CLINICAL STUDY PROTOCOL

Protocol Title:	Phase 1 Study to Determine the Safety and Tolerability of Ziftomenib Combinations for the Treatment of *KMT2A*-rearranged or *NPM1*-mutant Relapsed/Refractory Acute Myeloid Leukemia
Protocol Number:	KO-MEN-008
EU CTN:	2023-510288-37-00
Amendment Number:	4
Compound:	Ziftomenib
IND:	142028
Brief Title:	A Study to Investigate the Safety and Tolerability of Ziftomenib Combinations in Patients with Relapsed/Refractory Acute Myeloid Leukemia
Study Phase:	Phase 1
Sponsor Name:	Kura Oncology, Inc.
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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

AE	adverse events
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AST	aspartate aminotransferase
$AUC_{(0\text{-last})}$	area under the concentration-time curve from 0 to the time of the last quantifiable concentration
$AUC_{(0\text{-tau})}$	area under the concentration-time curve over a dosing interval
BID	twice daily
BM	bone marrow
BOR	best overall response
C_{max}	maximum plasma concentration
CFR	Code of Federal Regulations
CI	confidence interval
CL	clearance
CLIA	clinical laboratory improvement amendments
CNI	calcineurin inhibitor(s)
CNS	central nervous system
COVID-19	coronavirus disease 2019
CR	complete remission
CRF	case report form
CRh	complete remission with partial hematologic recovery
CRi	complete remission with incomplete hematologic recovery
CR_{MRD-}	complete remission without minimal residual disease
CSF	cerebrospinal fluid
CYP	cytochrome P450
DDI	drug-drug interactions
DIC	disseminated intravascular coagulation
DILI	drug-induced liver injury
DIPL	drug-induced phospholipidosis
DL	dose level
DLT	dose-limiting toxicity
DoR	duration of response
DS	differentiation syndrome
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EI	equivalence interval
ELN	European Leukemia Network

EOI	events of interest
EOT	end of treatment
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FISH	fluorescent in situ hybridization
FLAG-IDA	fludarabine + cytarabine + granulocyte colony-stimulating factor + idarubicin
FLT3	FMS-like tyrosine kinase 3
FLT3-m	FMS-like tyrosine kinase 3-mutated
G-CSF	granulocyte colony-stimulating factor
GCP	Good Clinical Practice
GvHD	graft-versus-host disease
HiDAC	high-dose cytarabine
HSCT	hematopoietic stem cell transplant
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonization
IDAC	intermediate-dose cytarabine
IDH	isocitrate dehydrogenase
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITD	internal tandem duplications
IV	intravenous(ly)
KM	Kaplan-Meier
KMT2A	lysine[K]-specific methyltransferase 2A
KMT2A-r	lysine[K]-specific methyltransferase 2A-rearranged
KMT2A-wt	lysine[K]-specific methyltransferase 2A-wild-type
LDAC	low-dose cytarabine
MFC	multiparameter flow cytometry
mITT	modified intent-to-treat
MLFS	morphologic leukemia-free state
MLL	mixed-lineage leukemia
MRD	measurable residual disease
MTD	maximum tolerated dose
mTOR	mammalian target of rapamycin
NCA	non-compartmental analysis
NCI CTCAE	National Cancer Institute Common Terminology for Adverse Events
NGS	next-generation sequencing

NPM1	nucleophosmin 1
NPM1-m	nucleophosmin 1-mutant
PCR	polymerase chain reaction
PDn	pharmacodynamic(s)
PK	pharmacokinetic(s)
PKAS	pharmacokinetic analysis set
PR	partial remission
PTD	partial tandem duplications
QD	once daily
QTcF	QT interval by Fredericia's formula
RP2D	recommended Phase 2 dose
R/R	relapsed/refractory
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous(ly)
SMC	Safety Monitoring Committee
SmPC	Summary of Product Characteristics
SoA	schedule of activities
SOC	standard-of-care
SOS	sinusoidal obstruction syndrome
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TLS	tumor lysis syndrome
T_{max}	time to maximum plasma concentration
USPI	United States Prescribing Information
VOD	veno-occlusive disease
WBC	white blood cell
WNL	within normal limits

1 PROTOCOL SUMMARY

1.1 Synopsis

Title	Phase 1 Study to Determine the Safety and Tolerability of Ziftomenib Combinations for the Treatment of *KMT2A*-rearranged or *NPM1*-mutant Relapsed/Refractory Acute Myeloid Leukemia
Short Title	A Study to Investigate the Safety and Tolerability of Ziftomenib Combinations in Patients with Relapsed/Refractory Acute Myeloid Leukemia
Study Number	KO-MEN-008
Phase	Phase 1
Study Design	This is a 2-part, multi-center Phase 1 dose escalation and expansion/validation study to assess the safety, tolerability, pharmacokinetics, and preliminary clinical activity of ziftomenib when combined with standard of care (SOC) therapies in adults with relapse or refractory (R/R) *NPM1*-m or *KMT2A*-r acute myeloid leukemia (AML). Patients with *NPM1*-m or *KMT2A*-r AML will be enrolled into separate arms to receive 1 of the following treatment combinations per investigator discretion: *NPM1*-m R/R AML: • Cohort A-1 (US only): Zifto/FLAG-IDA (intensive chemotherapy) • Cohort A-2: Zifto/LDAC (nonintensive chemotherapy) • Cohort A-3: Zifto/gilteritinib (*FLT3*-m targeted therapy for *NPM1*-m + *FLT3*-m R/R AML) *KMT2A*-r R/R AML: • Cohort B-1 (US only): Zifto/FLAG-IDA (intensive chemotherapy) • Cohort B-2: Zifto/LDAC (nonintensive chemotherapy) Note: Relapse is defined as reappearance of ≥5% blasts in the bone marrow (BM) or reappearance of blasts in the blood in ≥2 peripheral blood samples ≥1 week apart; or development of new extramedullary disease. Refractory is defined as patients who have failed at least 1 prior line of therapy. Each cohort within the respective arms is independent of the others and may open, close, and/or progress without dependence on the others. In any cohort, there is an option to expand enrollment if needed due to encouraging results and to provide a bridge to a future study. Dose Escalation (Part 1a) An i3+3 design will be employed in the Part 1a dose escalation to select the dose (or doses) of ziftomenib for each SOC combination within each arm for further characterization in Part 1b in order to identify the respective recommended Phase 2 dose (RP2D) of each combination. Patient assignment to a given arm and cohort should be based on investigator discretion, confirmation of eligibility criteria for the arm and cohort, and slot availability. Progression to the next dose level may occur after at least 6 patients have been reviewed by the Safety Monitoring Committee (SMC) at a given dose level (See Section 4.2.1). In each ziftomenib combination tested, only the ziftomenib dose should be escalated in combination with any appropriate adjustments per the label of the approved agent(s). Up to

	4 dose levels (DL) are planned for each intensive (IC) and nonintensive chemotherapy (NIC) combination and up to 5 DLs are planned for the gilteritinib combination. Dose Validation/Expansion (Part 1b) The safety, pharmacokinetics (PK), and preliminary clinical activity of 1 or more ziftomenib DLs for each combination identified in Part 1a will be examined in the Part 1b dose validation and expansion phase to determine the RP2D for each combination within each arm. As in Part 1a, patient assignment to a given arm and cohort should be based on investigator discretion. Up to approximately 15 patients will be enrolled per cohort at the DL chosen for validation. Independent Bayesian toxicity and futility monitoring will be employed in Part 1b to protect patient safety against excessive toxicity or lack of treatment effect. In addition, the safety data from each cohort will be reviewed continuously by the SMC and Independent Data Monitoring Committee (IDMC) with formal meetings scheduled as deemed necessary and per the respective SMC and IDMC charters (See Section 10.1.5). Following completion of the dose validation/expansion phase, the RP2D for each combination for the respective genotypes will be selected based on clinical activity, exposure, and other PK and pharmacodynamic (PD) effects in conjunction with the SMC and IDMC as described in Section 4.4.
Rationale	Ziftomenib is a potent and selective compound targeting the protein-protein interaction between menin and mixed-lineage leukemia (MLL)/lysine[K]-specific methyltransferase 2A (*KMT2A*), which blocks leukemic transformation and drives leukemic blasts towards terminal differentiation. The inhibitory activity of ziftomenib for the menin-MLL(*KMT2A*) interaction has been demonstrated preclinically in models of both *KMT2A*-r and *KMT2A*-wt/*NPM1*-m AML and ziftomenib has shown preliminary clinical activity in patients with R/R *NPM1*-m and *KMT2A*-r AML in the Phase 1 portion of KO-MEN-001. Due to ziftomenib's ability to target menin-dependent clones, ziftomenib in combination with SOC chemotherapies or the *FLT3* inhibitor, gilteritinib (for *NPM1*-m patients with a *FLT3* co-mutation), may provide additional benefit for patients with *NPM1*-m or *KMT2A*-r AML.

