Investigational Covalent FLT3 Inhibitor BMF-500 in Relapsed or Refractory (R/R) Acute Leukemia (AL): Preliminary Phase 1 Data from the Ongoing COVALENT-103 Study

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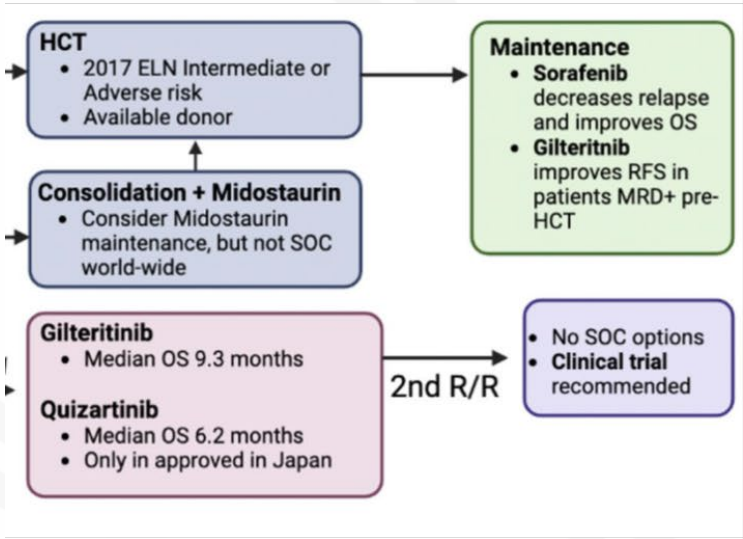
FLT3 Mutation in Acute Leukemia

- FLT3 mutations occur in up to 37% of patients with AML, and in ~ 5% of ALL patients and are associated with poor prognosis [1, 2]
- Once failing the only approved agent in the R/R setting, gilteritinib, patients have abysmal prognosis and very short survival (mOS ~1.8 months) 3; for example, no CRs were reported among the gilteritinib-experienced FLT3-mut AL patients treated with FF-10101, an investigational covalent FLT3 inhibitor which otherwise demonstrated efficacy in gilteritinib-naïve FLT3-mut AL[4]
- FLT3 abnormalities are most commonly ITD and TKD mutations; some approved FLT3 inhibitors are effective only for ITD mutations



- FLT3-mut patients post Gilt failure have no approved therapy
- Investigative agents have not demonstrated clinical success in this patient population to date

→ COVALENT-103
Dose Escalation Patients

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1.Bystrom et al. Curr Oncol Rep. 2023 Apr;25(4):369-378. 2. Zhang et al. Cancer Gene Ther. 27, 81–88 (2020)., 3. Abstract P1798 – EHA 2024. 4. Levis, et al. Blood Adv 2024; 8 (10): 2527–2535. 5. Law et al. ASH 2022 Abstract 2756.

BMF-500 Background

- BMF-500 is an orally bioavailable, selective, covalent, small-molecule investigational inhibitor of FLT3, including wild type, ITD, and TKD mutants, that is designed to retain potency against FLT3 inhibitor resistance mutations such as the F691 gatekeeper and D835 mutations
- BMF-500 has demonstrated high affinity for FLT3, lack of cKIT inhibition (therefore avoiding suppression of normal hematopoiesis), and sustained cell-killing capacity that persisted even after prolonged drug washout[5]
- BMF-500 has shown sustained tumor regression and improved survival in both subcutaneous and disseminated xenograft models of mutant FLT3-driven AML[5]
- BMF-500 is currently supplied as 5, 25 and 100 mg strength tablets for oral administration in clinical trials

COVALENT-103 Study Overview

- COVALENT-103 (NCT05918692) is an open-label, first-in-human, Phase I study evaluating the safety, tolerability, and clinical activity of twice daily oral BMF-500 in patients with R/R AL, with or without FLT3 mutations
- As of Nov 2024, the study is open for enrollment at 21 sites in the United States
- Study commenced in Q4 2023 and has dosed 20 patients to date; enrollment is ongoing

