biomea FUSION™

2023 Q2 Corporate Presentation

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Excellent Science - Combining Validated Targets with Breakthrough Chemistry

We aim to cure

- Experienced Management Team
- Novel FUSION™ System
- BMF-219 - Clinical Stage Lead Asset
- BMF-500 and additional Programs

biomea FUSION™ We Aim to Cure™

Biomea Fusion is a clinical-stage biopharmaceutical company focused on the discovery and development of **oral covalent small-molecule drugs** to treat patients with genetically defined cancers and metabolic diseases. We believe that our approach may lead to significant improvement and extension of life for patients. Our team is engaged in all phases of drug discovery and development, including target selection, small molecule design, and preclinical and clinical studies to develop innovative medicines.

Developing some of the most impactful medicines of our time

A long history of developing successful drugs together

Thomas Butler
Chairman & CEO

Veklury® remdesivir 100 MG FOR INJECTION
CO-INVENTOR

imbruvica® (ibrutinib)
560, 420, 280, 140 mg tablets | 140, 70 mg capsules

Ramses Erdtmann
President & COO

imbruvica® (ibrutinib)
560, 420, 280, 140 mg tablets | 140, 70 mg capsules

Naomi Cretcher
Chief of People

imbruvica® (ibrutinib)
560, 420, 280, 140 mg tablets | 140, 70 mg capsules

Heow Tan
Chief Technical & Quality Officer

imbruvica® (ibrutinib)
560, 420, 280, 140 mg tablets | 140, 70 mg capsules

Xtampza® ER (oxycodone) EXTENDED-RELEASE CAPSULES (II)

ZADAXIN

PLENAXIS

HylatopicPlus Cream

Steve Morris, M.D.
Chief Medical Officer

XALKORI® 250MG CAPSULES
CRIZOTINIB

ZYKADIA® ceritinib 150 mg tablets

LORBRENA® LORLATINIB | 100 mg tablets

ALECENSA® alectinib 150 mg capsules

ALUNBRIG™ BRIGATINIB 30mg TABLETS

Franco Valle
Chief Financial Officer

imbruvica® (ibrutinib)
560, 420, 280, 140 mg tablets | 140, 70 mg capsules

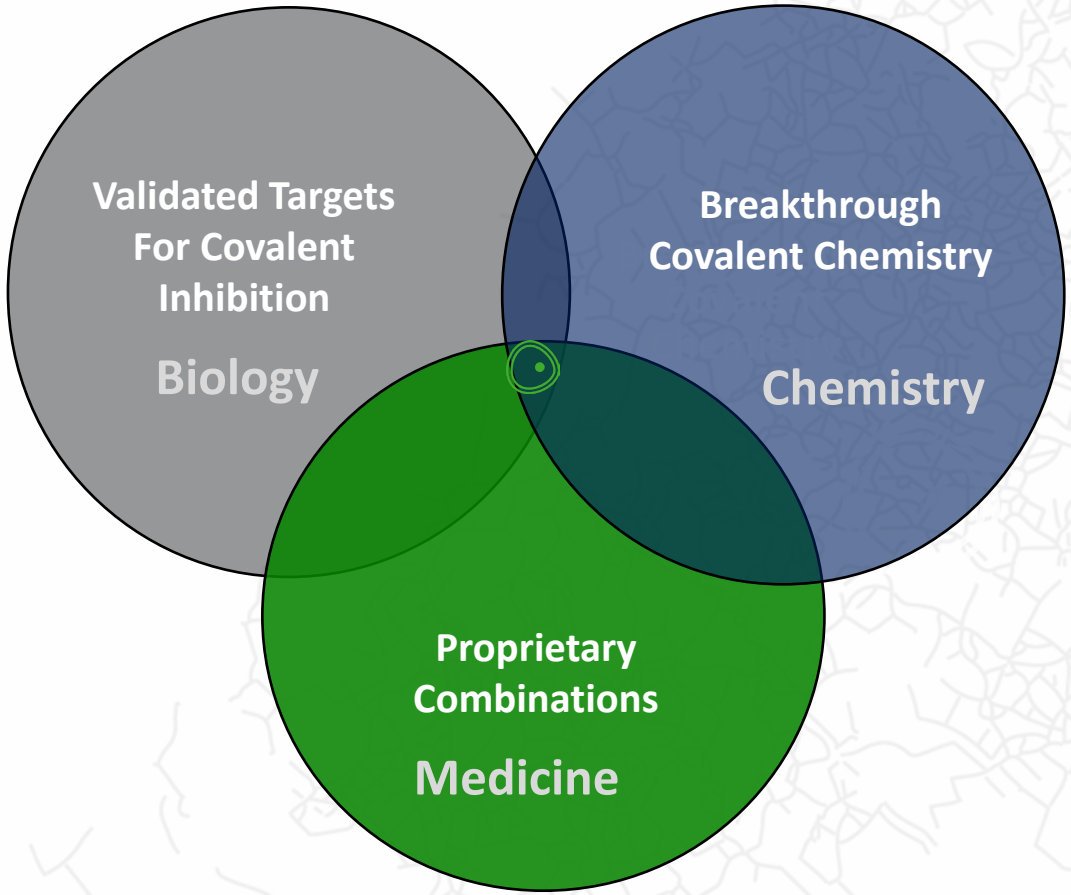
Thorsten Kirschberg, Ph.D.
EVP of Chemistry

HARVONI® ledipasvir / sofosbuvir
CO-LEAD

Jim Palmer, Ph.D.
VP of Drug Discovery

imbruvica® (ibrutinib)
560, 420, 280, 140 mg tablets | 140, 70 mg capsules
CO-INVENTOR

Biomea's Development Principles



Validated Targets

Drugs pursuing **Validated Disease Targets** have a ~2x higher likelihood of approval than molecules pursuing a new mechanism of action

Sources: Nelson et al. (2015) Nat Genet.; Thomas et al. (2016) BIO; In a Landscape of 'Me Too' Drug Development, What Spurs Radical Innovation? HBS Weekly Review (Jun 2018)

Covalent Inhibitors

Covalent Small Molecule Inhibitors provide deep target inactivation and a wider therapeutic window, allowing for longer duration on therapy

Sources: Singh et al. (2011) Nature Reviews Drug Discovery; Cheng et al. (2020) Journal of Hematology & Oncology; Strelow (2017) SLAS Discovery; Kalgutkar & Dalvie (2012) Expert Opin. Drug Discov.;

Proprietary Combinations

Combination Therapy with non-overlapping resistance mechanisms results in more durable responses and better outcomes

Sources: Palmer et al. (2019) eLife; Mokhtari et al. (2017) Oncotarget

Our Technology Platform – The FUSION™ SYSTEM

Biomea created the Fusion™ System specifically to address unique targets and rapidly create highly potent and safe covalent inhibitors for them.

- Protein-protein interactions
- Difficult to target kinases, including avoiding high homology family members
- Transcriptional factors
- Low expressing targets
- Scaffold proteins
- Small GTPases
- Shallow, limited, or dynamic binding sites
- High affinity competitive ligands
- Systemic tolerability issues at efficacious dose
- Targeting optimal confirmation
- Identify small molecules for new targets

Most proteins are considered undruggable because it's impossible to get high enough drug exposure to effectively silence the target without significant side effects… we believe our optimized covalent inhibitors uniquely solve that problem.

Our Technology Platform – The FUSION™ SYSTEM – provided 3 Program leads over the past 4 years!

Target identification to IND candidate in 18 months

Target to Hit

Target validation
Visual integration of crystal structures of target and reactive cysteine

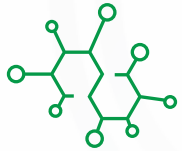
Utility:
Differentiated insights from X-ray crystal structures, identifying target cysteines

Custom Lead

Library of custom engagers
Proprietary AI platform with VR validation matches novel DRUG LIKE PROBES to cysteines; we do not screen via library probes.

Utility:
Library of covalent scaffolds provide for ~1,000 de novo scaffolds for AI/VR scoring

Lead Optimization



Custom scaffold creation
Custom built synthesis to create candidates with desired characteristics

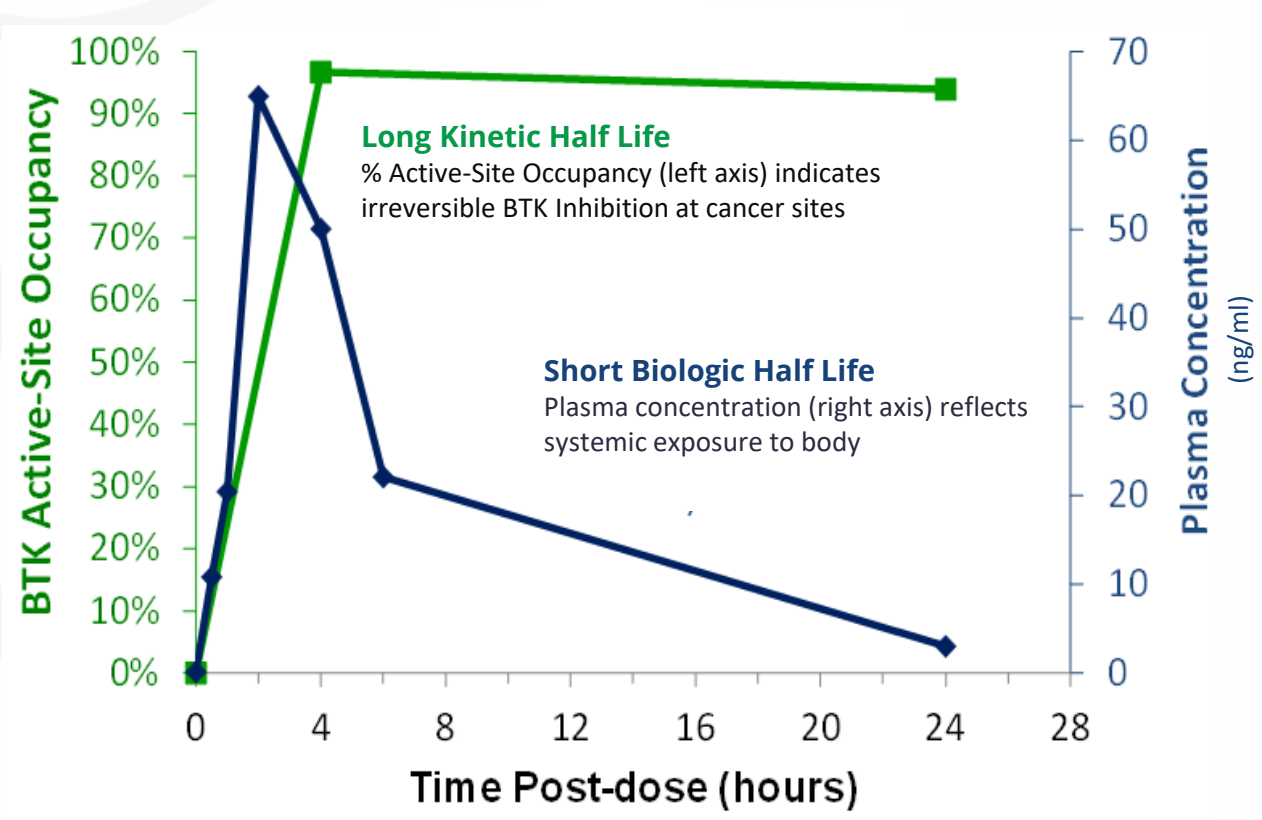
Utility:
AI/VR program platform yields over 300 scaffolds, which are synthesized for in vitro testing

IND

Refinement
Building in drug-like properties, optimizing PK/PD profile, and maintaining specificity

Utility:
Scaffolds are further refined with Mass spec, animal, and cell-based assays to two IND candidates

Imbruvica – a Covalent Inhibitor with Long Kinetic but very Short Biological Half Life



High Selectivity

Two-step inhibition: 1) Initial reversible binding followed by 2) covalent interaction, increasing target selectivity

Deep Target Inactivation

Permanent inactivation of bound protein drives target elimination through normal cellular degradation processes

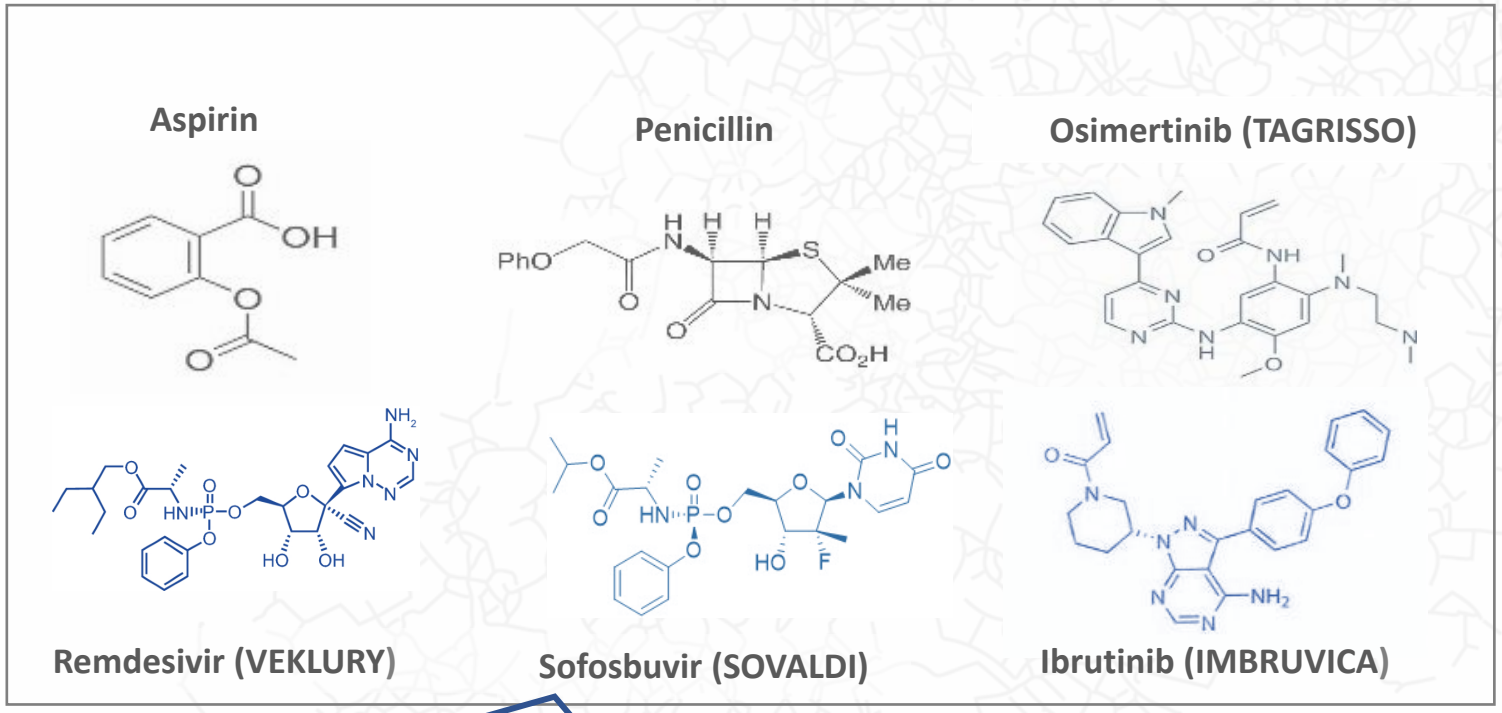
Greater Therapeutic Window

Designed to maintain an effect without sustained systemic exposure, unlike conventional non-covalent inhibitors

Covalent Chemistry creates very powerful results

Covalent Inhibitors - a History of Medical & Commercial Success

Notable Covalent Inhibitors

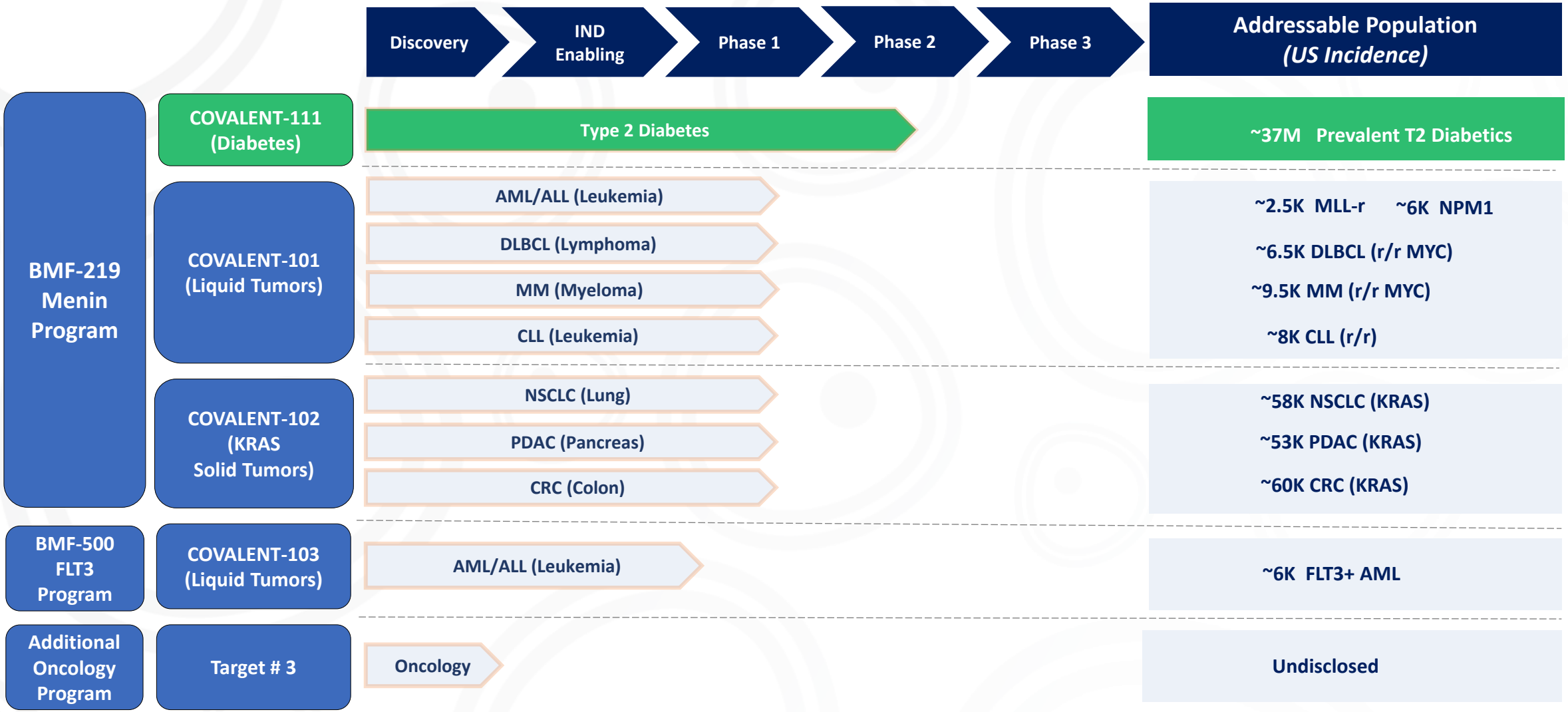


Compounds in Blue Were Co-Invented or Co-Developed by Biomea Fusion Senior Leadership

- **Aspirin** was the first commercialized covalent drug
- Notable precision oncology and infectious disease programs leverage covalent mechanisms
  - Precision Oncology**:** **Osimertinib** and **Ibrutinib** both target kinases and are used in subpopulations with specific genetic biomarkers
  - Antivirals**:** **Remdesivir** and **Tenofovir** both target reverse transcriptases and are leveraged to treat HCV and other viruses including HIV and COVID-19

Biomea Expanded into Eight Different Solid and Liquid Tumors as well as Type 2 Diabetes

Biomea's Pipeline as of January 2023



2023 and beyond expected to provide multiple Clinical Read Outs

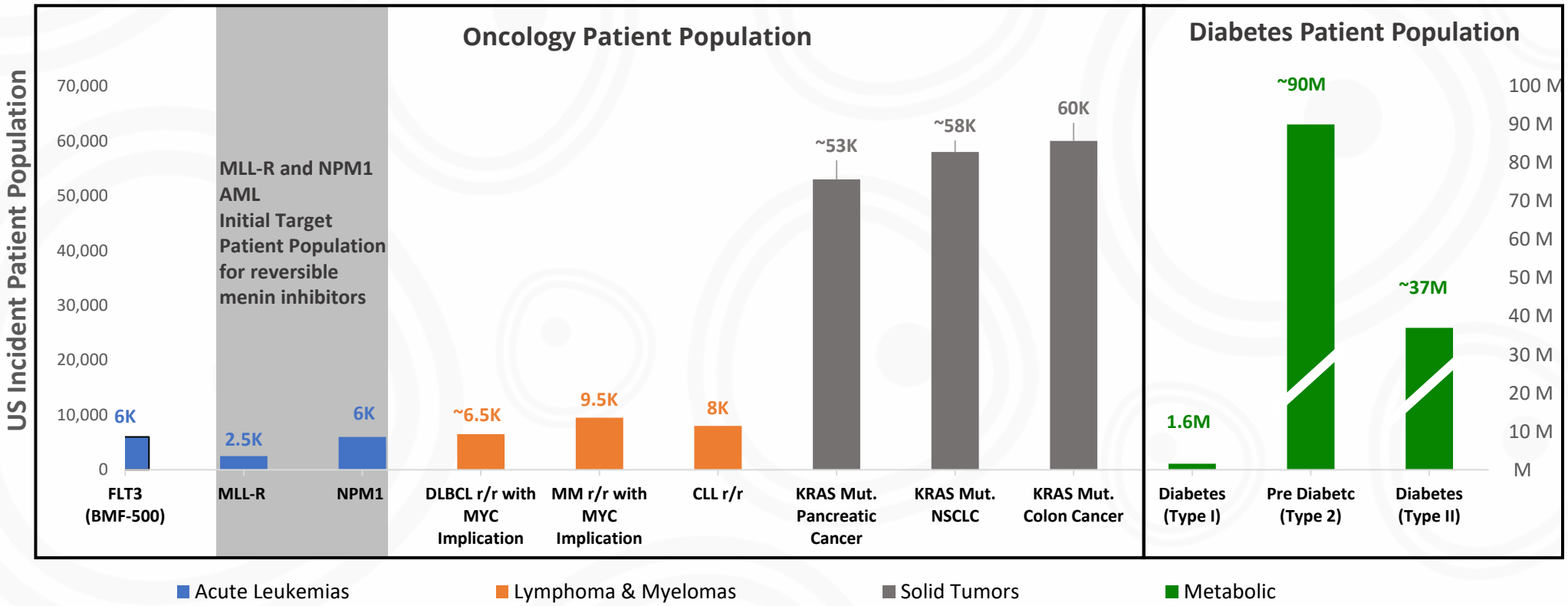
Near Term Expected Milestones – Biomea Fusion (NASDAQ: BMEA)

			Milestones	Expected Timeline
BMF-219 Menin Program	COVALENT-111 (Diabetes)	Type 2 Diabetes	Phase II: Next Clinical Data Update	Expected at ADA
	COVALENT-101 (Liquid Tumors)	AML/ALL (Leukemia)	Phase I Clinical Data in AML	1H 2023 first data set
		DLBCL (Lymphoma)	Enrolling in Phase I additional Cohort in DLBCL	In Progress
		MM (Myeloma)	Enrolling in Phase I additional Cohort in MM	In Progress
		CLL (Leukemia)	Enrolling in Phase I additional Cohort in CLL	In Progress
	COVALENT-102 (KRAS Solid Tumors)	NSCL (Lung)	Enrolling of Phase I KRAS Study in CRC, PDAC, NSCLC	In Progress
		PDAC (Pancreas)		
		CRC (Colon)		
BMF-500 FLT3 Program	COVALENT-103 (Liquid Tumors)	AML/ALL (leukemia)	Initiation of Phase I	In Progress
Additional Oncology Program	Target # 3	Oncology	Progress Update	1H 2023

BMF-219 and BMF-500 Patient Populations in the US

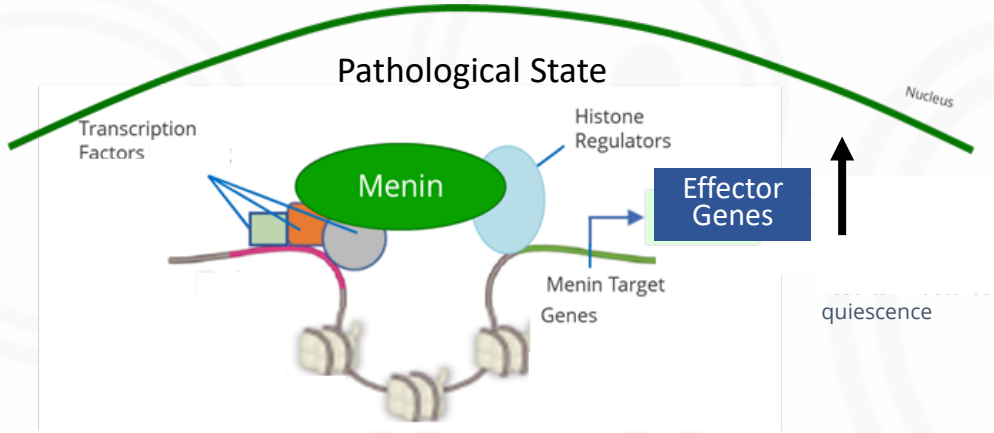
Cancer Indications: >200K and Diabetes: >125M

Addressable Annual US Patient Population for BMF-219



Sources: Jovanović, K. K., Roche-Lestienne, C., Ghobrial, I. M., Facon, T., Quesnel, B., & Manier, S. (2018). Targeting MYC in multiple myeloma. Leukemia, 32(6), 1295–1306. https://doi.org/10.1038/s41375-018-0036-x ; Riedell, P. A., & Smith, S. M. (2018). Double hit and double expressors in lymphoma: Definition and treatment. Cancer, 124(24), 4622–4632. https://doi.org/10.1002/cncr.31646; Kempf, E., Rousseau, B., Besse, B., & Paz-Ares, L. (2016). KRAS oncogene in lung cancer: focus on molecularly driven clinical trials. European respiratory review : an official journal of the European Respiratory Society, 25(139), 71–76. https://doi.org/10.1183/16000617.0071-2015; Lanfredini, S., Thapa, A., & O'Neill, E. (2019). RAS in pancreatic cancer. Biochemical Society transactions, 47(4), 961–972. https://doi.org/10.1042/BST20170521; Serna-Blasco, R., Sanz-Álvarez, M., Aguilera, Ó., & García-Foncillas, J. (2019). Targeting the RAS-dependent chemoresistance: The Warburg connection. Seminars in cancer biology, 54, 80–90. https://doi.org/10.1016/j.semcancer.2018.01.016; Park, W., Chawla, A., & O'Reilly, E. M. (2021). Pancreatic Cancer: A Review. JAMA, 326(9), 851–862. https://doi.org/10.1001/jama.2021.13027; NCI SEER Estimated 2021 Incidence <seer.cancer.gov>