Key Eligibility Criteria	Patients will be considered eligible if they meet the following key inclusion/exclusion criteria:
	
	Adults 18 years and older diagnosed with AML who relapsed or were refractory to ≥1 prior line of therapy with documented *NPM1*-m or *KMT2A*-r (excluding partial tandem duplications)
	
	• Adequate liver, renal, and cardiac function
	  ○ AST <3× ULN, ALT <3× ULN, total bilirubin <1.5× ULN (except for patients with known Gilbert's syndrome for which the total bilirubin must be <5× ULN)
	  ○ Creatinine Clearance (CLcr) ≥30 mL/min
	  ○ Ejection fraction by echocardiogram:
	  ▪ Cohorts A-1 and B-1: ≥50%
	  ▪ Cohorts A-2, B-2, and A-3: ≥40%
	• ECOG status ≤ 2
	• No active central nervous system (CNS) involvement by AML
	  ○ Those with CNS disease that is controlled (defined as clearance of cerebrospinal fluid (CSF) blasts and other evidence of CNS disease per the investigator) may be allowed and intrathecal therapy may be continued.

	• Recovered to Grade ≤1 (NCI CTCAE v5.0) or baseline from all nonhematological toxicities from prior AML therapies except for alopecia • No diagnosis of acute promyelocytic leukemia or blast phase chronic myeloid leukemia • Patients with active graft-vs-host disease (GvHD) requiring more than 0.5 mg/kg prednisone (or equivalent) or any new or increase in immunosuppressants in the prior 2 weeks for GvHD treatment (except adjustments of calcineurin or mammalian target of rapamycin (mTOR) inhibitors to maintain therapeutic trough levels) • No clinical signs/symptoms of leukocytosis or white blood cell count $>25\times10^9$/L
Number of Patients	Total: Approximately 171 patients Part 1a: Approximately 96 evaluable patients Part 1b: Up to 75 patients Per dose escalation cohort: At least 6 evaluable patients Per dose validation/expansion cohort: Up to approximately 15 patients
Length of Participation	On treatment: Up to approximately 2 years, with the potential to receive continued therapy via compassionate use. On study (including screening and follow-up): Up to approximately 2 years for all dosing combinations.
Intervention	Dosing regimens for each of the combinations are outlined below. All SOC backbone agents within the respective cohorts, in addition to any associated premedication, should be administered per institutional SOC and according to the respective manufacturer's prescribing information. Site protocols for the administration of backbone regimens can be shared in advance for Sponsor review to ensure that it remains in general alignment with the dosing regimens outlined below. Ziftomenib: Oral administration of 50 mg and/or 200 mg dose strengths of ziftomenib should be given once daily (QD) according to the patient's cohort schedule. Patients can self-administer ziftomenib. Ziftomenib should be taken at least 1 hour before or 2 hours after a meal with 8 oz of water. FLAG-IDA: Cohorts A-1 and B-1 (US Only): The components of FLAG-IDA (fludarabine + cytarabine + G-CSF + idarubicin) should be administered according to the details outlined in their respective prescribing information. Protocol recommended dosing is: fludarabine 30 mg/m^2/day intravenously (IV) on Days 1 to 4, idarubicin 6 to 10 mg/m^2/day (IV on Days 1 to 3, cytarabine 1500 to 2000 mg/m^2/day IV on Days 1 to 5, and G-CSF 300 mcg/m^2/day subcutaneous (SC) on Days 1 to 5. Additional G-CSF may be administered starting Day 6 following completion of chemotherapy until ANC > 1000/µL. G-CSF should be discontinued for at least 7 days prior to obtaining bone marrow to document remission. Cytarabine should be administered per the manufacturer's prescribing information and according to institutional standards. High-dose cytarabine (HiDAC) Consolidation (Cohorts A-1 and B-1 only): Patients indicated to receive HiDAC for treatment consolidation in combination with ziftomenib should receive a 3000 mg/m^2 dose of cytarabine by IV over 3 hours every 12 hours on Days 1, 3, and 5 (total dose 18,000 mg/m^2) per cycle. Ziftomenib should be administered on Days 1 to 28 of each consolidation cycle. The dose

	and/or schedule may be modified accordingly based on institutional practice and/or myelosuppression, per investigator discretion. Intermediate dose cytarabine (IDAC) Consolidation (Cohorts A-1 and B-1 only): Patients indicated to receive IDAC for treatment consolidation in combination with ziftomenib should receive a 1500 mg/m^2 dose of cytarabine by IV over 3 hours every 12 hours on Days 1, 3, and 5 (total dose 9000 mg/m^2) per cycle. Ziftomenib should be administered on Days 1 to 28 of each consolidation cycle. The dose and/or schedule may be modified accordingly based on institutional practice and/or myelosuppression, per investigator discretion. Low-dose cytarabine (LDAC; Cohorts A-2 and B-2): Patients indicated to receive LDAC in combination with ziftomenib should be administered a 20 mg dose of cytarabine twice a day (BID) SC on Days 1 to 10 of the 28-day cycle. Ziftomenib should begin on Day 8 of Cycle 1 and should be administered on Days 1 to 28 of Cycle 2 and beyond. The dose and/or schedule may be modified accordingly based on institutional practice and/or myelosuppression, per investigator discretion. • **NOTE:** LDAC is NOT a chemotherapy consolidation option for Cohorts A-1 and B-1. Gilteritinib (Cohort A-3): Gilteritinib should be administered according to the details outlined in the prescribing information.
Primary Objective and Primary Endpoint	Objective: To determine the safety and tolerability of each protocol-specified ziftomenib combination in patients with *KMT2A*-r or *NPM1*-m (± co-occurring *FLT3*-m) R/R AML. • Endpoints: o Rate of DLT per dose level o Descriptive statistics of AEs per the NCI-CTCAE v5.0.
Key Secondary Objective(s) and Corresponding Endpoint(s)	Objective: To evaluate the clinical activity for ziftomenib combinations in patients with *KMT2A*-r or *NPM1*-m (± co-occurring *FLT3*-m) R/R AML based on the European Leukemia Network (ELN) 2022. • Endpoints: o For Cohorts A-1, A-2, B-1, and B-2: CR rate o Cohorts A-3: the CR/CRh rate. Objective: To evaluate survival and disease control outcomes for protocol-specified ziftomenib combinations in patients with *KMT2A*-r or *NPM1*-m (± co-occurring *FLT3*-m) R/R AML. • Endpoints: o CRc (CR+CRi+CRh) and MLFS rates per 2022 ELN criteria o Overall Survival (OS); 6-month OS: Proportion of patients alive at 6 months; o Median event-free survival (EFS), 6-month EFS o Duration of remission o Measurable residual disease (MRD) assessment in the BM by flow cytometry and molecular analysis (PCR, NGS) o Proportion of patients that undergo hematopoietic stem cell transplant (HSCT) o Rate of transfusion independence. Objective: To characterize the PK of ziftomenib and metabolites administered in combination with SOC treatments in adults with R/R *NPM1*-m or *KMT2A*-r. • Endpoint: o Multiple dose PK: C_{max}, T_{max}, $AUC_{(0\text{-last})}$, $AUC_{(tau)}$

	Objective: To evaluate the PK of gilteritinib when administered concurrently with ziftomenib in adults with R/R *NPM1*-m (+ co-occurring *FLT3*-m). • Endpoint: o Multiple dose PK: C_{max}, T_{max}, $AUC_{(0\text{-}last)}$, $AUC_{(tau)}$
Number of Sites	Approximately 52 sites globally (40 in US and 12 in EU)
Study Duration	Estimated start date: Q4 2023 Projected end date: Q3 2027 Estimated duration: approx. 4 years
Safety Monitoring Committee	An SMC composed of investigators, Sponsor personnel, and independent advisor(s), if applicable will review patient data to assess the safety and help determine the dose level advancement in Part 1a, and any further mitigations that may be needed for the respective combinations. The composition of the committee is dependent upon the scientific skills and knowledge required for monitoring this study. Details are available in Section 10.1.5.1 and in the SMC charter.
Independent Data Monitoring Committee	The IDMC will support the SMC at certain key milestones within the study, including a data review following completion of the dose escalation portion in Part 1a to support the selection of dose(s) to be further investigated in the dose validation/expansion portion in Part 1b and for the ultimate selection of the respective combination RP2Ds. Upon completion of Part 1a, the IDMC will convene approximately every 4 months to provide ongoing oversight. The IDMC may make recommendations regarding whether adjustments to ziftomenib dose are warranted, as well as whether to continue the study as planned. The IDMC may also formulate recommendations relating to the selection, recruitment, and retention of patients and their management. Additional details regarding the responsibility of the IDMC/its chair is provided in Section 10.1.5.2 and in the IDMC charter.