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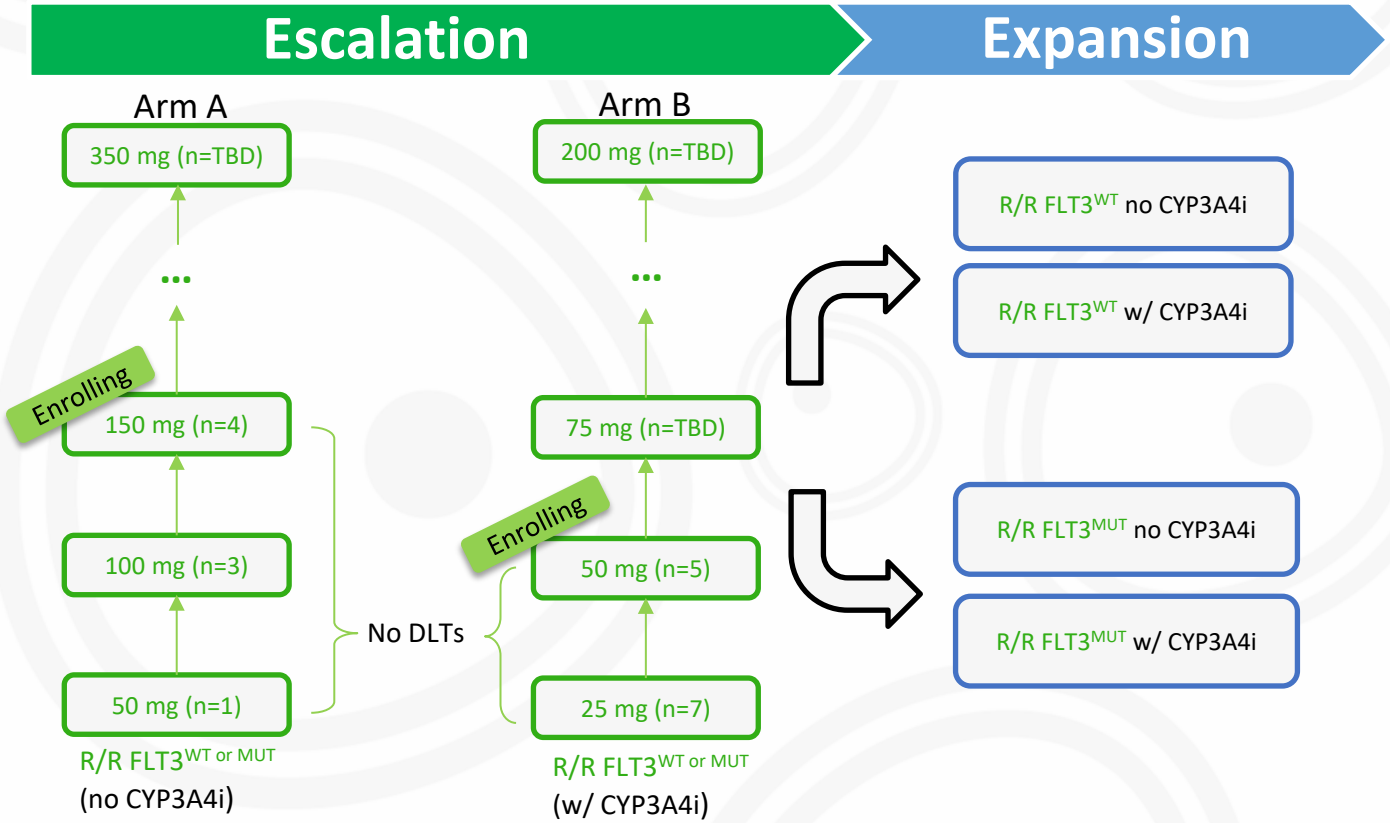
1.Bystrom et al. Curr Oncol Rep. 2023 Apr;25(4):369-378. 2. Zhang et al. Cancer Gene Ther. 27, 81–88 (2020)., 3. Abstract P1798 – EHA 2024. 4. Levis, et al. Blood Adv 2024; 8 (10): 2527–2535. 5. Law et al. ASH 2022 Abstract 2756.