Restoring Balance in Menin Dependents Diseases is Context Specific

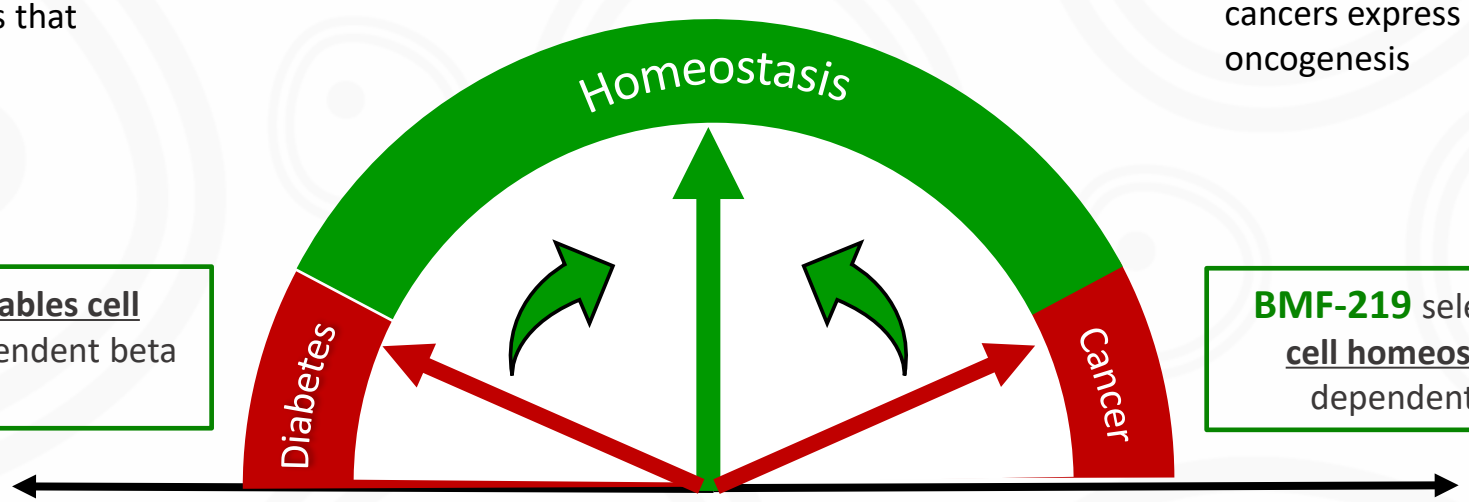


Treating Diabetes

Menin dependent effector genes in beta-cells express proteins that repress beta-cell growth

Treating Cancer

Menin dependent effector genes in certain cancers express or regulate proteins that drive oncogenesis



BMF-219 selectively **enables cell homeostasis** of menin dependent beta cells

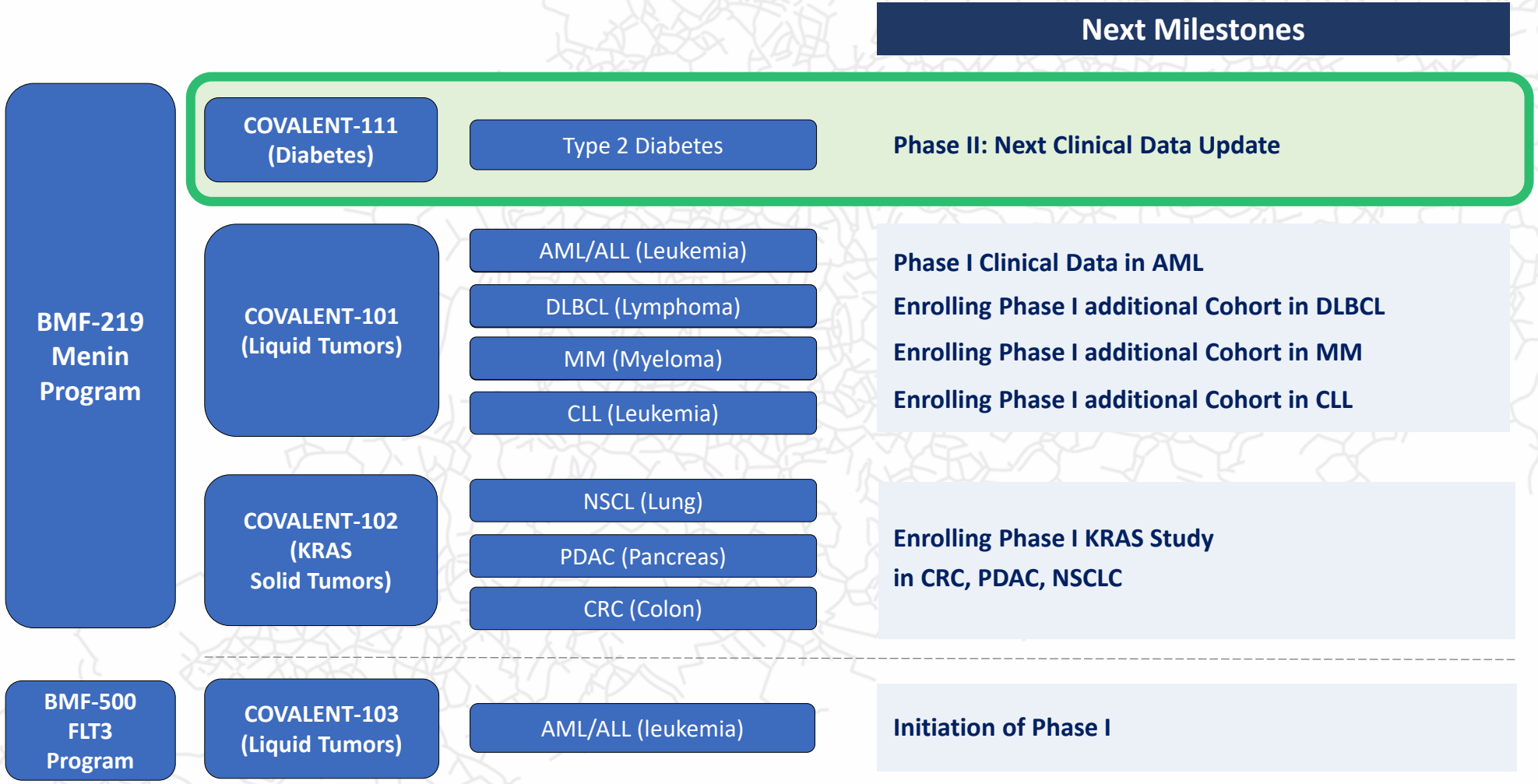
BMF-219 selectively **enables cell homeostasis** of menin dependent cancer cells

Menin **suppressing** cell homeostasis

Menin **disrupting** cell homeostasis

Novel Covalent Inhibitor of Menin

Pipeline-in-a-Pill – Single Agent for Multiple Indications



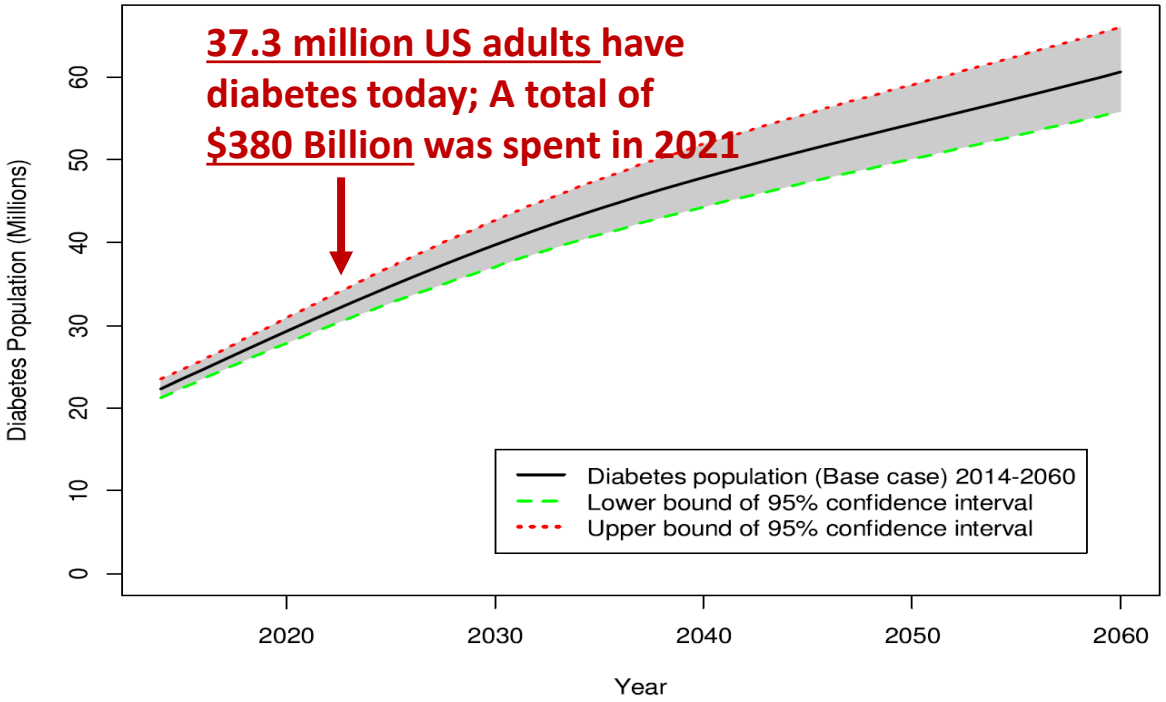
Diabetes – the biggest epidemic of the 21st century

2 in 5 Americans will develop Diabetes in their life

- One of the largest economic burdens on the US health care system and the 7th leading cause of death in the US Source: Diabetes.org

- 80% of people with diabetes will die from this disease. Premature mortality caused by diabetes results in an estimated 12-14 years of life lost. Source: National library of Medicine 1(2); 2007 Jul PMC3068646

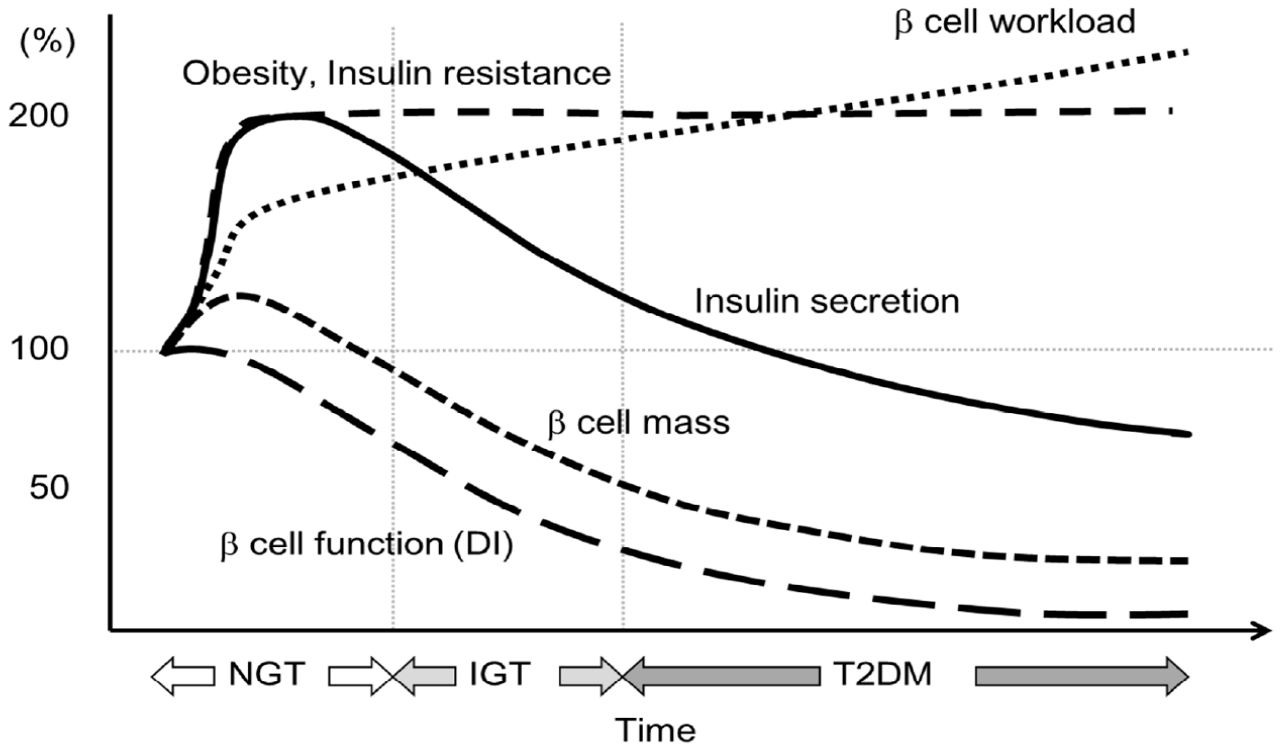
- In the United States $1 out of every $4 in US health care costs is being spent on caring for people with diabetes. In 2021 the US spent $380 Billion to treat diabetes.



- According to the CDC, worldwide 537 million adults have diabetes. In the United States alone, 37.3 million adults have diabetes, 11.3% of the population. 96 million adults (more than 1 in 3) in the US have prediabetes.

= ***Diabetes is an uncontrolled disease despite the availability of current medication. There is a significant need for the treatment and care of diabetes patients.***

Diabetes Progression of Type 1 and Type 2 Driven by Beta Cell Loss



Prior Paradigm	Type 1 diabetes	Type 2 diabetes
	β cell destruction β cell mass ↓↓ Insulin secretion ↓↓	Obesity Insulin resistance Hyperinsulinemia
Current Paradigm	Type 1 diabetes	Type 2 diabetes
	β cell destruction β cell mass ↓↓ Insulin secretion ↓↓	β cell loss β cell mass ↓ Insulin secretion ↓
Causes	Autoimmune	Insulin resistance β cell overwork

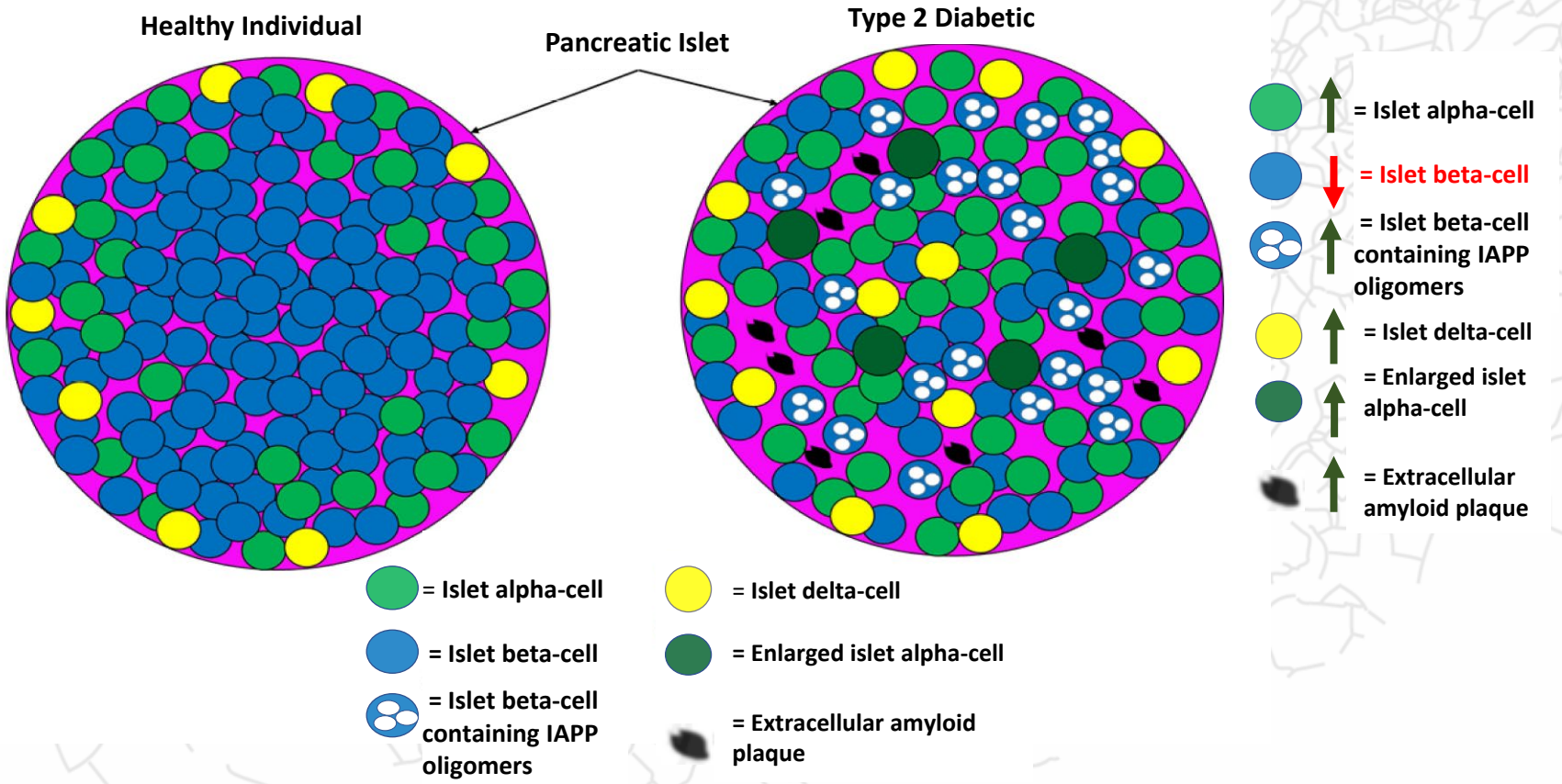
Insulin Resistance leads to an increase in Beta Cell Workload which ultimately leads to Beta Cell Failure and Death and the Progression of Type 2 Diabetes.

Type 1 and Type 2 Diabetes results in Beta Cell Loss and Reduction in Beta Cell Mass

Int. J. Mol. Sci.* **2016, *17*, 744; doi:10.3390/ijms17050744

Diabetes – the biggest epidemic of the 21st century

Types 2 Diabetes Progression: Beta Cell Loss

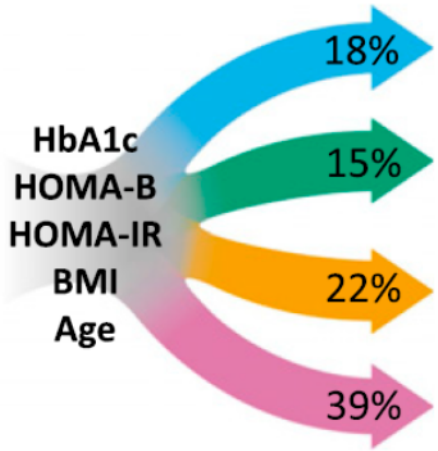


- Type 1 and Type 2 Diabetes results in Beta Cell Loss and a Reduction in Beta Cell Mass
- Standard of Care Agents are not addressing the Loss of Beta Cells
- Type 1 and Type 2 Diabetes Patients remain un-controlled and continue to progress

Int. J. Mol. Sci.* **2016, *17*, 744; doi:10.3390/ijms17050744`

Diabetes Patient Subtype Characteristics

		Patient Population	Potential BMF-219 MOA
Pre-Diabetes	**Initial Decline in Glycemic Control** Increasing HbA1c, Increasing Insulin Resistance Decreasing beta cell numbers and function	~90M	Beta Cell Preservation Beta Cell Growth
T2D (HbA1c, HOMA-B, HOMA-IR, BMI, Age)	**SIDD = Severe Insulin Deficient Diabetes** Low insulin secretion, poor metabolic control, increased risk of retinopathy and neuropathy	~6M	Beta Cell Reactivation Beta Cell Growth
	SIRD = Severe Insulin Resistant Diabetes Insulin resistance, obesity, late onset, increased risk of nephropathy and fatty liver	~5M	Beta Cell Reactivation Beta Cell Preservation
	MOD = Mild Obesity-Related Diabetes Obesity, early onset	~8M	Beta Cell Reactivation Beta Cell Growth
	MARD = Mild Age-Related Diabetes Late onset, low risk of complications	~14M	Beta Cell Reactivation Beta Cell Preservation
T1D	**Initial Diagnosis/Disease – Stage 2/Stage 3** Increasing HbA1c, Initial Reduction in Insulin Significant Decrease in beta cell numbers	~1.5M	Beta Cell Growth Beta Cell Preservation



E. Ahlqvist,1 et., Diabetes 2020;69:2086–2093

Diabetes – the biggest epidemic of the 21st century

BMF-219 Value Proposition in Beta Cell Health & Diabetes

First-in-class molecule with paradigm shifting potential for the treatment of diabetes

Oral Treatment for the Regeneration, Preservation, and Reactivation of Beta Cells

- **Disease modification** first treatment to potentially provide remission of diabetes via restoration of beta cell homeostasis
- **Potential reduction in insulin dependence** for advanced Type 2 and Type 1 patients
- **Synergistic/additive with current standard of care (SOC) including GLP-1 based treatments**
- **Potential utility in:**
  - Prevention of T2DM (there are 96M prediabetic patients in the US)
  - T2DM with beta cell impact and T2DN patients on SOC but not at target A1C
  - T1D
  - Diabetic patients at risk for hypoglycemia
- **MOA (inhibition of menin) could positively impact:**

  NASH, CKD, CV benefit; Weight loss as monotherapy or in combination; Patients at risk for hypoglycemia under current SOC; Reduction of glucose excursions; Additional impact on diabetes associated co-morbidities and indirect economic burden

Natural History: During Pregnancy the Hormone Prolactin Down-Regulates Menin Levels Allowing for Beta Cell Expansion

- During pregnancy, maternal pancreatic islets grow to match dynamic physiological demands.
- Menin has been found to control islet growth in pregnant mice. Pregnancy stimulated proliferation of maternal pancreatic islet b-cells that was accompanied by reduced islet levels of menin and its targets.
- Prolactin, a hormonal regulator of pregnancy, repressed islet menin levels and stimulated b-cell proliferation.
- Transgenic expression of menin in maternal b-cells prevented islet expansion and led to hyperglycemia and impaired glucose tolerance, hallmark features of gestational diabetes.

Dr. SK Kim. Department of Developmental Biology, Pathology and Medicine Stanford University
www.sciencemag.org/cgi/content/full/318/5851/806/DC1

REPORTS

Menin Controls Growth of Pancreatic β-Cells in Pregnant Mice and Promotes Gestational Diabetes Mellitus

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During pregnancy, maternal pancreatic islets grow to match dynamic physiological demands, but the mechanisms regulating adaptive islet growth in this setting are poorly understood. Here we show that menin, a protein previously characterized as an endocrine tumor suppressor and transcriptional regulator, controls islet growth in pregnant mice. Pregnancy stimulated proliferation of maternal pancreatic islet β-cells that was accompanied by reduced islet levels of menin and its targets. Transgenic expression of menin in maternal β-cells prevented islet expansion and led to hyperglycemia and impaired glucose tolerance, hallmark features of gestational diabetes. Prolactin, a hormonal regulator of pregnancy, repressed islet menin levels and stimulated β-cell proliferation. These results expand our understanding of mechanisms underlying diabetes pathogenesis and reveal potential targets for therapy in diabetes.

Maternal pancreatic islet expansion in rodents and humans (*1*–*3*) suggests that adaptive islet cell growth is a mechanism for ensuring metabolic balance in pregnancy, a physiological state marked by increased insulin demand. Descriptive studies with rats (*2*, *3*) support the hypothesis that proliferation of insulin-secreting islet β-cells is the principal mechanism of β-cell expansion in pregnancy, but the molecular basis of facultative maternal β-cell proliferation is unknown. Moreover, it is unclear if impaired maternal β-cell proliferation leads to reduced insulin levels and gestational diabetes (*4*).

To investigate the mechanisms controlling maternal islet expansion, we examined β-cell mass in pregnant C57Bl6 mice. We found that maternal β-cell mass increased by twofold (fig. S1A), accommodating increases in maternal body mass (fig. S1B). After parturition, maternal β-cell mass and body mass returned to prepartum levels (fig. S1, A and B). To assess maternal islet cell proliferation, we performed labeling studies with bromodeoxyuridine (BrdU). β-cell proliferation increased in pregnant mice until 15 days postcoitum (dpc) and then declined to prepartum levels (Fig. 1, A to C). Thus, maternal islet β-cell expansion and mass are dynamic in mice.

Hyperplasia of the maternal pituitary (*5*) and islets in pregnancy is reminiscent of endocrine proliferation in multiple endocrine neoplasia type 1 (MEN1), a human cancer syndrome characterized by synchronous tumors of the pituitary, endocrine pancreas, and parathyroid. Most MEN1 cases result from mutation of *Men1*, whose protein product is menin (*6*, *7*). In mice and humans, mutation and pathological *Men1* loss promote neuroendocrine tumors, including islet β-cell tumors (*7*, *8*). Thus, we postulated that physiological changes in *Men1* expression might regulate facultative maternal β-cell growth in pregnancy. Immunohistology, Western blotting, and real-time reverse transcription polymerase chain reaction (RT-PCR) studies of maternal islets isolated during gestation revealed that islet levels of *Men1* mRNA and menin decreased in pregnancy (Fig. 1, D to G), then increased to prepartum levels by 1 week after birth of the pups (Fig. 1, F and G). By contrast, we did not detect changes in maternal islet levels of mRNA encoding mixed lineage leukemia-1 (MLL1), a protein that associates with menin (Fig. 1F). Thus, attenuated *Men1* expression corresponded with increased β-cell proliferation in maternal islets.

Menin functions in a histone methyltransferase protein complex containing MLL (*9*, *10*). This complex promotes trimethylation of histone H3 on lysine 4 (H3K4), an epigenetic mark associated with transcriptionally active chromatin. Menin-dependent histone methylation maintains expression of $p27^{Kip1}$ and $p18^{INK4C}$ (hereafter, *p27* and *p18*), which encode cyclin-dependent kinase (CDK) inhibitors that prevent islet proliferation (*11*–*14*). Consistent with our previous findings in islet tumors (*11*), reduced islet menin levels in pregnancy after 8 dpc were accompanied by reduced *p27* and *p18* mRNA and protein levels (Fig. 1G and fig. S1C) and, as revealed by chromatin immunoprecipitation (ChIP), by decreased levels of menin and trimethyl H3K4 associated with *p27* and *p18* expression (Fig. 1H). Thus, attenuated menin levels and function reduced pancreatic islet *p27* and *p18* expression in pregnant mice.

To determine whether adaptive maternal β-cell proliferation might require reduced *Men1* expression, we generated mice that permitted conditional *Men1* expression in β-cells. Transgenic mice producing hemagglutinin-tagged menin under control of the tetracycline response element (TRE-*Men1*) (*15*) were generated and mated with mice expressing the reverse tetracycline trans-activator (rtTA) in β-cells directed by the rat insulin promoter (RIP) (*16*). In bi-transgenic RIP-*rtTA*, TRE-*Men1* mice (abbreviated βMen1), administration of doxycycline (Dox) allows rtTA binding to the TRE element and stimulates β-cell expression of *Men1* mRNA and menin protein (fig. S2, A and B). Exposure of RIP-*rtTA* or TRE-*Men1* single transgenic mice to Dox did not induce changes in menin levels (fig. S2, A

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with the ANOVA analysis, and T. Vemous for discussions concerning GO enrichment. We also thank N. Provart, J. Harer, T. Mitchell-Olds, B. Schores, and members of the Benfey lab for reviewing the manuscript. S.M.B. received partial support from a postdoctoral fellowship from the Natural Science and Engineering Research Council of Canada. J.R.D. is supported by a Ruth Kirschstein National Research Service Award postdoctoral fellowship (NIH). U.O. is an Alfred P. Sloan Fellow in Computational Molecular Biology. This work was funded in large part by an NSF AT2010 grant to P.N.B. (0209754) and by NSF 0618304 to P.N.B. and U.O.