1.2 Schedule of Activities (SoA)

Table 1 Ziftomenib Combined with FLAG-IDA (Cohorts A-1 and B-1)

		Induction Cycle 1 [Induction Cycle 2 (if applicable)]						Recovery[a,b]	Consolidation (each cycle) [up to 2 cycles permitted]			Maintenance	EOT[e]	Safety Follow-up	Survival Follow-up
Protocol Activity	**Screening D-28 – D-1**	**D1[a]**	**D8**	**D14**	**D21**	**D28**	**D35, 42+, as app.**	**Either End of Induction C1 or Induction C2**	**D-1[a,c]**	**Weekly D8-28[d]**	**Recovery**	**(Monotherapy/ post-HSCT) See Table 7**		**Occurs 28 days after last dose**	**Monthly[f]**
			±2d	**±2d**	**±3d**	**±3d**	**±7d**		**+1d**				**±7d**	**±7d**	**±14d**
Informed Consent[g]	X														
Inclusion/ Exclusion Criteria[h]	X														
Cytogenetics/ Molecular Assessment[i]	X														
Med/Surg History[j]	X	X[k]													
Disease History	X														
Demographics	X														
Physical Exam[l]	X	X	X	X	X	X			X	X			X		
Height and Weight[m]	X	X	X	X	X	X			X	X			X		
Vital Signs[n]	X	X	X	X	X	X			X	X			X		
ECOG PS[o]	X	X[p]							X				X		
12-Lead ECG[q]	X	X[r]	X[s]										X		

		Induction Cycle 1 [Induction Cycle 2 (if applicable)]						Recovery[a, b]	Consolidation (each cycle) [up to 2 cycles permitted]			Maintenance	EOT[e]	Safety Follow-up	Survival Follow-up
Protocol Activity	**Screening D-28 – D-1**	**D1[a]**	**D8**	**D14**	**D21**	**D28**	**D35, 42+, as app.**	**Either End of Induction C1 or Induction C2**	**D-1[a,c]**	**Weekly D8-28[d]**	**Recovery**	**(Monotherapy/ post-HSCT) See Table 7**		**Occurs 28 days after last dose**	**Monthly[f]**
			±2d	**±2d**	**±3d**	**±3d**	**±7d**		**+1d**				**±7d**	**±7d**	**±14d**
ECHO/MUGA[t]	X														
Chest X-ray[u]	X														
Hematology, Chemistry, and Safety Laboratory Tests[v, w]	X	X	X	X	X	X	(X)	X	X	X	X		X		
Cystatin C[x]	X	X[y]							X						
Coagulation Laboratory Tests[v]	X	(X)[y]	X	X	X	X									
Inflammatory markers[v]	X	(X)[y]	X	X	X	X									
Urinalysis[v]	X	X							X				X		
DS and TLS monitoring[z]		During Cycle 1 Induction (and, if applicable, Cycle 2 Induction)													
Pregnancy Test (WOCP)[aa]	X	X							X				X		
Lumbar Puncture[bb]	(X)														
CNS/PNS/ EMD[cc]	(X)	Table 2													

		Induction Cycle 1 [Induction Cycle 2 (if applicable)]						Recovery[a, b]	Consolidation (each cycle) [up to 2 cycles permitted]			Maintenance	EOT[e]	Safety Follow-up	Survival Follow-up
Protocol Activity	**Screening D-28 – D-1**	**D1[a]**	**D8**	**D14**	**D21**	**D28**	**D35, 42+, as app.**	**Either End of Induction C1 or Induction C2**	**D-1[a,c]**	**Weekly D8-28[d]**	**Recovery**	**(Monotherapy/ post-HSCT) See Table 7**		**Occurs 28 days after last dose**	**Monthly[f]**
			±2d	**±2d**	**±3d**	**±3d**	**±7d**		**+1d**				**±7d**	**±7d**	**±14d**
Evaluate Extent of Disease and Response to Treatment[dd]		Table 2													
TLS and DS Prophylaxis[ee]		TLS prophylaxis per institutional standards													
FLAG-IDA Admin.[ff]		Table 13													
HiDAC/IDAC Admin[gg]								Table 13							
Ziftomenib Admin. Continuous[hh]		Table 13													
PK Sampling		Table 18, Table 19, and Table 20													
Biomarker Sampling (BMA and Blood)		Table 5													
Dispense Patient Diary[ii]			X						X						
Collect Zifto Patient Diary						X			X				X		

		Induction Cycle 1 [Induction Cycle 2 (if applicable)]						Recovery[a, b]	Consolidation (each cycle) [up to 2 cycles permitted]			Maintenance	EOT[e]	Safety Follow-up	Survival Follow-up
Protocol Activity	**Screening D-28 – D-1**	**D1[a]**	**D8**	**D14**	**D21**	**D28**	**D35, 42+, as app.**	**Either End of Induction C1 or Induction C2**	**D-1[a,c]**	**Weekly D8-28[d]**	**Recovery**	**(Monotherapy/ post-HSCT) See Table 7**		**Occurs 28 days after last dose**	**Monthly[f]**
			±2d	**±2d**	**±3d**	**±3d**	**±7d**		**+1d**				**±7d**	**±7d**	**±14d**
AEs/SAEs[jj]	Every Visit (during the Screening Period, report SAEs only)												X	X	
Con Meds/ Procedures[kk]	Every Visit												X	X	
Transfusion Data[ll]	Every Visit												X	X	
New Antineoplastic Therapy[mm]													X	X	X
Survival Assessment															X

Abbreviations: AE=adverse event; AESI= adverse event of special interest; ANC=absolute neutrophil count; BM=bone marrow; CNS=central nervous system; D=day; DS=differentiation syndrome; ECG=electrocardiogram; ECHO/MUGA=echocardiogram/multi-gated acquisition scan; ECOG=Eastern Cooperative Oncology Group; EOT=end of treatment; FEV1=forced expiratory volume in 1 second; FLAG-IDA=fludarabine + cytarabine + granulocyte colony-stimulating factor + idarubicin; GvHD=graft vs host disease; HSCT=hematopoietic stem cell transplant; *KMT2A*-r=lysine[K]-specific methyltransferase 2A-rearranged; *NPM1*-m=nucleophosmin 1-mutant; PK=pharmacokinetic(s); PNS=peripheral nervous system; RBC=red blood cell; SAE=serious adverse event; SOS= sinusoidal obstruction syndrome; TLS=tumor lysis syndrome; VOD= veno-occlusive disease.