Study Design

- **Dose Escalation** using Accelerated Titration Design (ATD) followed by classical "3+3"); Arm A / B (not taking / taking CYP3A4i) enrolled in parallel
- **Dose Expansion** to explore at least two dose levels



BMF-500 orally twice daily administered in continuous 28-day cycles
N=~141

Total n= 20 as of Nov-2024 (enrollment ongoing)

Study Objectives

- Evaluate safety and tolerability
- Determine OBD/RP2D
- Evaluate efficacy per ELN2017 as assessed by PI
- Characterize on-treatment PD effects
- Evaluate changes in molecular profiling

Key Eligibility Criteria

- Adults (≥18 years), ECOG ≤2, life expectancy >3 months
- R/R FLT3-mutant AML, ALL, MPAL, and R/R wild type FLT3 AML, ALL, MPAL (≤33% per Arm)
- Must be R/R and progressed after SOC
- FLT3-mutant patients must have failed treatment with approved FLT3 inhibitor(s)
- Adequate organ function: Bilirubin ≤1.5 x ULN; ALT/AST ≤2.0 x ULN, eCrCl ≥60 mL/min
- Absence of significant CV disease (LVEF >45%, mean QTcF or QTcB of <470 ms)

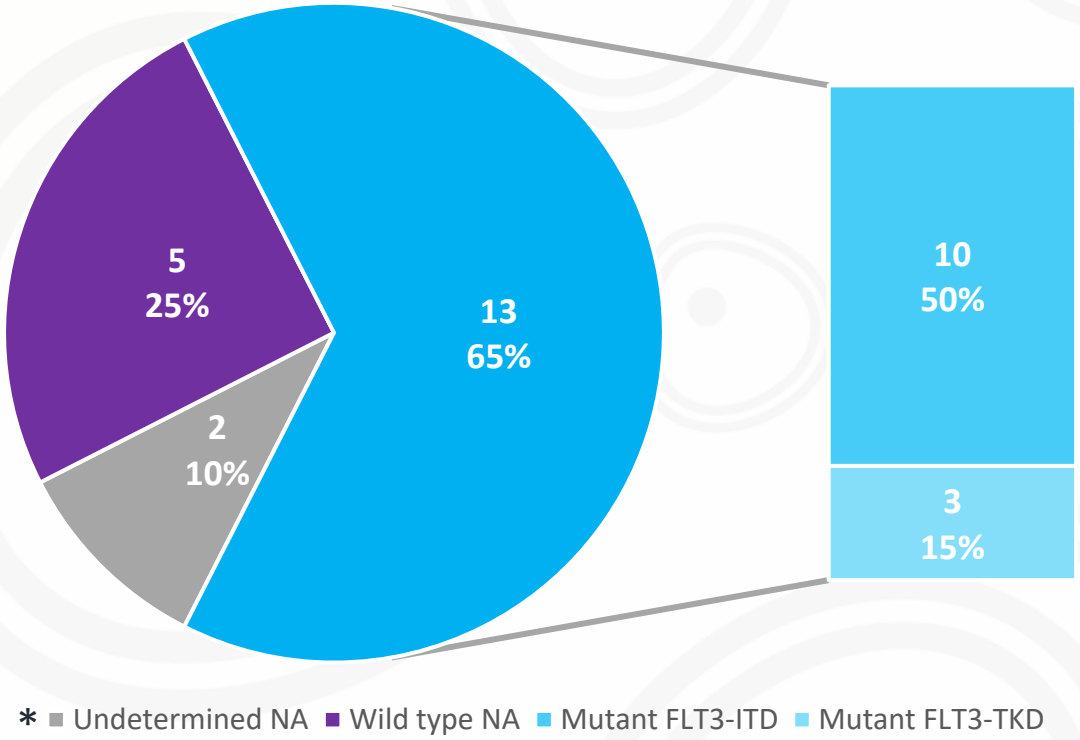
Baseline Characteristics

	Arm A (N=8)	Arm B (N=12)	Total (N=20)
Median age, years (range)	57.9 (34, 69)	53.3 (23, 78)	55.2 (23,78)
ECOG Performance Status			
0	1 (12.5 %)	3 (25.0%)	4 (20.0%)
1	4 (50.0%)	6 (50.0%)	10 (50.0%)
2	3 (37.5%)	3 (25.0%)	6 (30.0%)
Gender			
Female, n (%)	3 (37.5%)	5 (41.7%)	8 (40.0%)
Male, n (%)	5 (62.5%)	7 (58.3%)	12 (60.0%)
Prior Therapies			
Median # prior therapies (range)	4 (2,10)	4 (1,8)	4 (1,10)
Prior treatment with intensive therapy	5 (62.5%)	8 (66.7%)	13 (65.0%)
Prior Hematopoietic Stem Cell Transplant (HSCT)	3 (37.5%)	6 (50.0%)	9 (45.0%)
Prior Venetoclax-containing regimen	7 (87.5%)	11 (91.7%)	18 (90.0%)