References and Notes

1. M. Levine, E. H. Davidson, *Proc. Natl. Acad. Sci. U.S.A.* **102**, 4936 (2005).
2. P. N. Benfey, B. Scheres, *Curr. Biol.* **10**, R813 (2000).
3. K. Birnbaum *et al.*, *Science* **302**, 1956 (2003).
4. J.-Y. Lee *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **103**, 6055 (2006).
5. S. M. Brady, S. Song, K. S. Dhugga, J. A. Rafalski, P. N. Benfey, *Plant Physiol.* **143**, 172 (2007).
6. L. Laplaze *et al.*, *Plant Physiol.* **143**, 2433 (2005).
7. A. Imlau, E. Truernit, N. Sauer, *Plant Cell* **11**, 309 (1999).
8. T. Nawy *et al.*, *PLoS Biol.* **4**, e143 (2006).
9. M. P. Levesque *et al.*, *Plant Cell* **17**, 1908 (2005).
10. Materials and methods are available as supporting material on *Science* Online.
11. E. Yakir, D. Hilman, Y. Harir, R. M. Green, *FEBS J.* **274**, 335 (2007).
12. H. Maamar, A. Raj, D. Dubnau, *Science* **317**, 526 (2007).
13. J. D. Storey, *J. R. Stat. Soc. Ser. B. Method.* **64**, 479 (2002).
14. T. R. O'Connor, C. Dyreson, J. J. Wyrick, *Bioinformatics* **21**, 4411 (2005).
15. M. A. Jones, M. J. Raymond, N. Smirnoff, *Plant J.* **45**, 83 (2006).
16. M. Menges, S. M. de Jager, W. Gruissem, J. A. H. Murray, *Plant J.* **41**, 546 (2005).
17. D. Sadowsky, B. Winkel-Shirley, *Plant J.* **27**, 37 (2001).
18. M.-L. Dequéant *et al.*, *Plant Cell* **17**, 3035 (2005).
19. S. Vanneste *et al.*, *Development* **134**, 681 (2007).
20. I. De Smet *et al.*, *Bioinformatics* **21**, i159 (2005).
21. J. Ernst, G. J. Nau, Z. Bar-Joseph, *Bioinformatics* **21**, i159 (2005).
22. J. L. Celenza *et al.*, *Plant Physiol.* **137**, 253 (2005).
23. K. Birnbaum *et al.*, *Nat. Methods* **2**, 615 (2005).
24. M. Bonke, S. Thitamadee, A. P. Mahonen, M.-T. Hauser, Y. Helariutta, *Nature* **426**, 181 (2003).
25. We thank K. Birnbaum for providing the J2501 data set and B. Parfett and L. Nussaume for the RM1000 data set, members of the Duke Center for Systems Biology and L. Brady for useful discussions, M. Levesque for assistance

Supporting Online Material

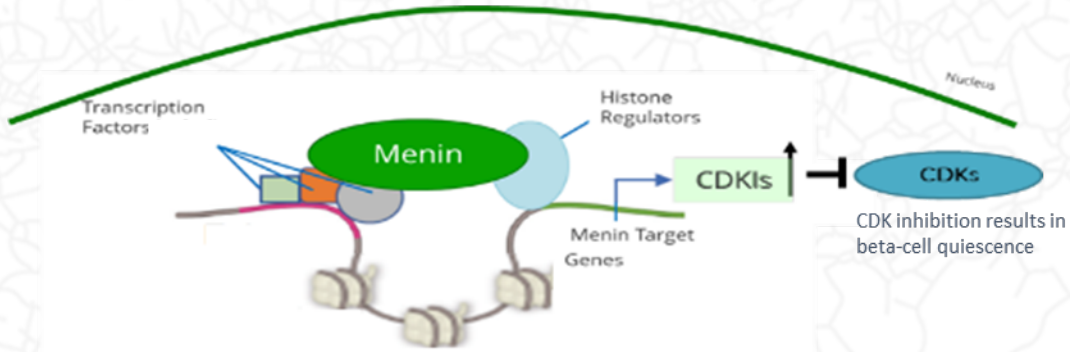
www.sciencemag.org/cgi/content/full/318/5851/801/DC1
Materials and Methods
Figs. S1 to S21
Tables S1 to S14
References
Folders S1 to S6

8 June 2007; accepted 2 October 2007
10.1126/science.1146265

Menin: a Key Checkpoint for Beta Cell Homeostasis
An Important Target for Type 1 and Type 2 Diabetes

- Menin functions in a histone methyltransferase protein complex.
- This complex promotes trimethylation of histone H3 on lysine 4 (H3K4), which is associated with transcriptionally active chromatin
- Menin dependent histone methylation maintains expression of p27 and p18, two key members of cyclin-dependent kinase (CDK) inhibitor family that prevent β-cell proliferation

Menin regulates beta-cell quiescence



Menin inhibition by BMF-219 allows for beta-cell restoration and glucose homeostasis

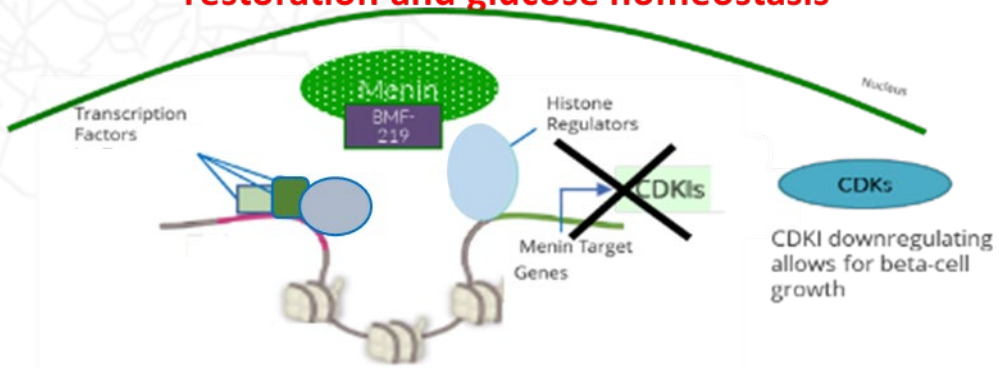
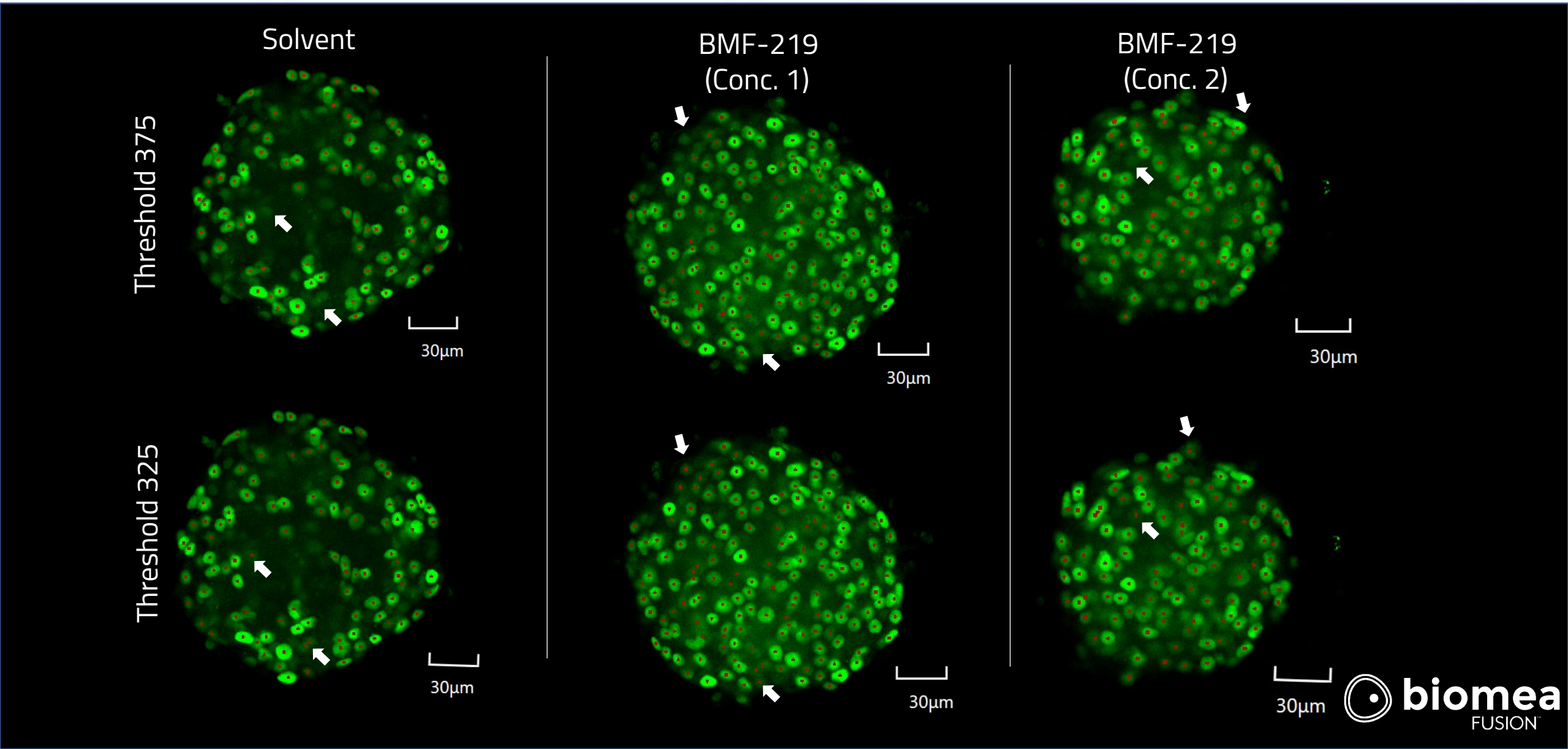


Figure adapted from Issa et al. Leukemia **35**, 2482–2495 (2021).

Human Donor Islets (Ex-Vivo): Statistically significant increase in beta cells with BMF-219



COVALENT-111 Trial Design

COVALENT-111: A Phase 1/2 Randomized, Double-Blind, Placebo-Controlled Single and Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of BMF-219, an Oral Covalent Menin Inhibitor, in Healthy Adult Subjects and in Adult Subjects with Type 2 Diabetes Mellitus (NCT05731544)

Phase 1 (SAD)

SAD C1 to SAD C4 (HVs)
Total N=40
Dose [100, 200, 400, and 600 mg]

Phase 2 (MAD)

MAD C1 (HVs)
Total N = 16

MAD C2 to MAD C8 (T2DM)
Total N=108

Dose [100, 200, 300, 400, 600 mg]

In Phase 2, COVALENT-111 is enrolling subjects with an HbA1c of 7-10% despite being on standard of care (up to three T2DM agents).

Study Treatment: BMF-219

- A covalent small molecule menin inhibitor, administered orally daily in 28 day cycles

Primary Objective:

- Evaluate safety and tolerability of BMF-219

Secondary Objectives:

- Evaluate PK of BMF-219
- Evaluate the effect on BMF-219 on glycemic parameters (HbA1c, PG) and few additional parameters using OGTT, 7-day CGM
- Evaluate the changes in beta cell function
- Evaluate impact on lipid parameters, body weight etc.

Exploratory Objectives:

- To assess the durability of response to glycemic parameters

COVALENT-111 Dosing Scheme

Dose Escalation Phase (Oral, Daily Dosing X 28 days) as of March 28, 2023

Dosing Scheme

400 mg → Coming soon

200 mg → In progress

100 mg → Completed

- **Cohort 1** Healthy Volunteer
- **Cohort 2** Taken w/ food
- **Cohort 3** Taken w/o food

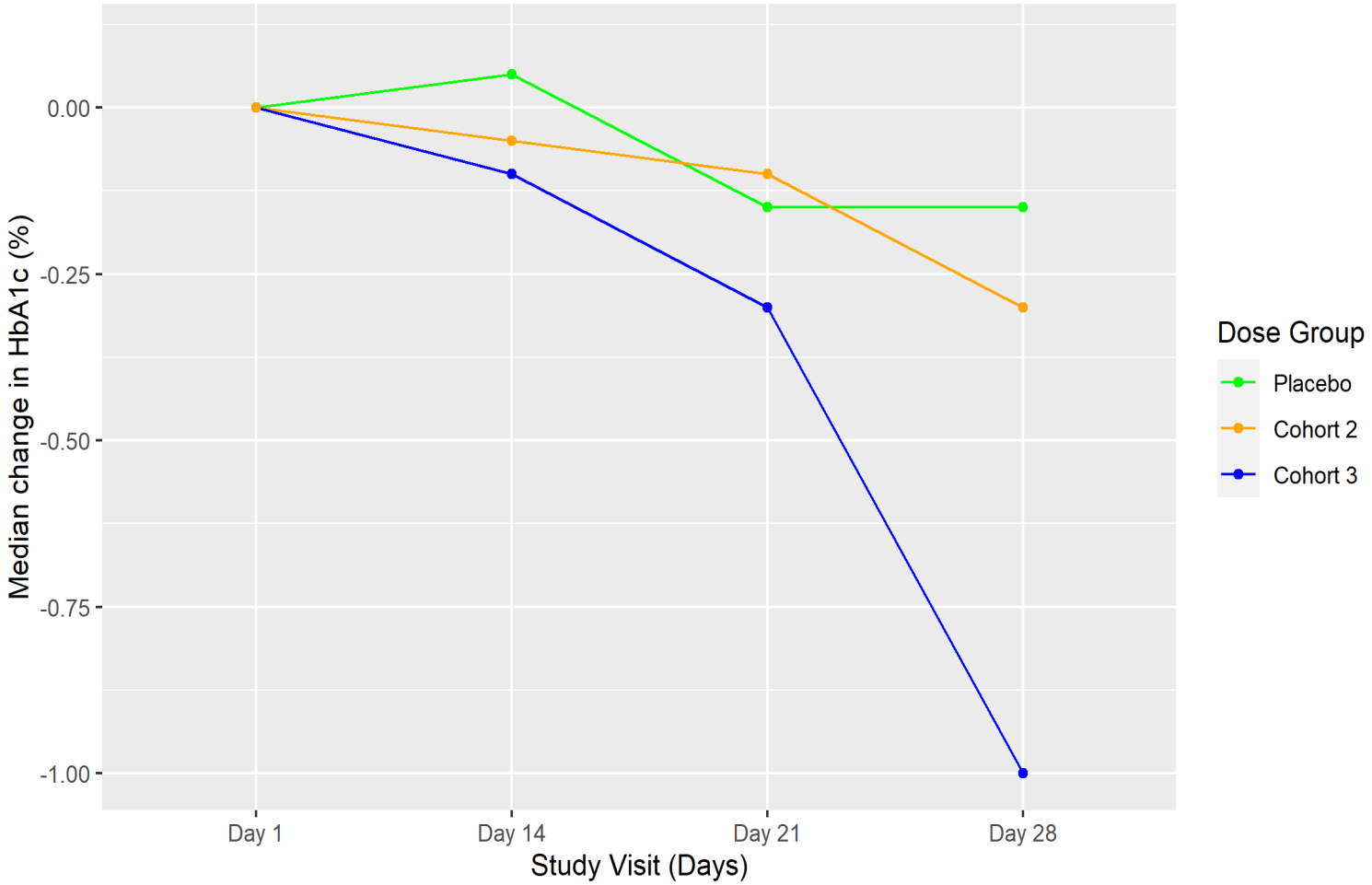
- Dose Escalation Phase (Total N) = 60 Type 2 Diabetes
  - Each dose cohort [N=10 active, 2 placebo]
  - Key Inclusion criteria: HbA1c= 7-10%; Time since diagnosis within 15 yrs. on stable anti-diabetic regimen (up to 3 agents) for at least 2 months prior to enrollment.
  - (H.V.) Study treatment duration – once daily dosing for 14 days
  - (T2DM) Study treatment duration – once daily dosing for 28 days
  - Follow-up duration – 5 months post completion of study treatment
- Dose Expansion Phase at two dose levels (Total N) = 24 Type 2 Diabetes

COVALENT-111 Baseline Patient Characteristics

	Cohort 2		Cohort 3	
	BMF-219	**Placebo**	**BMF-219**	**Placebo**
Number of Subjects	10	2	10	2
Age (min, max)	35, 60	40, 53	38, 63	35, 61
Sex (M, F)	7, 3	2, 0	6, 4	2, 0
Time since T2DM diagnosis (min, max)	4 yrs, 14 yrs	~1 yrs, 5 yrs	6 mo, 9 yrs	9 mo, 9 yrs
Concurrent Medications for T2DM	▪ Metformin (7/10) ▪ Janumet (1/10) ▪ Jardiance [Metformin + Empagliflozin] (1/10) ▪ Synjardy [Metformin + Empagliflozin] (1/10)	▪ Metformin alone (1/2) ▪ Janumet [Metformin + Sitagliptin] (1/2)	▪ Metformin alone (9/10) ▪ Janumet and Farxiga [Dapagliflozin] (1/10)	▪ Metformin (2/2)

Note: **Cohort 2** – 100 mg BMF-219 or placebo daily for 4 weeks taken with food
Cohort 3 – 100 mg BMF-219 or placebo daily for 4 weeks taken without food

Observed HbA1c Lowering of BMF-219 as presented on March 28, 2023



Cohort 2

Response Rate

70% of patients responded to BMF-219

HbA1c (all pts)

Median Baseline: 7.9%

Median Δ: - 0.3% (at week 4)

Cohort 3

Response Rate

89% of patients responded to BMF-219

HbA1c (all pts)

Median Baseline: 7.8%

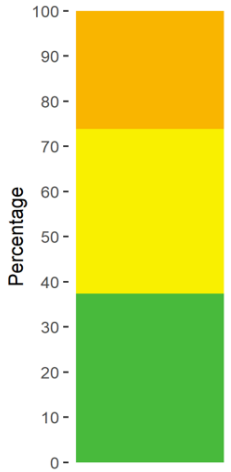
Median Δ: - 1.0% (at week 4)

COVALENT-111 HbA1c Summary Results at Week 4 as presented on March 28, 2023

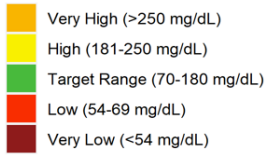
	Cohort 2 (100 mg with food)		**Cohort 3** (100 mg without food)	
	BMF-219	**Placebo**	**BMF-219**	**Placebo**
Number of Subjects	10	2	10	2
HbA1c (%) at Baseline	7.1 – 9.1		7.0 – 9.8	
Exposure: C_{max} (ng/mL)/ AUC (hr*ng/mL)	34.8 / 84.3	-	94.2 / 224	-
Median HbA1c (Mean) (%) at Baseline	7.9 (8.0)	8.4 (8.4)	**7.8 (8.1)**	7.8 (7.8)
Number of Subjects with Reduction in HbA1c at week 4	7/10 (70%)	1/2	**8/9 (89%)***	1/2
≥0.5% Reduction in HbA1c at Week 4	3/10 (30%)	1/2	**7/9 (78%)***	0
≥1% Reduction in HbA1c at Week 4	0	0	**5/9 (56%)***	0
Median Change in HbA1c at Week 4 (Mean) (%)	-0.3 (-0.25)	-0.1 (-0.1)	**-1.0 (-0.81)**	-0.15 (-0.15)

*Note: The active group denominator in Cohort 3 is 9 because the week 4 sample for one patient was unable to process.

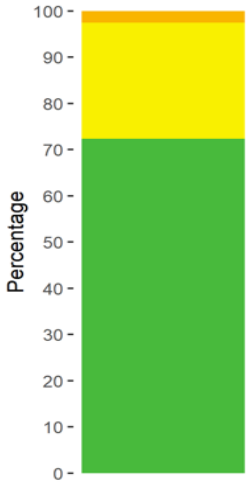
Case Report Cohort 3 Patient Results (Patient A): Glycemic Parameters (March 28, 2023)



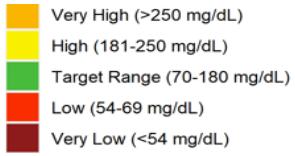
Continuous Glucose Monitoring
Baseline



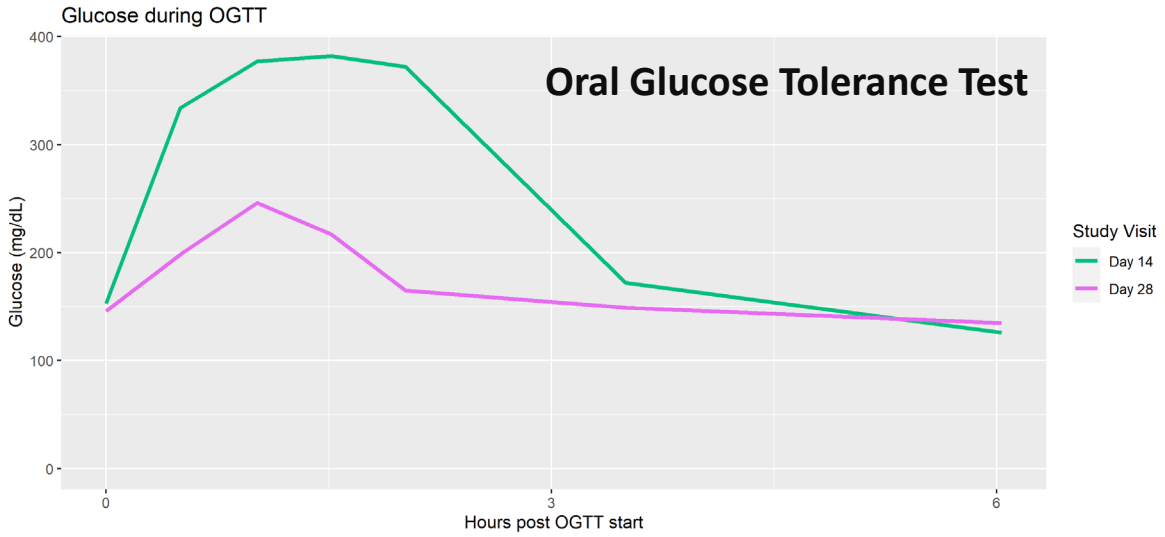
- Average glucose 205 mg/dL
- 37% time in Target Range

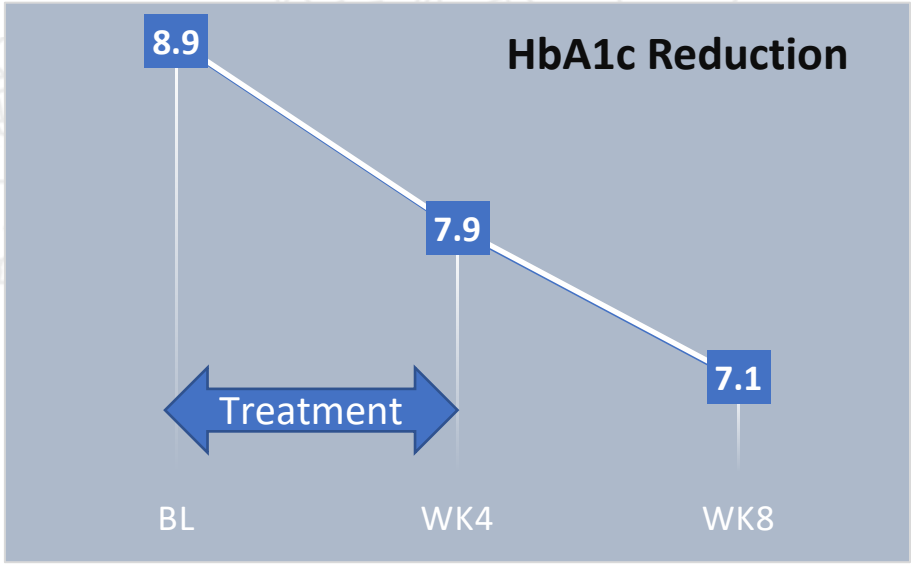


Continuous Glucose Monitoring
Week 4

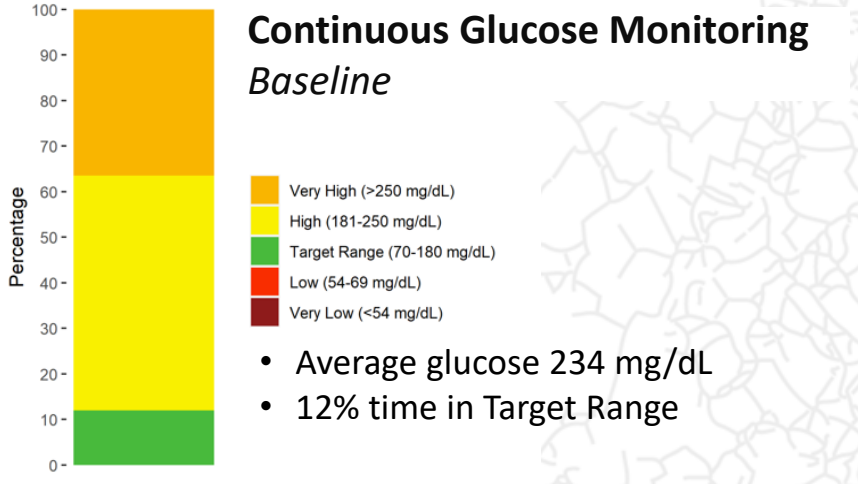


- Average glucose 169 mg/dL
- 72% time in Target Range



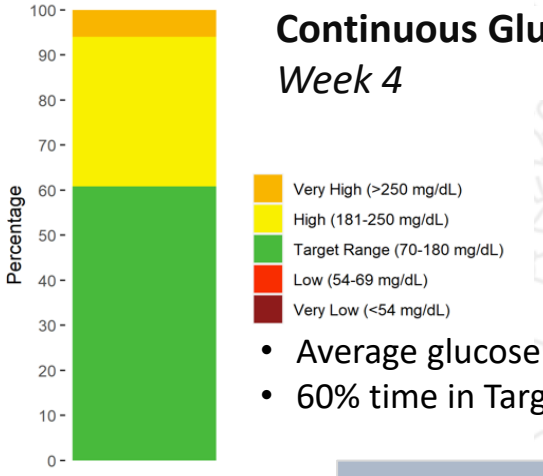


Case Report Cohort 3 Patient Results (Patient B): Glycemic Parameters (March 28, 2023)