(X) = if clinically indicated

a. The assessments at these visits (i.e., Day 1 of Cycle 2) may be combined with the prior respective End of Cycle visit for patient convenience. If the visits are combined for convenience, all required assessments for both visits are required.
b. Recovery is defined as peripheral ANC $\geq 1\times10^9$/L and platelets at least $\geq 50\times10^9$/L (but preferably $\geq 100\times10^9$/L) and signs of a cellular BM. Note: It is not mandatory to obtain more than 1 BM examination after remission Induction Cycle 1, as long as the indicated assessments were completed, and the BM examination was performed at the time of recovery.
c. The assessments at the D-1 visit can occur on D1 of consolidation.
d. There should be 3 visits during this period: 1 each between D8-14, D15-21, and D22-28.
e. For patients who do not proceed to maintenance and permanently discontinue all study treatment, EOT assessments should be conducted within the specified window, and patients should proceed to Safety and Survival Follow-up per this table. Those going on to maintenance therapy should follow the schedule presented in Table 7 and should complete the EOT visit, Safety Follow-up and Survival Follow-up following maintenance therapy completion.
f. After the Safety follow-up visit, all patients should enter survival follow-up and be contacted monthly for assessment of survival status including HSCT and initiation of other new antineoplastic therapies from the discontinuation of study treatment until death, withdrawal of consent, lost to follow-up, or end of study.
g. Refer to Section 10.1.3
h. Refer to Section 5.
i. Cytogenetic and/or molecular testing for *KMT2A*-r and *NPM1*-m should be performed locally as part of SOC and may take place outside of the 28-day screening period as long as the most recent results are obtained after the last therapy and provided to the Sponsor to confirm eligibility. Patients must also submit a BM aspirate prior to C1D1 for determination of baseline BM blast counts and to meet other biomarker requirements (see Section 8.4.1 for further information).
j. A thorough family history is needed to identify potential myeloid neoplasms with germline predisposition. On Cycle 1 Day 1, additional medical history that is observed after signing of the informed consent but prior to initial study drug administration and not considered related to study-required procedures should be recorded in the patient's medical history.
k. Medical/Surgical History is only required for Cycle 1 Induction. Note: See footnote kk regarding Con Meds and Con Procedures. See footnote jj regarding AE/SAE reporting.
l. A complete physical examination will be performed at Screening and EOT; otherwise, a limited symptom-directed physical examination will be performed at all other visits. See Section 8.2.2.
m. Weight should be recorded at all visits as indicated. Cycle X Day 1 weight may be collected up to 3 days prior to enable time for study drug preparation and/or dispensation. Height recorded at Screening only.
n. If vital signs are performed after blood collection for laboratory tests, there should be at least 30 minutes in between. See Section 8.2.3.
o. ECOG assessment should be performed at the timepoints indicated and at regular visits or if a change in ECOG status occurs. See Section 8.2.5.
p. ECOG assessment applicable for patients who receive a second round of induction.
q. 12-lead ECG in triplicate (all 3 collected within a 10-minute period) to be performed at Screening and during the study visit on Cycle 1 Day 8, Cycle 2 Day 1, and EOT. On Cycle 1 Day 8, triplicate 12-lead ECGs will be collected at predose (relative to ziftomenib), and at 2 hours (± 15 minutes) following ziftomenib administration. Patients should be supine for at least 5 minutes before the 12-lead ECG is performed. Beyond Cycle 2 Day 1 (with the exception of the EOT ECG), additional ECGs may be performed as clinically indicated. See Section 8.2.4.
r. 12-lead triplicate ECG applicable for patients who receive a second round of induction.
s. 12-lead triplicate ECG on Day 8 is only required during Cycle 1 Induction. See footnote 'q' for details.
t. ECHO/MUGA must be performed at Screening to determine eligibility and may be performed during the study as clinically indicated.
u. To determine eligibility and as clinically indicated thereafter.

v. See Appendix 1 for the respective analytes/laboratory parameters. For patients requiring Induction Cycle 2, obtain on Cycle 2 Day 1 and then as clinically indicated thereafter.
w. In the absence of active or residual leukemia, if a patient has not had count recovery by Day 28 of induction, CBCs are required weekly until ANC $\geq 1\times10^9$/L or platelets $\geq 50\times10^9$/L, and as clinically indicated thereafter.
x. Cystatin C to be collected during Screening, Cycle 1 Day 1 induction, Cycle 2 Day 1 induction (for patients who receive a second cycle of induction), and D-1 (or D1) of each consolidation cycle.
y. Required on Day 1 of Induction Cycle 2 only.
z. Monitor for DS and TLS until the absence of active or residual leukemia as per the DS and hyperleukocytosis guidance in Section 6.5.4.1 and Appendix 5. See Appendix 1 for laboratory parameters if DS is suspected and Section 8.2.1.
aa. In women with childbearing potential, a serum pregnancy test at screening should be performed within 72 hours of Cycle 1 Day 1; at all other timepoints, a urine or serum pregnancy test is acceptable.
bb. Required in patients with clinical symptoms suspicious of active CNS involvement; lumbar puncture considered optional in other settings (eg, high white blood cell count).
cc. Radiological confirmation is required in patients with clinical symptoms suspicious of active PNS involvement (eg, intracranial bleeding), leptomeningeal disease, or extramedullary disease; the choice of diagnostic imaging modality will be as determined most appropriate by the investigator and should remain consistent throughout the study. Whenever possible, the same instrument should be used. Those patients with evidence of prior CNS disease controlled (defined as clearance of cerebrospinal fluid (CSF) blasts and other evidence of CNS disease per the investigator) at enrollment or who are at high risk of developing CNS disease may continue to receive intrathecal chemotherapy as treatment or begin prophylaxis, respectively, as per institutional practices.
dd. Local disease response assessments should be assessed at the timepoints in Table 2, using the ELN 2022 criteria (Table 17). Response assessments for patients who discontinue for reasons other than disease progression should be entered until the start of the next non-HSCT therapy.
ee. Only applicable for Cycle 1 induction. TLS prophylaxis is per institutional practice and guidance as per the TLS section of the DS and hyperleukocytosis guidance in Section 6.5.4.1.1 #3. It is recommended to continue TLS prophylaxis through Day 14 to account for the first week with the addition of ziftomenib. Patients may be hospitalized or brought into clinic to receive TLS prophylaxis starting any time prior to starting SOC backbone therapy as per institutional standards. Suggested treatment of electrolyte abnormalities are provided but should be per site SOC. See Appendix 5.
ff. Refer to Section 6.1.2.
gg. Refer to Section 6.1.3.
hh. See Section 6.1.1.
ii. For Cycle 1, diaries should be dispensed on the day of discharge from the hospital or at the in-clinic visit around C1D8 (or later as needed). For patients who go on to receive a second Induction Cycle, diaries should be dispensed at the C1D28 or the C2D1 visit.
jj. AEs will be monitored and recorded starting at the time of dosing of study drug (C1D1 or upon study entry (sign off on the subject eligibility form) if starting SOC therapy outside of the study). SAEs will be monitored and recorded starting at the time of signing the informed consent. Refer to Appendix 6 for further information on AE reporting requirements. The DLT evaluation period will begin on Cycle 1 Day 8 and will end on Study Day 35 for patients achieving leukemic clearance. Otherwise, the DLT period will end at the start of Cycle 2 for any patients with residual disease after Cycle 1. For patients who undergo HSCT, AEs/SAEs should continue to be collected for 28 days following the last dose of ziftomenib, ***excluding any common transplant-related events***. Any ziftomenib-related SAEs should continue to be reported regardless of timing. Following the start of conditioning, only the following AESIs should be collected until ziftomenib is restarted post HSCT: VOD/SOS, acute graft vs host disease (aGvHD) (Grade II-IV per MAGIC criteria, Appendix 7), chronic graft vs host disease (cGvHD) (Jagasia et al, 2015). Refer to Section 6.1.5 for further information.
kk. Collected continuously from informed consent throughout the safety follow-up period.
ll. Information on RBC and platelet transfusions (eg, dates and units administered) and associated hemoglobin, RBC, and/or platelet levels should be collected from at least the 28 days prior to the first dose of study treatment through the safety follow-up period.
mm. Documentation of new antineoplastic therapies including HSCT and associated conditioning therapies.

Table 2 Disease Response Assessments – Cohorts A-1 and B-1

Protocol Activity	Screening Days -28 to -1	Induction Cycles 1-2 (as applicable)		Consolidation Treatment (each cycle, as applicable)		Post-HSCT maintenance or ziftomenib monotherapy (up to 2 years)		EOT Visit (+7d)	Post EOT Follow-up
		Day 28 (±7d)	At Recovery	Day -1	At Recovery	Day -1	Q3 Cycles (±7d)		Per SOC[j]
Local Investigator Disease Response Assessment by Blood, BM Aspirate or BM Core Biopsy[a]	X[b]	X[c]	X[d]	X[g]	X[e,f]	X[e,f,g]	X[f]	X[f,i]	X
Local MRD Assessment[h]		X	X[d]	X[g,h]	X[e,f]	X[e,f,g]	X[f]	X[i,f]	X
Imaging Assessments for Patients with Extramedullary Disease Only[k]	X	Disease response to be assessed per institutional SOC							

Abbreviations: ANC=absolute neutrophil count; BM=bone marrow; BMA=bone marrow aspiration; CR=complete remission; CRi=complete remission with incomplete hematologic recovery; CR_{MRD+}=complete remission with measurable residual disease; CR_{MRD-}=complete remission without measurable residual disease; d=days; EDC=electronic data capture; EOT=end of treatment; HiDAC=high-dose cytarabine; HSCT= hematopoietic stem cell transplant; IDAC=intermediate-dose cytarabine; *KMT2A*-r=lysine[K]-specific methyltransferase 2A-rearranged; MFC=multiparameter flow cytometry; MLFS=morphologic leukemia-free state; MRD=measurable residual disease; *NPM1*-m=nucleophosmin 1-mutant; Q3=every 3; qPCR=quantitative polymerase chain reaction; qRT-PCR=quantitative reverse transcription polymerase chain reaction; SOC=standard-of-care.

