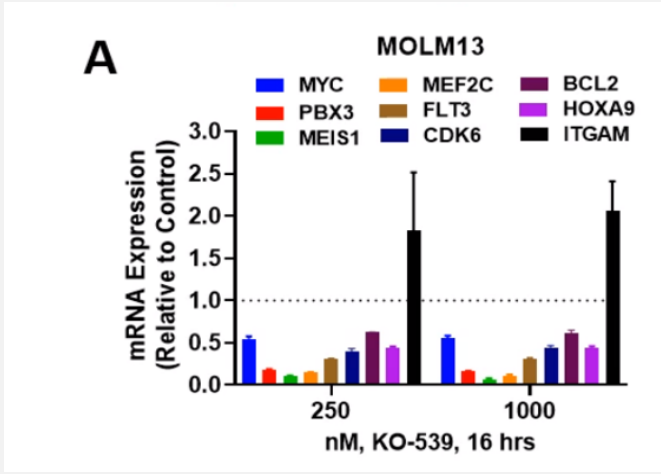
BMF-219 Increases Differentiation Followed by Induction of Cell Death in MLL-Rearranged AML Cell Line

Relative Gene Expression (MOLM-13) – BMF-219



HOXA9: ~90% Reduction

Relative Gene Expression – Clinical Reversible Inhibitor

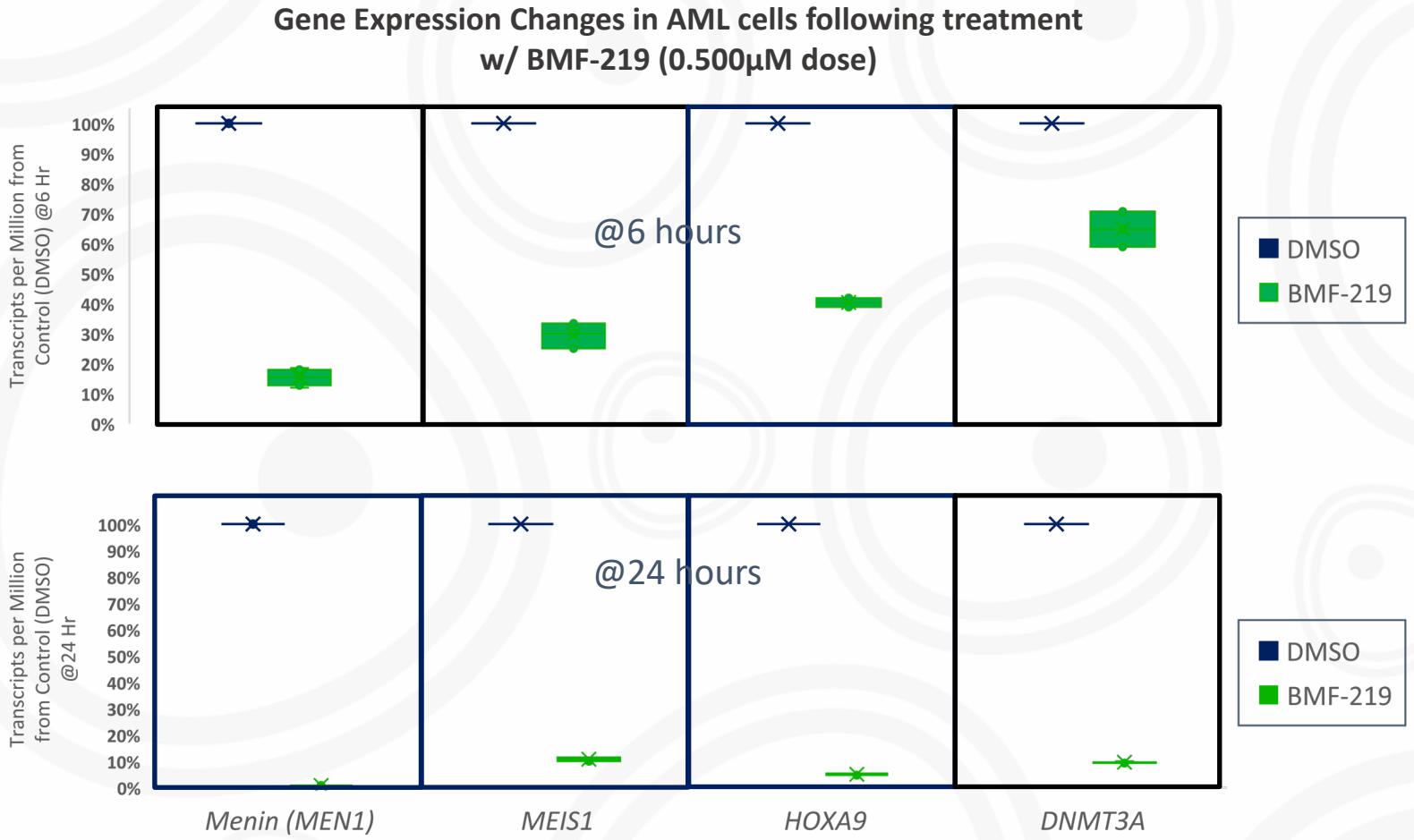


HOXA9: ~50% Reduction

***Blood* (2021) 138 (Supplement 1): 3357.**

- Differentiation marker, ITGAM, expression increases 2-3 fold at 6 hrs post- BMF-219 treatment, followed by a decrease at 24 hrs
- Anti-apoptotic marker, BCL2, remains largely unaltered at 6 hrs post-treatment with BMF-219, and is reduced by ~20 to 30-fold at 24 hrs post-treatment with BMF-219
- HOXA9 expression is reduced by ~15-fold at 24 hrs post treatment with BMF-219
- MYC expression is reduced ~100-200 fold at 6 hrs and 24 hrs post-treatment with BMF-219

BMF-219 Demonstrated Rapid and Pronounced Reduction of Oncogene Expression



(Transcripts per Million is a measure of gene expression)

- Covalent inhibitor, BMF-219, downregulated expression of Menin (via the target *MEN1* gene) and critical leukemogenic genes (e.g., *MEIS1* and *HOXA9*)
  - *MEIS1* is a gene that can be an accelerator of leukemic transformation (along with *HOXA9*)
  - *HOXA9* is a gene involved in myeloid differentiation and can be leukemogenic
  - *DNMT3A* is a gene that codes for a methyltransferase, which can be leukemogenic when mutated
- BMF-219 demonstrated up to 80% reduction in readout genes by 6 hours and approximately 90%+ reduction at 24 hours

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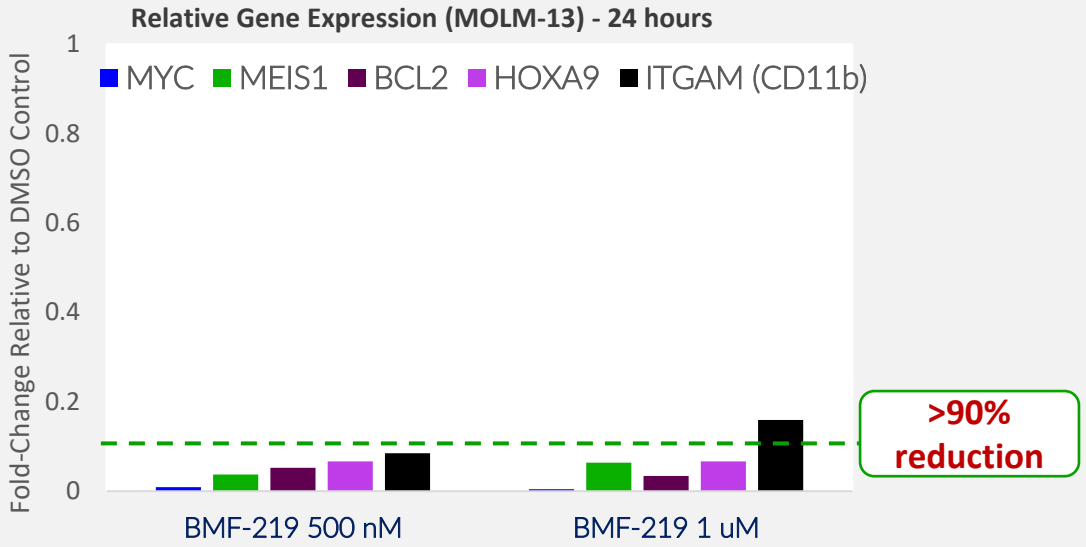
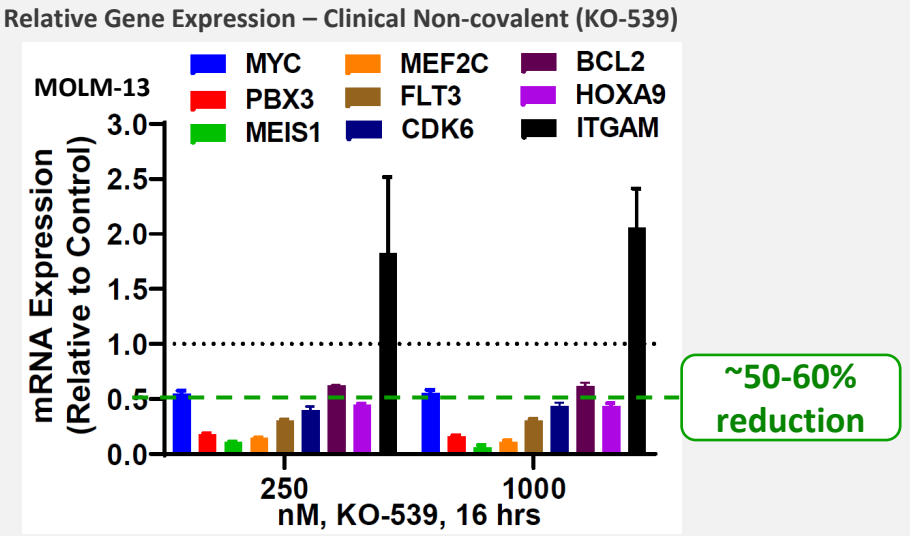
First Development Success with BMF-219 in MLL Fusion and NPM1 Driven Tumors

BMF-219 Displayed Superior Impact on Key Gene Signatures in MLL-Rearranged AML Cell Line