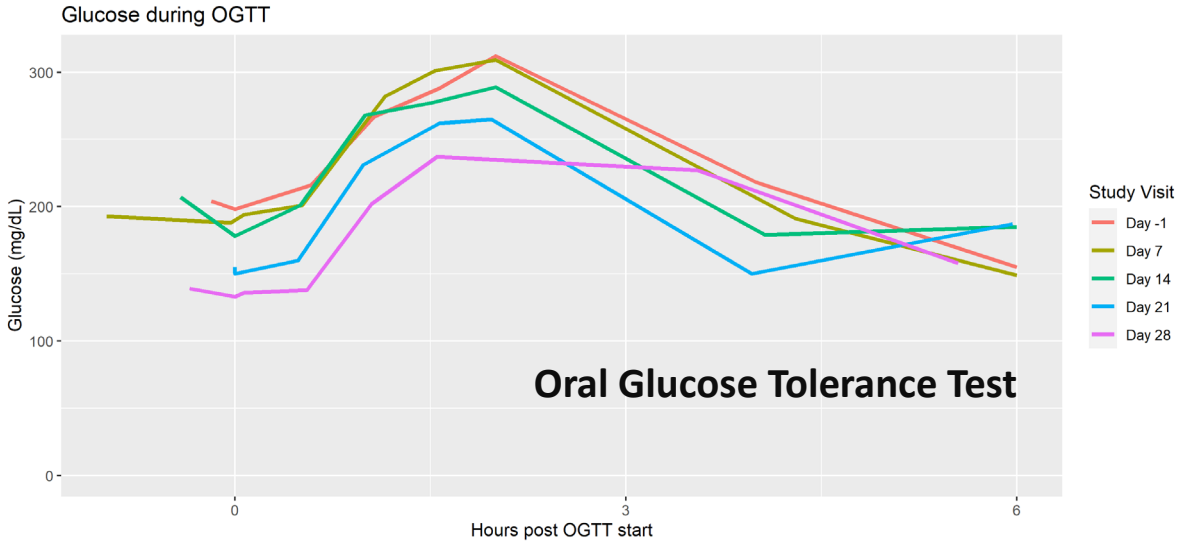
Continuous Glucose Monitoring
Baseline

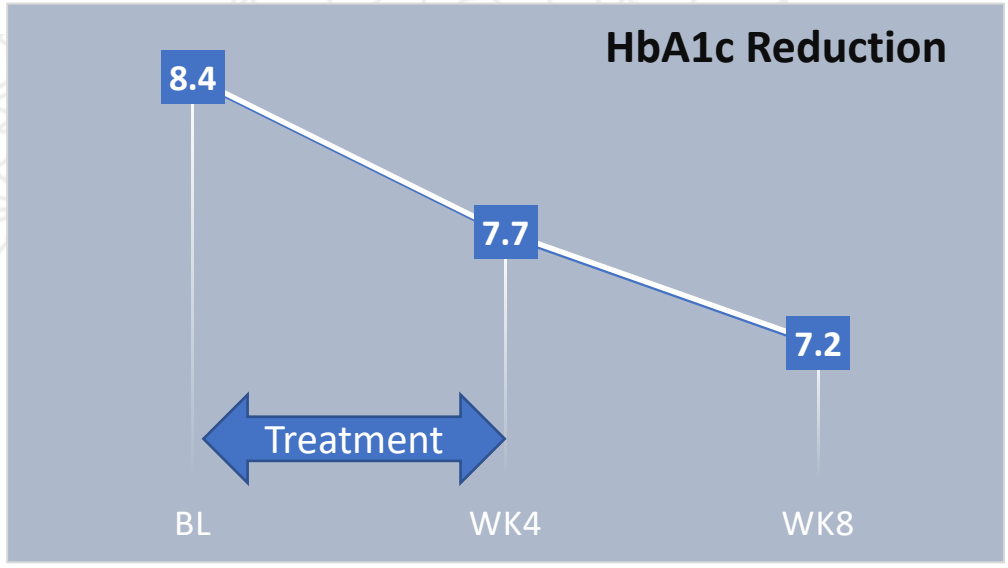
- Average glucose 234 mg/dL
- 12% time in Target Range



Continuous Glucose Monitoring
Week 4

- Average glucose 174 mg/dL
- 60% time in Target Range





COVALENT-111 Cohort 1 All Treatment Emergent Adverse Events (TEAEs) (March 28, 2023) (Healthy Volunteers, n=16; *100 mg once daily for 14 days*)

Preferred Term for TEAE	BMF-219 (N=12)	Placebo (N=4)	Total (N=16)
Subjects with ≥1 TEAE	2 (16.7%)	1 (25%)	3 (18.8%)
Headache	1 (8.3%)	1 (25%)	2 (12.5%)
Sharp left eye pain	1 (8.3%)	0	1 (6.3%)

*All TEAEs were Grade 1

COVALENT-111 Cohort 2 & 3 All TEAEs (March 28, 2023) (Type 2 Diabetes n=24; 100 mg once daily dosing X 4 weeks)

Preferred Term for TEAE	BMF-219 (N=20)	Placebo (N=4)	Total (N=24)
Subjects with ≥1 TEAE	7 (35%)	2 (50%)	9 (38%)
Abdominal bloating	2 (10%)	0	2 (8.4%)
Elevated pancreatic polypeptide in plasma	0	2 (50%)	2 (8.4%)
Cough	1 (5%)	1 (25%)	2 (8.4%)
Elevated GGT	1 (5%)	0	1 (4.2%)
Elevated AST	1 (5%)	0	1 (4.2%)
Elevated ALT	1 (5%)	0	1 (4.2%)
Sore throat	1 (5%)	0	1 (4.2%)
Non-specific GI symptoms	1 (5%)	0	1 (4.2%)
Decreased interleukin-6	1 (5%)	0	1 (4.2%)
Swollen lymph nodes	0	1 (25%)	1 (4.2%)
Elevated lipase	1 (5%)	0	1 (4.2%)
Intermittent headaches	1 (5%)	0	1 (4.2%)
Contact dermatitis	1 (5%)	0	1 (4.2%)

All TEAEs are Grade 1 except Elevated Lipase (Grade 2)

Summary of Data as presented on March 28, 2023

Safety

- BMF-219 demonstrated a well-tolerated safety profile
- No dose discontinuations
- All 20 subjects completed 4 weeks of treatment and continue in 5-month follow-up period
- No severe or serious TEAEs were observed
- No episodes of symptomatic hypoglycemia occurred in any patients

Well-tolerated safety profiles are contributed by the fact that BMF-219 does not extinguish menin protein completely, it decreases the levels of menin protein transiently; BMF-219 is designed for short dosing period; newly created beta cells post treatment with BMF-219 have normal levels of menin protein

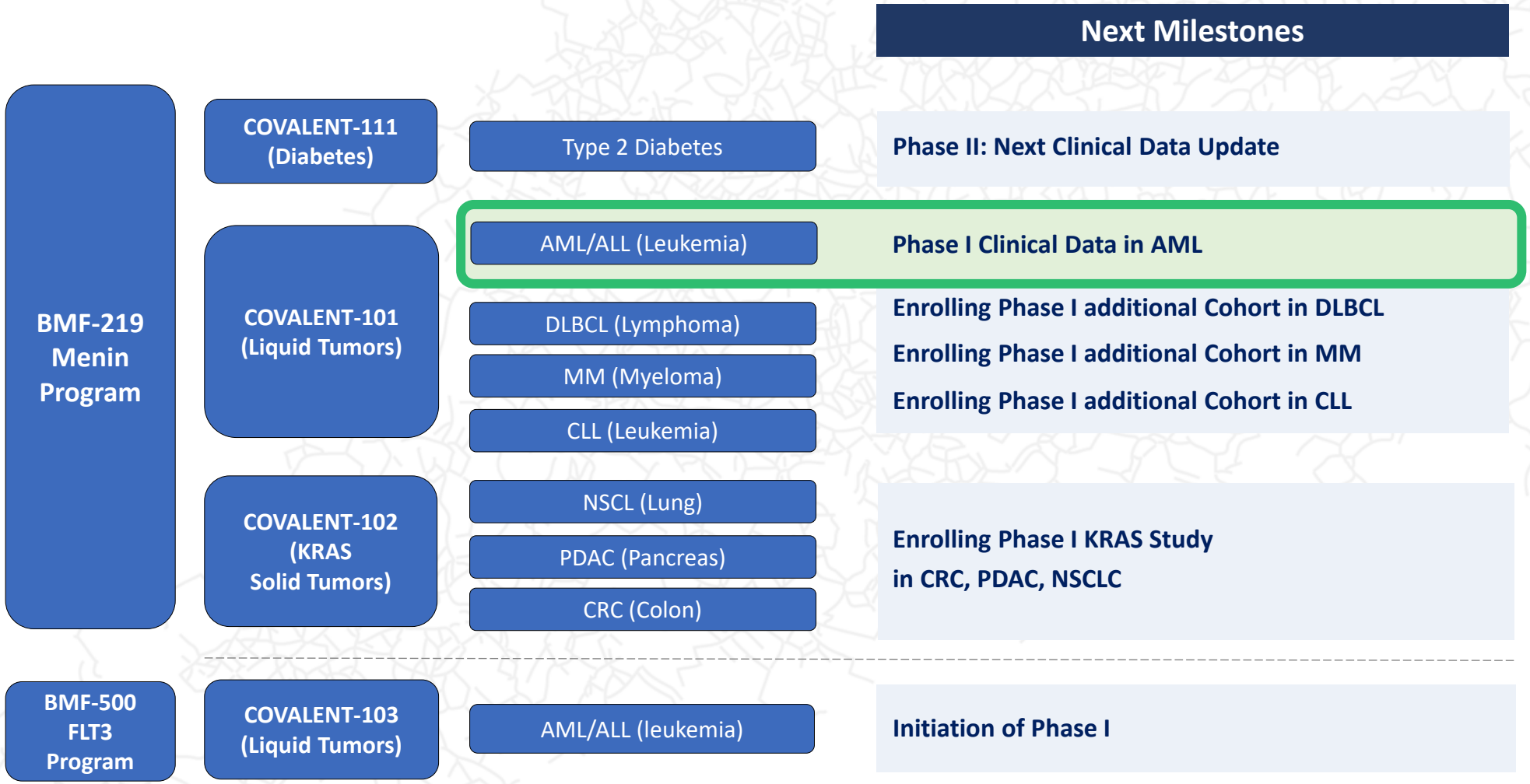
Efficacy

Cohort 3 highlights

- 89% pts achieved a reduction in HbA1c
- 78% pts achieved ≥ 0.5% reduction in HbA1c
- 56% pts achieved ≥ 1% reduction in HbA1c
- Positive trend in OGTT and CGM parameters

Novel Covalent Inhibitor of Menin

Pipeline-in-a-Pill – Single Agent for Multiple Indications



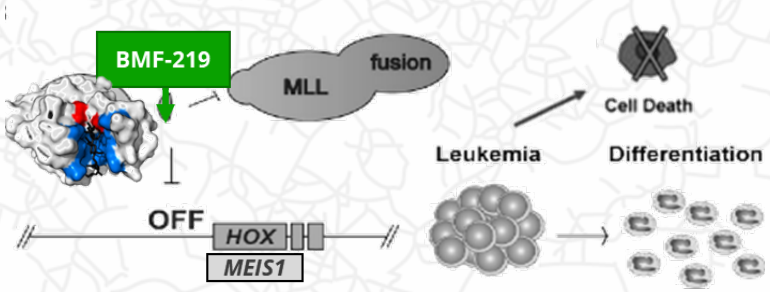
First Development Success with BMF-219 in MLL Fusion and NPM1 Driven Tumors

In Acute Leukemia

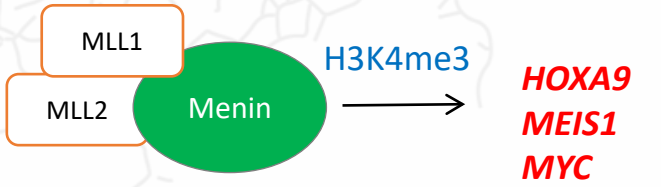
Development Stage:
Phase I Clinical Trial (COVALENT-101) enrolling patients with relapsed/refractory acute leukemia

Key Facts	MOA	Relevant Pathway
Estimated Addressable Population	BMF-219 covalently blocks menin / MLL interaction	Menin / MLL interaction can modify chromatin, activating key leukemic genes

Acute Leukemia (Mutation)	Estimated US Patient Population (Annual Incidence)
MLL-r	~2,500
NPM1 mutant	~6,000
Ras Driven	~6,000



- 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)

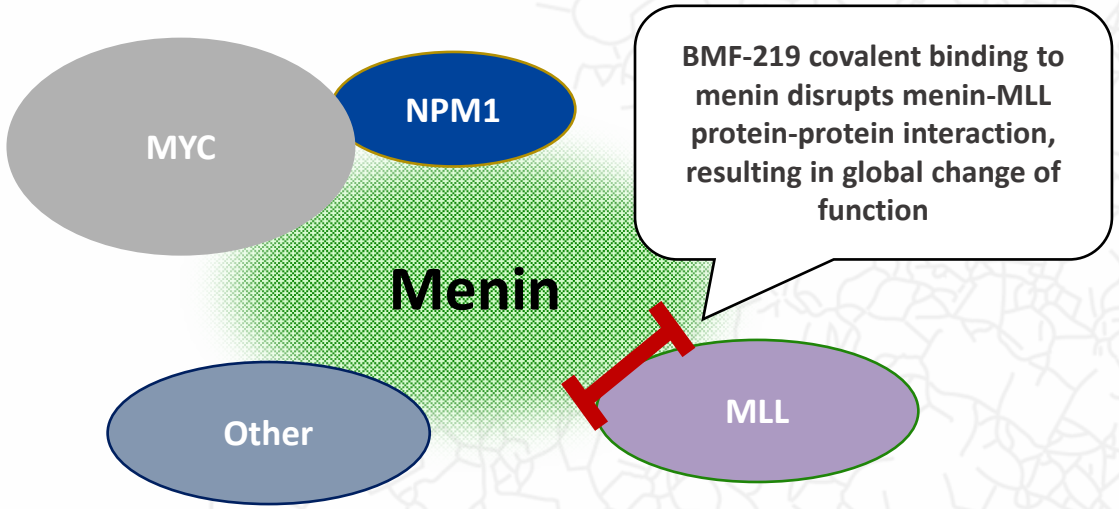


Menin / MLL complex forms and modifies chromatin at histone H3, activating *HOXA9* and *MEIS1*

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

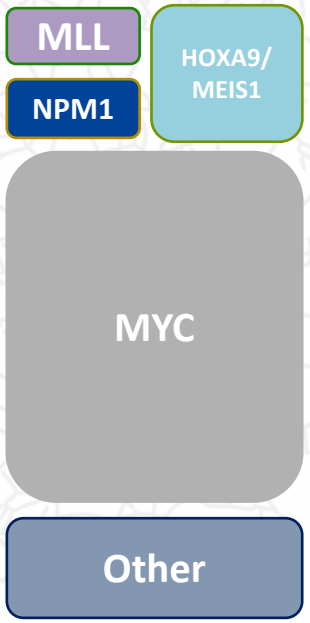
BMF-219 has the Potential to Impact Important Binding Partners in Multiple Tumors

Mechanism of Action



Resulting change of function of menin impacts important binding partners involved in oncogenesis

Target Patient Population



- Acute Leukemia: MLL-r
- Acute Leukemia: NPM1 mutant
- Acute Leukemia: Ras mutant
- DLBCL: DHT / DEL
- Multiple Myeloma: MYC addicted
- KRAS mutant Solid Tumors:
  Colorectal
  Lung
  Pancreatic
- CLL: r/r population
- Liquid and Solid Tumors

BMF-219 has the potential to address additional patient populations with tumors that are dependent on menin or some of its binding partners

BMF-219 Was Highly Selective in Key Screening and Safety Panels

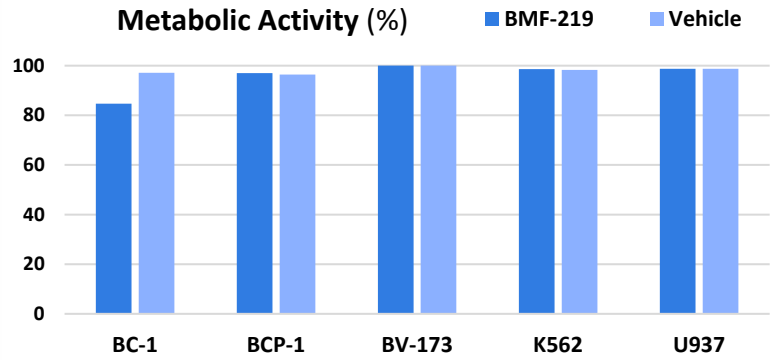
No Histopathology Findings Were Observed with BMF-219 in GLP and non-GLP IND-Enabling Toxicology Studies

✓ Kinase Screening

169 kinases screened; only **two** showed >50% inhibition with BMF-219

✓ Oncopanel Screen

Minimal impact of BMF-219 on cell metabolism in leukemia and lymphoma cell lines that have **wild type MLL1**



✓ Safety Screen

SafetyScreen44 panel (CEREP/Eurofins Discovery)* showed **no meaningful impact** (>50% activation or inhibition)

*SafetyScreen44 *in-vitro* panel of 44 common selected targets to identify significant off-target interactions

✓ Glutathione Reactivity

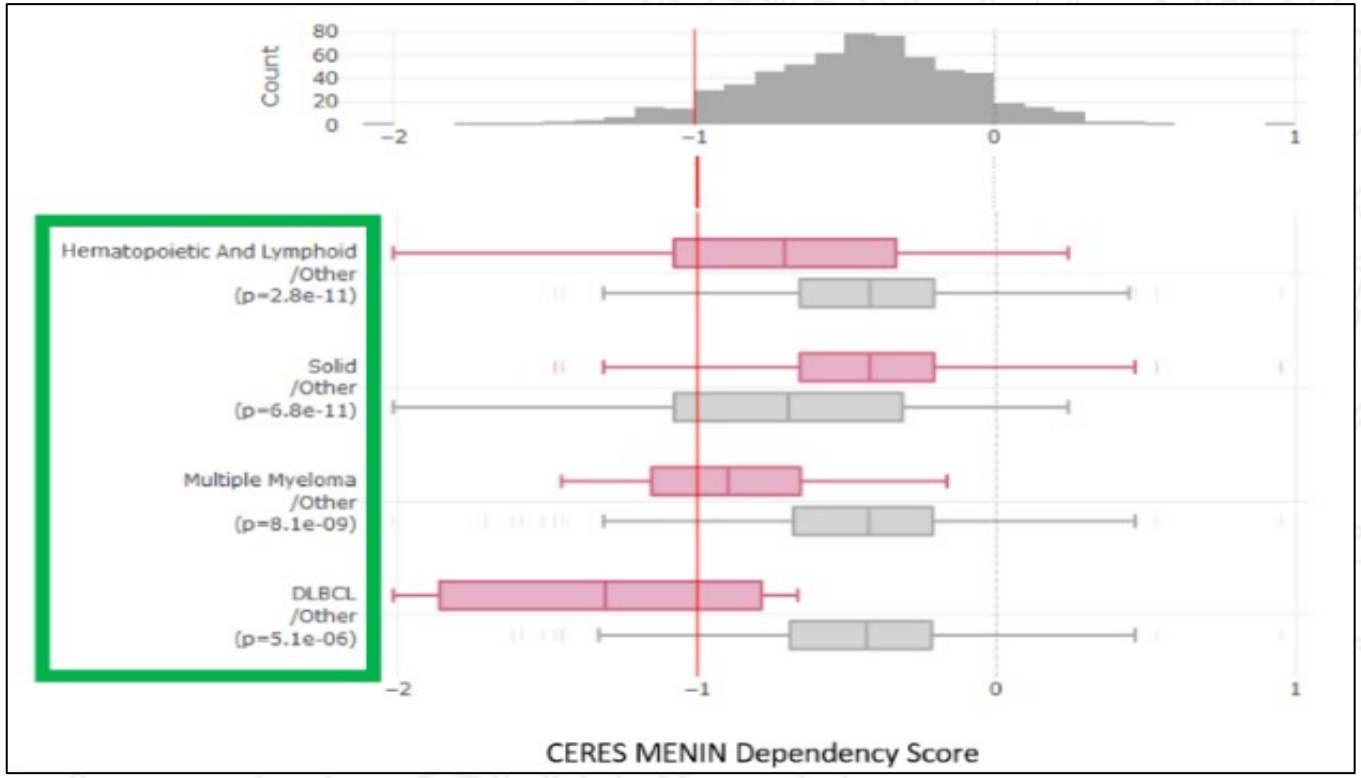
BMF-219 had **less reactivity than the approved covalent drugs omeprazole and neratinib**

Drug	Mean half-life (min)
Omeprazole	123.3
Neratinib	197.7
Ibrutinib	>360
BMF-213	322.3
BMF-214	>360
BMF-219	>360

Menin Dependencies Observed in Multiple Tumors

Acute Leukemia, DLBCL, MM & Other Tumor Types Have High Menin Dependency Based on Broad Institute DEPMAP Dataset

BROAD Institute Cancer Dependency Map (DEPMAP) for Menin (*MEN1*)

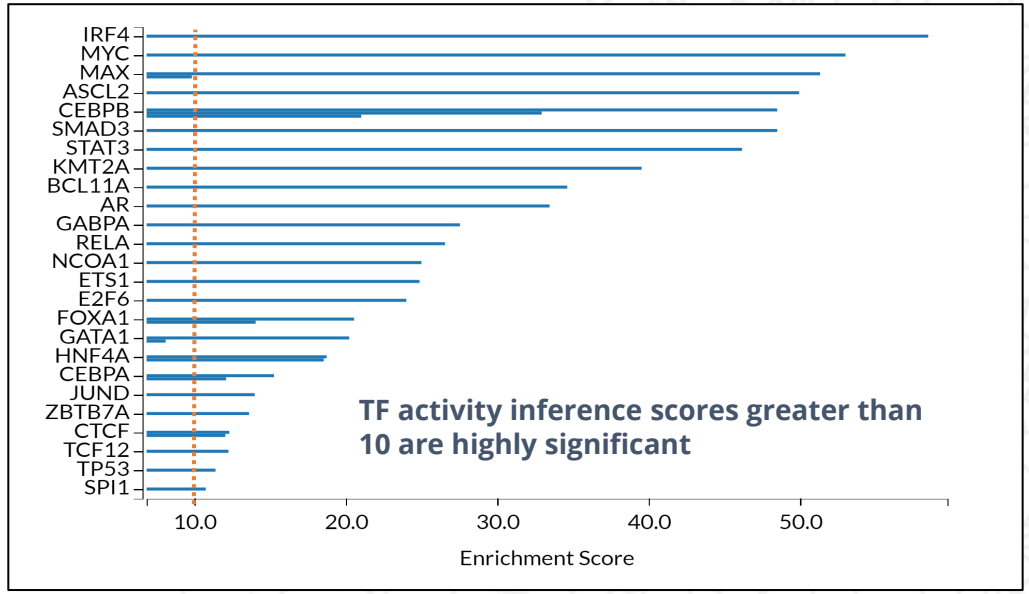


- Cell viability scores have shown that **menin** plays a key role in **survival of multiple tumors**
- **High menin dependency in liquid and solid tumors,** beyond acute leukemias, provides rationale for further analysis in dependent tumor types
- Biomea is exploring the potential for **covalent inhibition of menin in a variety of liquid and solid tumor types**

Note: CERES MENIN Dependency scores less than -1 in various tumor types imply that menin is considered essential for cell survival in those tumor types

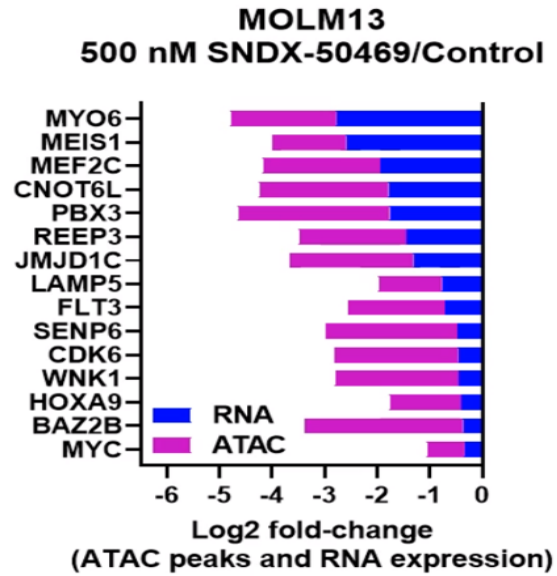
BMF-219 Shown to Disrupt MYC Genomic Function via Broad Impact on the Complexes Surrounding Menin

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.