a. Disease response assessments should be performed locally by the investigator to ensure rapid patient treatment and triage during this study. A portion of the BM aspirate or blood or BM core biopsy from each disease assessment (including assessments that occur at nonprotocol specified times) should be submitted to the study per instructions in the Laboratory Manual (see Table 5). If a BM assessment is not required due to response status in the prior BM, the investigator assessment of disease status is still required using all available clinical data, including recent complete blood count and differential.

b. BM aspirate samples and/or core biopsy should be collected for all patients at Screening to establish baseline disease (BM blast counts, local cytogenetics, local *NPM1*-m or *KMT2A*-r molecular screening results). BM aspirates performed prior to the Screening period as SOC will be accepted for baseline disease assessment if within 28 days prior to C1D1 if it is not clinically feasible or within institutional standards to repeat.

c. BM aspirate or BM core biopsy sample for hematopathology should be taken on Day 28 (±7d) of Induction Cycle 1, with the recommendation to repeat per SOC only if results are equivocal. For patients receiving an additional induction cycle, repeat response assessment at the end of Induction Cycle 2, as described for Induction Cycle 1. If the local disease response assessment is repeated after Cycle 1 Day 28 prior to the start of Cycle 2, then the BMA and blood for biomarkers should be repeated as well.

d. If there is no evidence of hematologic recovery by Day 42 of the respective induction cycle, a BM aspirate or BM core biopsy sample should be performed at this time to assess underlying disease status and for MRD status. If there is no evidence of hematologic recovery by Day 56, a BM aspirate or BM core biopsy sample should be performed at this time to assess underlying disease status and for MRD status. If the optional Induction Cycle 2 is administered, response assessment should be done after recovery of blood counts, similar to Induction Cycle 1.

Protocol Activity	Screening Days -28 to -1	Induction Cycles 1-2 (as applicable)		Consolidation Treatment (each cycle, as applicable)		Post-HSCT maintenance or ziftomenib monotherapy (up to 2 years)		EOT Visit (+7d)	Post EOT Follow-up
		Day 28 (±7d)	At Recovery	Day -1	At Recovery	Day -1	Q3 Cycles (±7d)		Per SOC[j]

e. Bone marrow and peripheral blood analysis for response assessment after consolidation should be performed preferably at early hematologic recovery before the start of maintenance treatment (early hematologic recovery is defined as ANC $\geq 0.5\times10^9$/L platelets $\geq 20\times10^9$/L). For patients receiving HiDAC or IDAC consolidation, the response assessment should include an assessment of MRD after completion of each consolidation cycle or sooner if chemotherapy is discontinued due to intolerance or other reasons (see Section 8.1).

f. MRD assessment should be performed by molecular MRD analysis (eg, qRT-PCR, qPCR, and/or next-generation sequencing) and/or MFC, as dictated by institutional practices. Molecular MRD, if available, should be chosen over MFC. In addition to the prespecified timepoints, local MRD assessment should be performed at the time of CR, CRh, CRi, or MLFS during consolidation and every 3 cycles during maintenance therapy to confirm continued MRD status, as well as just prior to any HSCT. In the event of a CR_{MRD-} response at a given cycle, a confirmatory BM sample should be collected after 1 additional cycle. In the event of a CR_{MRD+} response at a given cycle, a BM sample should be collected upon completion of the subsequent cycle to evaluate conversion to an MRD- response. Otherwise, during maintenance therapy, BM assessments should be performed every 3 cycles (q84 ± 7 days) and at EOT or as needed based on evidence of suspected relapse (cytopenias, increased transfusion requirements, etc.) or for suspected response (ie, the peripheral blood count of leukemia blasts drops to <5%).

g. If consolidation or maintenance treatment is initiated <4 weeks after a response assessment, a repeated “Day -1” (“D-1”) assessment before start of consolidation or maintenance is not required.

h. An MRD assessment should be performed just prior to the start of consolidation, including any HSCT.

i. If disease progression has been documented through blood or BM assessment during the study treatment period, additional response and/or MRD assessment at the EOT visit is not required.

j. Evaluations should be collected per SOC for patients who discontinue study treatment without progression.

k. Patients with extramedullary disease present should have a complete imaging assessment of baseline disease burden per institutional standards by CT or PET scan, with PET scan preferred where appropriate. Once on study, tumor imaging and investigator assessment of response should be performed per institutional practice. All imaging performed on study should use identical techniques and equipment, where possible. Imaging response assessments may be performed in place of, or in addition to, blood and BM aspirate or BM core biopsy sampling for disease response assessments at the investigator’s discretion. Blood collection for study-related biomarker analyses should still be collected as shown in Table 5.

Table 3 Ziftomenib Combined with LDAC [Cohorts A-2 and B-2] or Ziftomenib Combined with Gilteritinib [Cohort A-3]

Protocol Activity		Cycle 1								Cycle 2					Cycle 3 and beyond			Maintenance[b]	EOT[c]	Safety Follow-Up	Survival Follow-up
	Screening d-28 to d-1	D1	D4	D8	D10	D15	D21	D28	D35, 42+, as app.	D1[a]	D4	D10	D28	D35, 42+, as app	D1[a]	Q28d	Q84d (every 3rd cycle)	Mono/ Post-HSCT Table 7		28 days after EOT	Monthly[d]
			±2 d	±2 d	±2d	±2d	±3d	±3d	±7d	+2d	±2d	±2d	±7d	±7d	+1d	±7d	±7d		±7d	±7d	±14d
Informed Consent[e]	X																				
Inclusion/ Exclusion Criteria[f]	X																				
Cytogenetics/ Molecular Assessment[g]	X																				
Med/Surg History[h]	X	X																			
Disease History	X																				
Demographics	X																				
Physical Exam[i]	X	X	X	X		X				X	X		X		X						
Height and Weight[j]	X	X				X				X					X				X		
Vital Signs[k]	X	X	X	X		X				X	X		X		X						
ECOG PS[l]	X	X								X							X		X		

Protocol Activity		Cycle 1								Cycle 2					Cycle 3 and beyond			Maintenance[b]	EOT[c]	Safety Follow-Up	Survival Follow-up
	Screening d-28 to d-1	D1	D4	D8	D10	D15	D21	D28	D35, 42+, as app.	D1[a]	D4	D10	D28	D35, 42+, as app	D1[a]	Q28d	Q84d (every 3rd cycle)	Mono/ Post-HSCT Table 7		28 days after EOT	Monthly[d]
			±2 d	±2 d	±2d	±2d	±3d	±3d	±7d	+2d	±2d	±2d	±7d	±7d	+1d	±7d	±7d		±7d	±7d	±14d
12-Lead ECG[m] (Cohort A-2, B-2)	X			X						X									X		
12-Lead ECG[m] (Cohort A-3)	X	X		X		X				X					X				X		
ECHO/MUGA[n]	X																				
Chest Radiograph[o]	X																				
Hematology, Chemistry and other safety laboratory tests[p,q]	X	X		X	X	X	X	X	(X)	X	X	X	X	(X)	X	X			X		
Cystatin C	X	X								X					X						
Creatine Phosphokinase[r] (Cohort A-3 only)		X				X				X					X						
Urinalysis[p]	X	X								X					X				X		

Protocol Activity		Cycle 1								Cycle 2					Cycle 3 and beyond			Maintenance[b]	EOT[c]	Safety Follow-Up	Survival Follow-up
	Screening d-28 to d-1	D1	D4	D8	D10	D15	D21	D28	D35, 42+, as app.	D1[a]	D4	D10	D28	D35, 42+, as app	D1[a]	Q28d	Q84d (every 3rd cycle)	Mono/ Post-HSCT Table 7		28 days after EOT	Monthly[d]
			±2 d	±2 d	±2d	±2d	±3d	±3d	±7d	+2d	±2d	±2d	±7d	±7d	+1d	±7d	±7d		±7d	±7d	±14d
Coags and Inflammatory Markers (Cohorts A-2 and B-2)[s]	X			X	X	X				(X)[s]		(X)[s]			(X)[s]	(X)[s]					
Coags and Inflammatory Markers (Cohort A-3)[s]	X	X		X	X	X				(X)[s]		(X)[s]			(X)[s]	(X)[s]					
TLS and DS Monitoring[t]		Section 6.5.4.1																			
Pregnancy Test (WOCP)[u]	X	X								X					X		X		X		
Lumbar Puncture[v]	(X)																				
CNS/PNS/EMD[w]	(X)	Table 4																			
Evaluate Extent of Disease and Response to Treatment[x]		Table 4																			
TLS and DS Prophylaxis (Cohorts A-2, B-2, and A-3)[y, z]		Per section 6.5.4.1.1																			