Somanath et al., ASCO 2022 Abstract 7541

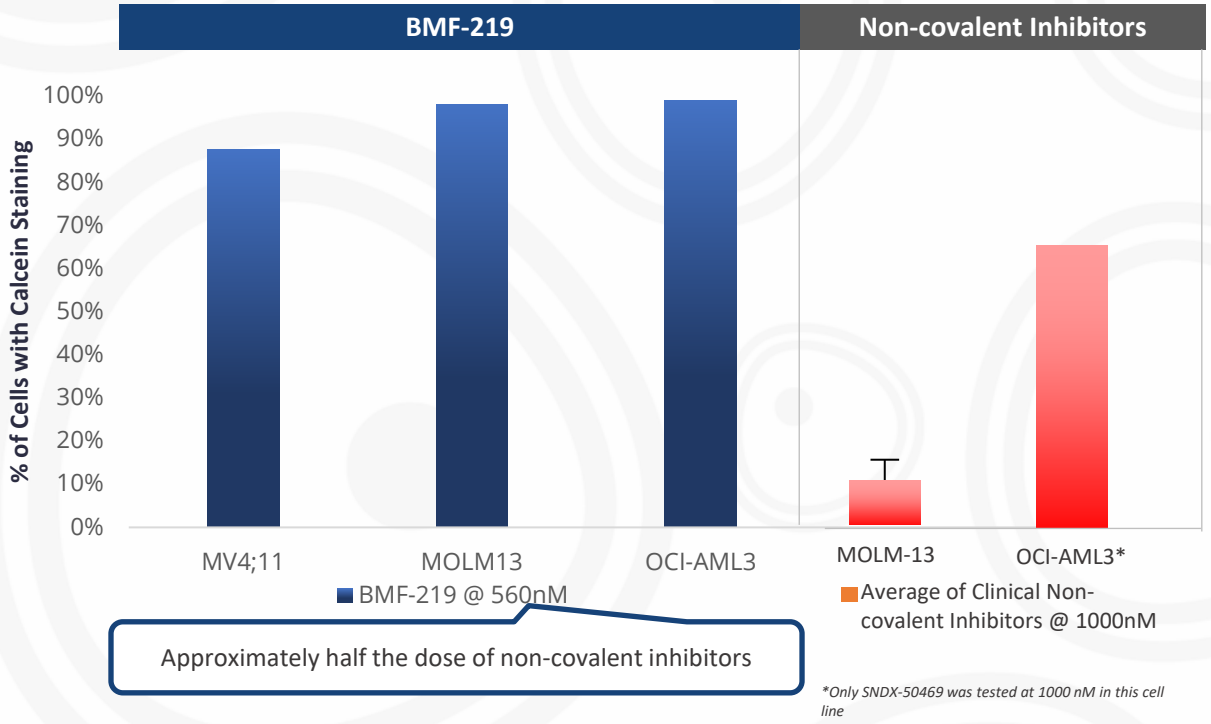


Blood (2021) 138 (Supplement 1): 3357

- Differentiation marker, *ITGAM (CD11b)*, expression increases 2 to 3-fold at 6 hours, followed by ***~8 to 10-fold*** reduction at 24 hours with BMF-219
- *MEIS1* expression is reduced ***~10 to 20-fold*** at 24 hrs with BMF-219
- *HOXA9* expression decreases ***~15-fold*** at 24 hrs with BMF-219
- *BCL2* expression decreases ***~20 to 30-fold*** at 24 hrs post-treatment with BMF-219
- *MYC* expression is reduced ***~100 to 200-fold*** at both 6 and 24 hrs post-treatment with BMF-219

First Development Success with BMF-219 in MLL Fusion and NPM1 Driven Tumors

BMF-219 Superior Cell Killing of the Target AML Cell Lines at Half the Dose vs Reversible Competitive Menin Inhibitors



*Only SNDX-50469 was tested at 1000 nM in this cell line

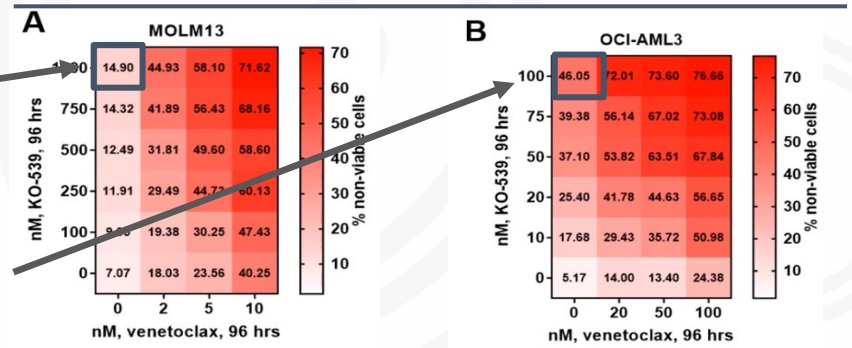
- BMF-219 **killed >90% of AML cells** in MLL-rearranged and NPM1 mutant cell lines at 4 days post-treatment
- Non-covalent menin inhibitors generally report significantly less cell killing of AML cell lines as a single agent

Source Data from ASH 2021 Publications

KO-539 is 15% effective @ 1000nM in MOLM-13 cells and 46% effective @ 1 100nM in OCI-AML3 cells

15% effective @ 1000nM

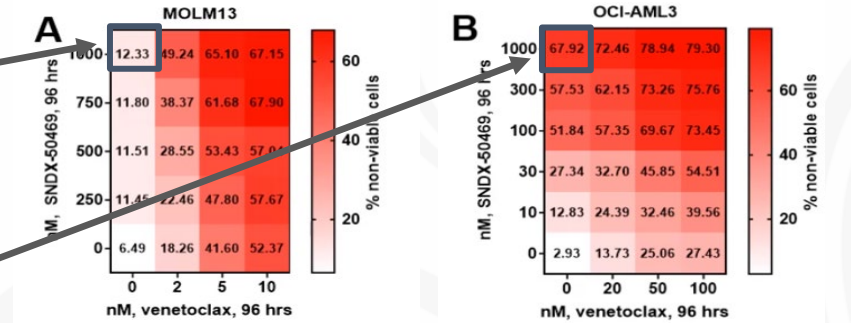
46% effective @ 100nM



SNDX-50469 is 12% effective @ 1000nM in MOLM-13 cells And 68% effective @ 1000nM in OCI-AML3 cells

12% effective @ 1000nM

68% effective @ 1000nM



Blood (2021) 138 (Supplement 1): 3340., ASH 2021.

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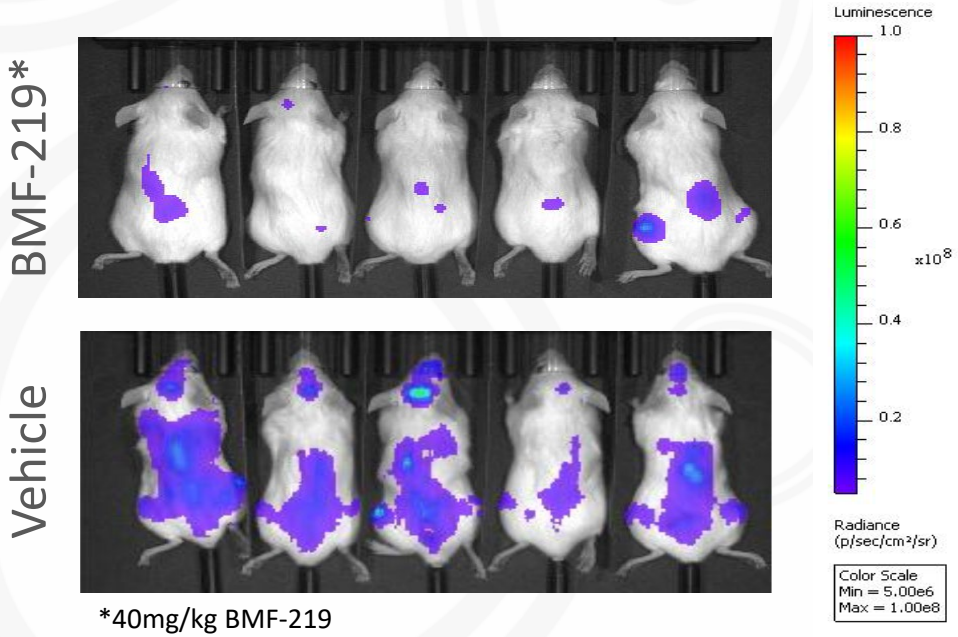
First Development Success with BMF-219 in MLL Fusion and NPM1 Driven Tumors

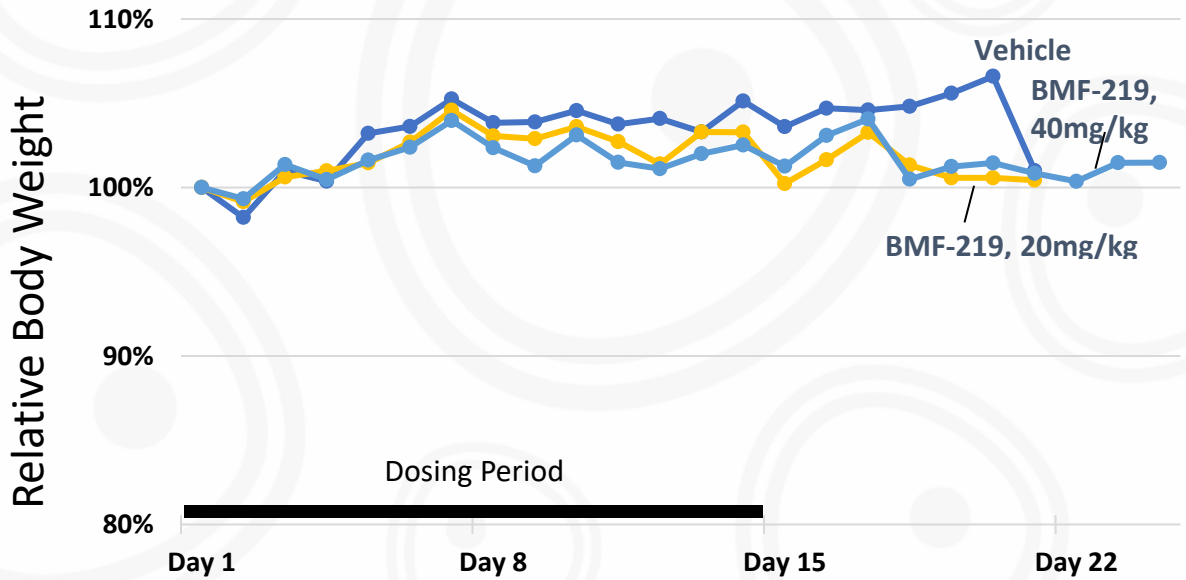
BMF-219 Achieved Significant Survival Benefit in A Disseminated Leukemia Xenograft Model