Non-Covalent Menin Inhibitor – SNDX-50469



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

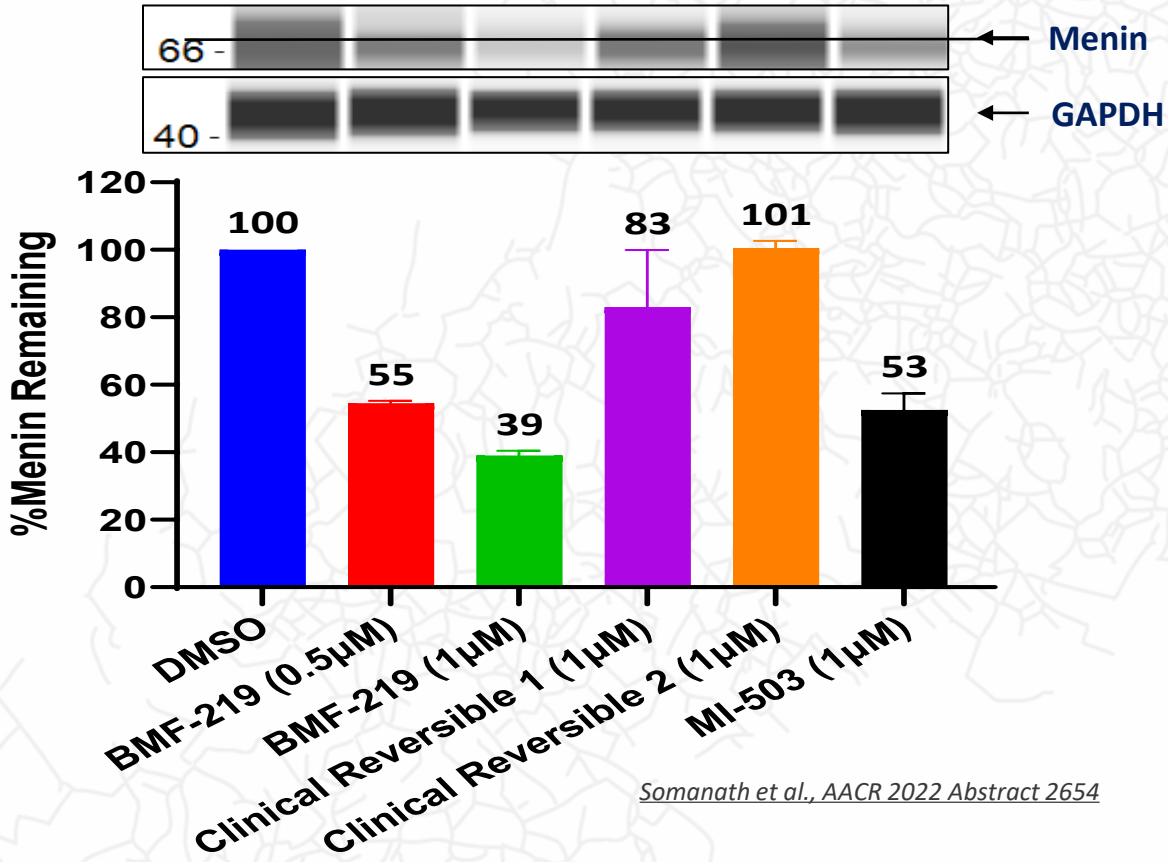
- **In MOLM-13 cells treated with BMF-219, the top transcription factors regulating gene expression are MYC and MAX**
- IRF4, MYC, and MAX are known drivers for some forms of DLBCL, (addicted) multiple myeloma, and multiple additional tumors

- **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

BMF-219 Significantly Reduced Menin Protein in DLBCL Cell Line

Menin Protein Levels in BMF-219 Toledo (DLBCL- DHL) cell line

14 hours



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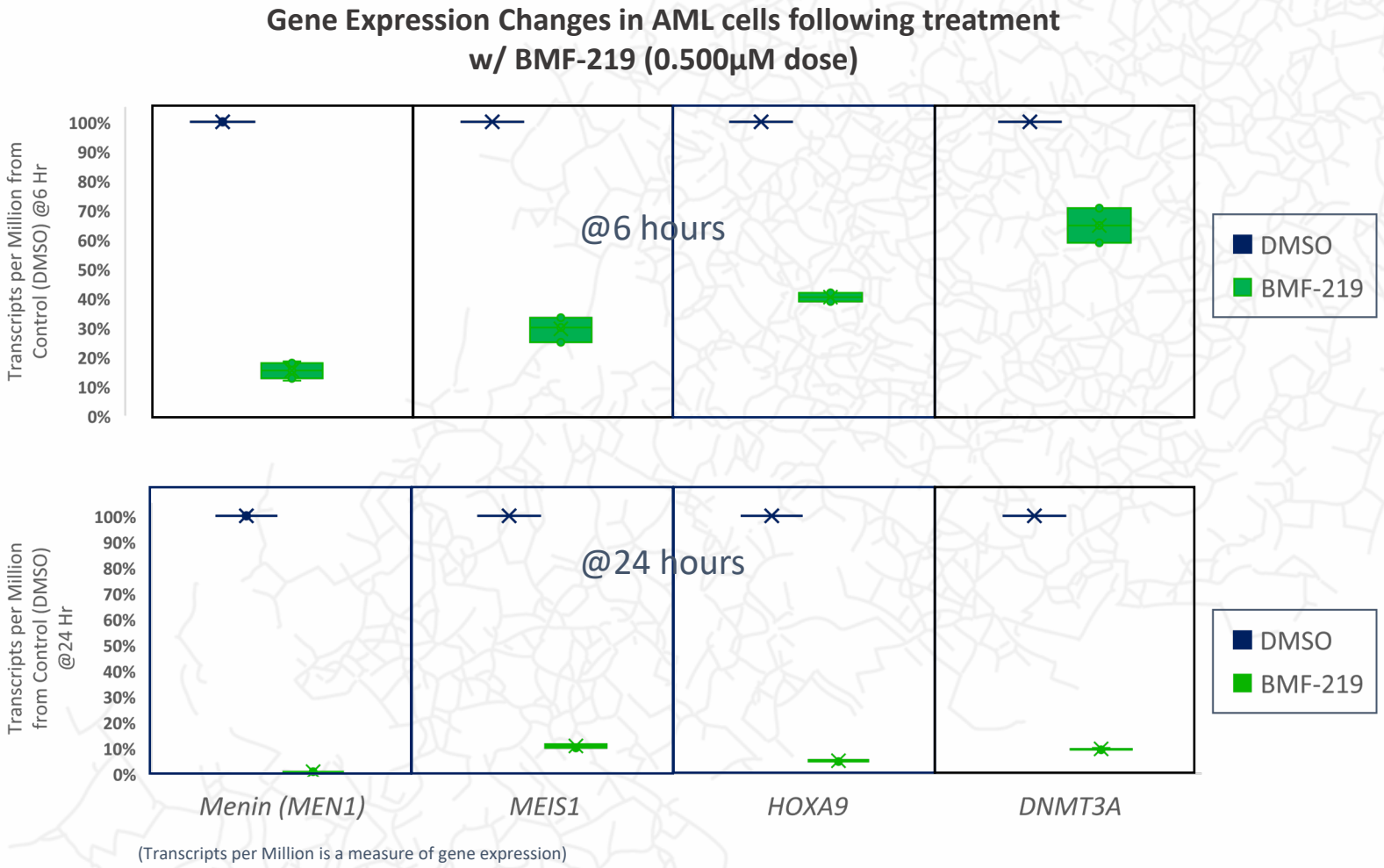
- Covalent inhibitor, BMF-219, at 1µm concentration achieves >60% reduction of menin protein at 14hrs
- Clinical reversible (non-covalent) inhibitors of menin achieved less than 20% reduction of menin protein at the same concentration

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

BMF-219 Demonstrated Rapid and Near Complete Reduction of Expression of Oncogenes

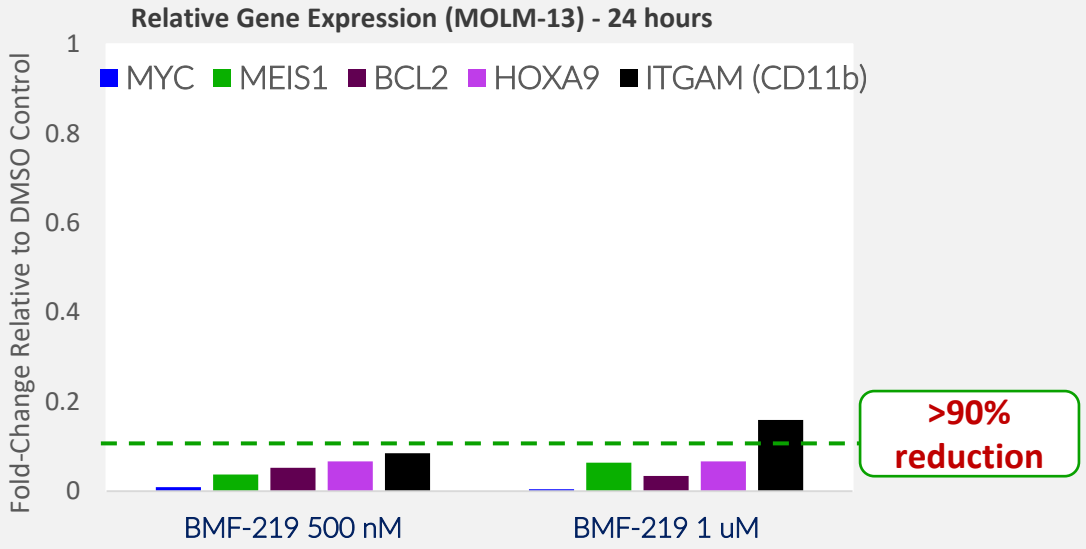


(Transcripts per Million is a measure of gene expression)

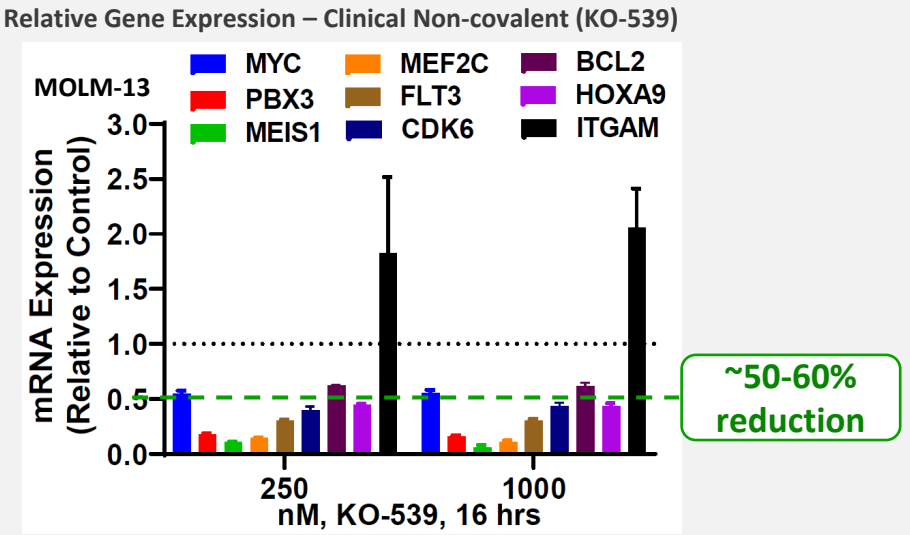
- Covalent inhibitor, BMF-219, downregulates expression of Menin (via the target *MEN1* gene) and critical leukemogenic genes (e.g., *MEIS1* and *HOXA9*)
  - *MEIS1* is a gene that can be an accelerator of leukemic transformation (along with *HOXA9*)
  - *HOXA9* is a gene involved in myeloid differentiation 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

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

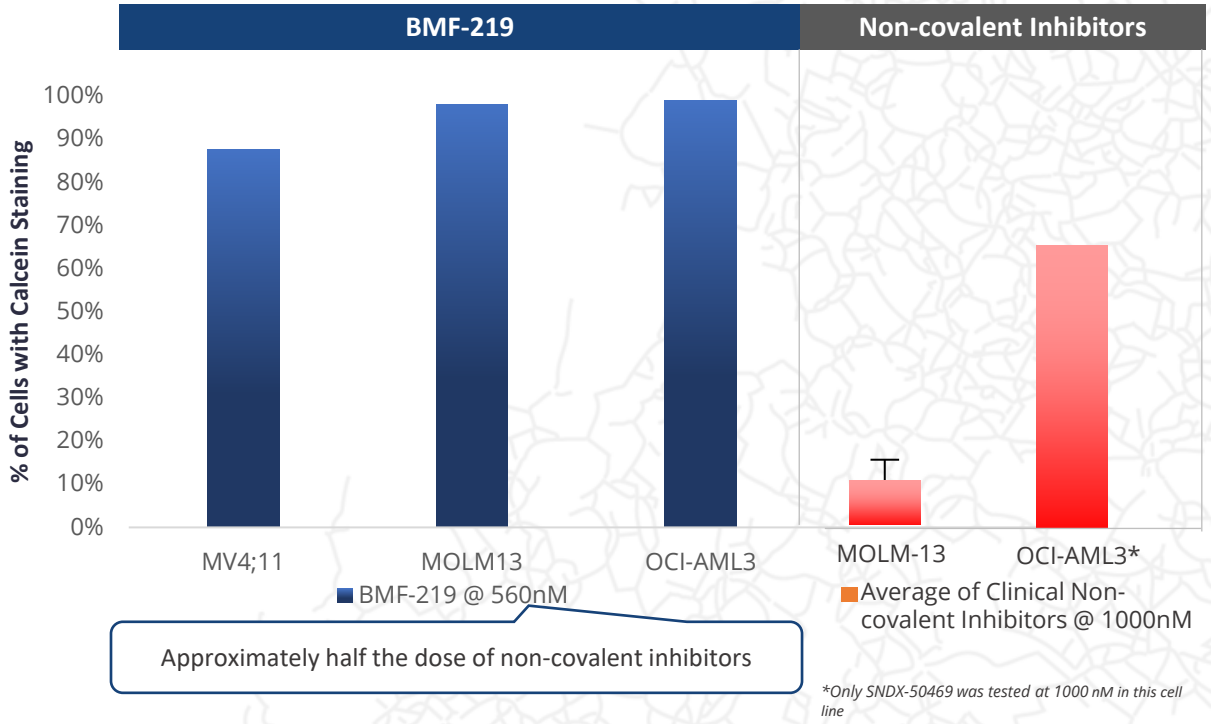


Blood (2021) 138 (Supplement 1): 3357

- 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

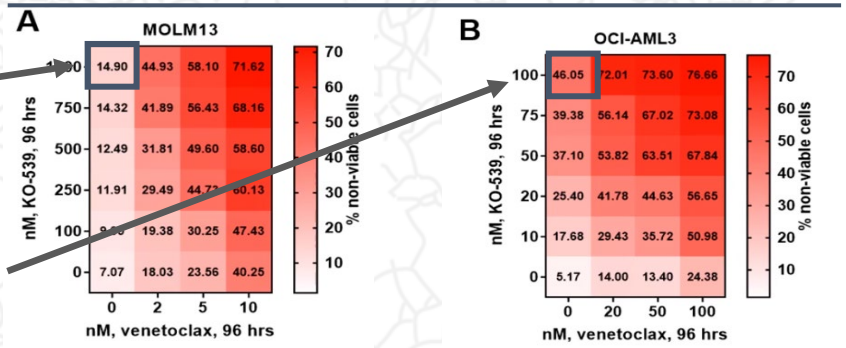
- BMF-219 **killed >90% of AML cells** in MLL-rearranged and NPM1 mutant cell lines at 4 days post-treatment
- Non-covalent menin inhibitors generally report significantly less cell killing of AML cell lines as a single agent

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

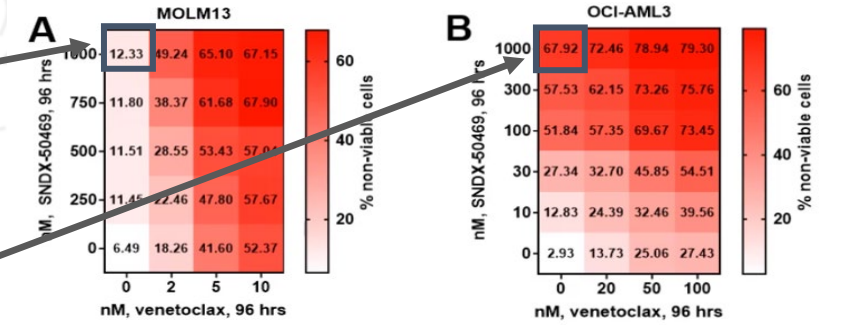
46% effective @ 100nM



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

12% effective @ 1000nM

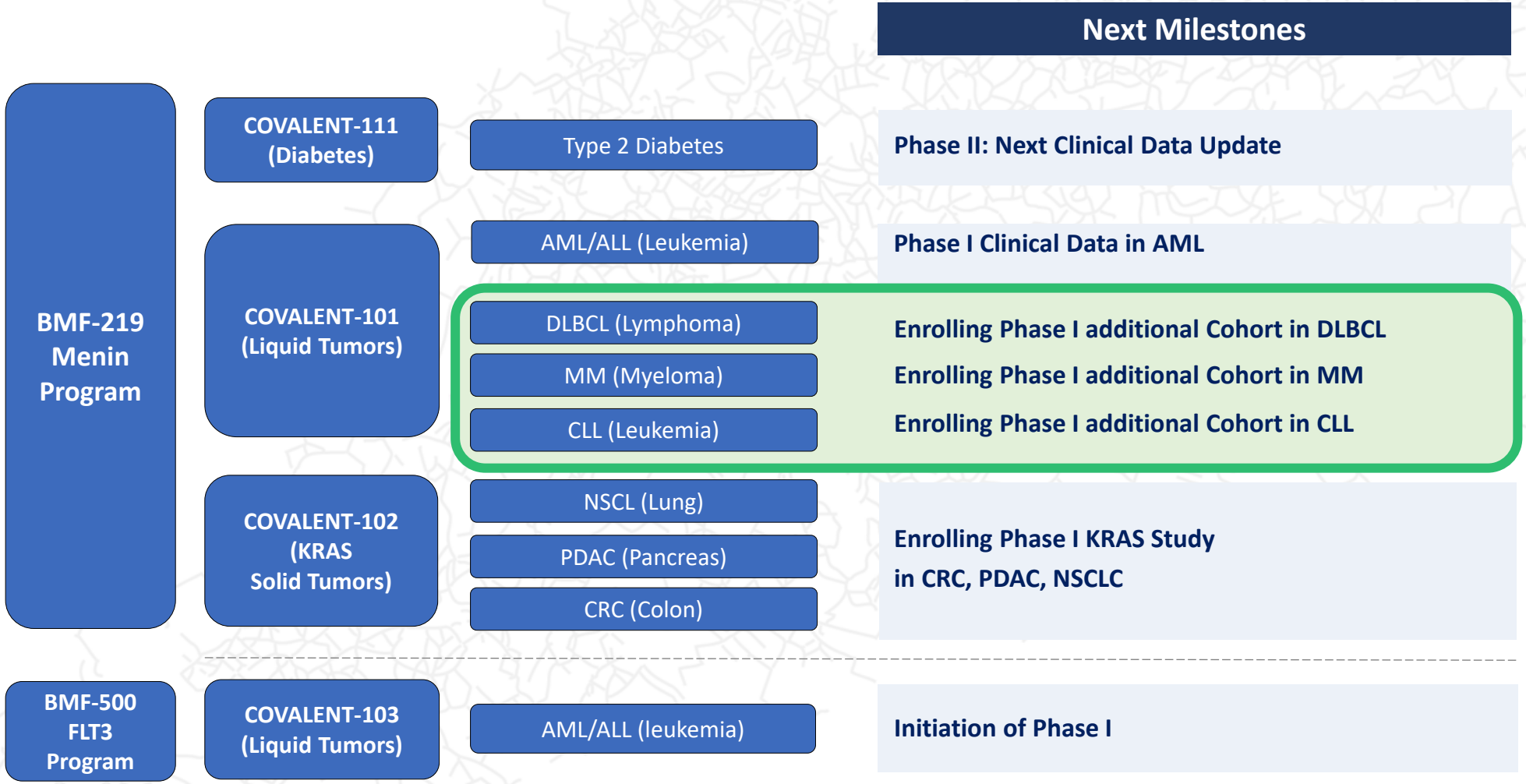
68% effective @ 1000nM



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

Novel Covalent Inhibitor of Menin

Pipeline-in-a-Pill – Single Agent for Multiple Indications



First Development Success with BMF-219 in MYC Addicted and MYC Driven Tumors

In 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

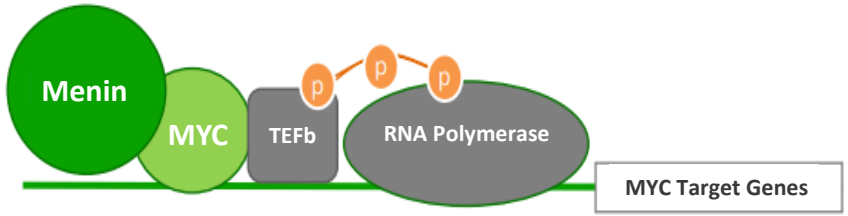
Estimated Addressable Population

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

- 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

MOA

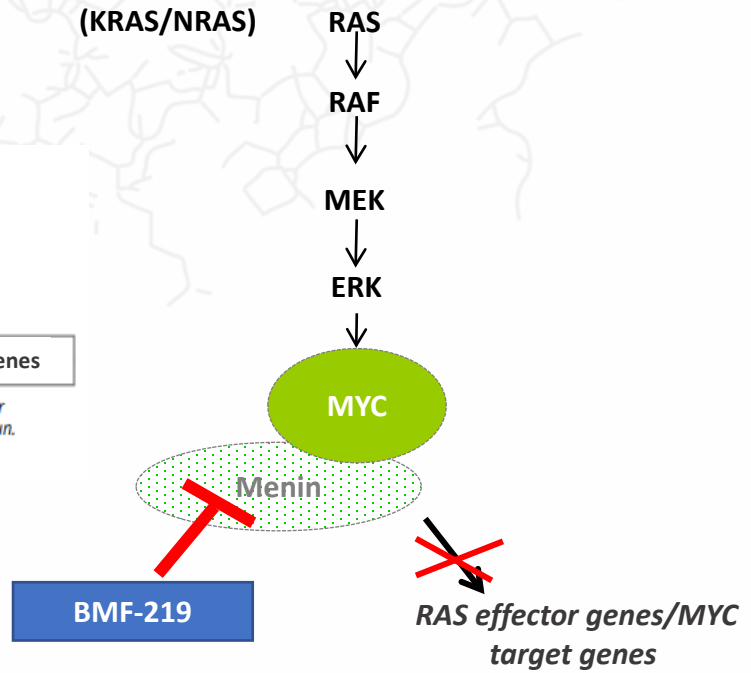
Menin complexes with MYC in the expression of MYC target genes. BMF-219 robustly decreases MYC gene expression and genomic function.
(Blood (2021) 138 (Supplement 1): 4318.)



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



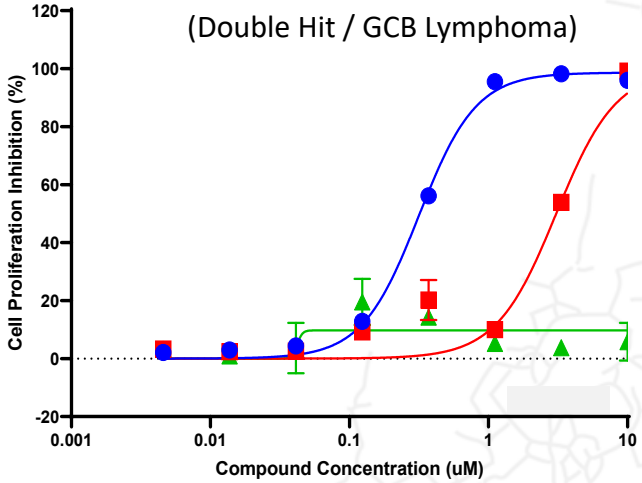
First Development Success with BMF-219 in MYC Addicted and MYC Driven Tumors

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)

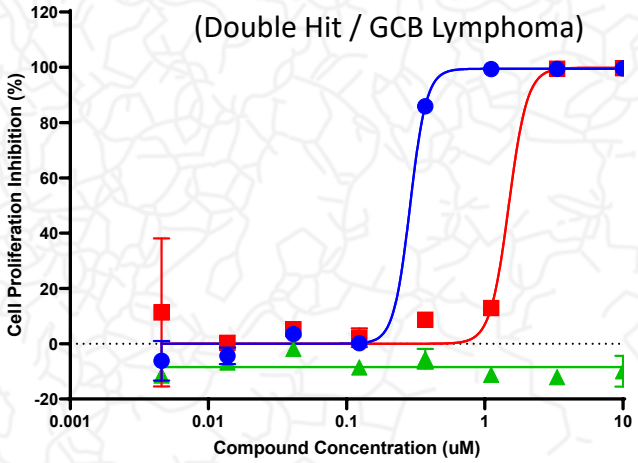


	IC50 (µM)	%Max
BMF-219	0.316	98.64
Clinical Non-covalent Inhibitor-1	3.07	100
Clinical Non-covalent Inhibitor-2	No Resp.	9.7

DB and Toledo cells were incubated with compounds for 4 days

TOLEDO

(Double Hit / GCB Lymphoma)



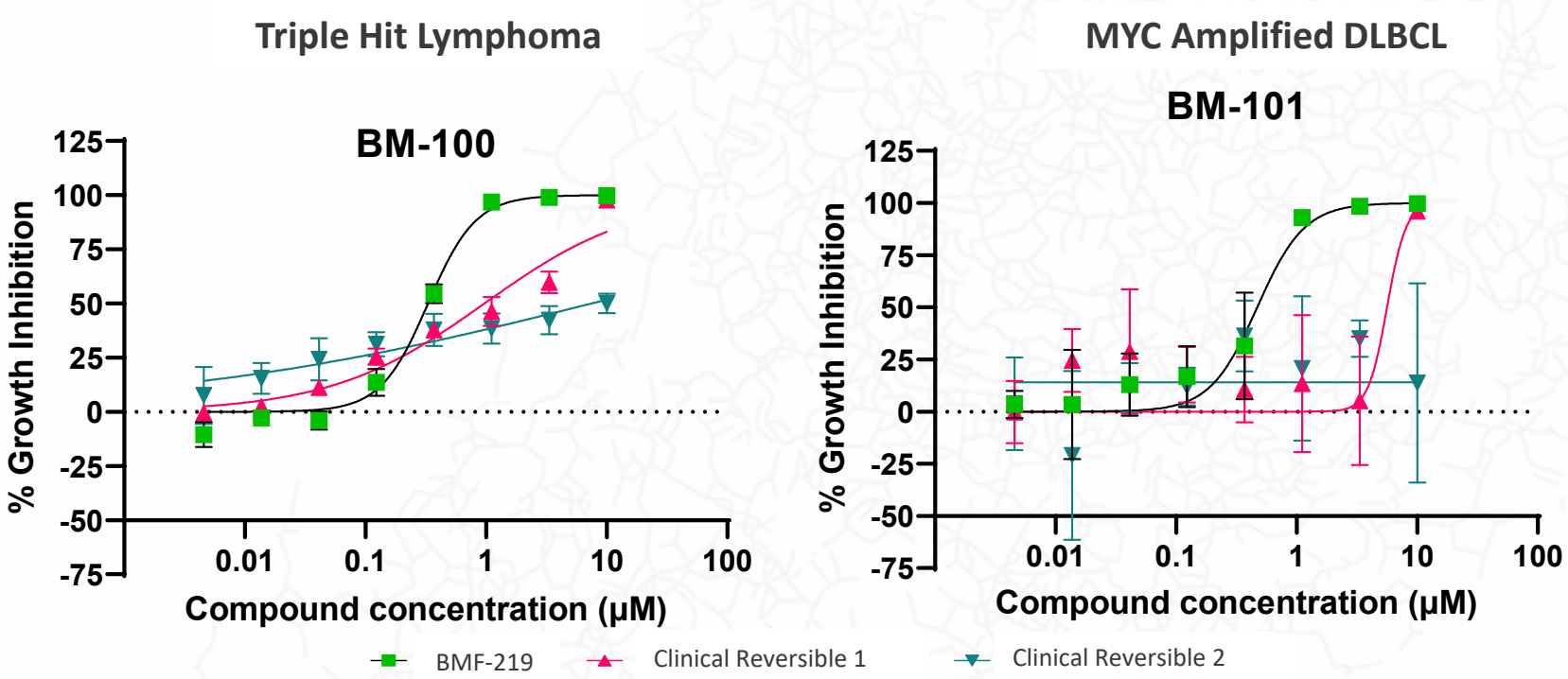
	IC50 (µM)	%Max
BMF-219	0.2877	99.47
Clinical Non-covalent Inhibitor-1	1.49	99.84
Clinical Non-covalent Inhibitor-2	No Resp.	-8.4

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 Led to near Complete Inhibition of Growth at 1µM in DLBCL in ex-vivo Samples



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

- At ~1µM exposure, 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

Somanath et al., AACR 2022 Abstract 2654

First Development Success with BMF-219 in MYC Addicted and MYC Driven Tumors

BMF-219 Exerts 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 were significantly less effective (20-35% cell killing with 3 µM MI-503)

In Chronic Lymphocytic Leukemia (CLL)

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

Key Facts

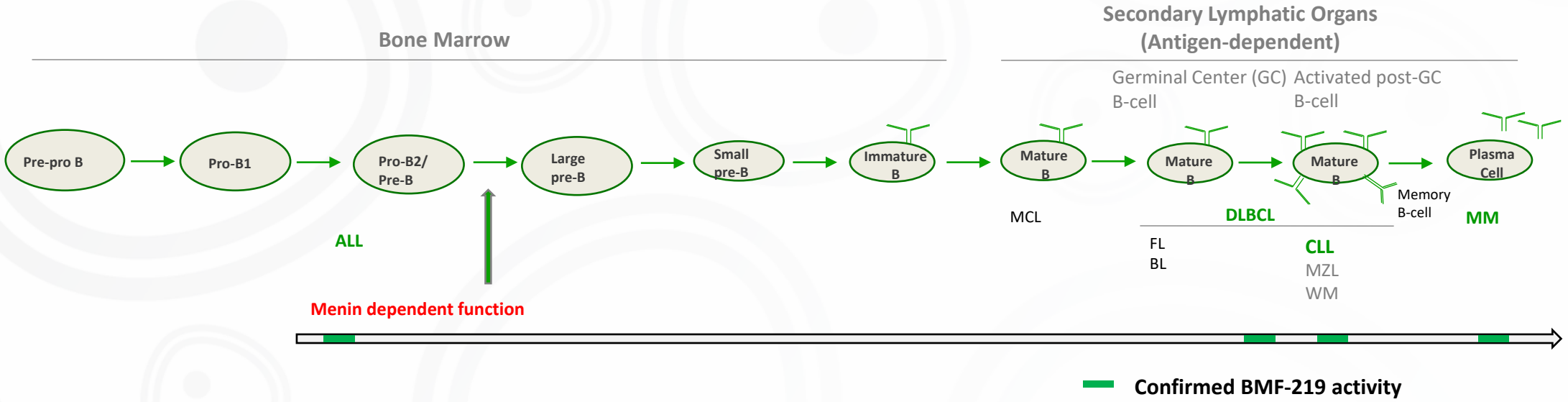
Disease	Estimated US Patient Population (Annual Incidence)
CLL (r/r)	~8,000

MOA

Menin complexes with MYC in expression of MYC target genes. BMF-219 robustly decreases MYC gene expression and downregulates the expression of BCL2 in cells.