Protocol Activity		**Cycle 1**								**Cycle 2**					**Cycle 3 and beyond**			**Maintenance[b]**	**EOT[c]**	**Safety Follow-Up**	**Survival Follow-up**
	Screening d-28 to d-1	**D1**	**D4**	**D8**	**D10**	**D15**	**D21**	**D28**	**D35, 42+, as app.**	**D1[a]**	**D4**	**D10**	**D28**	**D35, 42+, as app**	**D1[a]**	**Q28d**	**Q84d (every 3rd cycle)**	**Mono/ Post-HSCT Table 7**		**28 days after EOT**	**Monthly[d]**
			±2 d	**±2 d**	**±2d**	**±2d**	**±3d**	**±3d**	**±7d**	**+2d**	**±2d**	**±2d**	**±7d**	**±7d**	**+1d**	**±7d**	**±7d**		**±7d**	**±7d**	**±14d**
LDAC Admin. (Cohorts A-2 and B-2 only)[aa]		Table 13																			
Gilteritinib Admin. Continuous (Cohort A-3)[bb]		Table 13																			
Ziftomenib Admin. Continuous[cc]		Table 13																			
PK Sampling		Table 18, Table 19, and Table 20																			
Biomarker Sampling (BMA and Blood)		Table 6																			
Dispense Patient Diary[dd]		X		(X)						X					X				X		
Collect Zifto Patient Diary[ee]										X					X						
AEs/SAEs[ff]		Every Visit (during the Screening Period, report SAEs only)																	X	X	
Con Meds/ Procedures[gg]		Every Visit																	X	X	

Protocol Activity		Cycle 1								Cycle 2					Cycle 3 and beyond			Maintenance[b]	EOT[c]	Safety Follow-Up	Survival Follow-up
	Screening d-28 to d-1	D1	D4	D8	D10	D15	D21	D28	D35, 42+, as app.	D1[a]	D4	D10	D28	D35, 42+, as app	D1[a]	Q28d	Q84d (every 3rd cycle)	Mono/ Post-HSCT Table 7		28 days after EOT	Monthly[d]
			±2 d	±2 d	±2d	±2d	±3d	±3d	±7d	+2d	±2d	±2d	±7d	±7d	+1d	±7d	±7d		±7d	±7d	±14d
Transfusion data[hh]	Every Visit																		X	X	
New Antineoplastic Therapy[ii]																			X	X	X
Survival Assessment																					X

Abbreviations: AE=adverse events; AESI= adverse event of special interest; BM=bone marrow; CNS=central nervous system; D=day; DS=differentiation syndrome; ECG=electrocardiogram; ECHO/MUGA=echocardiogram multi-gated acquisition scan; ECOG=Eastern Cooperative Oncology Group; EOT=end of treatment; FLT3=FMS-like tyrosine kinase 3; GvHD= graft vs host disease; HSCT=hematopoietic stem cell transplant; *KMT2A*-r=lysine[K]-specific methyltransferase 2A-rearranged; *NPM1*-m=nucleophosmin 1-mutant; PK=pharmacokinetic(s); PNS=peripheral nervous system; Q3=every 3; RBC=red blood cell; SAE=serious adverse event; SOC=standard-of-care; SOS= sinusoidal obstruction syndrome; TLS=tumor lysis syndrome; VOD= veno-occlusive disease.

(X) = if clinically indicated.

a. The assessments at these visits (i.e., Day 1 of Cycle 2 and beyond) may be combined with the prior respective End of Cycle visit for patient convenience.
b. For maintenance/monotherapy SoA, please refer to Table 7.
c. For patients who do not proceed to maintenance and permanently discontinue all study treatment. EOT assessments should be conducted within the specified window, and patients should proceed to Safety and Survival Follow-up per this table. Those going on to maintenance therapy should follow the schedule presented in Table 7 and should complete the EOT visit, Safety Follow-up and Survival Follow-up following maintenance therapy completion.
d. After the Safety follow-up visit, all patients should enter follow-up and be contacted monthly for assessment of survival status including HSCT and initiation of other new antineoplastic therapies since the discontinuation of study treatment until death, withdrawal of consent, lost to follow-up, or end of study.
e. Refer to Section 10.1.3.
f. Refer to Section 5.
g. Cytogenetic and/or molecular testing for *KMT2A*-r and *NPM1*-m should be performed locally as part of SOC and may take place outside of the 28-day screening period as long as the most recent results are obtained after the last therapy and provided to the Sponsor to confirm eligibility. Patients must also submit a BM aspirate prior to C1D1 for determination of baseline BM blast counts and to meet other biomarker requirements (see Section 8.4.1 for further information).
h. A thorough family history is needed to identify potential myeloid neoplasms with germline predisposition. On Cycle 1 Day 1, additional medical history that is observed after signing of the informed consent but prior to initial study drug administration and not considered related to study-required procedures should be recorded in the patient's medical history. Medical/Surgical history is only required for Cycle 1. Note: See footnote gg regarding Con Med and Con Procedures. See footnote ff regarding AE/SAE reporting.
i. A complete physical examination will be performed at Screening and EOT; otherwise, a limited symptom-directed physical examination will be performed at all other visits. See Section 8.2.2.

Protocol Activity		Cycle 1								Cycle 2					Cycle 3 and beyond			Maintenance[b]	EOT[c]	Safety Follow-Up	Survival Follow-up
	Screening d-28 to d-1	D1	D4	D8	D10	D15	D21	D28	D35, 42+, as app.	D1[a]	D4	D10	D28	D35, 42+, as app	D1[a]	Q28d	Q84d (every 3rd cycle)	Mono/ Post-HSCT Table 7		28 days after EOT	Monthly[d]
			±2 d	±2 d	±2d	±2d	±3d	±3d	±7d	+2d	±2d	±2d	±7d	±7d	+1d	±7d	±7d		±7d	±7d	±14d

j. Weight should be recorded at all visits as indicated. Cycle X Day 1 weight may be collected up to 3 days prior to enable time for study drug preparation and/or dispensation. Height recorded at screening only.
k. If vital signs are performed after blood collection for laboratory tests, there should be at least 30 minutes in between. See Section 8.2.3.
l. ECOG assessment should be performed at the timepoints indicated and at regular visits, or if a change in ECOG status occurs. See Section 8.2.5.
m. 12-lead ECG in triplicate (all 3 collected within a 10-minute period) to be performed at Screening and during the study visits as follows: **Cohorts A-2 and B-2**: Cycle 1 Day 8 (triplicate ECG to be performed predose (relative to ziftomenib) and 2 hours (± 15 minutes) following drug administration), Cycle 2 Day 1, and EOT. **Cohort A-3:** Cycle 1 Day 1 (triplicate ECG to be performed predose (relative to ziftomenib) and 2 hours (± 15 minutes) following drug administration), Cycle 1 Day 8, Cycle 1 Day 15, Cycle 2 Day 1, Cycle 3 Day 1, and EOT. ECGs beyond these timepoints may be performed as clinically indicated. Patients should be supine for at least 5 minutes before the 12-lead ECG is performed. See Section 8.2.4.
n. ECHO/MUGA must be performed at Screening to determine eligibility and may be performed as clinically indicated thereafter.
o. To determine eligibility and as deemed clinically necessary during study participation.
p. See the table in Appendix 1 for respective analytes/laboratory parameters.
q. In the absence of active or residual leukemia, if a patient has not had count recovery during Cycle 1, CBCs are required weekly until ANC $\geq 1\times10^9$/L or platelets $\geq 50\times10^9$/L.
r. For Cohort A-3 only. Creatine phosphokinase performed locally on Cycle 1 Day 1, Cycle 1 Day 15, and Day 1 of every subsequent cycle.
s. Coagulation studies and inflammatory markers are only for patients who have evidence of persistent AML at the end of the preceding cycle. See the table in Appendix 1 for respective analytes/ laboratory parameters.
t. Monitor for DS and TLS until the absence of active or residual leukemia as per the DS and hyperleukocytosis guidance in Section 6.5.4.1 and Appendix 5. See Appendix 1 for laboratory parameters if DS is suspected and Section 8.2.1.
u. In women with childbearing potential, a serum pregnancy test at screening must be performed within 72 hours of Cycle 1 Day 1; at all other timepoints, a urine or serum pregnancy test is acceptable.
v. Required in patients with clinical symptoms suspicious of CNS involvement; lumbar puncture considered optional in other settings (eg, high white blood cell count).
w. Radiological confirmation is required in patients with clinical symptoms suspicious of active PNS involvement (eg,intracranial bleeding), leptomeningeal disease, or extramedullary disease; the choice of diagnostic imaging modality should be as determined most appropriate by the investigator and should remain consistent throughout the study. Whenever possible, the same instrument should be used. Those patients with evidence of prior CNS disease controlled (defined as clearance of cerebrospinal fluid (CSF) blasts and other evidence of CNS disease per the investigator) at enrollment or who are at high risk of developing CNS disease continue to receive intrathecal chemotherapy as treatment or to begin prophylaxis, respectively, as per institutional practices.
x. Local disease response assessments should be assessed at the timepoints in Table 4, using the ELN 2022 criteria (Table 17). Response assessments for patients who discontinue for reasons other than disease progression should be entered until the start of the next non-HSCT therapy.
y. For patients in Cohorts A-2 and B-2: TLS prophylaxis is per institutional practice and guidance as per the TLS section of the DS and hyperleukocytosis guidance in Section 6.5.4.1.1 #3. It is recommended to continue TLS prophylaxis through Day 14 to account for the first week with the addition of ziftomenib. Patients may be hospitalized or brought into clinic to receive TLS prophylaxis starting on D-1 or any time prior to starting SOC backbone therapy as per institutional standards. For treatment of electrolyte abnormalities while on treatment see Appendix 5.