Anti-Tumor Effect



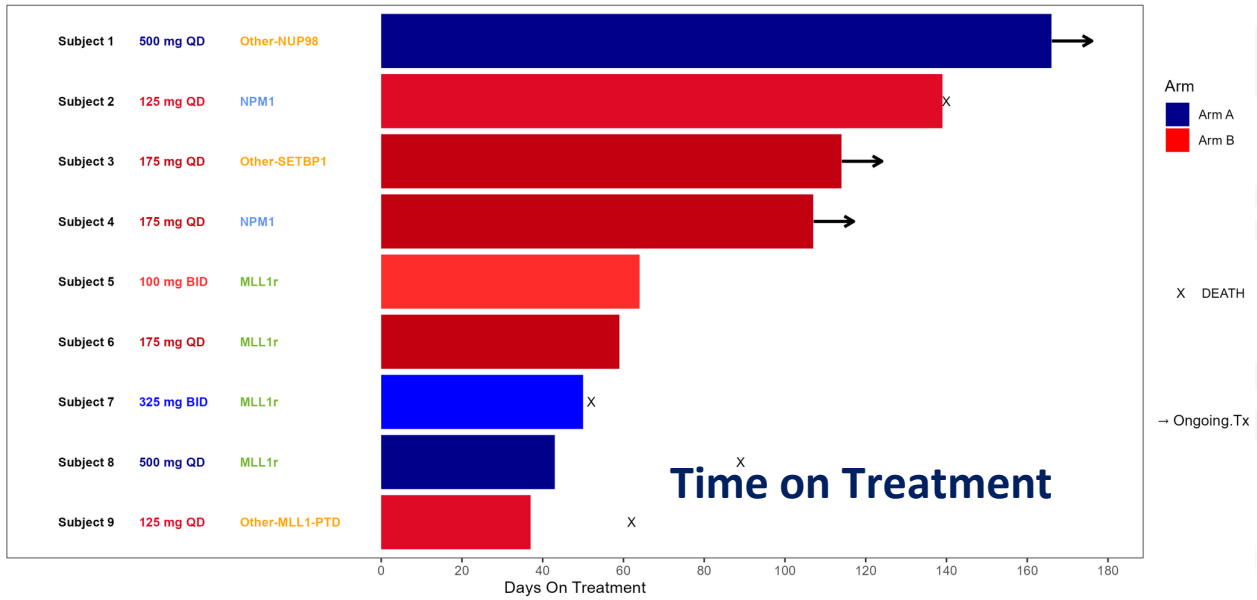
*40mg/kg BMF-219

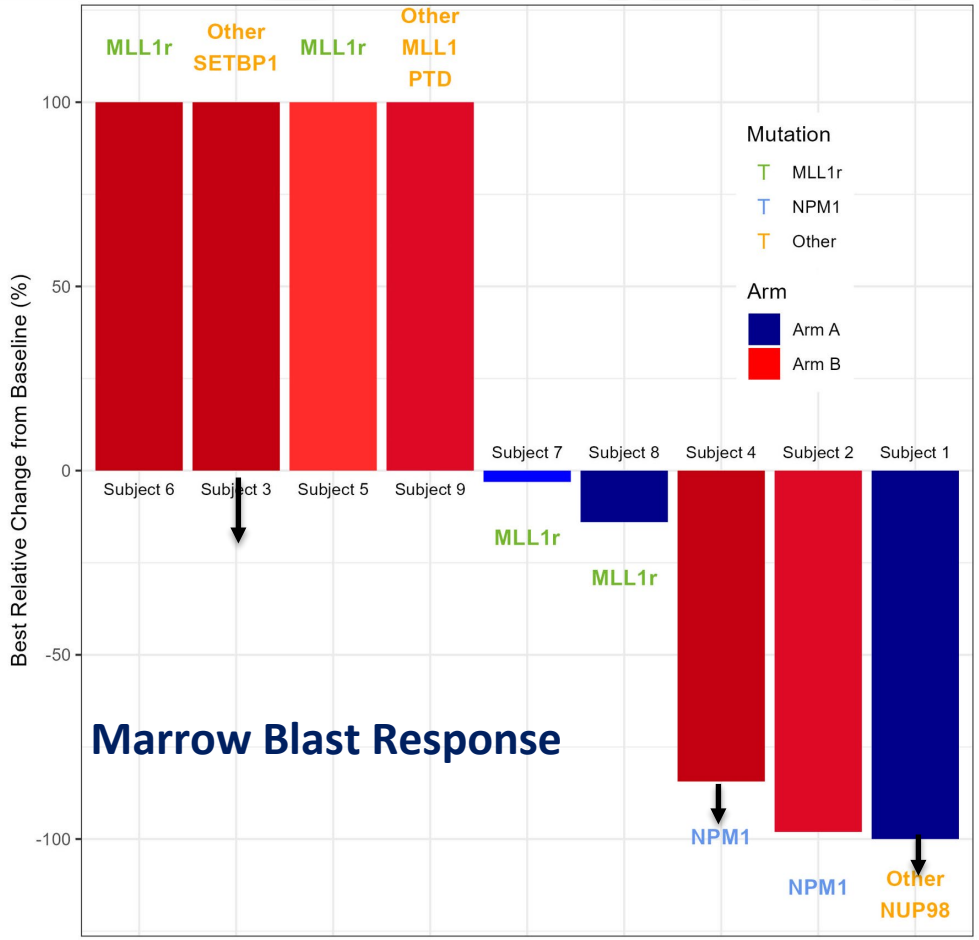
Body Weight



- Mice were inoculated with xenograft cancer cells at high levels ($1x10^7$ MV4;11-luc) with greater than 90% viability
- BMF-219 treatment showed notable reduction in tumor burden and **survival benefit over vehicle control (72% at 20mg/kg and 94% at 40mg/kg)**
- Daily dosing for 14 days was well-tolerated and caused **minimal body weight changes**

Early Signs of Clinical Efficacy Was Shown in AML Patients Treated with BMF-219





- Efficacy evaluable population is defined as DLT-evaluable patients with AML bearing mutation(s) believed to be menin-inhibitor sensitive who received treatment with BMF-219 at ≥500 mg QD (Arm A) or ≥125 mg QD (Arm B)
- Data cutoff included all patients who initiated treatment on or before 06 Sep 2023; responses assessed as per PI using ELN2017 criteria.

- For patients who received at least 2 cycles of therapy: CR/CRi rate = 2/7 (29%); mean time to response = 1.8 months; minimal residual disease negativity achieved in the first CR
- Duration of treatment (months): mean 2.84 (range: 1.2 - 5.5) ; 3/9 (33%) patients continued treatment as of cutoff date of 31 Oct2023
- BMF-219 was generally well-tolerated with no dose-limiting toxicities observed and without treatment discontinuations due to toxicity.

BM blast response for efficacy-evaluable patients (n=9), as described above patients with best relative change from baseline >100% are trimmed

BMF-219 - MYC Dysregulation is Believed to Play an Important Role in Multiple Tumors:

Diffuse Large B-cell Lymphoma (DLBCL), Multiple Myeloma (MM) and Chronic Lymphocytic Leukemia (CLL)

Development Stage: Phase I Clinical Trial (COVALENT-101) enrolling patients with relapsed/refractory DLBCL, MM and CLL

Key Facts

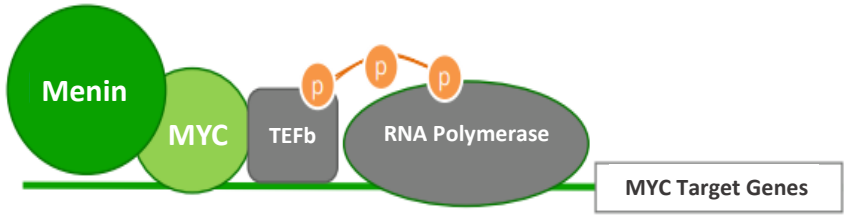
Estimated Addressable Population

Disease (r/r with MYC Implication)	Estimated US Patient Population (Annual Incidence)
DLBCL	~6,500
MM	~9,500
CLL	~8,000

- MYC addiction tends to increase with stage and line of therapy
- ~20-50% MYC dysregulation or translocations in newly diagnosed MM patients
- ~50-70% of advanced r/r MM patients have MYC dysregulation
- ~10,000 (40%) of DLBCL patients are Double and Triple Hit and Double expressors (BCL2 and MYC overexpression)
- >50% of relapsed/refractory DLBCL are double expressors

Proposed MOA

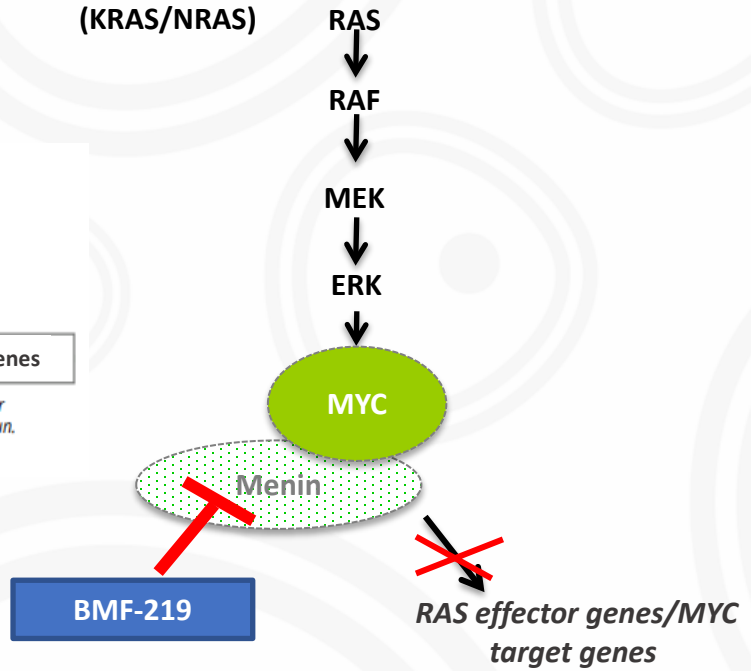
Menin complexes with MYC in the expression of MYC target genes. BMF-219 robustly decreases MYC gene expression and genomic function.
(Blood (2021) 138 (Supplement 1): 4318.)