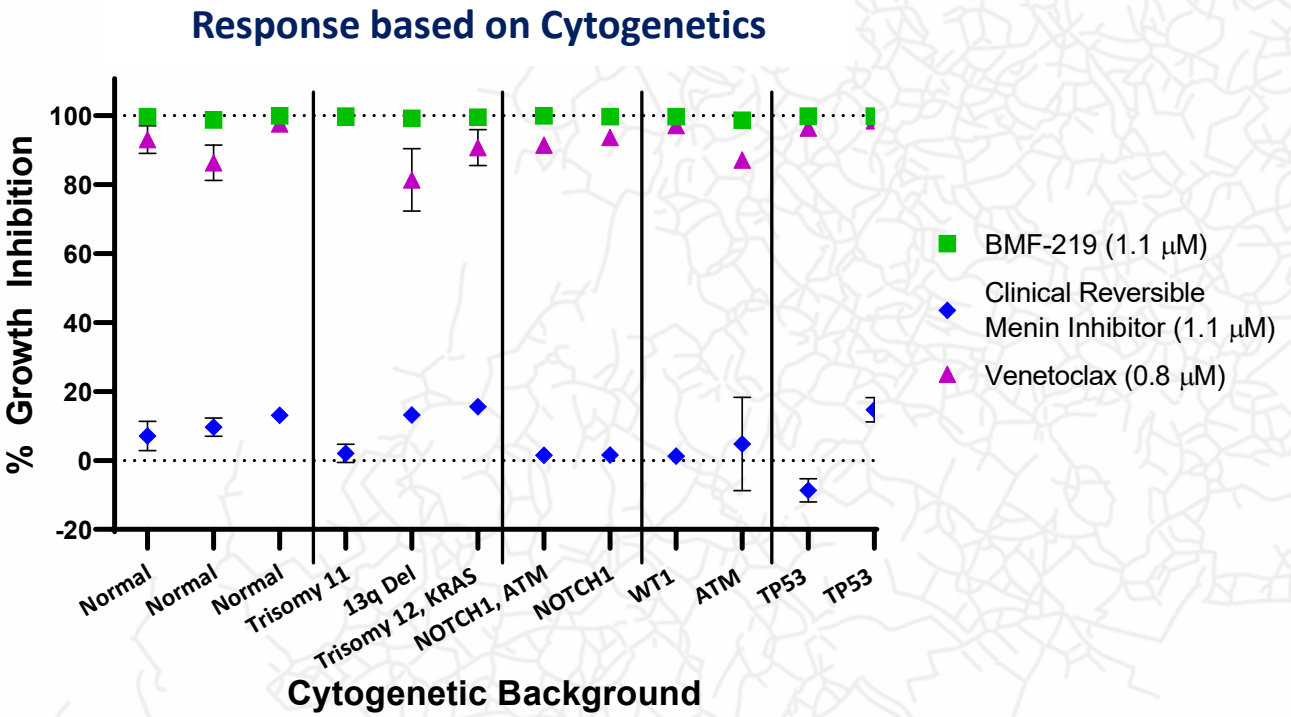
Relevant Pathway

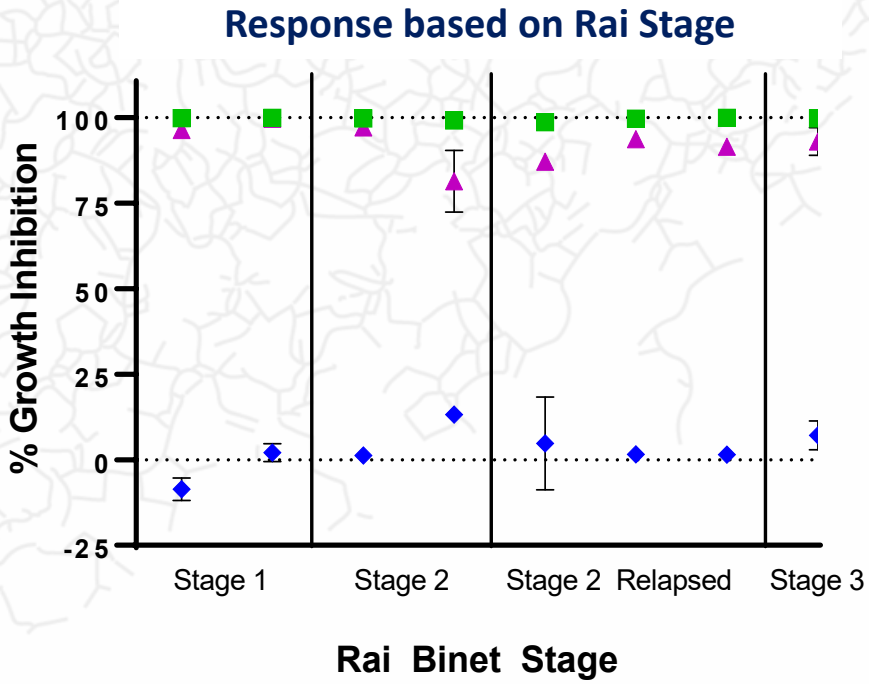
Tumor leverages the MAPK pathway



BMF-219 Achieves >98% Cell Lethality Against Diverse CLL ex vivo models

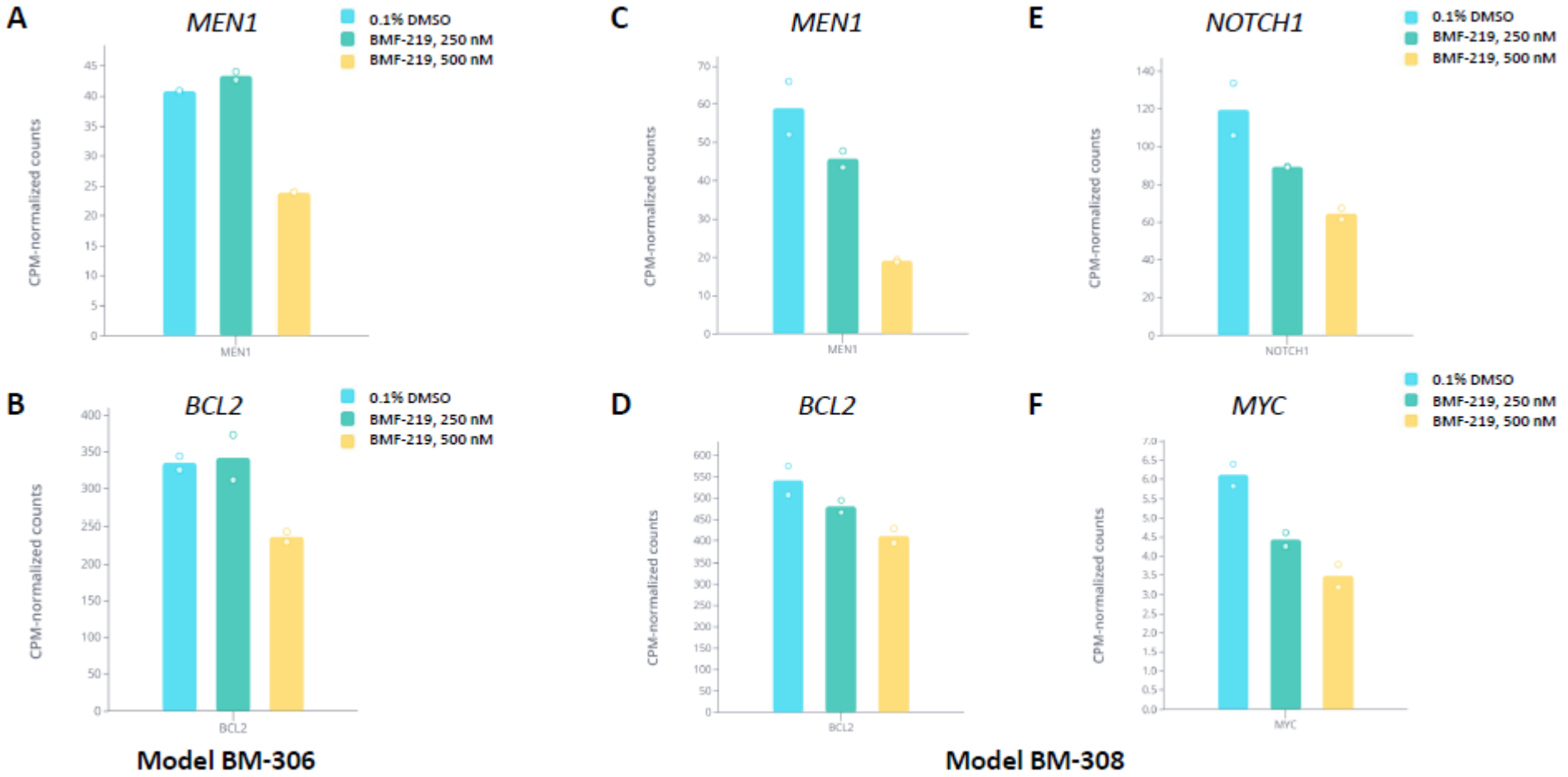
Growth inhibition of BMF-219 in CLL *ex vivo* models grouped by genetic background and Rai stage





Somanath et al., ASCO 2022 Abstract 7541

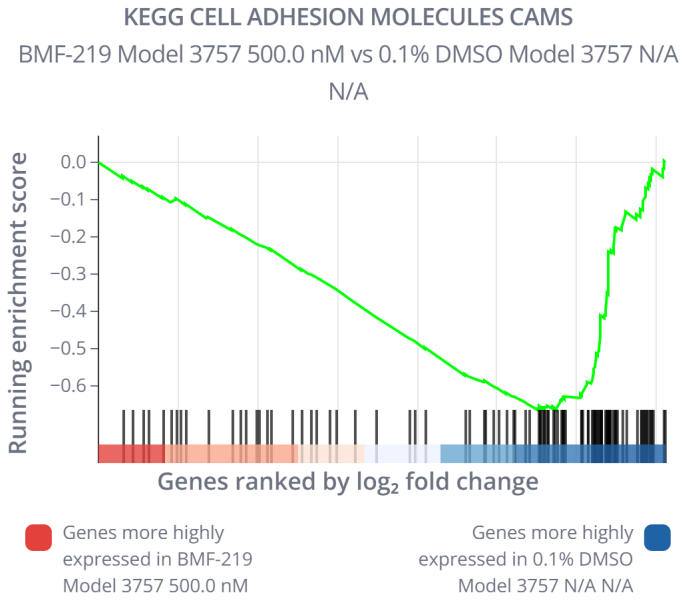
BMF-219 exerts dose dependent reduction of menin target genes in CLL patient samples

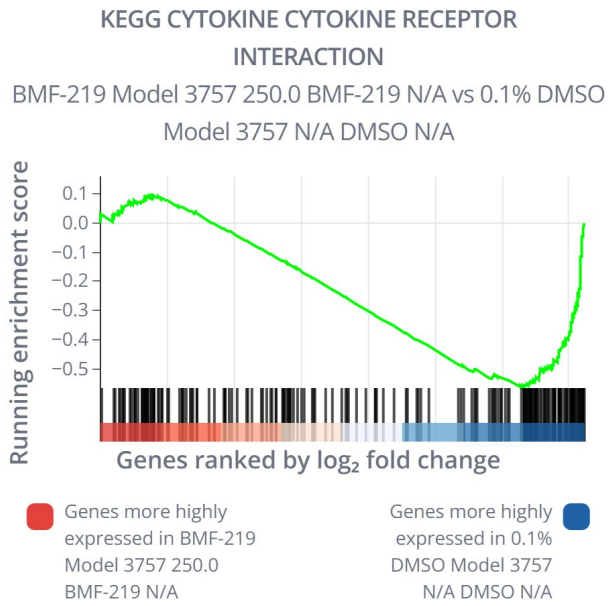


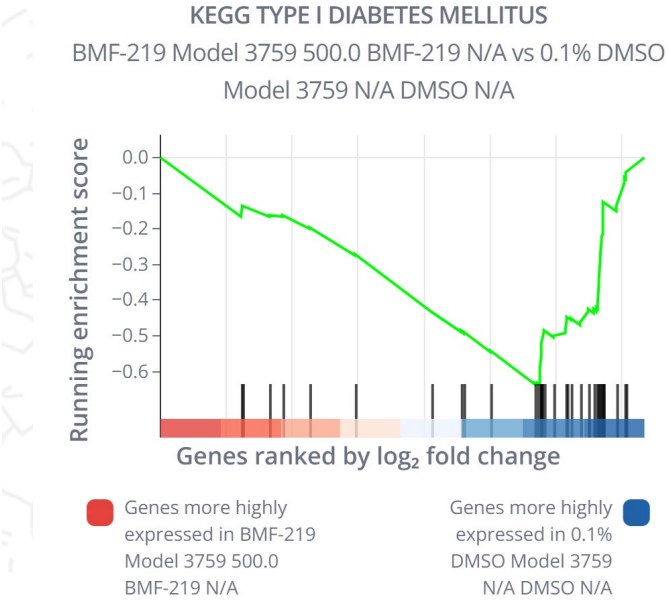
Somanath P., et al. AACR 2023 (#473)

First Development Success with BMF-219 in MYC Addicted and MYC Driven Tumors

BMF-219 downregulates cell adhesion, cytokine signaling and autoimmune pathways in CLL patient samples





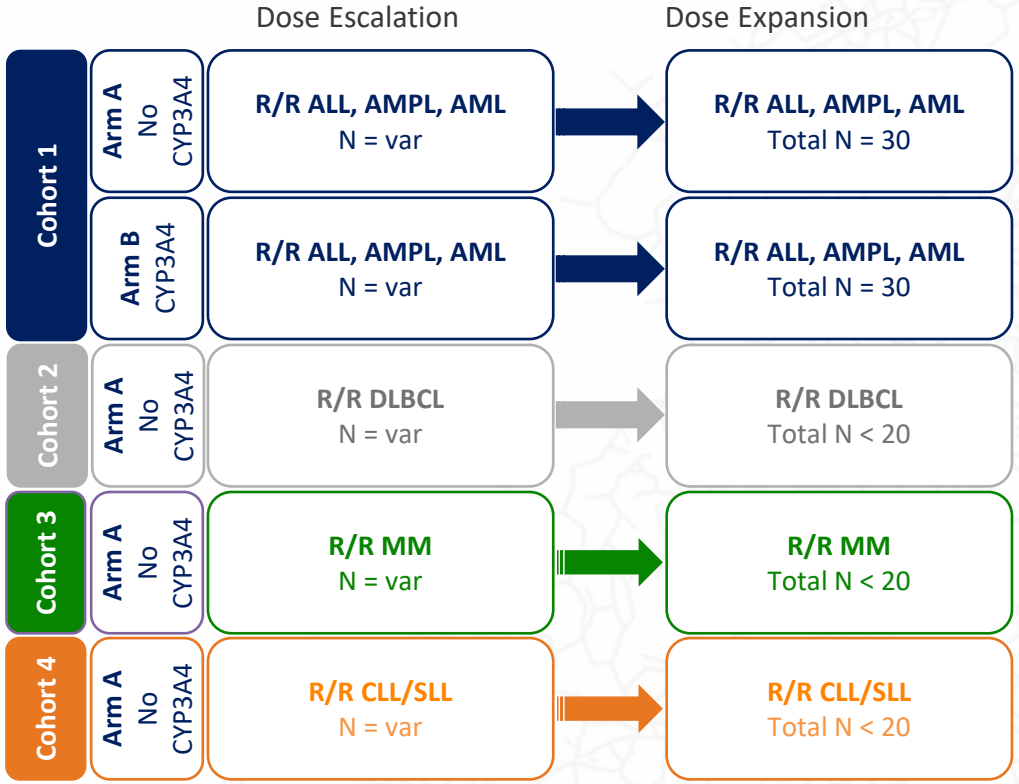


- Gene set enrichment analysis (GSEA) highlighted novel molecular pathways altered by BMF-219 belonging to cell adhesion and cytokine receptor signaling including the CXC chemokine family.
- Other notable pathways downregulated by BMF-219 included autoimmune function pathways such as Type 1 Diabetes Mellitus, with reduction of IL1B

Somanath P., et al. AACR 2023 (#473)

COVALENT-101 (ENROLLING 4 COHORTS)

Phase I First-in-Human Dose-Escalation and Dose-Expansion Study of BMF-219 Enrolling Adult Patients with R/R Acute Leukemia, R/R Diffuse Large B Cell Lymphoma, R/R Multiple Myeloma, and R/R Chronic Lymphocytic Leukemia (CLL) (NCT05153330)



Accelerated titration design followed by classical 3+3

Cohort 1 for R/R AML/AMPL/AML patients
Cohort 2 for R/R DLBCL with ≥ 2L of prior therapy
Cohort 3 for R/R MM with ≥ 3L of prior therapy
Cohort 4 for R/R CLL/SLL with ≥ 2L of prior therapy

Study Treatment: BMF-219

- A covalent small molecule menin inhibitor, administered orally daily in 28-day cycles

Objectives

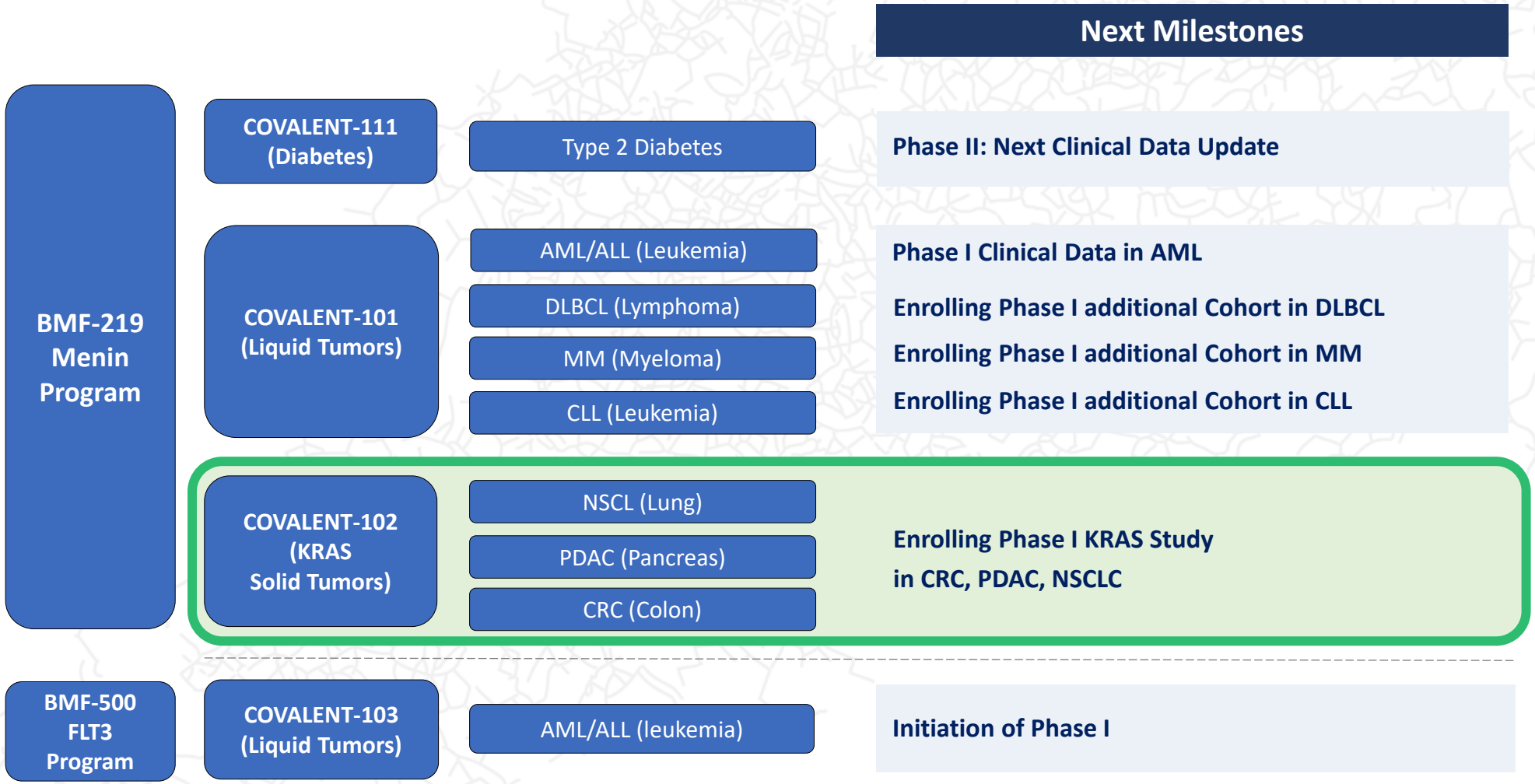
- Primary: Determine OBD & RP2D of BMF-219 monotherapy independently for each Cohort and Arm
- Secondary: Evaluate safety and tolerability of BMF-219
  Determine PK/ PD parameters of BMF-219
  Explore additional evidence of efficacy and antitumor activity

BMF-219 is being studied in seven different blood cancers. The design of COVALENT-101 is the following: Dose escalation of each cohort is done in parallel followed by independent dose selection and dose expansion phase.

Abbreviations: ALL Acute Lymphoblastic Leukemia AML Acute Myeloid Leukemia AMPL Acute Mixed-Phenotype Leukemia CYP3A4 Cytochrome 450 OBD Optimal biologic dose DLBCL diffuse large B-cell lymphoma MM multiple myeloma R/R Relapsed/Refractory

Novel Covalent Inhibitor of Menin

Pipeline-in-a-Pill – Single Agent for Multiple Indications



First Development Success with BMF-219 in RAS/RAF Driven Solid Tumors

In KRAS Mutant Solid Tumors (Lung, Colon, Pancreatic)

Development Stage: Phase I/Ib Clinical Trial (COVALENT-102) enrolling patients with relapsed/refractory KRAS mutant Solid Tumors

Key Facts

Estimated Addressable Population

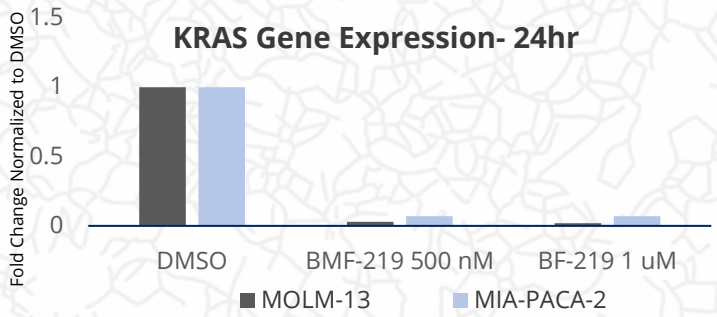
Tumor Type (KRAS Mutant)	Estimated US Patient Population (Annual Incidence)
Lung (NSCLC)	~58,000
Colon (CRC)	~60,000
Pancreatic (PDAC)	~53,000

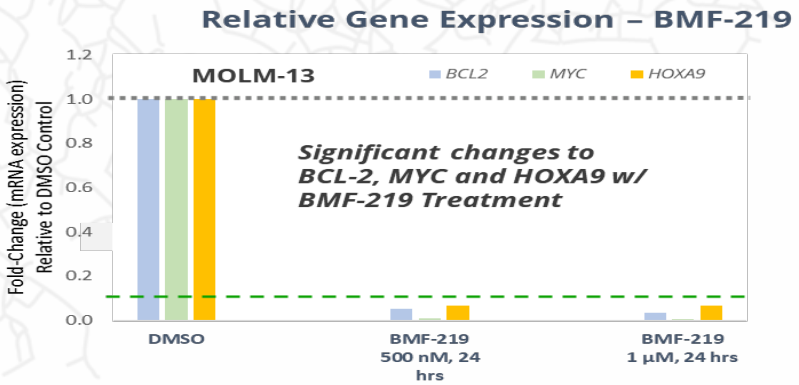
- MYC is a major downstream effector of the MAPK pathway in KRAS-activated tumors
- BMF-219 robustly decreases MYC gene expression and genomic function and drives cell killing in numerous MYC driven ex-vivo tumor samples.

MOA

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

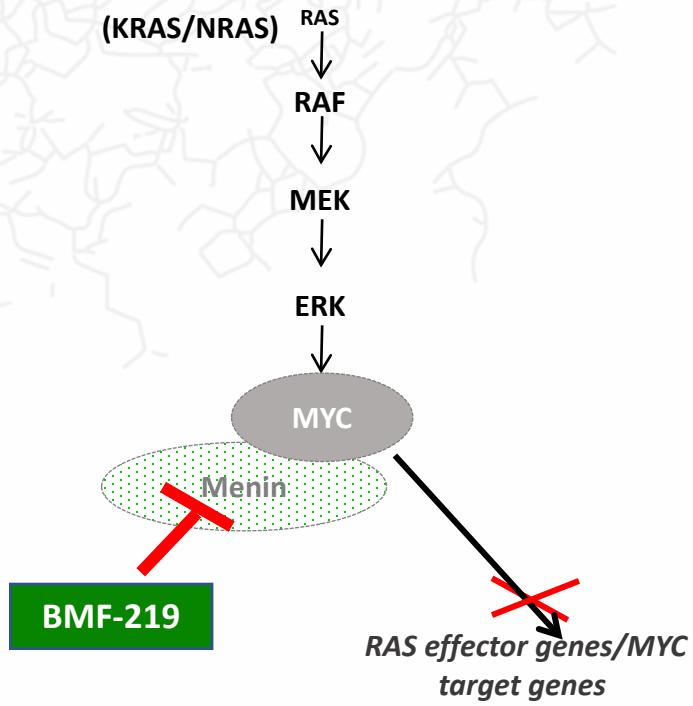
(Blood (2021) 138 (Supple. 1): 4318.)