- Overall balanced patient population between the two Arms
- Nearly half (~45%) post HSCT
- Large majority (~90%) had prior venetoclax-containing regimen
- Median prior lines of therapy: 4 (range 1 to 10)

FLT3 Mutational Status at Study Entry

FLT3 mutational status at study entry as determined by Central Lab (n=20)



** Central lab FLT3 mutational status not available*

- As per protocol, at each dose level up to 33% of patients may be wild type FLT3
- 100% (n=13) FLT3-mutant patients had progressed on or after a gilteritinib-containing regimen
- 5 of 13 had received at least two FLT3 inhibitors prior to study entry

BMF-500 Was Generally Well Tolerated

TEAEs with Preferred Term (Incidence ≥ 20%)	Related	Unrelated	All
	(N = 20)	(N = 20)	(N = 20)
Participants with at least one TEAE	**4 (20.0%)**	**20 (100.0%)**	**20 (100.0%)**
Anaemia	0	4 (20.0%)	4 (20.0%)
Dyspnoea	0	4 (20.0%)	4 (20.0%)
Febrile neutropenia	0	5 (25.0%)	5 (25.0%)
Hypocalcaemia	0	4 (20.0%)	4 (20.0%)
Hypokalaemia	0	4 (20.0%)	4 (20.0%)
Hypophosphataemia	0	4 (20.0%)	4 (20.0%)
Hypotension	1 (5.0%)*	4 (20.0%)	5 (25.0%)
Hypoxia	0	4 (20.0%)	4 (20.0%)
Nausea	0	4 (20.0%)	4 (20.0%)
Oedema peripheral	0	5 (25.0%)	5 (25.0%)
Platelet count decreased	0	4 (20.0%)	4 (20.0%)
Tachycardia	0	4 (20.0%)	4 (20.0%)

*Grade 2 per CTCAE as assessed by PI

- BMF-500 has shown a generally well-tolerated safety profile across all dose levels explored as of the data cut-off
- No DLTs reported, no dose reductions as of the data cut-off
- No treatment-related cytopenias were observed as of the data cut-off
- No QTc prolongation reported as of the data cut-off