Source: *Madden et al., Molecular Cancer volume 20, Article number: 3 (2021); Martínez-Martín et al. Cancer Drug Resist 2021;4:842-65; Xia Y. et al., Acta Haematol 2020;143:520–528; Zhu L., et al. (2017).. Nat. Commun. 8, 15278.; Musti et al., Oncogene . 2002 Sep 19;21(42):6434-45.*

Relevant Pathway

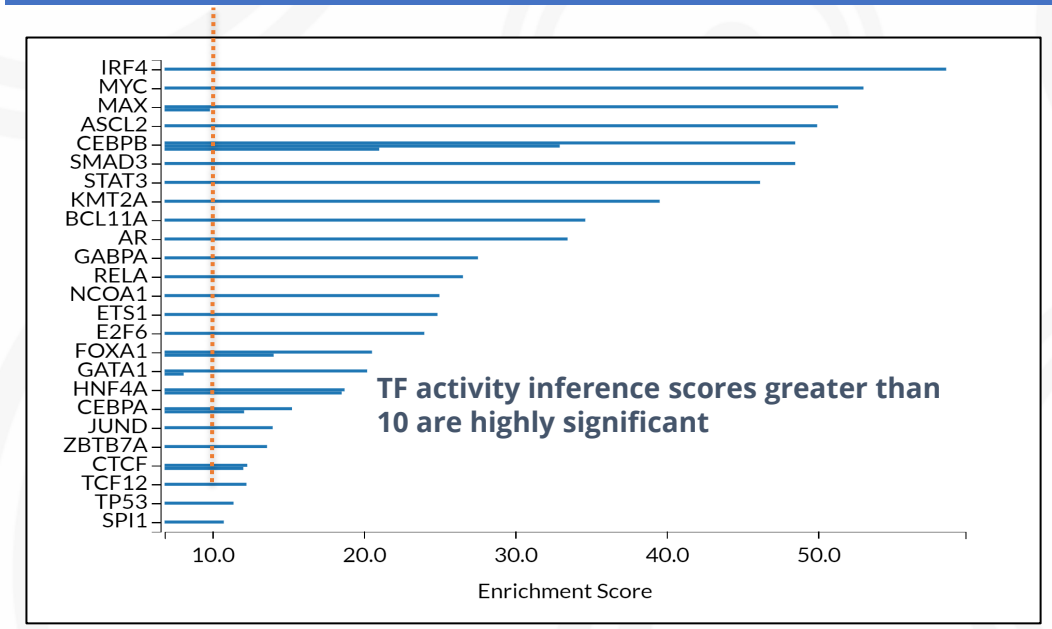
Tumor leverages MAPK pathway



Xia et al.. 2020;143(6):520-528. doi: 10.1159/000505892. Epub 2020 Feb 19
Crump et al. Blood (2017) 130 (16): 1800–1808. doi.org/10.1182/blood-2017-03-769620

BMF-219 Disrupts Multiple Binding Partners of Menin, including MYC, MLL, and JUND

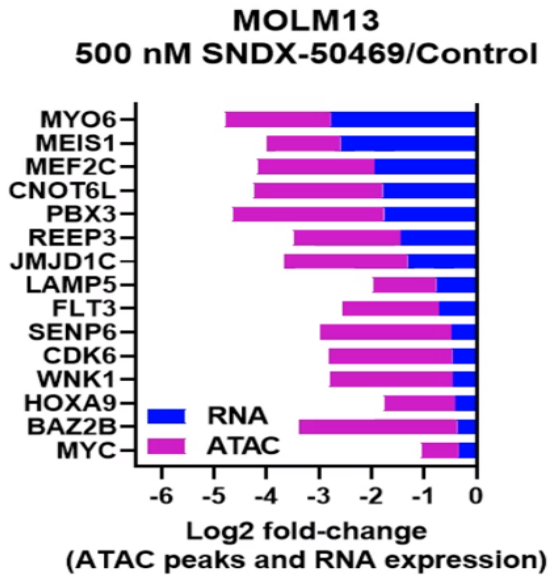
Covalent Menin Inhibitor – BMF-219



TF activity inference using ChIP-seq of differentially expressed genes in MOLM-13 cells incubated with 500 nM BMF-219 at 24 hours. Each bar represents a study in the GEO repository using the specified TF antibody.

- **In MOLM-13 cells treated with BMF-219, the top transcription factors regulating gene expression are MYC and MAX**
- IRF4, MYC, and MAX are known drivers for some forms of DLBCL, (addicted) multiple myeloma, and multiple additional tumors

Non-Covalent Menin Inhibitor – SNDX-50469



Blood **(2021) 138 (Supplement 1): 3340.**

- **Significantly less impact on *MYC* expression** (2x fold) and genomic function by clinical non-covalent menin inhibitor
- In contrast, **BMF-219 treatment led to a ~100-200x reduction in *MYC*** expression at 24 hours

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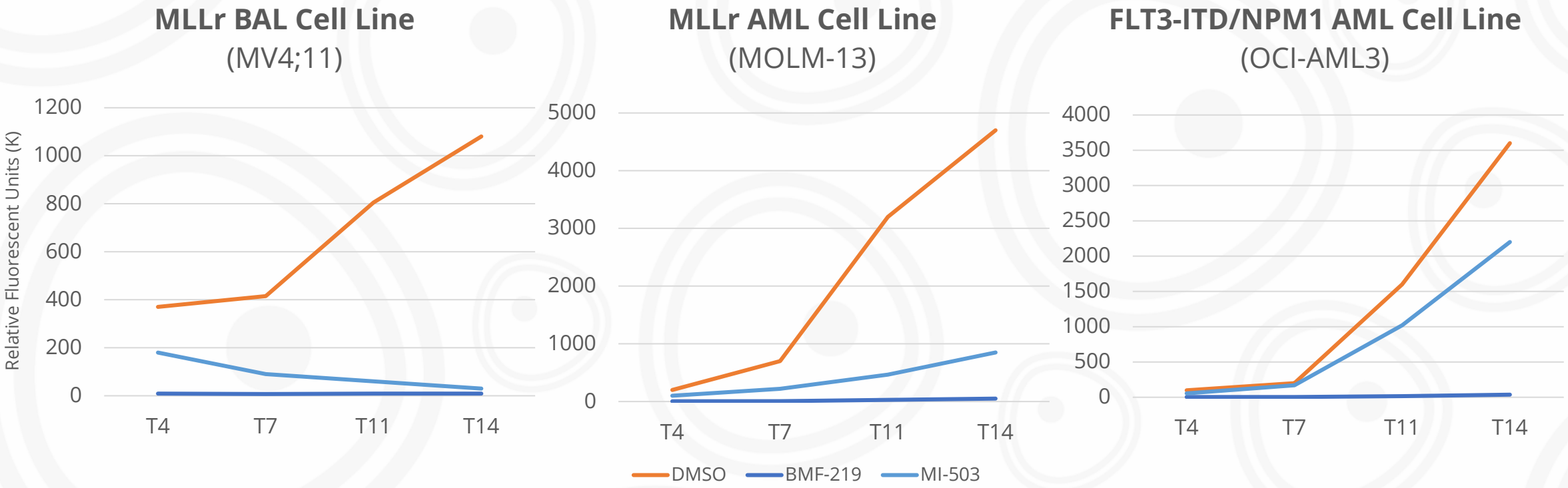
BMF-219 Shows Strong Cell-Growth Inhibition Across Menin Dependent Cell Lines

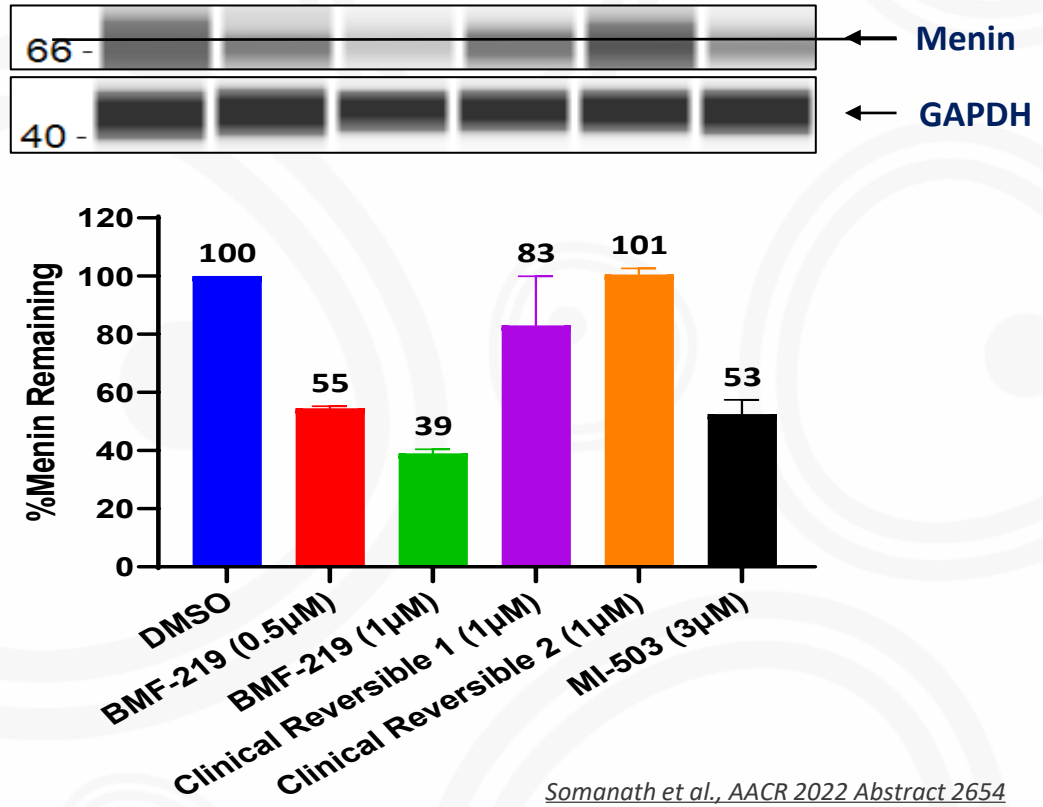


- BMF-219 demonstrated rapid shut down of metabolic activity, sustained over the 14-day study duration
- BMF-219 responses were superior to a tested reversible menin inhibitor (MI-503) with respect to both onset and durability of metabolic suppression