Protocol Activity		Cycle 1								Cycle 2					Cycle 3 and beyond			Maintenance[b]	EOT[c]	Safety Follow-Up	Survival Follow-up
	Screening d-28 to d-1	D1	D4	D8	D10	D15	D21	D28	D35, 42+, as app.	D1[a]	D4	D10	D28	D35, 42+, as app	D1[a]	Q28d	Q84d (every 3rd cycle)	Mono/ Post-HSCT Table 7		28 days after EOT	Monthly[d]
			±2 d	±2 d	±2d	±2d	±3d	±3d	±7d	+2d	±2d	±2d	±7d	±7d	+1d	±7d	±7d		±7d	±7d	±14d

z. For patients in Cohort A-3: TLS prophylaxis is per institutional practice and guidance as per the TLS section of the DS and hyperleukocytosis guidance in Section 6.5.4.1.1. It is recommended to continue TLS prophylaxis through Day 7 to account for the first week with the addition of ziftomenib. Patients may be hospitalized or brought into clinic to receive TLS prophylaxis starting on D-1 as per institutional standards. For treatment of electrolyte abnormalities while on treatment, see Appendix 5.

aa. See Section 6.1.3.

bb. See Section 6.1.4.

cc. See Section 6.1.1.

dd. Diaries should be dispensed on C1D1 (Cohort A-3) or on the day of discharge from the hospital or at the in-clinic visit around C1D8 (Cohorts A-2 and B-2). For patients who continue on therapy beyond Cycle 1, diaries should be dispensed at the end of the current cycle or the start of the next cycle (if visits are combined for patient convenience).

ee. Diaries should be collected on D1 of every subsequent cycle.

ff. AEs should be monitored and recorded starting at the time of dosing of study drug (Cycle 1 Day 1 for Cohort A-3) or upon study entry (sign off on the subject eligibility form for Cohorts A-2 and B-2) if starting SOC therapy outside of the study. SAEs should be monitored and recorded starting at the time of signing the informed consent. Refer to Appendix 6. For patients who undergo HSCT, AEs/SAEs should continue to be collected for 28 days following the last dose of ziftomenib at the start of conditioning, ***excluding any common transplant-related events***. Any ziftomenib related SAEs should continue to be reported regardless of timing. Following the start of conditioning, only the following AESIs should be collected until ziftomenib is restarted post HSCT: VOD/SOS, acute graft vs host disease (aGvHD) (Grade II-IV per MAGIC criteria, Appendix 7), chronic graft vs host disease (cGvHD) NIH Consensus Criteria (Jagasia et al, 2015). Refer to Section 6.1.5 for further information. For Cohorts A-2 and B-2, the DLT evaluation period will begin on Cycle 1 Day 8 upon administration of ziftomenib and will close on Study Day 35 for patients achieving leukemic clearance. Otherwise, the DLT period will close upon the start of Cycle 2 for patients with residual disease after Cycle 1. For Cohort A-3, the DLT evaluation period will begin upon administration of ziftomenib on Cycle 1 Day 1 and close on Cycle 1 Day 28.

gg. Collected continuously from informed consent throughout the safety follow-up period.

hh. Information on RBC and platelet transfusions (eg, dates and units administered) and associated hemoglobin, RBC, and/or platelet levels should be collected from at least the 28 days prior to the first dose of study treatment through the safety follow-up period.

ii. Documentation of new antineoplastic therapies including HSCT and associated conditioning therapies.

Table 4 Disease Response Assessments – Cohorts A-2, A-3, and B-2

Protocol Activity	Screening Days -28 to -1	Cycle 1 D28 (±7d)	Cycle 2 D28 (±7d)	Cycle 3 D28 (±7d)	Cycle 4/Q3 Cycles/q84 days (± 7 days) D28 (±7d)	Post-HSCT maintenance or ziftomenib monotherapy (up to 2 years) D-1[a]	Post-HSCT maintenance or ziftomenib monotherapy (up to 2 years) Q3 Cycles/q84 days (±7d)	EOT (±7d[b])	Post-EOT Follow-up As per SOC[h,]
Local Investigator Disease Response Assessment of Blood, BM, aspirate, and/or BM Core Biopsy Samples[c]	X[d]	X[e,f]	X[e,f]	X[e,f]	X[e,f]	X[f,i]	X[e,f]	X[f, g]	X
Local MRD Assessment[f]		Upon CR, CRi, CRh, MLFS or q3 Cycles[f]				X[f,i]	X[f]	X[f, g]	X
Imaging Assessments for Patients with Extramedullary Disease Only[j]	X	Disease response to be assessed per institutional SOC							

Abbreviations: BM=bone marrow; BMA=bone marrow aspiration; CR=complete remission; CRc=composite complete remission; CRh=complete remission with partial hematologic recovery; CRi=complete remission with incomplete hematologic recovery; CR_{MRD+}=complete remission with measurable residual disease; CR_{MRD-}=complete remission without measurable residual disease; EDC=electronic data capture; EOT=end of treatment; HSCT= hematopoietic stem cell transplant; *KMT2A*-r=lysine[K]-specific methyltransferase 2A-rearranged; MFC=multiparameter flow cytometry; MLFS=morphologic leukemia-free state; MRD=measurable residual disease; *NPM1*-m=nucleophosmin 1-mutant; Q3=every 3; qPCR=quantitative polymerase chain reaction; qRT-PCR=quantitative reverse transcription polymerase chain reaction; SOC=standard-of-care.

a. In the case where consolidation or maintenance treatment is initiated <4 weeks after a response assessment, a repeated "Day -1" ("D-1") assessment before the start of consolidation or maintenance is not required.
b. BM samples are required at EOT if the patient has not had a disease assessment in the prior 28 days.
c. Disease response assessments should be performed locally by the investigator to ensure rapid patient treatment and triage during this study. A portion of the BM aspirate or blood or BM core biopsy from each disease assessment (including assessments that occur at non-protocol specified times) should be submitted to the study per instructions in the Laboratory Manual (see Table 6). If a BM assessment is not required due to response status in the prior BM, the investigator assessment of disease status is still required using all available clinical data, including recent complete blood count and differential.