Early Evidence of Clinical Activity

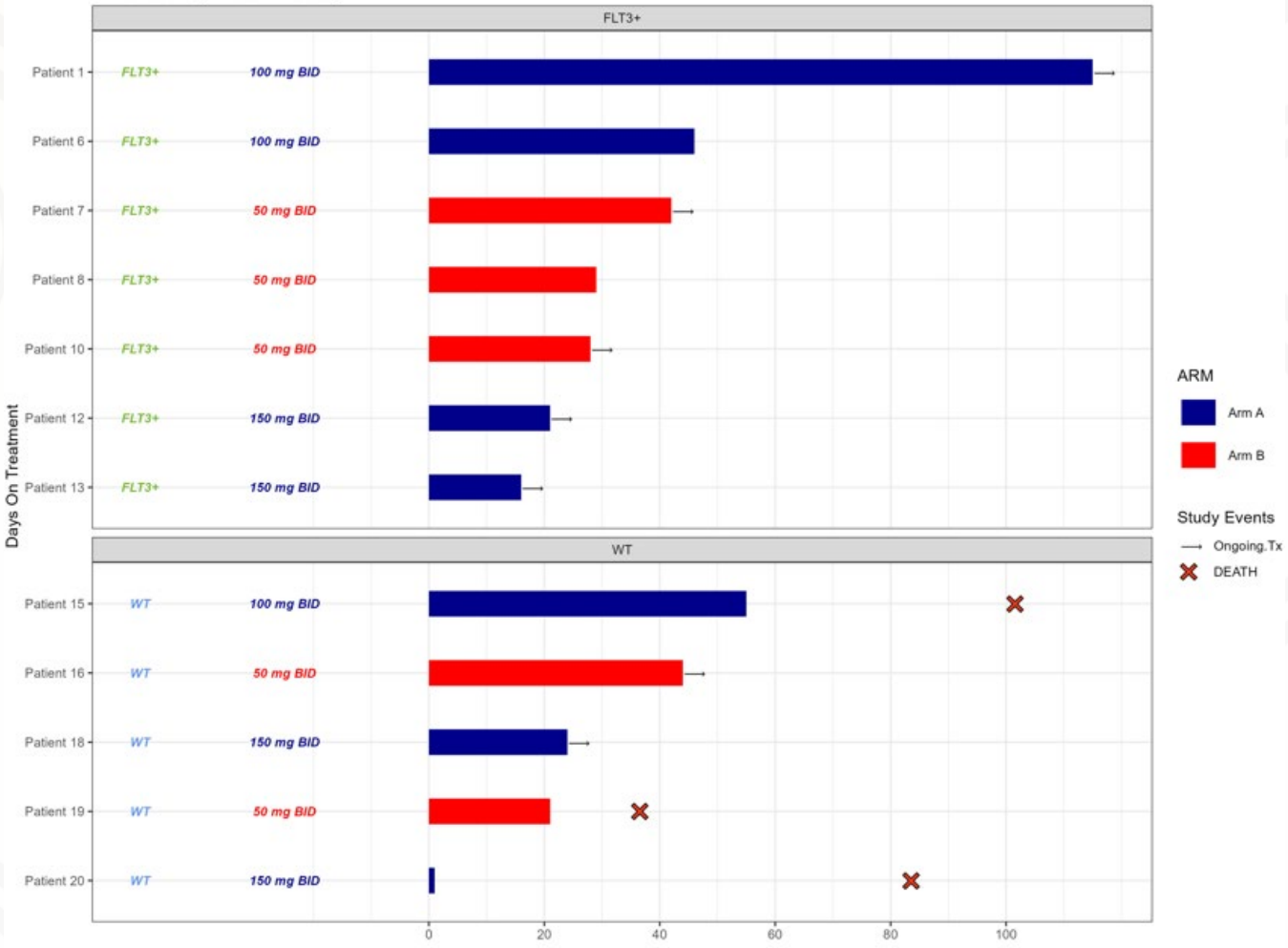
Evidence of Clinical Activity Observed in 11 Patients (Efficacy Evaluable population[#] n= 12)

Dose	Patient ID	FLT3 mutational status	Mutational Profile	CYP3A4 Inhibitor	# Prior Lines Therapy	Clinical Activity
100 mg BID	Patient 15	FLT3-wild type	ASXL1, IKZF1, NF1, RUNX1, SF3B1	No	3	Reduced BM blasts
	Patient 1	FLT3-mutation	ASXL1, IDH2, PHF6, RUNX1, SRSF2, **FLT3-ITD**	No	4	CRi (see case study)
	Patient 6	FLT3-mutation	ASXL1, **FLT3-TKD**, MSH3, NF1, RUNX1, SRSF2	No	8	>50% reduced BM blasts, clearance of PBs, reduced transfusion frequency
50 mg BID	Patient 17	Undetermined	Not available	No	4	None
	Patient 19	FLT3-wild type	ASXL1, CCND2, KIT, RUNX1, TET2	Yes	4	>50% reduced PBs
	Patient 7	FLT3-mutation	CDKN2A, CREBBP, **FLT3-ITD**, WT1	Yes	8	Reduced BM blasts, Clearance of PBs, reduced Hydrea use
	Patient 16	FLT3-wild type	Not available	Yes	3	Clearance of PBs
	Patient 10	FLT3-mutation	CHEK2, **FLT3-ITD**, NRAS, NSD1, RUNX1, WT1	Yes	8	Reduced BM blasts, reduced Hydrea use
25 mg BID	Patient 14	Undetermined	Not available	Yes	1	Reduced BM blasts
	Patient 4	FLT3-mutation	ASXL1, **FLT3-ITD**, KIT, KRAS, PTPN11, SRSF2, TP53, WT1	Yes	4	Reduced BM blasts, >50% reduced PBs
	Patient 2	FLT3-mutation	CBL, **FLT3-TKD**, FOXP1, KMT2A, KRAS G12A, PTEN, RUNX1, SETD2, STAG2	Yes	5	Clearance of PBs
	Patient 9	FLT3-mutation	**FLT3-ITD**, NSD1-NUP98 fusion, PMS2, WT1	Yes	7	Reduced Hydrea use