BMF-219 Significantly Reduced Menin Protein in DLBCL Cell Line

Menin Protein Levels in BMF-219 Toledo (DLBCL- DHL) Cell Line

14 hours



Somanath et al., AACR 2022 Abstract 2654

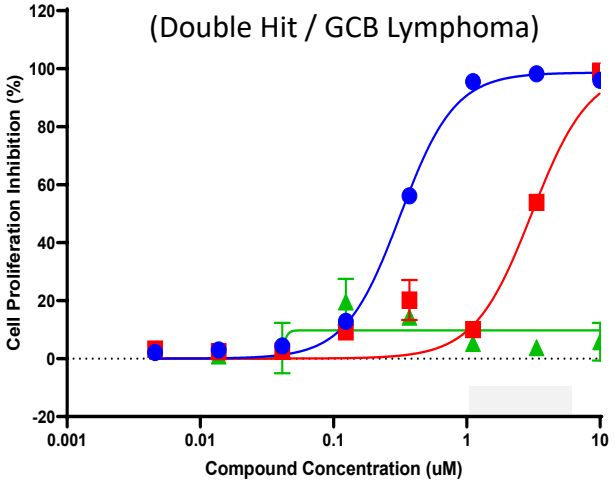
- Covalent inhibitor, BMF-219, at 1µm concentration achieves >60% reduction of menin protein at 14hrs
- Clinical reversible (non-covalent) inhibitors of menin achieved less than 20% reduction of menin protein at the same concentration

BMF-219 Led to Near Complete Inhibition of Growth at 1µM in DLBCL Cell Lines

BMF-219 Growth Inhibition in DLBCL Cell Lines, ASH 2021

DB

(Double Hit / GCB Lymphoma)

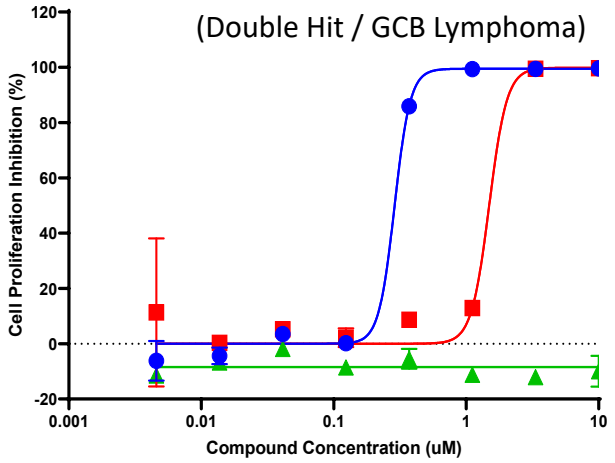


	IC50 (µM)	%Max
BMF-219	0.316	98.64
Clinical Non-covalent Inhibitor-1	3.07	100
Clinical Non-covalent Inhibitor-2	No Resp.	9.7

DB and Toledo cells were incubated with compounds for 4 days

TOLEDO

(Double Hit / GCB Lymphoma)



	IC50 (µM)	%Max
BMF-219	0.2877	99.47
Clinical Non-covalent Inhibitor-1	1.49	99.84
Clinical Non-covalent Inhibitor-2	No Resp.	-8.4

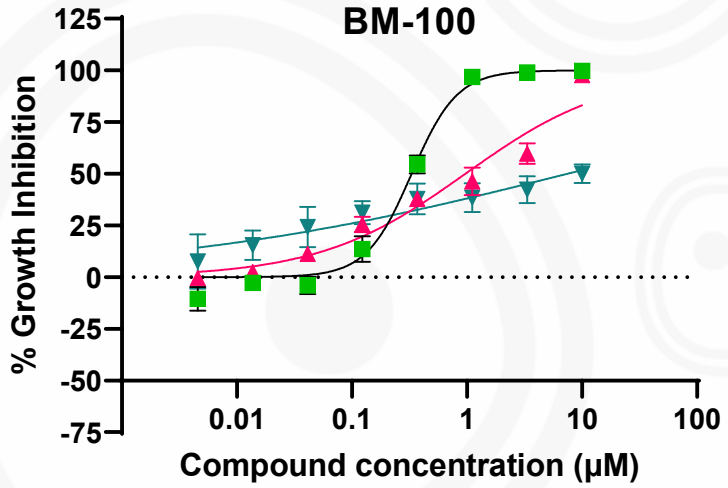
Source: Blood (2021) 138 (Supplement 1): 4318. ASH, 2021.

- Covalent menin inhibition by BMF-219 led to marked growth inhibition in multiple DLBCL cell lines
- We believe this is due to disruption of Menin-MYC
- One of the clinical stage non-covalent menin inhibitors tested displayed activity, but at 5-10x higher concentration
- The other clinical non-covalent inhibitor did not achieve IC50 in the tested cell lines at any concentration tested

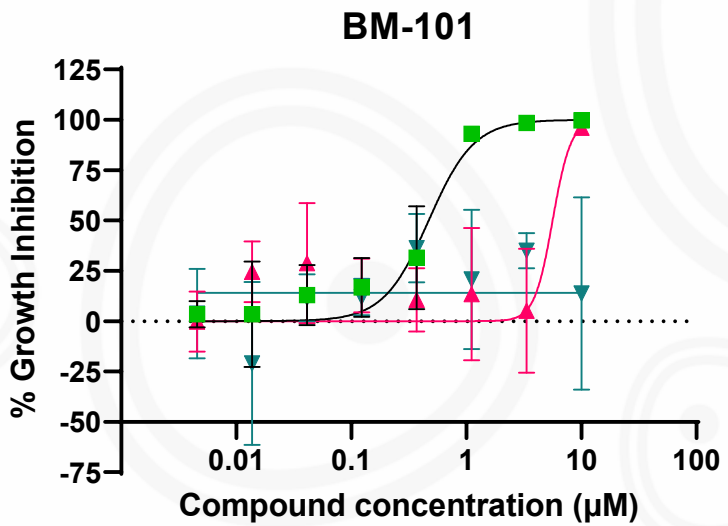
Cell Lines	Cell Type	Translocations
DB	GCB-DLBCL	MYC/BCL2
TOLEDO	GCB-DLBCL	MYC/BCL2

BMF-219 Produced Near Complete Inhibition of Growth at 1µM in DLBCL ex-vivo Samples

THL - Responded, then progressed on R-EPOCH



MYC Amplified DLBCL - Responded, then progressed on R-CHOP

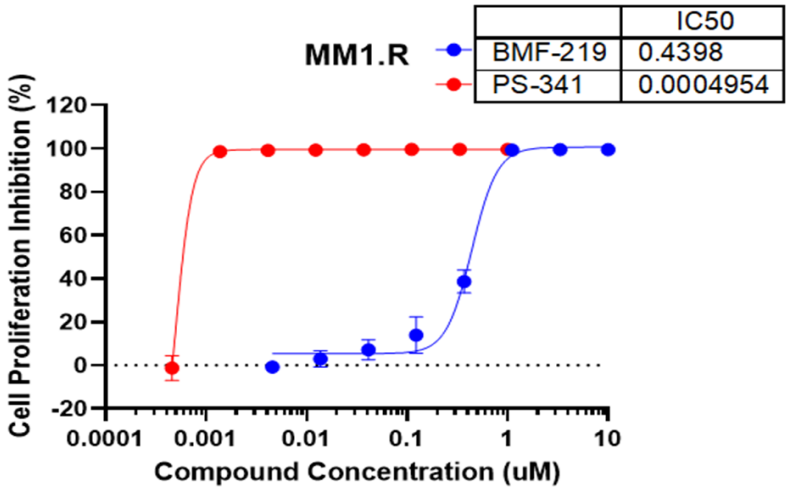


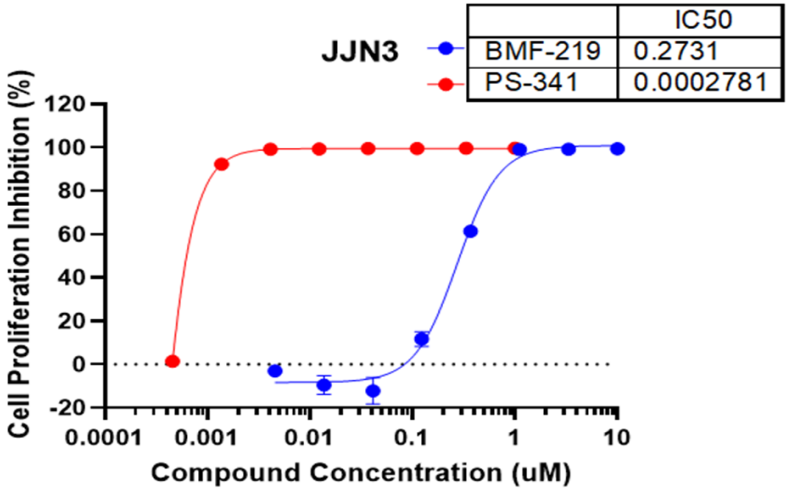
BMF-219 Clinical Reversible 1 Clinical Reversible 2

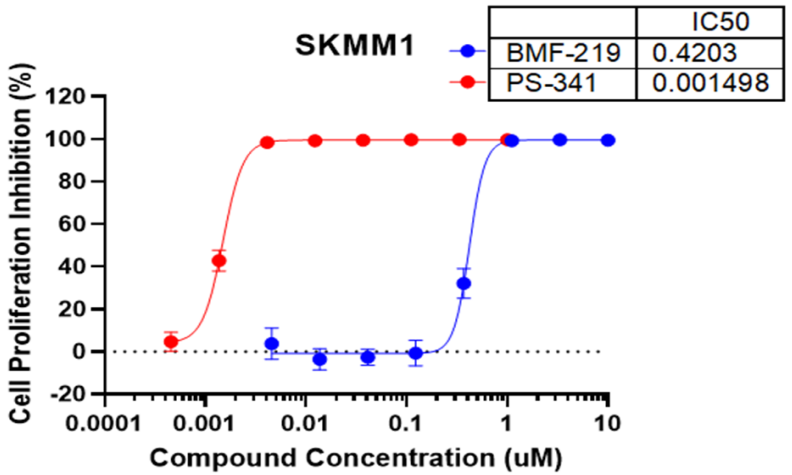
	Growth Inhibition IC_{50} (µM)	
Treatment	BM100	BM101
BMF-219	0.250	0.151
Clinical Reversible-1	0.969	5.63
Clinical Reversible-2	6.31	Max killing <30%