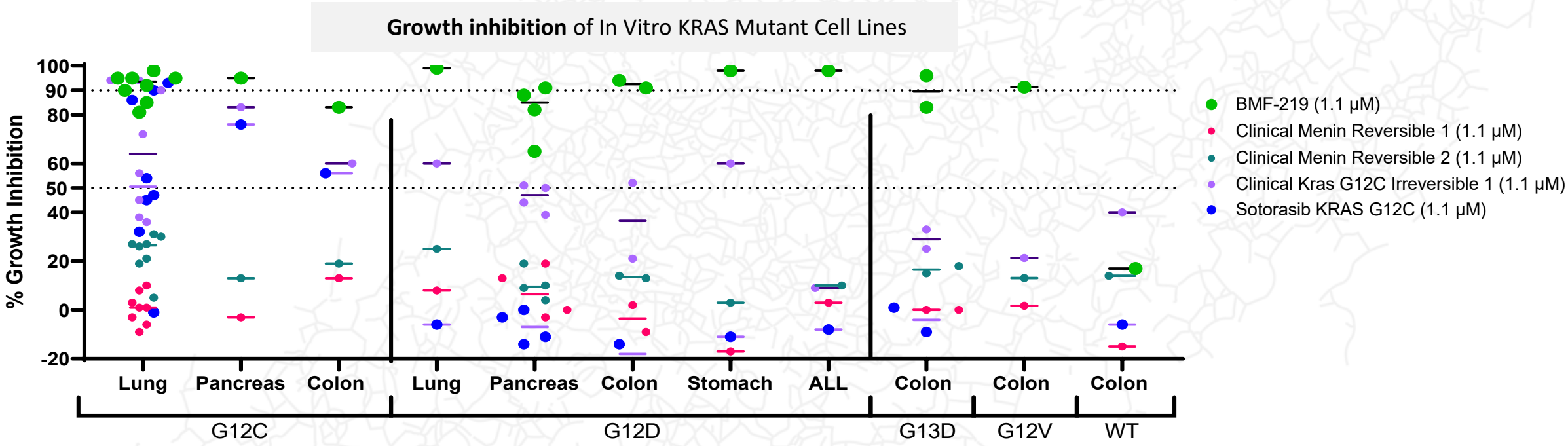


Relevant Pathway

Tumor leverages MAPK pathway



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

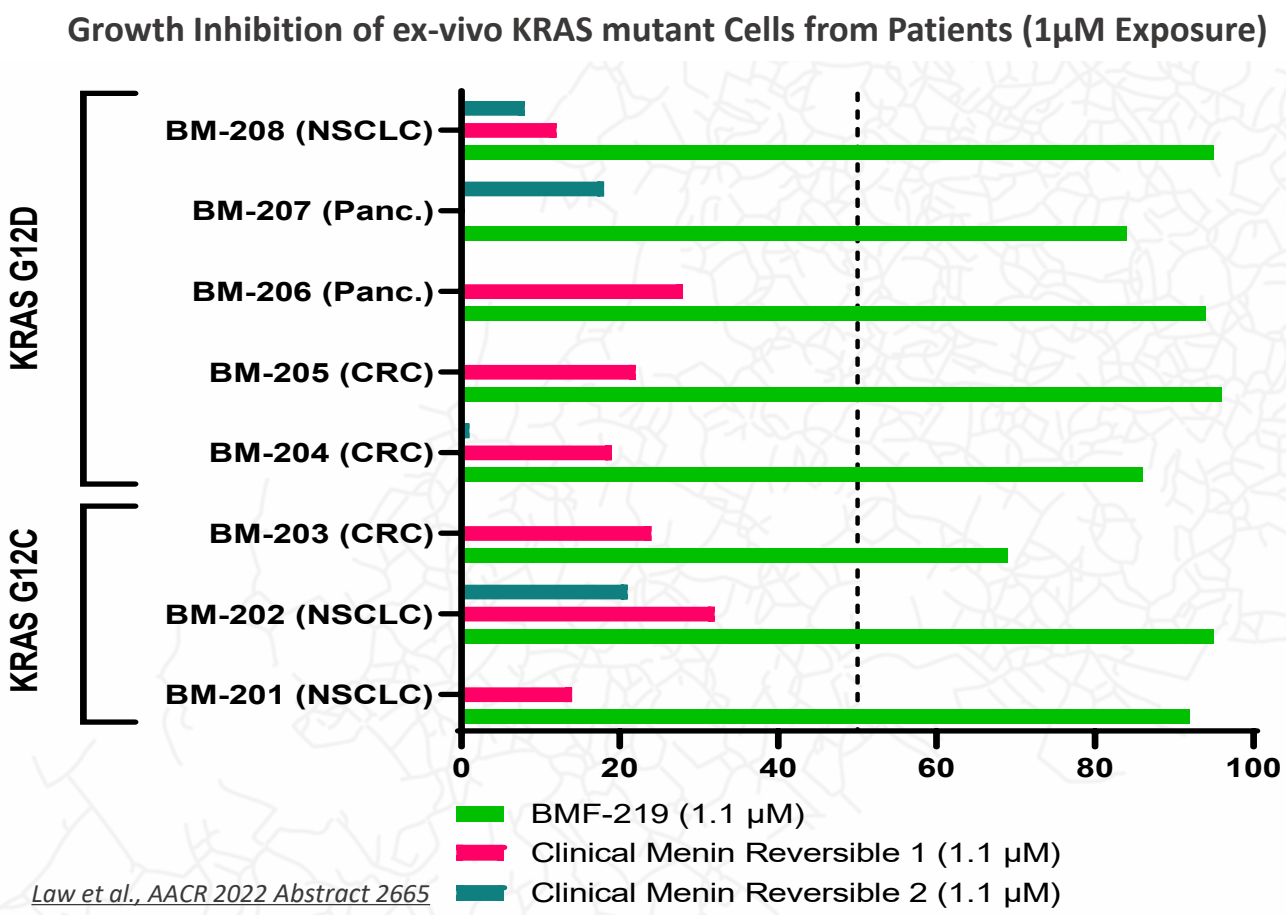


- Covalent menin inhibition by BMF-219 led to robust growth inhibition, comparable to clinical G12C inhibitors in G12C cell lines
- In non-G12C cell lines, BMF-219 achieved robust growth inhibition, higher than clinical KRAS G12C inhibitors
- Clinical reversible (non-covalent) inhibitors did not achieve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

Law et al., AACR 2022 Abstract 2665

First Development Success with BMF-219 in RAS/RAF Driven Solid Tumors

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

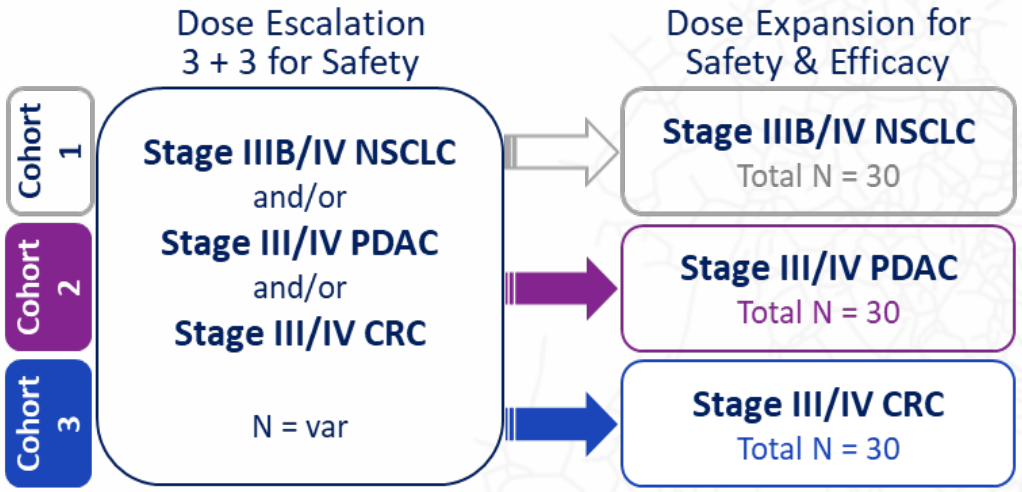


Law et al., AACR 2022 Abstract 2665

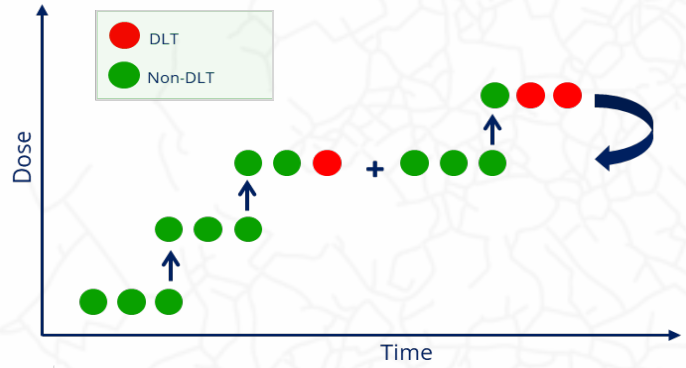
- 1.1µM exposure of BMF-219 produces robust growth inhibition in both G12C and G12D ex-vivo cell lines
- BMF-219 responses were superior to clinical reversible (non-covalent) inhibitors with respect to cell growth inhibition at the concentrations tested

COVALENT-102 (ENROLLING 3 COHORTS)

Phase I/Ib Study of BMF-219, an Oral Covalent Menin Inhibitor, in Patients with KRAS Mutant, Unresectable, Locally Advanced, or Metastatic Non-Small Cell Lung Cancer (NSCLC), Pancreatic Cancer (PDAC), and Colorectal Carcinoma (CRC) (NCT05631574)



Classical 3+3 dose escalation design



Study Treatment: BMF-219

- A covalent small molecule menin inhibitor, administered orally daily in 28 day cycles

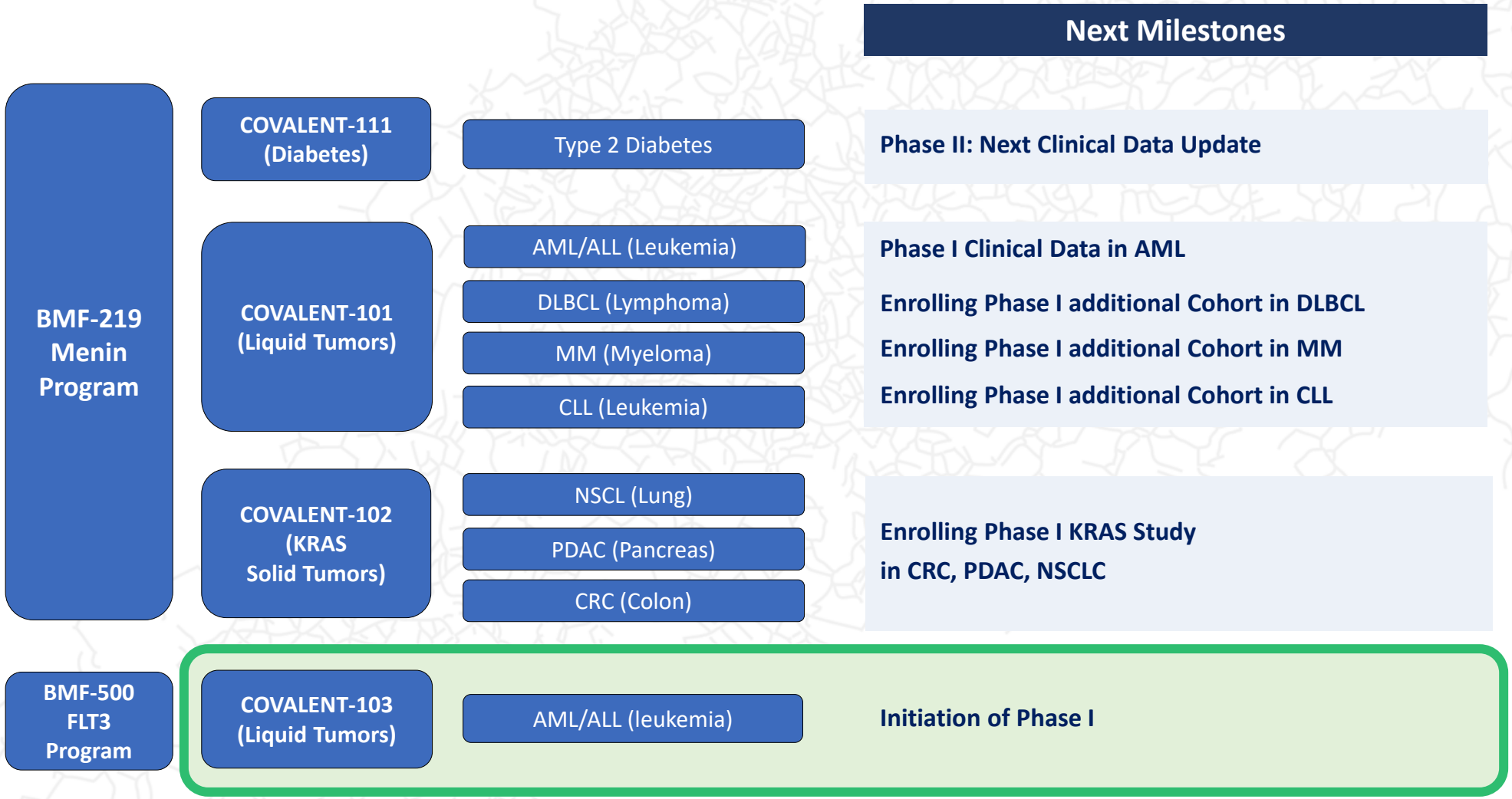
Objectives

- Primary:
  - Determine OBD & RP2D of BMF-219 monotherapy independently for each Cohort / Indication
- Secondary:
  - Evaluate safety and tolerability of BMF-219
  - Determine PK/ PD parameters of BMF-219
  - Explore additional evidence of efficacy and antitumor activity

Abbreviations: NSCLC Non-Small Cell Lung Cancer PDAC Pancreatic Cancer CRC Colorectal Carcinoma OBD optimal biologic dose RP2D recommended phase 2 dose PK/PD pharmacokinetic/pharmacodynamic ECOG Eastern Cooperative Oncology Group var variable L prior line of systemic therapy

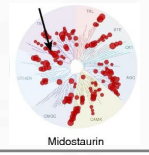
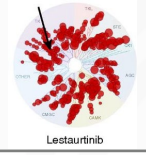
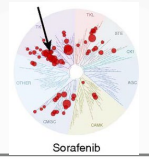
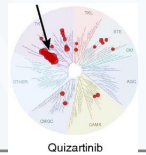
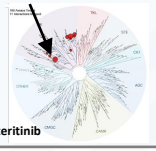
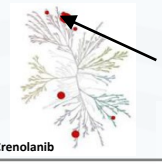
Novel Covalent Inhibitor of Menin

Pipeline-in-a-Pill – Single Agent for Multiple Indications



Second Development Success with BMF-500

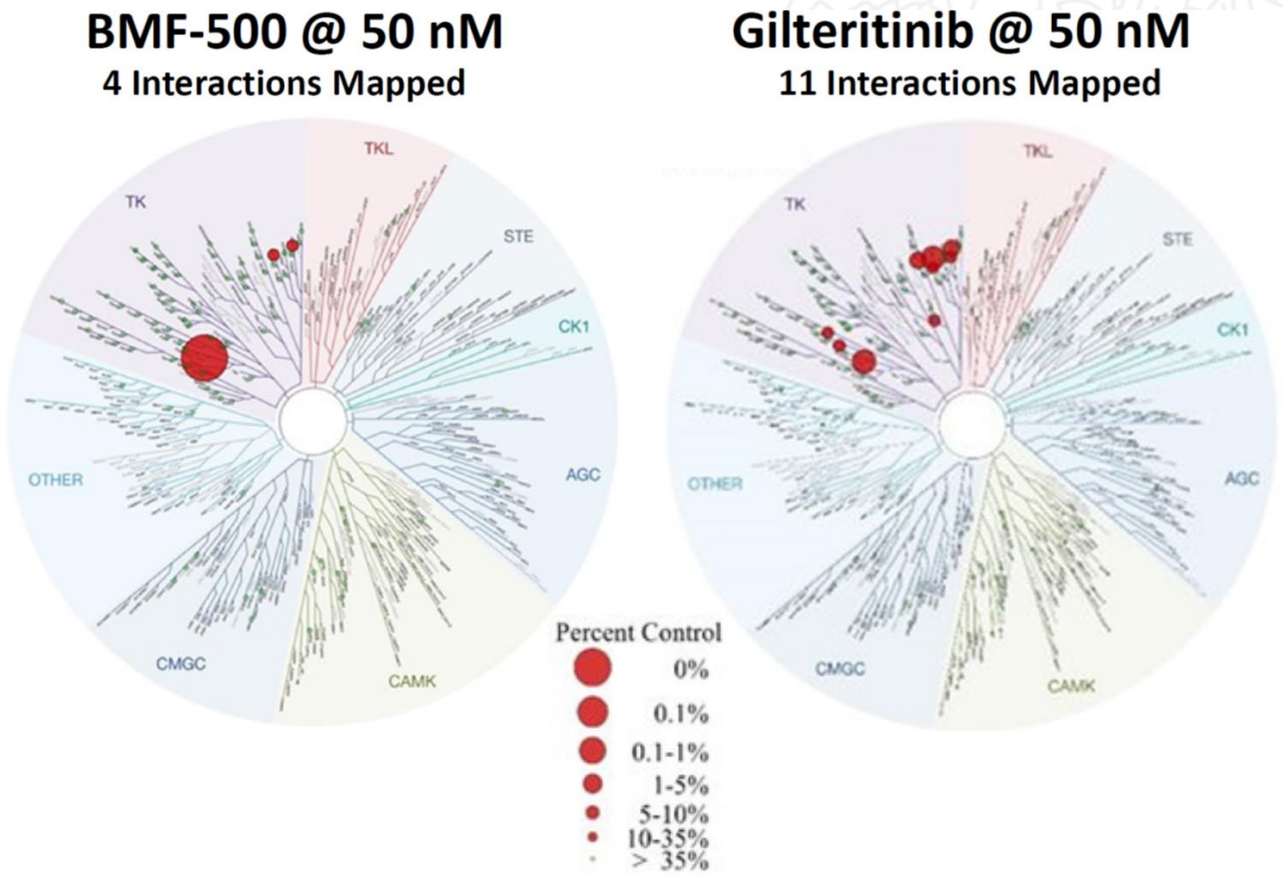
BMF-500 A Covalent FLT3 Inhibitor

Generation of FLT3 Inhibitor	First Generation FLT3 / multi-kinase Inhibitors			Second Generation FLT3 Inhibitors			Third Generation FLT3 Inhibitors
Products	**Midostaurin** *(FDA Approved as RYDAPT)*	**Lestaurtinib** *(Failed in clinical trials)*	**Sorafenib** *(FDA Approved as NEXAVAR)*	**Quizartinib** *(FDA Rejected due to Cardiotox)*	**Gilteritinib** *(FDA Approved as XOSPATA)*	**Crenolanib** *(Phase 3 in US)*	**BMF-500** *(Covalent Inhibitor, Preclinical)*
Benefits	• *In vitro* potency against FLT3 • Oral route of administration			• More selective for FLT3	• Improved PK properties	• Improved potency D835 • Reduced KIT inhibition	• Drives cell death • Improved FLT3 potency and selectivity • Improved activity in known resistance mechanisms • Limited impact on cKIT at projected physiological dose
Challenges	• Poor kinase selectivity • Challenging pharmacokinetic (PK) profile • Low steady state free drug concentration • Low potency resulting from challenging PK at tolerable doses			• Adverse Events • QTc impact • Cytopenia	• Drives Differentiation • Myelo-suppression • Frequent Dose Adj • QTc impact	• TID Dosing • F619 Resistance • Drives Differentiation	• Limited history of covalent FLT3 experience in the clinic • Novel scaffold with emerging profile
Kinome Selectivity	 Midostaurin	 Lestaurtinib	 Sorafenib	 Quizartinib	 Gilteritinib	 Crenolanib	 **BMF-500**

Sources: Levis M. (2017). Midostaurin approved for FLT3-mutated AML. *Blood*, *129*(26), 3403–3406. https://doi.org/10.1182/blood-2017-05-782292; Drugs@FDA.gov

Second Development Success with BMF-500

BMF-500 Highly Selective to FLT3



Law et al., ASH 2022 (#2756)

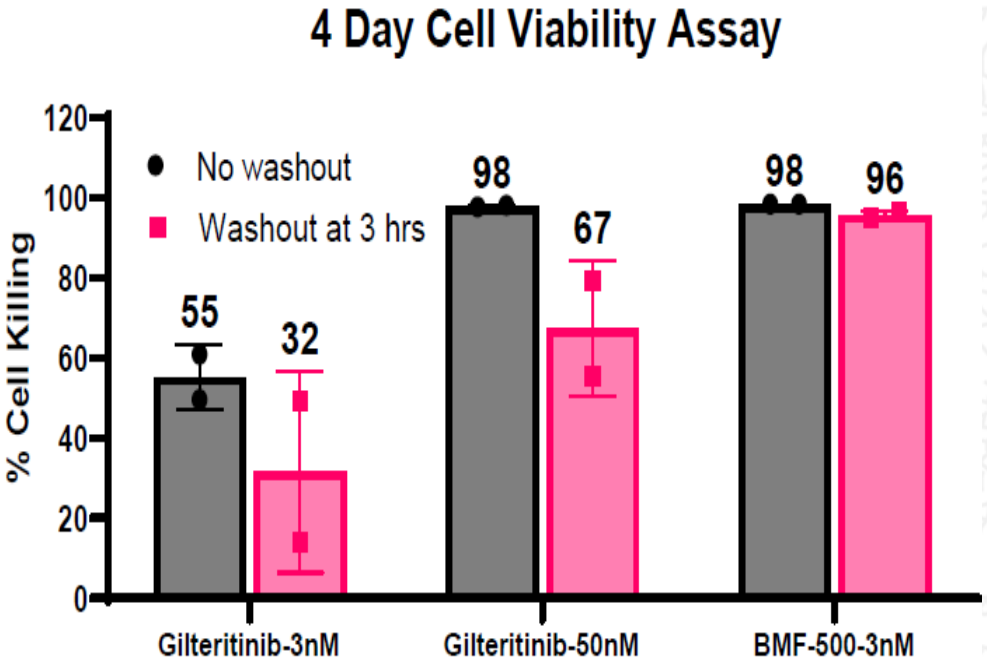
5-Day Cytotoxicity Profile (IC_{50}, uM)

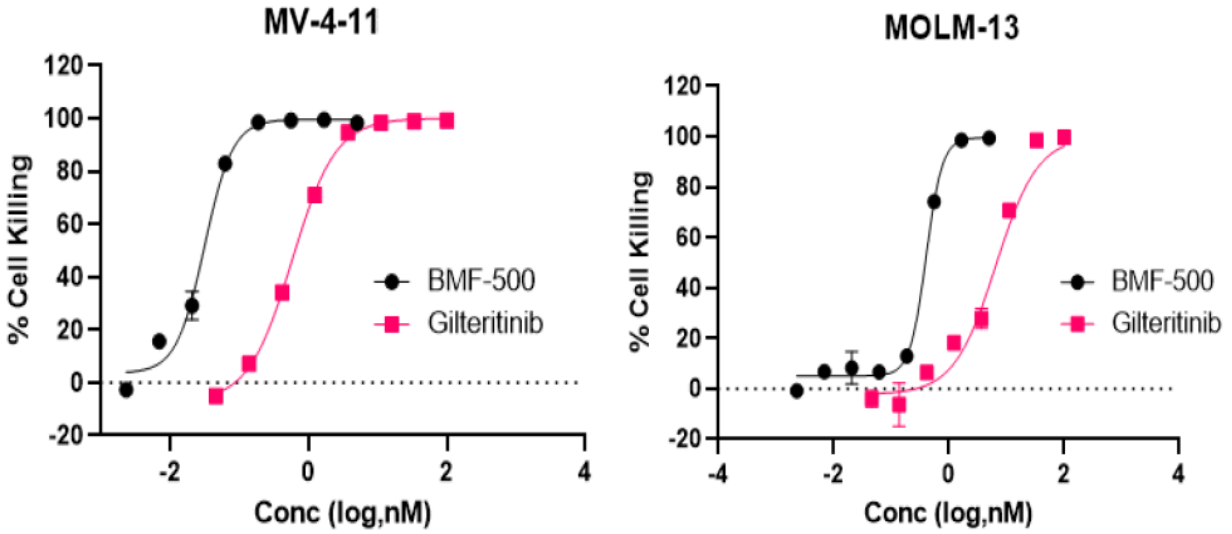
Cell Line	Tumor Type	BMF-500	Gilteritinib
MCF7	Adenocarcinoma	>1	>1
MV-4-11	Leukemia (acute myelomonocytic	**<0.001**	**0.003**
RS4;11	Leukemia (acute lymphoblastic)	>1	0.233
SaOS2	Osteosarcoma	>1	0.236
SK-N-AS	Neuroblastoma	>1	>1
SKOV3	Adenocarcinoma	>1	0.804
Thp1	Leukemia (acute monocytic)	>1	>1
WiDr	Colorectal adenocarcinoma	>1	0.268
CCRFCEM	Leukemia (acute lymphoblastic)	>1	>1
RL95-2	Carcinoma	>1	0.868

Cell Line	Tumor Type	BMF-500	Gilteritinib
SW684	Fibrosarcoma	>1	>1
A549	NSCLC	>1	0.278
BV-173	Leukemia (CML)	>1	0.740
CGTH-W-1	Carcinoma, metastatic	>1	0.455
Daudi	Burkitt's lymphoma	>1	>1
HCT-116	Carcinoma	>1	>1
Jurkat	Acute T-cell leukemia	>1	0.947
HL-60	Leukemia, acute promyelocytic	>1	0.445
LS411N	Carcinoma, Duke's type B	>1	>1
MOLT-4	Leukemia (ALL)	>1	>1

Second Development Success with BMF-500

BMF-500 Highly Effective FLT3 Inhibitor Even After Drug Wash-Out





Compound ID	MV-4-11 IC_{50} (nM)	MOLM-13 IC_{50} (nM)
BMF-500	0.03	0.30
Gilteritinib	1.7	6.5

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BMF-500 Highly Effective FLT3 Inhibitor Against Resistance Mutations

NanoBRET Target Engagement Assay, IC_{50} (nM)

Cmpd ID	FLT3 WT	FLT3 (D835H)	FLT3 (D835V)	FLT3 (D835Y)
BMF-500	0.31	0.18	0.22	0.25
Gilteritinib	23.4	1.45	1.1	1.4