[#] Efficacy Evaluable population (defined as all patients enrolled who received at least one dose and had at least one disease assessment

Early Efficacy Data and Time on Treatment

Dose levels 2 and 3 from Arms A/B



- 7 of 12 (58%) patients remain on treatment
- 5 of 7 of FLT3-mut continue treatment at the time of reporting
- 1 of 2 FLT3-mut at dose level 2 (100mg BID) in Arm A (not taking CYP3A4i) achieved CRi
- 2 of 3 FLT3-mut at dose level 2 (50mg BID) in Arm B (taking CYP3A4i) showed BM blast reduction after first cycle and continue on study treatment

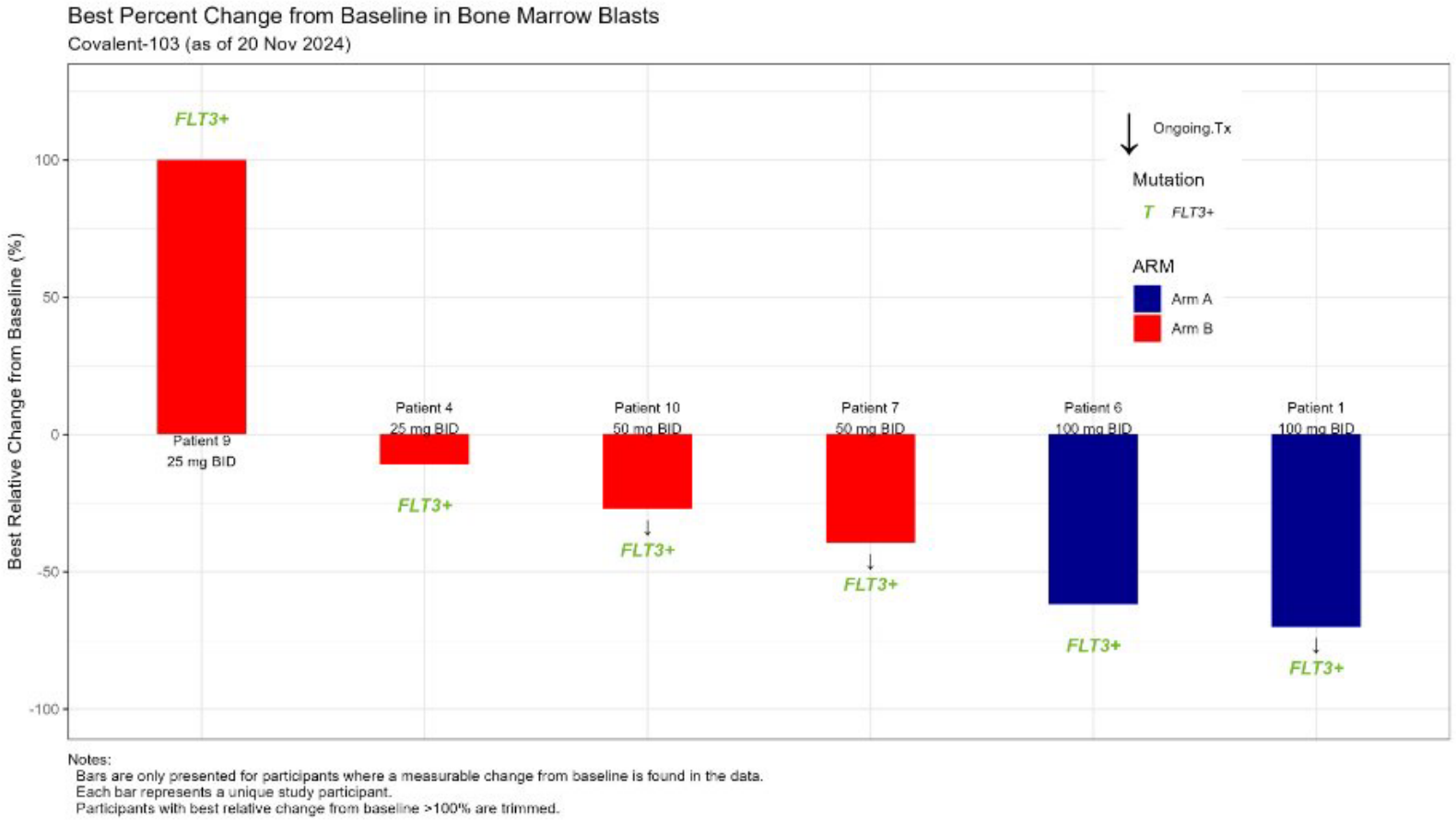
*** Study patient population:** reference prognostic parameters[1]:

- The mOS for R/R AML pts post gilteritinib: ~1.8 mo after gilteritinib discontinuation
- Pts who failed gilteritinib and received no subsequent treatment had mOS of 0.28 mo

[1]EHA 2024 Abst P1798 Type: e-Poster Presentation

The Safety Population is defined as all subjects who receive the 1st dose or partial dose of study drug.
NA = Not Available per Central Lab.

Early Efficacy Data: Bone Marrow Blasts % Change



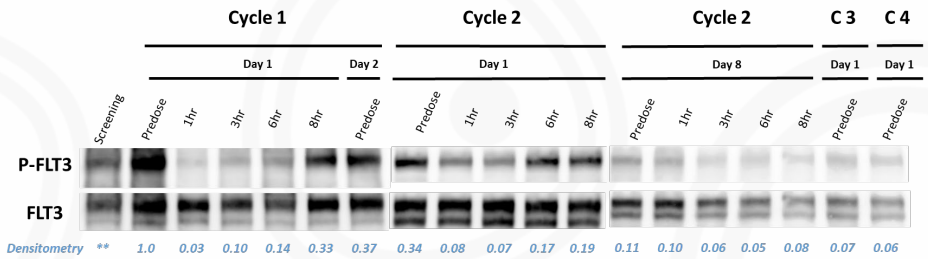
Notes:
Bars are only presented for participants where a measurable change from baseline is found in the data.
Each bar represents a unique study participant.
Participants with best relative change from baseline >100% are trimmed.

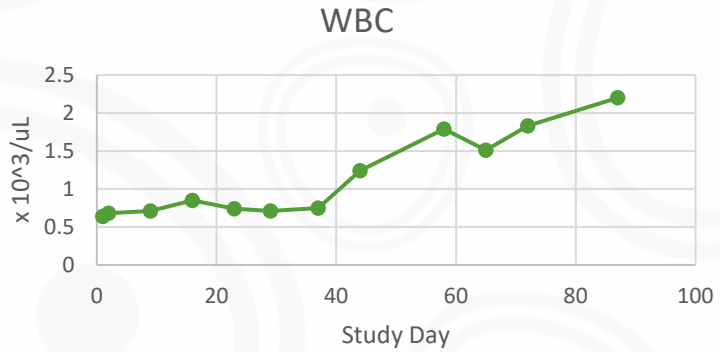
- 54% (7 of 13 of FLT3 mutated) were deemed efficacy-evaluable# as of the cut-off date, with only 6 displayed here*
- 83% (5 of 6) FLT3 mutated efficacy-evaluable# patients had a reduction in bone marrow (BM) blasts

*EDC data entry pending for 1 patient
#Efficacy Evaluable population (defined as all patients enrolled who received at least one dose and had at least one disease assessment

61-year-old male FLT3-mutant patient treated with BMF-500 100 mg BID achieved sustained CRi

Acute Leukemia	Primary AML
Mutations detected at study entry	**FLT3-ITD**, ASXL1, IDH2, PHF6, RUNX1, SRSF2
# of prior therapies	4 (including venetoclax and gilteritinib-containing regimens)
Prior HSCT	Yes