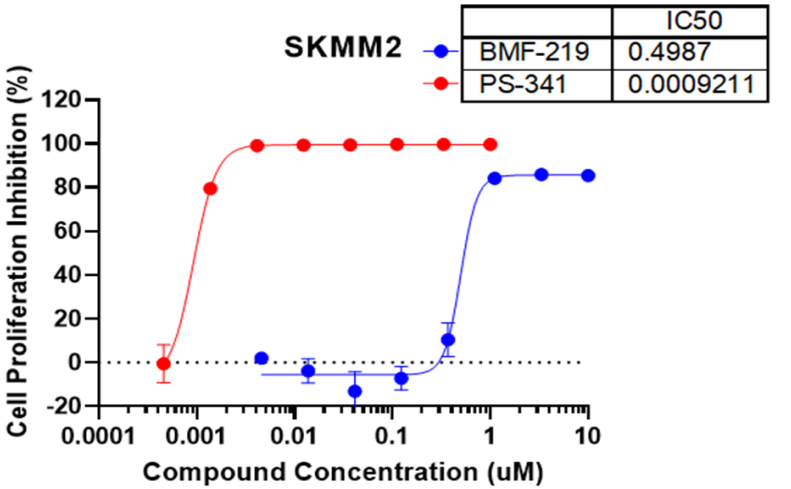
- ~1µM exposure of BMF-219 produces robust growth inhibition in both THL (triple hit lymphoma) and MYC amplified DLBCL ex-vivo cell lines
- BMF-219 responses were superior to clinical reversible (non-covalent) inhibitors with respect to cell growth inhibition at the concentrations tested

BMF-219 exerts lethality against MM cell lines at clinically relevant concentrations and Bortezomib as a positive control





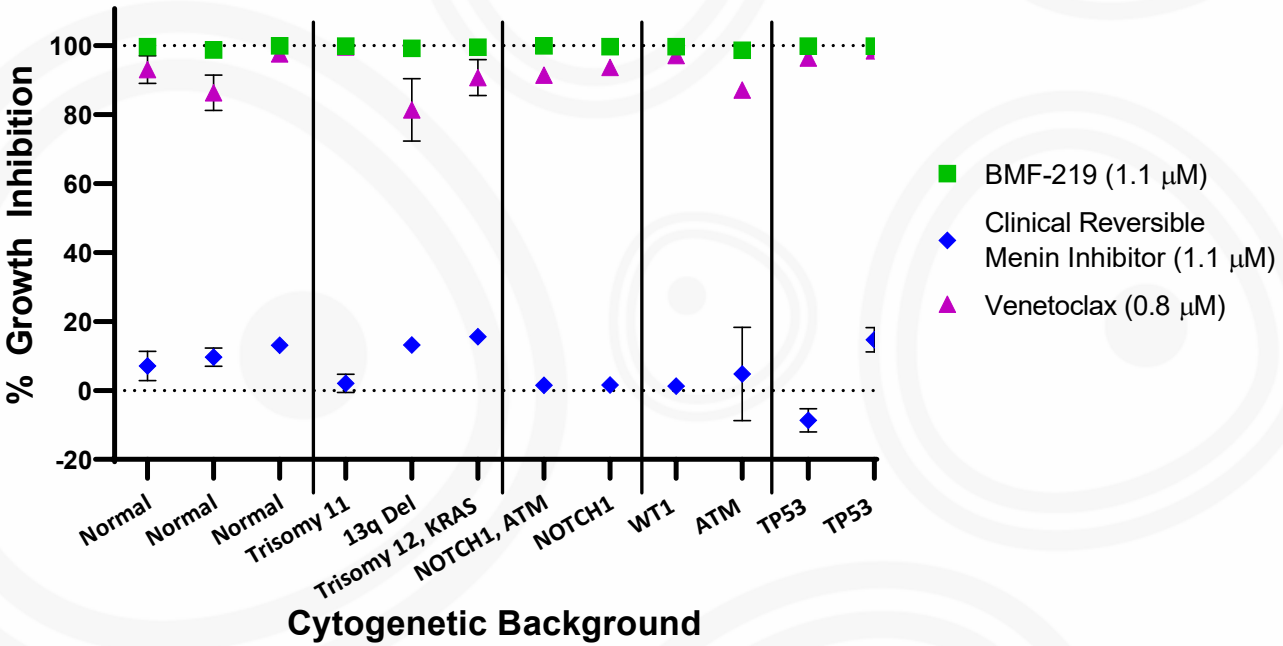




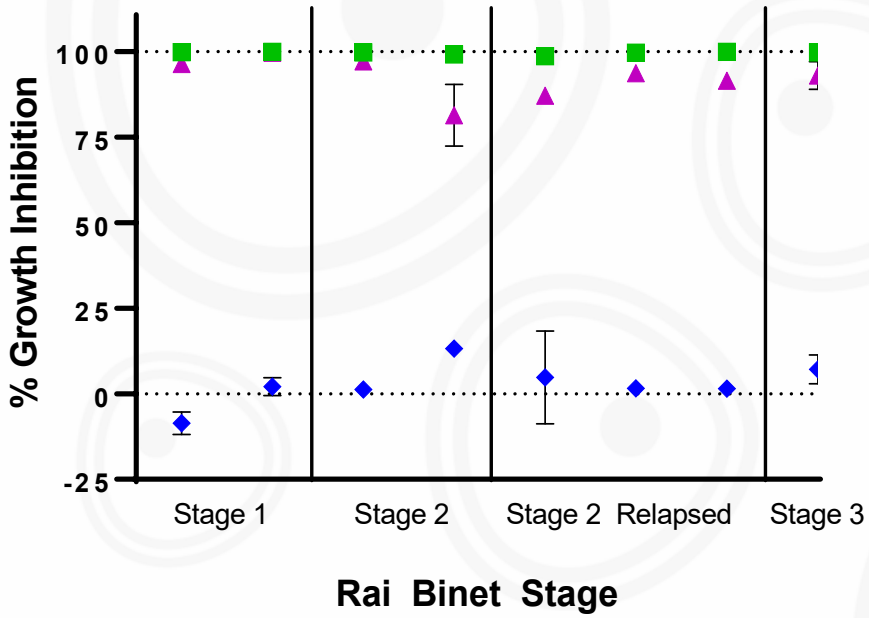
BMF-219 Achieved >98% Cell Lethality against Diverse CLL *ex vivo* Models

Growth inhibition of BMF-219 in CLL *ex vivo* models grouped by genetic background and Rai stage

Response based on Cytogenetics

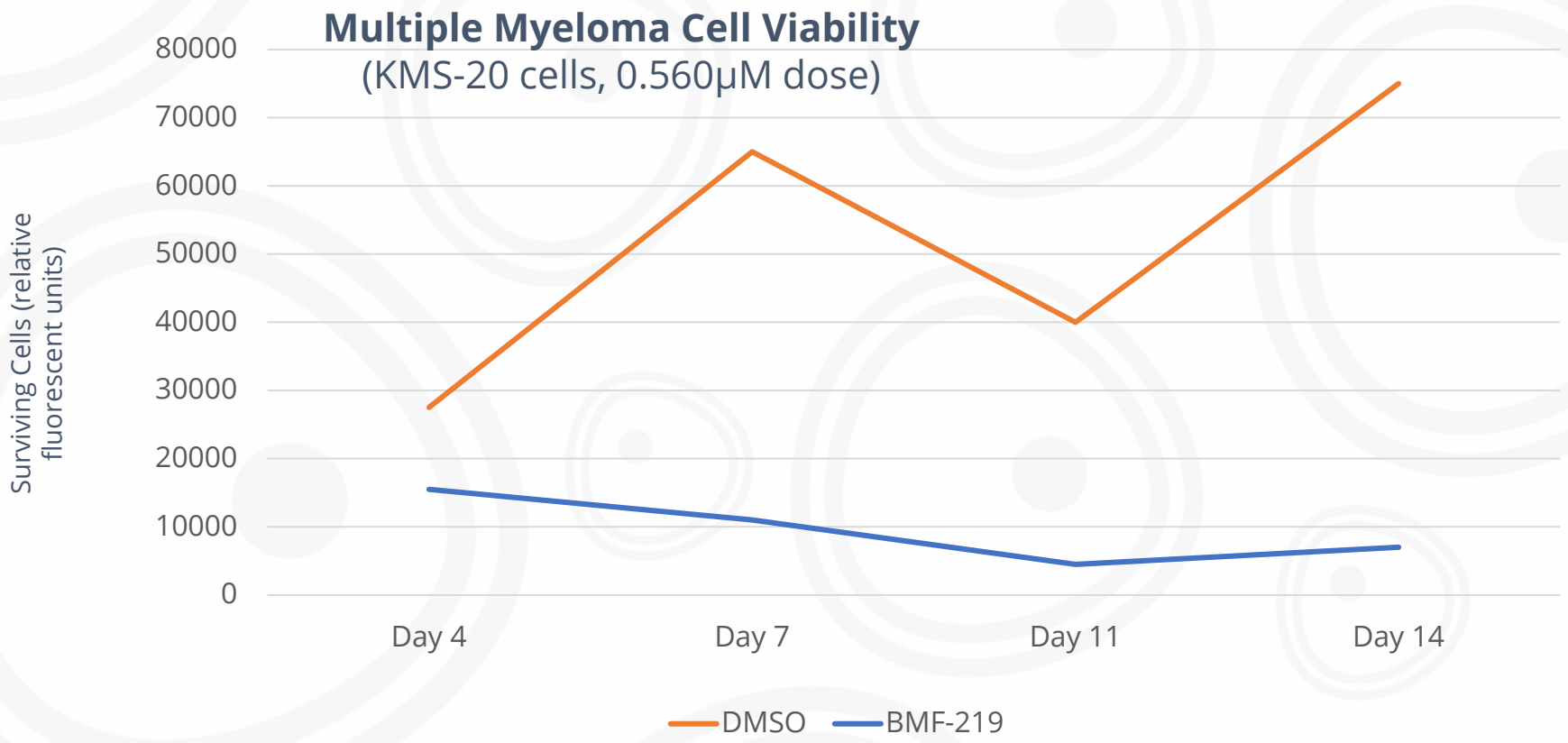


Response based on Rai Stage



Somanath et al., ASCO 2022 Abstract 7541

BMF-219 Impairs Growth in Multiple Myeloma Cell Lines



Impairment of survival in multiple myeloma model (KMS-20 cell line, 0.56µM doses) by irreversible menin inhibitor BMF-219

BMF-219 Exerted Potent Lethality against Representative DLBCL (Toledo & U2932) & MM Cell Lines (SKMM1 & OPM2)

% Cell Death	SKMM1					OPM2				
	BMF-219			Clin Rev	MI-503	BMF-219			Clin Rev	MI-503
Conc.	0.4 µM	0.5 µM	1 µM	1 µM	3 µM	0.4 µM	0.5 µM	1 µM	1 µM	3 µM
14 hr	-	15	25	0	13	-	8	57	0	14
72 hr	27	-	**86%**	4	33	22	-	**80%**	3	21

% Cell Death	TOLEDO					U2932				
	BMF-219			Clin Rev	MI-503	BMF-219			Clin Rev	MI-503
Conc.	0.4 µM	0.5 µM	1 µM	1 µM	3 µM	0.4 µM	0.5 µM	1 µM	1 µM	3 µM
14 hr	-	18	12	0	11	-	19	36	0	7
72 hr	32	-	**97%**	0	35	29	-	**86%**	3	34

Lu et al., IMS 2022

To measure cell killing, cells were cultured in the presence of menin inhibitor for 72hr or 14hr and viable cell count measured by CellTiter-Glo® (CTG) readout. The % cell killing relative to untreated cultures was measured at 72hr and 14hr. Data tabulated was averaged from 2 independent experiments.