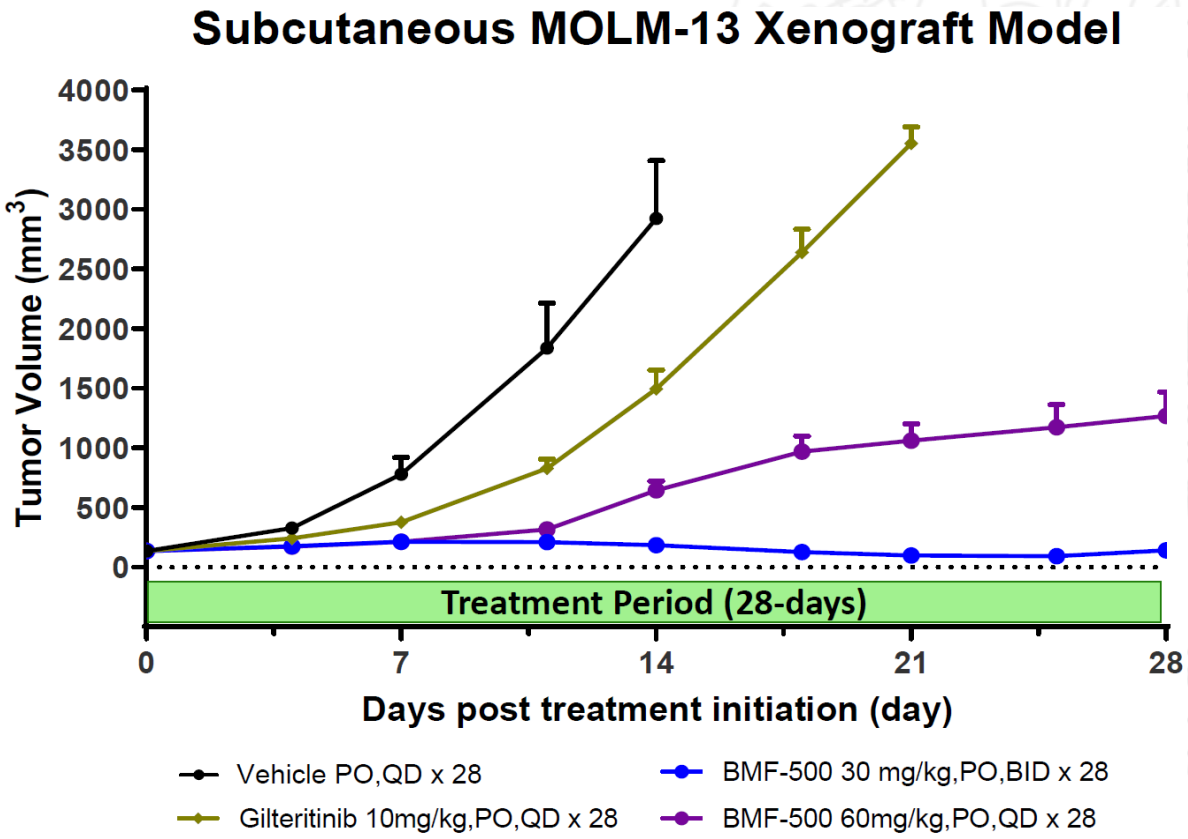
FLT3 Inhibitor Resistance Mutations Coverage, IC_{50} (nM)

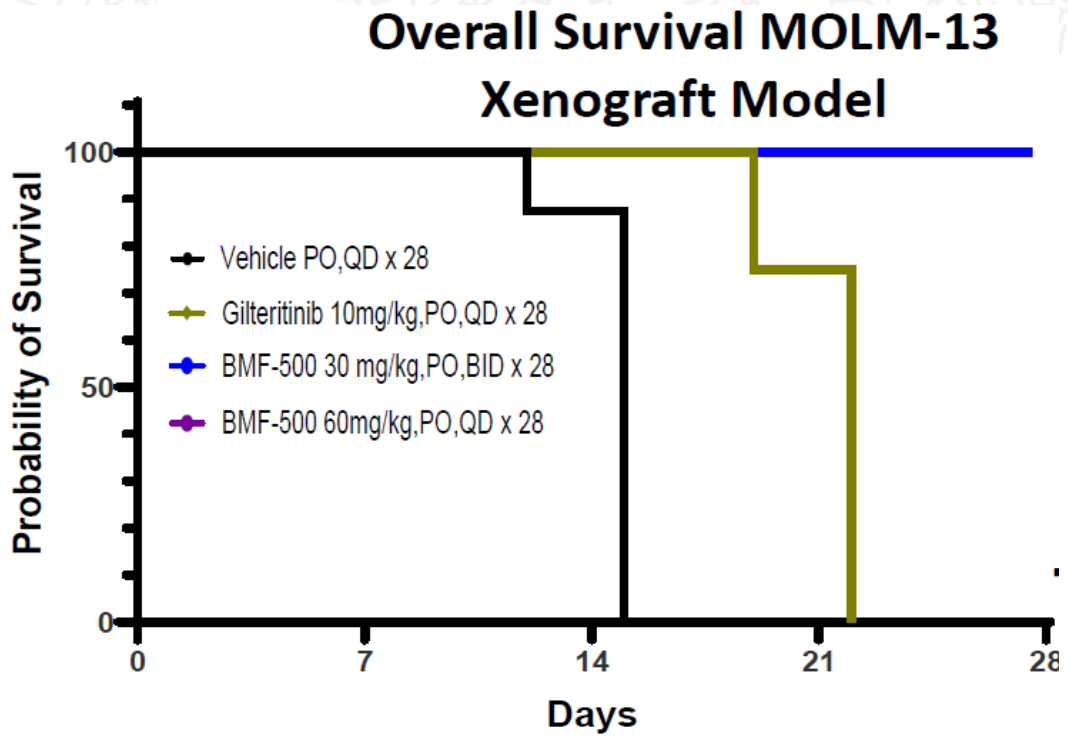
Cmpd ID	FLT3-ITD	FLT3-ITD-D835Y	FLT3-ITD-F691L
BMF-500	2 nM	5 nM	7 nM
Gilteritinib	7 nM	19 nM	98 nM

Law et al., ASH 2022 (#2756)

Second Development Success with BMF-500

BMF-500: Highly Potent and Durable FLT3 Inhibitor



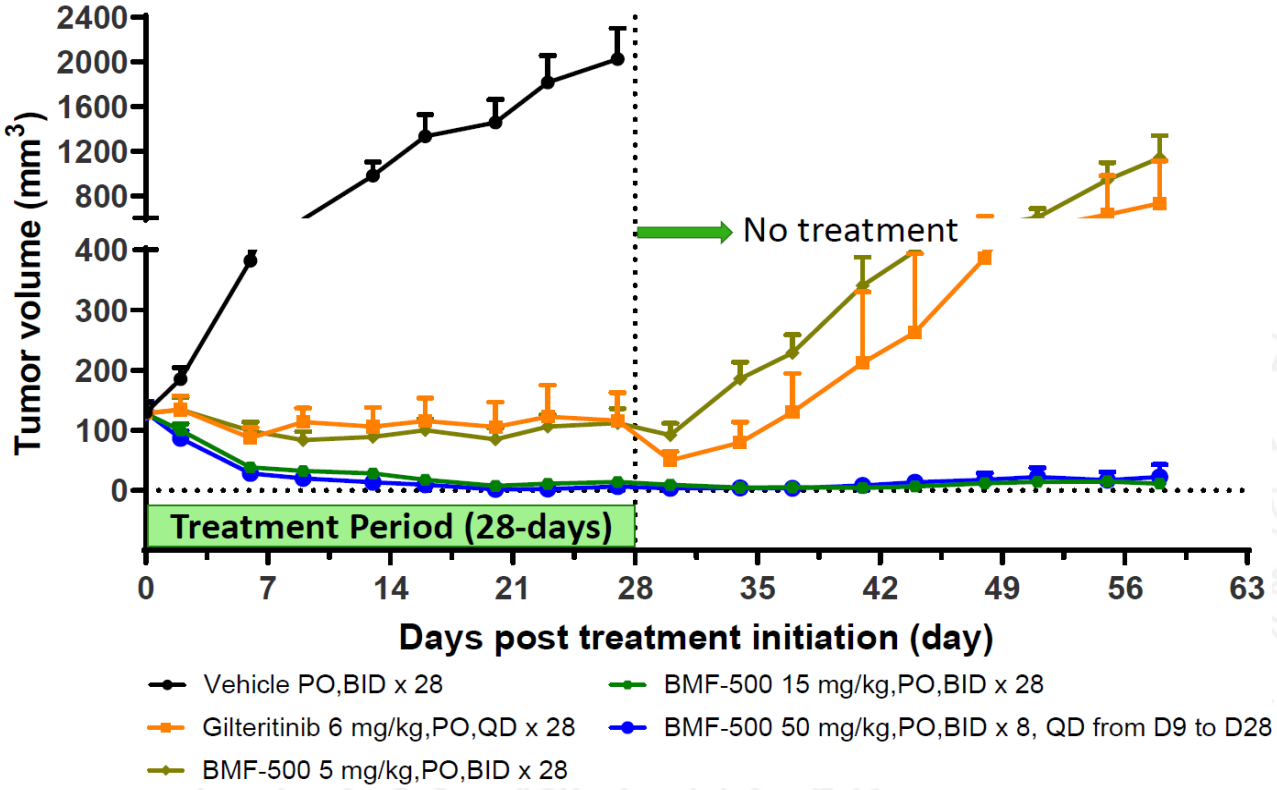


Law et al., ASH 2022 (#2756)

Second Development Success with BMF-500

BMF-500: Highly Potent and Durable FLT3 Inhibitor

Subcutaneous MV-4-11 Xenograft Model



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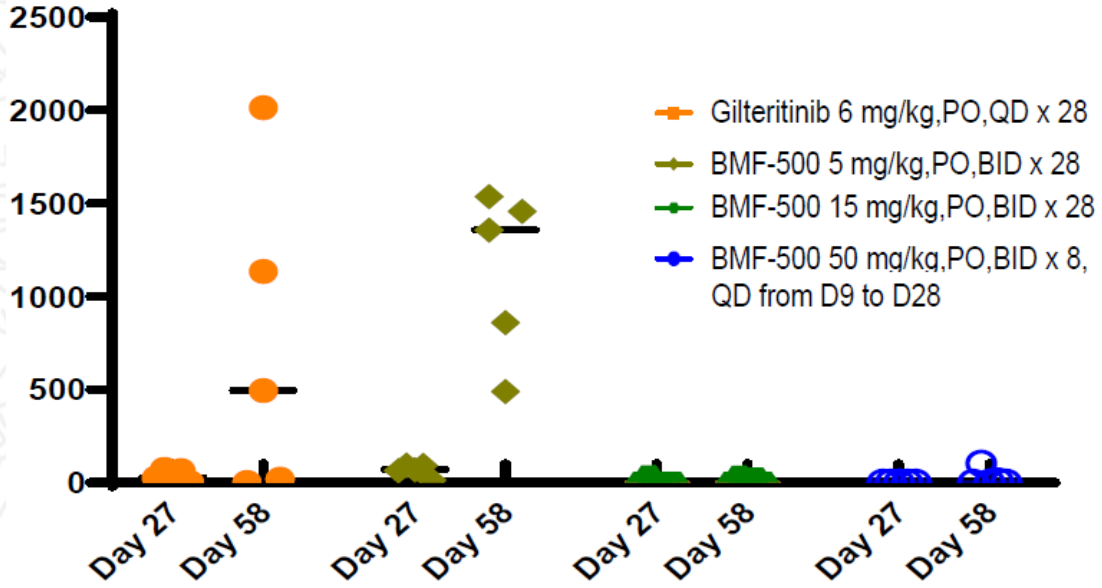
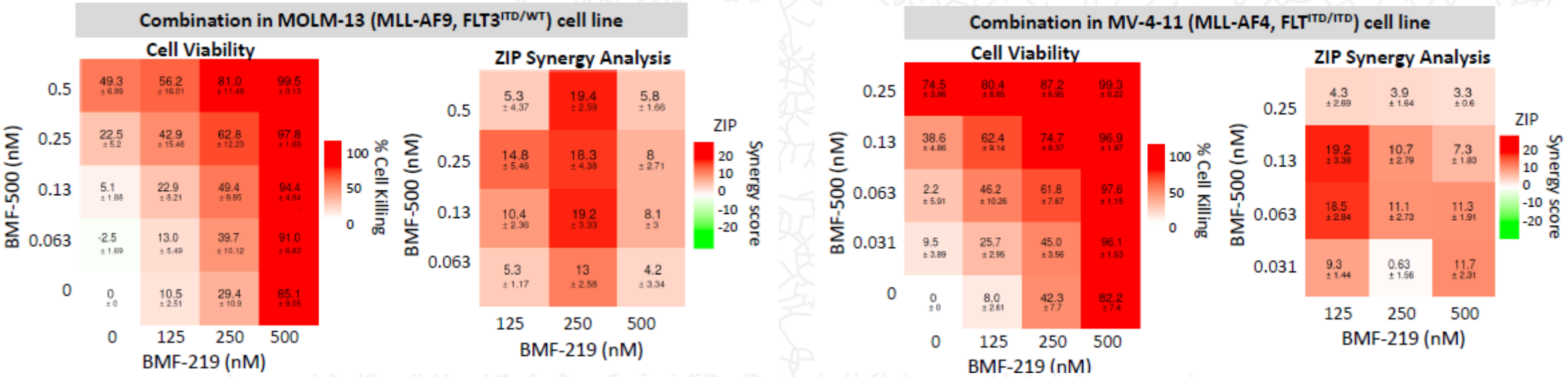
Individual Tumor Volume MV-4-11 Xenograft Model



Second Development Success with BMF-500

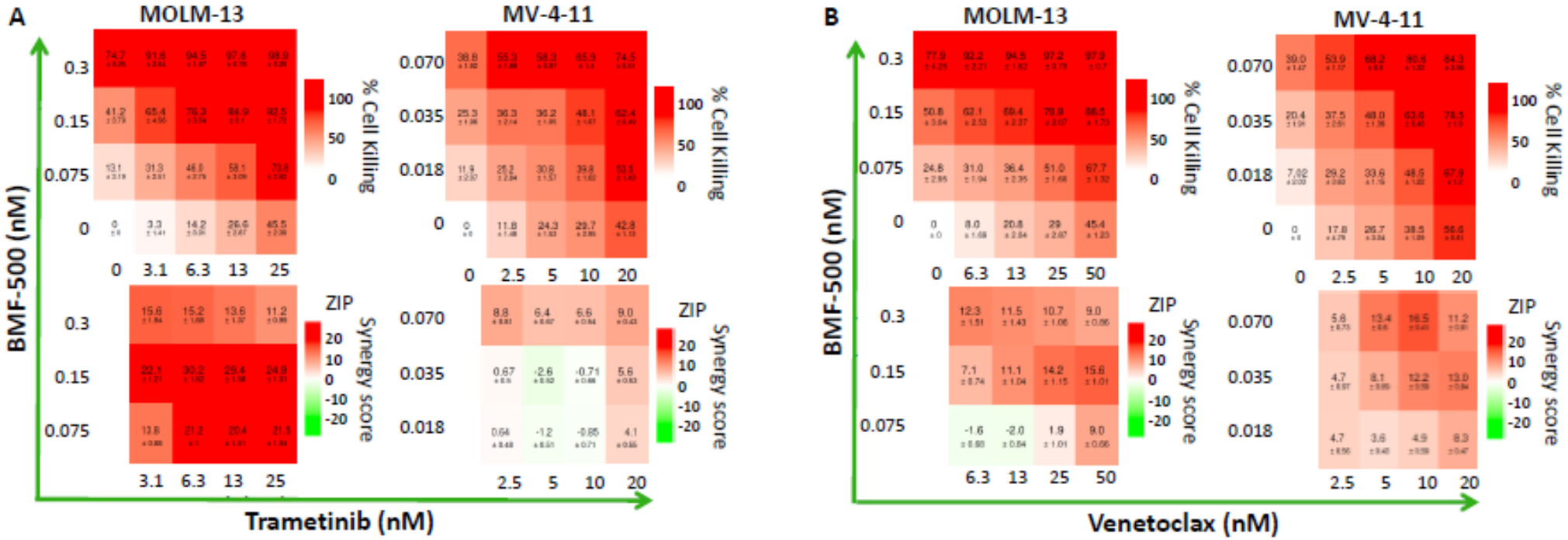
BMF-219 and BMF-500 in combination induced higher cell killing at lower single agent concentrations



BMF-219 and BMF-500 in combination shows beneficial effects affording higher cell killing at lower concentrations.

Law et al., AACR 2023 (#4939)

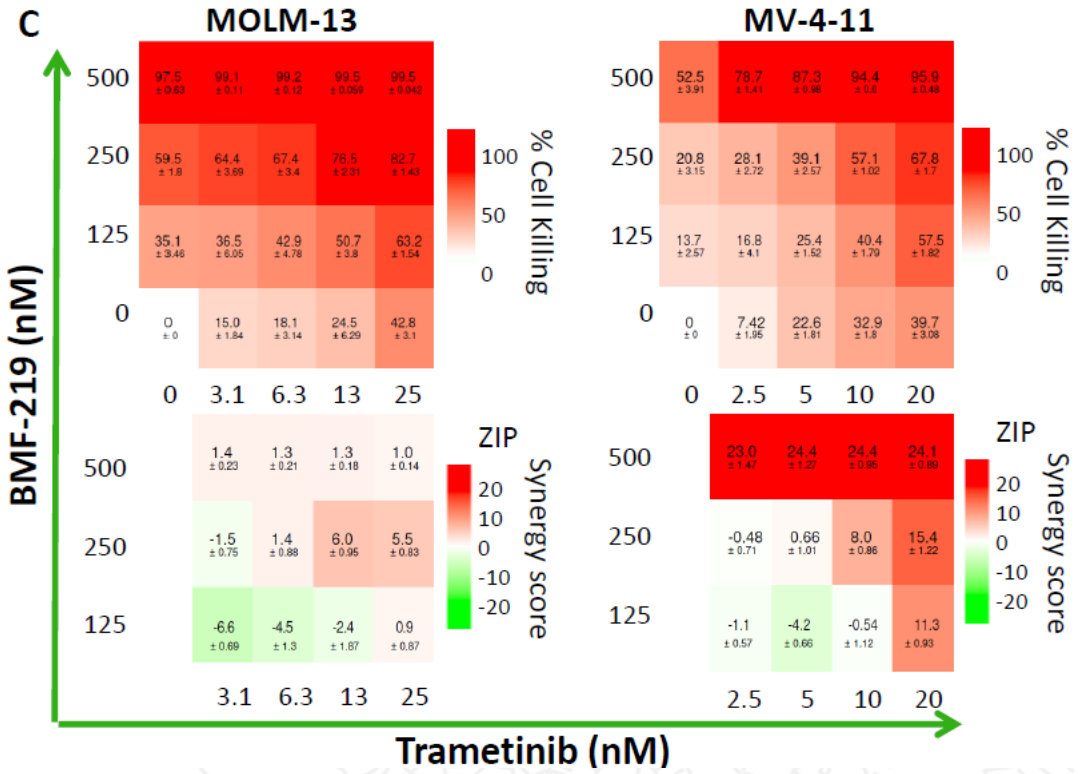
BMF compounds combined with MEK or BCL2 inhibitors elicit additivity

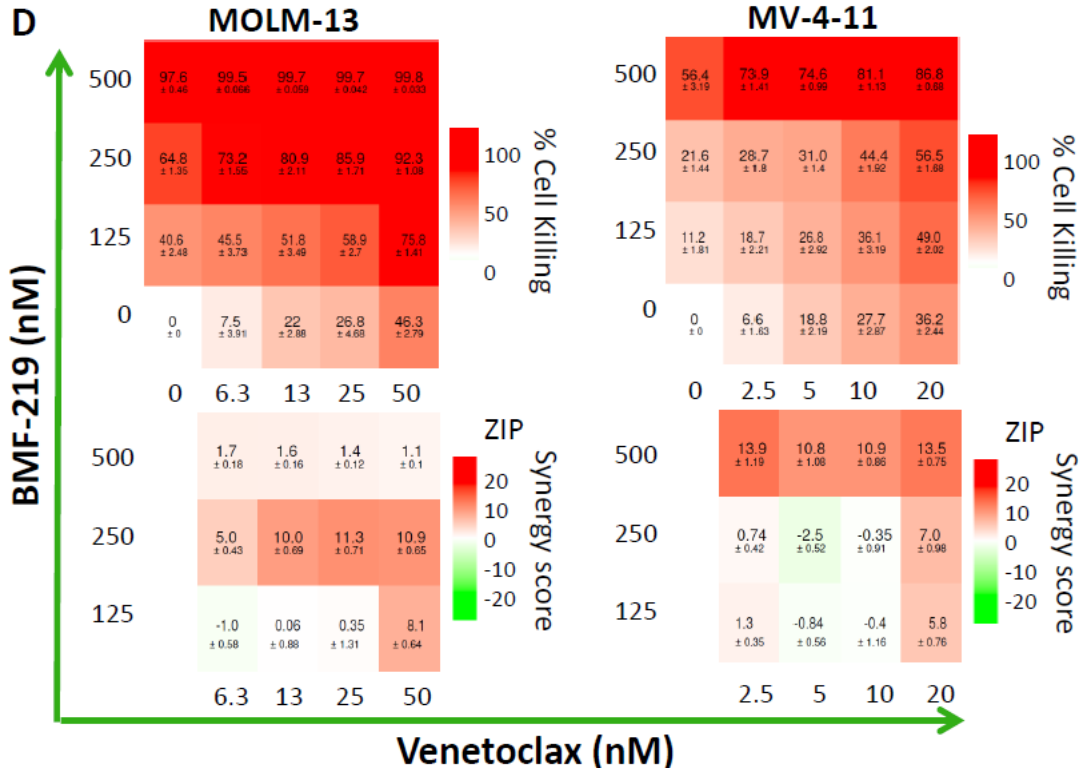


- BMF-500 combined with the MEK inhibitor, trametinib achieved more than additive cell killing in the MOLM-13 cells vs MV4-11.
- BMF-500 combined with the BCL2 inhibitor, venetoclax achieved additive cell killing in both cell lines.
- Our results demonstrate the utility of combination approaches of menin and FLT3 covalent inhibitors with MEK and BCL2 blockade to achieve higher antileukemic cell killing with lower drug concentrations.

Law et al., AACR 2023 (#4939)

BMF compounds combined with MEK or BCL2 inhibitors elicit additivity





Law et al., AACR 2023 (#4939)

2023 and beyond expected to provide multiple Clinical Read Outs

Near Term Expected Milestones – Biomea Fusion (NASDAQ: BMEA)

			Milestones	Expected Timeline
BMF-219 Menin Program	COVALENT-111 (Diabetes)	Type 2 Diabetes	Phase II: Next Clinical Data Update	Expected at ADA
	COVALENT-101 (Liquid Tumors)	AML/ALL (Leukemia)	Phase I Clinical Data in AML	1H 2023 first data set
		DLBCL (Lymphoma)	Enrolling in Phase I additional Cohort in DLBCL	In Progress
		MM (Myeloma)	Enrolling in Phase I additional Cohort in MM	In Progress
		CLL (Leukemia)	Enrolling in Phase I additional Cohort in CLL	In Progress
	COVALENT-102 (KRAS Solid Tumors)	NSCL (Lung)	Enrolling of Phase I KRAS Study in CRC, PDAC, NSCLC	In Progress
		PDAC (Pancreas)		
		CRC (Colon)		
BMF-500 FLT3 Program	COVALENT-103 (Liquid Tumors)	AML/ALL (leukemia)	Initiation of Phase I	In Progress
Additional Oncology Program	Target # 3	Oncology	Progress Update	1H 2023

Expected 2023 Milestones : Exploring 8 Different Tumor Types and Type II Diabetes in the Clinic

- [x] Present initial Phase II clinical data in Type 2 Diabetes: 1Q 2023
- [ ] Present initial Phase I clinical data in Acute Leukemia: 1H 2023
- [x] File IND and initiate Phase I Trial for BMF-500: 1H 2023
- [ ] Announce update on third pipeline asset from FUSION™ platform technology: 1H 2023
- [ ] Continue enrolling patients in COVALENT 101 exploring BMF-219 utility in liquid tumors (AML/ALL, MM, CLL, DLBCL)
- [ ] Continue enrolling patients in COVALENT 102 exploring BMF-219 utility in KRAS driven Solid Tumors (PDAC, NSCLC, CRC)
- [ ] Continue enrolling patients in COVALENT 111 exploring BMF-219 utility in Type 2 Diabetes
- [ ] Provide next clinical update at American Diabetes Association in June 2023 and at the European Association for the Study of Diabetes in October 2023
- [x] **Cash as of 31 March 2023: $259M (incl. $172M raised on March 28, 2023)**

As of March 31, 2023

Company Financials (NASDAQ: BMEA)

	Three Months Ended March 31, 2023
Operating expenses:	
R&D	$ 24,395
G&A	$ 5,636
Total Operating Expenses	$ 30,031
Loss from operations	($ 30,031)
Interest and other income, net	$ 980
Net loss	($29,051)
Other comprehensive loss:	
Changes in unrealized gain on short term investments, net	$ 1
Comprehensive loss	($ 29,050)
Net loss per common share, basic and diluted	($ 0.98)
Weighted-average number of common shares used to compute basic and diluted net loss per common share	$ 29,586,468

Cash as of 31 Dec 2022	$ 113.4M
Net Cash Burn Q1 2023	$ 26.7M
Cash as of 31 March 2023	**$259.2M**
($ 86.7M + 172.5M from public offering)	

THANK YOU

biomea FUSION™ | We Aim to Cure™

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biomeafusion.com

Publications & Presentations

Biomea Fusion's Conference Publications & Presentations

Presentation Title	Conference	Date	Link
Combinatorial approach using covalent menin inhibitor, BMF-219, and/or covalent FLT3 inhibitor, BMF-500, with MEK or BCL2 blockade potentiates therapeutic use in AML	American Association for Cancer Research (AACR)	April 18, 2023	Poster
Covalent menin inhibitor, BMF-219, impacts key gene signatures and molecular pathways in Chronic Lymphocytic Leukemia patient-derived models	American Association for Cancer Research (AACR)	April 16, 2023	Poster
BMF-500: An Orally Bioavailable Covalent Inhibitor of FLT3 with High Selectivity and Potent Antileukemic Activity in FLT3-Mutated AML	American Society of Hematology (ASH)	Dec 11, 2022	Poster
Oral long-acting menin inhibitor normalizes type 2 diabetes in two rat models	European Association for the Study of Diabetes (EASD)	Sept 22, 2022	Oral Presentation
Oral Menin Inhibitor, BMF-219, displays a significant and durable reduction in HbA1c in a Type 2 Diabetes Rat Model	European Association for the Study of Diabetes (EASD)	Sept 20, 2022	Oral Presentation
Anti-tumor Activity of Covalent Menin Inhibitor, BMF-219, in High Grade B-Cell Lymphoma and Multiple Myeloma Preclinical Models	International Myeloma Society Annual Meeting (IMS)	Aug 26, 2022	Poster
Phase 1 first-in-human dose-escalation and dose-expansion study of BMF-219, an oral, covalent, menin inhibitor, in adult patients with acute leukemia (AL), diffuse large B-cell lymphoma (DLBCL), and multiple myeloma (MM)	International Myeloma Society Annual Meeting (IMS)	Aug 26, 2022	Poster
Oral Long-Acting Menin Inhibitor, BMF-219, Normalizes Type 2 Diabetes Mellitus in Two Rat Models	American Diabetes Association (ADA)	June 6, 2022	Poster
Oral Menin Inhibitor, BMF-219, displays a significant and durable reduction in HbA1c in a Type 2 Diabetes Mellitus Rat Model	American Diabetes Association (ADA)	June 6, 2022	Poster (Late Breaking)
Preclinical Activity of irreversible menin inhibitor, BMF-219, in Chronic Lymphocytic Leukemia	American Society of Clinical Oncology (ASCO)	June 4, 2022	Poster
Irreversible menin inhibitor, BMF-219, inhibits the growth of KRAS-mutated solid tumors	American Association for Cancer Research (AACR)	April 12, 2022	Poster
Anti-tumor activity of irreversible menin inhibitor, BMF-219, in high-grade B-cell lymphoma and multiple myeloma preclinical models	American Association for Cancer Research (AACR)	April 12, 2022	Poster
COVALENT-101: A Phase 1 study of BMF-219, a novel oral irreversible menin inhibitor as a single agent in patients with R/R ALL/AML, DLBCL, and MM	American Association for Cancer Research (AACR)	April 12, 2022	Poster