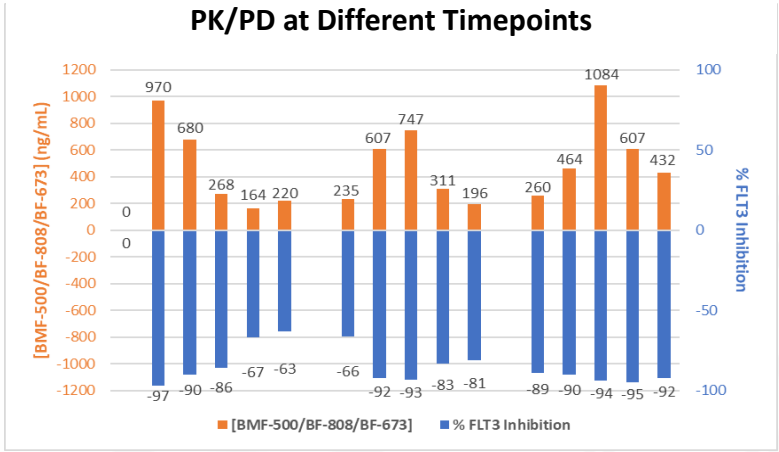


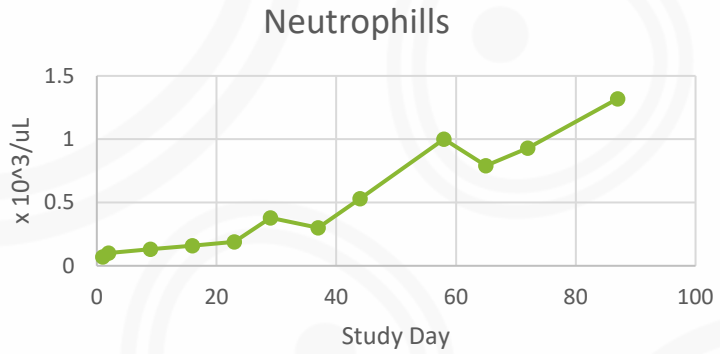


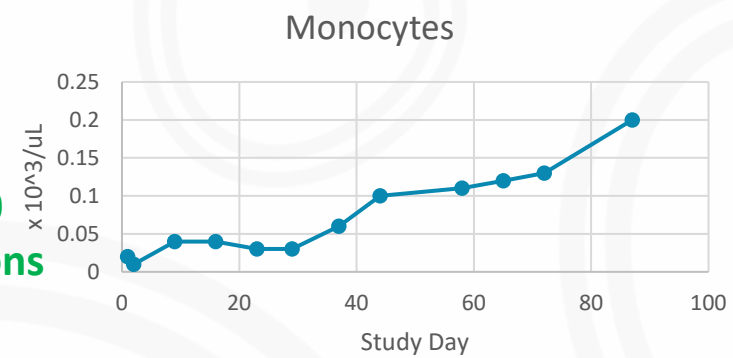
Timepoint: **Screening** **C2D1** **C3D1** **C4D1** **C5D1**

Response	-	**MLFS**	**CRi**	**CRi**	**CRi**
BM blasts (%):	**10%**	**5%**	**3%**	**5%**	**5%**
Allelic Ratio:	**0.1**	-	-	-	
MFC MRD:	-	-		**3.82%**#	**<0.1%***

 # Based on Bone Marrow assessment
**Based on peripheral blood assessment*







- **The magnitude of FLT3 inhibition correlated with the plasma concentration of BMF-500**
- **Study treatment was generally well tolerated with no interruptions or dose modifications**
- **Best Objective Response of CRi, as assessed by PI per ELN2017**

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Summary

Safety and tolerability data:

- No significant safety or tolerability issues observed to date (i.e. no QT prolongations or cytopenias) and no DLTs reported
- BMF-500 has been generally well tolerated, and the escalation continues without safety restrictions

Early clinical activity data:

- Ability to induce response by end of C1 and achievement of CRi at dose levels explored
- Ability to induce reduction of bone marrow blasts for the majority of efficacy-evaluable patients at the dose levels explored
- Other evidence of clinical activity observed in majority of patients treated (e.g. clearance of peripheral blasts, reduction of transfusion frequency, reduction in use of hydroxyurea etc.)

PK/PD markers confirm on-target inhibition of FLT3:

- Ability to induce dose-proportional FLT3 inhibition
- Ability to achieve near complete FLT3 inhibition on first day of dosing at dose levels explored
- BMF-500 and its major metabolites have shown similar concentrations in bone marrow compared to plasma suggesting good compartmental penetration

Collectively, these data support the ongoing development of BMF-500, the only covalent FLT3 inhibitor currently in the clinic

Acknowledgments & Legal Disclaimer

We would like to thank the patients, their families, physicians, healthcare professionals and research teams for participating and their contributions

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