BMF-219 at 1 µM induced potent killing inducing 80-97% cell death following 72hr drug treatment. In comparison, the reversible menin inhibitors MI-503 and a clinical reversible menin inhibitor exhibited significantly less killing (20-35% cell killing with 3 µM MI-503)

BMF-219 Preclinical and Clinical Results in Solid Tumors

Menin-MYC Interaction is Observed to Play an Important Role in KRAS Mutant Solid Tumors (Lung, Colon, Pancreatic)

Key Facts

Estimated Addressable Population

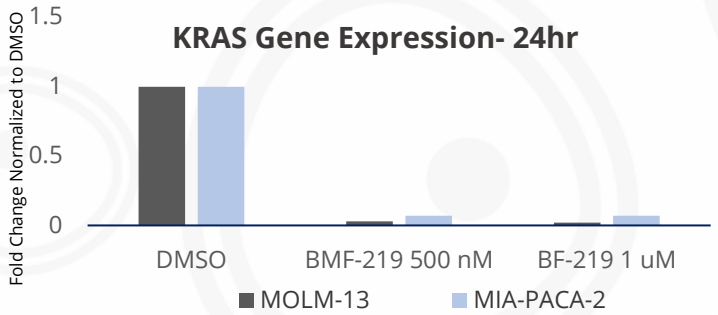
Tumor Type (KRAS Mutant)	Estimated US Patient Population (Annual Incidence)
Lung (NSCLC)	~58,000
Colon (CRC)	~60,000
Pancreatic (PDAC)	~53,000

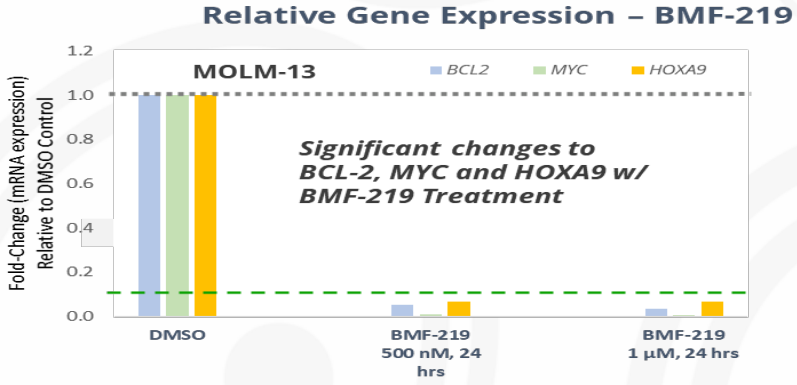
- MYC is a major downstream effector of the MAPK pathway in KRAS-activated tumors
- BMF-219 robustly decreased MYC gene expression and genomic function and drove cell killing in numerous MYC driven ex-vivo tumor samples.

Proposed MOA

BMF-219 inhibits the menin/ MYC interaction and downregulates expression of MYC and MYC target genes, including KRAS

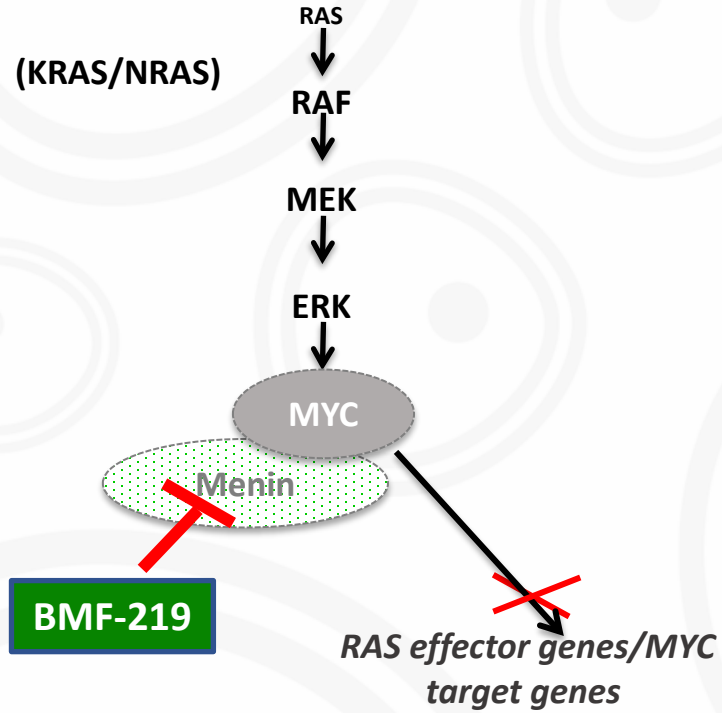
(Blood (2021) 138 (Supple. 1): 4318.)





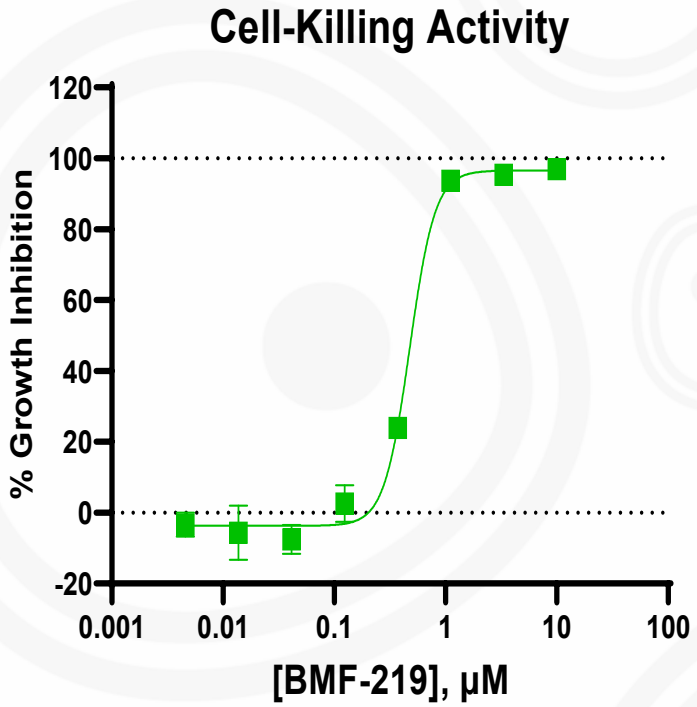
Relevant Pathway

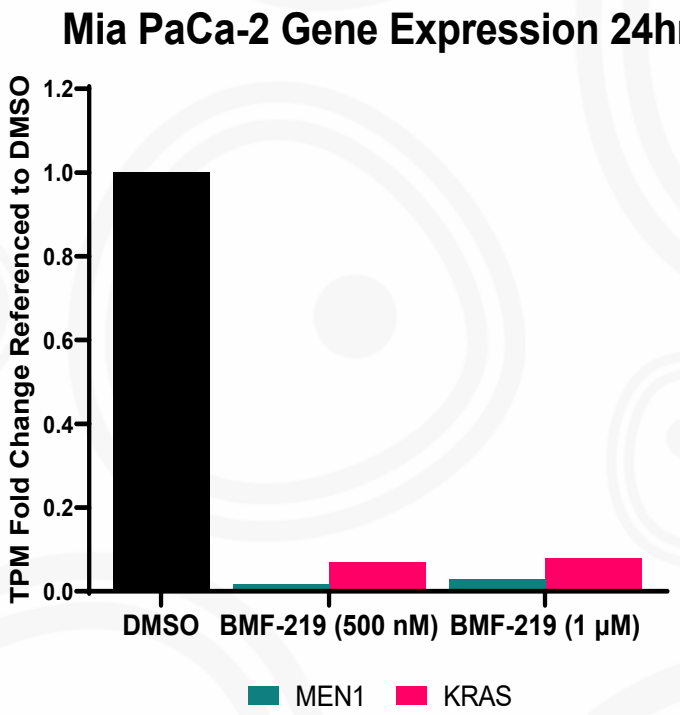
Tumor leverages MAPK pathway



BMF-219 Achieves Robust Cell Killing and Downregulation of MEN1 and KRAS Expression in KRAS G12C mutant Cell Lines

BMF-219 activity in MIA PaCa-2 KRAS G12C cell line





- Covalent inhibitor, BMF-219, at 1µm concentration achieves robust cell killing activity and downregulates expression of *MEN1* and *KRAS* at 24hrs
- *KRAS* and *MEN1* expression reduced by ≥90% at both 0.5 µm and 1µm

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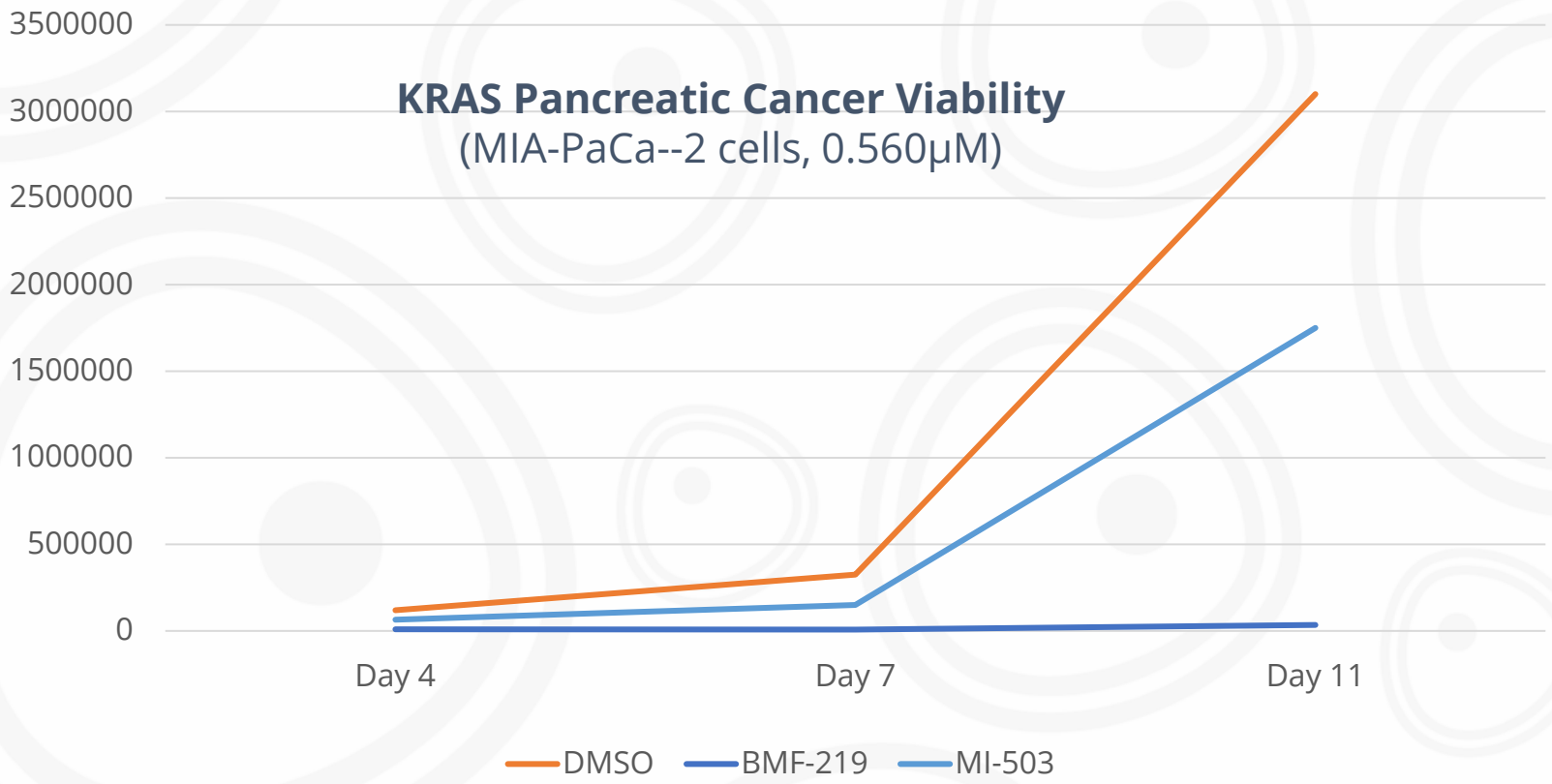
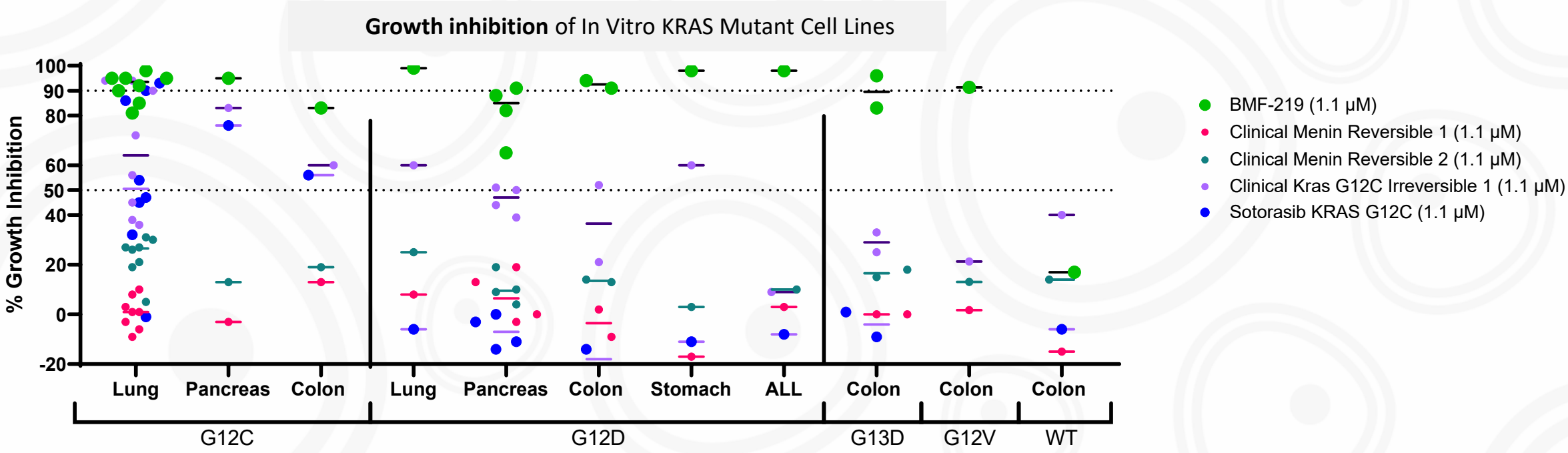
BMF-219 Impairs Growth in KRAS Solid Tumor Cell Lines



Impairment of survival in G12C KRAS mutation driven pancreatic cancer model (MIA-PaCa-2, 0.56µM doses) by irreversible menin inhibitor BMF-219 versus a reversible menin inhibitor (MI-503)

BMF-219 Produced Near Complete Inhibition of Growth at 1.1µM Across KRAS G12C, G12D, G13D, and G12V Mutant Cell Lines but not WT KRAS



- Covalent menin inhibition by BMF-219 led to robust growth inhibition, comparable to clinical G12C inhibitors in G12C cell lines
- In non-G12C cell lines, BMF-219 achieved robust growth inhibition, higher than clinical KRAS G12C inhibitors
- Clinical reversible (non-covalent) inhibitors did not achieve greater than 30% growth inhibition in any cell lines at the concentrations tested

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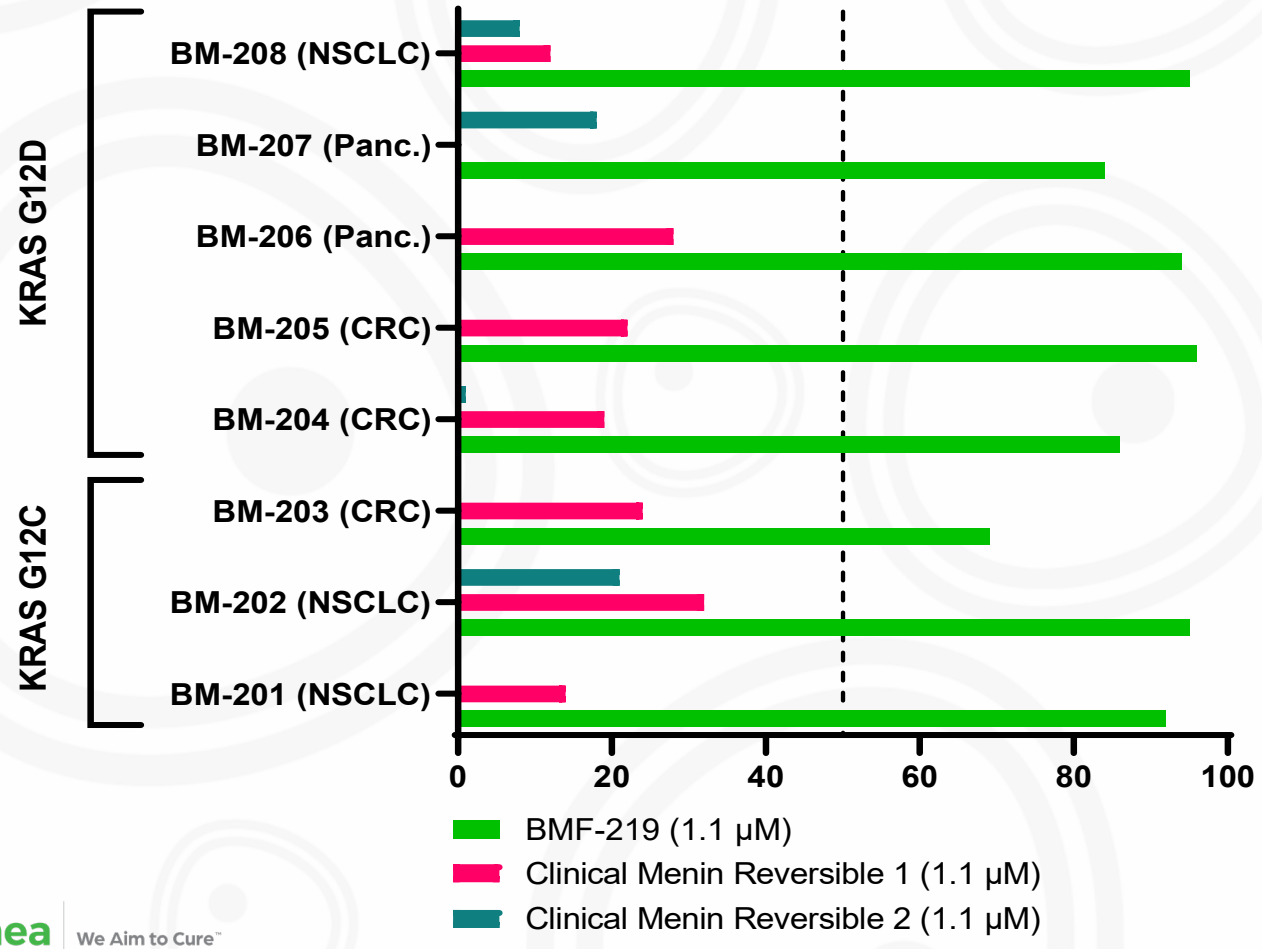
BMF-219 Produced Near Complete Inhibition of Growth at 1.1µM in KRAS G12C and G12D ex-vivo Samples

Growth Inhibition of ex-vivo KRAS mutant Cells from Patients (1µM Exposure)



- 1.1µM exposure of BMF-219 produces robust growth inhibition in both G12C and G12D ex-vivo cell lines
- BMF-219 responses were superior to clinical reversible (non-covalent) inhibitors with respect to cell growth inhibition at the concentrations tested

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THANK YOU

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