d. BM aspirate samples and/or core biopsy should be collected for all patients at Screening to establish baseline disease (BM blast counts, local cytogenetics, local *NPM1*-m or *KMT2A*-r molecular screening results). BM aspirates performed prior to the Screening period as SOC will be accepted for baseline disease assessment if within 28 days prior to C1D1 if it is not clinically feasible or within institutional standards to repeat.
e. End of Cycle 1 BM aspirate or biopsy should be performed at Cycle 1 Day 28 ±7 days. For subsequent cycles, assessments should be performed monthly until leukemic clearance (eg, CR, CRh, CRi, or MLFS) and then Q3 cycles thereafter until end of treatment or as needed based on evidence of suspected relapse (cytopenias, increased transfusion requirements, etc.).
f. MRD assessment should be performed by molecular MRD analysis (eg, qRT-PCR, qPCR, and/or next-generation sequencing) and/or multiparameter flow cytometry, as dictated by institutional practices. Molecular MRD, if available, should be chosen over MFC. In addition to the prespecified timepoints, local MRD assessment should be performed at the time of CR, CRi, or MLFS and every 3 cycles during maintenance therapy to confirm continued MRD status, as well as just prior to any HSCT. In the event of a CR_{MRD-} response at a given cycle, a confirmatory BM sample should be collected after 1 additional cycle. In the event of a CR_{MRD+} response at a given cycle, a BM sample should be collected upon completion of the subsequent cycle to evaluate conversion to an MRD- response. Otherwise, during maintenance therapy, BM assessments should be performed every 3 cycles and at EOT or as needed based on evidence of suspected relapse (cytopenias, increased transfusion requirements, etc.) or for suspected response (ie, the peripheral blood count of leukemia blasts drops to <5%).
g. If disease progression has been documented through blood or BM assessment during study treatment, additional response and/or MRD assessment at the EOT visit is not required.
h. Local disease response evaluations (including MRD status when available) should be collected for patients who discontinue study treatment without progression. Evaluations should be collected per SOC for patients who discontinue study treatment without progression.
i. In the case where consolidation or maintenance treatment (including post-transplant maintenance) is initiated <4 weeks after, a disease response assessment should be performed prior to initiating maintenance therapy.
j. Patients with extramedullary disease should have a complete imaging assessment of baseline disease burden per institutional standards by CT or PET scan, with PET scan preferred where appropriate. Once on study, tumor imaging and investigator assessment of response should be performed per institutional standard practice. All imaging performed on study should use identical techniques and equipment, where possible. Imaging response assessments may be performed in place of, or in addition to, blood and BM aspirate or BM core biopsy sampling for disease response assessments at the investigator's discretion. Blood collection for study-related biomarker analyses should still be collected as shown in Table 6.

Table 5 Sample Collection for Study-related Biomarkers for Cohorts A-1 and B-1

Protocol Activity[a]	Screening Day-28 to -1	Induction Cycles 1-2 (as applicable)		Consolidation Treatment (Each cycle, if applicable)		Post-HSCT Maintenance or ziftomenib monotherapy (Up to 2 years)		EOT Visit (+7 days)
		Day 28 (±7d)	At Recovery	Day -1[b]	At Recovery	Day -1[b]	Q3 Cycles/q84 days (±7 days)	
BM Aspirate for *NPM1*-m and *KMT2A*-r[c]	X							
Archival Frozen Samples for *NPM1*-m and *KMT2A*-r[c]	X							
Archival BM Core for *NPM1*-m and *KMT2A*-r[c]	X							
BM Aspirate Sample for Mutational Analysis[c]	X							
BM Aspirate Sample for MRD Assessment[d]		X	X	X	X	X	X	X
BM Aspirate Sample for Biomarkers[c,d]	X	X	X	X	X	X	X	X
Blood Sample for Biomarkers[e]	X	X	X	X	X	X	X	X
BM Aspirate Sample for Pharmacodynamic Analysis[c,d]	X	X						X
Blood Sample for Pharmacodynamic Analysis[e]	X	X						X

Abbreviations: BM=bone marrow; EOT=end of treatment; FFPE=formalin-fixed paraffin-embedded; *KMT2A*-r=lysine[K]-specific methyltransferase 2A-rearranged; MRD=measurable residual disease; *NPM1*-m=nucleophosmin 1-mutant; Q3=every 3.

a. Blood and BM should be collected for all patients. Please refer to the Laboratory Manual for details regarding instructions and container type for collecting blood and BM samples.

b. In the case consolidation or maintenance treatment is initiated <4 weeks after a response assessment, a repeated "Day -1" ("D-1") assessment before start of consolidation or maintenance is not required.

c. For all patients, a portion of the BM aspirate collected for molecular screening evaluations and local investigator assessments (see Table 2) must be submitted to the study for retrospective central confirmation of the local test results for *NPM1*-m and *KMT2A*-r and additional study-related biomarker analysis. Patients that have started their SOC backbone treatment prior to screening, must submit a BMA sample for retrospective central confirmation and storage and the most recent archival sample (if available) prior to ziftomenib dosing at Cycle 1 Day 8. For all patients, if the collection of the BM sample is not clinically feasible and/or results in a dry tap, a peripheral blood sample for storage and a BM core (eg, trephine) biopsy must be collected and submitted. For all patients who do not undergo BM aspirate collection, the investigator should also attempt to obtain and submit the most recent archived BM sample if available (eg, frozen BM, viable frozen cells, cell pellet, frozen DNA, FFPE slides, FFPE block). Refer to the Laboratory Manual for details regarding submission of BM core FFPE block or FFPE slides.

d. For all patients, a portion of the BM aspirate collected for on-study local investigator assessments, including assessments that occur at non-protocol specified times must be submitted for central MRD assessment and additional biomarker analysis (see Table 2). If the collection of the BM sample is not clinically feasible and/or results in a

Protocol Activity[a]	Screening Day-28 to -1	Induction Cycles 1-2 (as applicable)		Consolidation Treatment (Each cycle, if applicable)		Post-HSCT Maintenance or ziftomenib monotherapy (Up to 2 years)		EOT Visit (+7 days)
		Day 28 (±7d)	At Recovery	Day -1[b]	At Recovery	Day -1[b]	Q3 Cycles/q84 days (±7 days)	

dry tap, a peripheral blood sample for storage and a BM core (eg, trephine) biopsy must be collected and submitted. Refer to the Laboratory Manual for details regarding submission of BM core FFPE block or FFPE slides.

e. Peripheral blood for study-related biomarker analysis of leukemia cells and pharmacodynamic analysis should be collected at each timepoint.

Table 6 Sample Collection for Study-related Biomarkers for Cohorts A-2, A-3, and B-2

Protocol Activity[a]	Screening Day-28 to-1	Cycle 1			Cycle 2		Cycle 3 and Beyond	Post-HSCT maintenance or ziftomenib monotherapy (Up to 2 years)		EOT Visit (+7 days)
		Cohorts A-3 ONLY: Day 8 (±2d)	All Cohorts: Day 15 (±2d)	All Cohorts: Day 28 (±7d)	All Cohorts: Day 4 (±2d)	All Cohorts: Day 28 (±7d)	All Cohorts: Day 28 (±7d) until leukemic clearance; Q3 Cycles/q84 days (± 7 days) thereafter	Day -1[e]	Q3 Cycles/q84 days (± 7 days)	All Cohorts
BM Aspirate for *NPM1*-m and *KMT2A*-r[b]	X									
Archival Frozen Samples for *NPM1*-m and *KMT2A*-r[b]	X									
Archival BM Core for *NPM1*-m and *KMT2A*-r[b]	X									
BM Aspirate Sample for Mutational Analysis[b]	X									
BM Aspirate Sample for MRD Assessment[c]				X		X	X	X	X	X
BM Aspirate Sample for Biomarkers[b,c]	X			X		X	X	X	X	X
Blood Sample for Biomarkers[d]	X	X	X	X	X	X	X	X	X	X
BM Aspirate Sample for Pharmacodynamic Analysis[b,c]	X			X						X
Blood Sample for Pharmacodynamic Analysis[d]	X			X						X

Abbreviations: BM=bone marrow; EOT=end of treatment; FFPE=formalin-fixed paraffin-embedded; *KMT2A*-r=lysine[K]-specific methyltransferase 2A-rearranged; MRD=measurable residual disease; *NPM1*-m=nucleophosmin 1-mutant; Q3=every 3; SOC=standard-of-care.

a. Blood and BM should be collected for all patients. Please refer to the Laboratory Manual for details regarding instructions and container type for collecting blood and BM samples.
b. For all patients, a portion of the BM aspirate collected for clinical and molecular screening evaluations and local investigator assessments (see Table 4) must be submitted to the study for retrospective central confirmation of the local test result for *NPM1*-m and *KMT2A*-r. Patients in Cohorts A-2 and B-2 who are receiving LDAC per SOC and patients on gilteritinib per SOC intending to enroll into Cohort A-3 prior to screening, must submit a BMA sample for storage and the most recent archival sample (if available) prior to ziftomenib dosing in Cycle 1 Day 8 (Cohorts A-2 and B-2) or prior to Cycle 1 Day 1 (Cohort A-3). For all patients, if the collection of the BM sample is not clinically feasible and/or results in a dry tap, a peripheral blood sample for storage and a BM core (eg, trephine) biopsy must be collected and submitted. For all patients who do not undergo BM aspirate collection, the investigator should also attempt to obtain and submit the most recent archived BM sample if available (eg, frozen BM, viable frozen cells, cell pellet, frozen DNA, FFPE slides, FFPE block). Refer to the Laboratory Manual for details regarding submission of BM core FFPE block or FFPE slides.
c. For all patients, a portion of the BM aspirate collected for on-study local investigator assessments, including assessments that occur at non-protocol specified times, must be submitted for central MRD assessment and additional study-related biomarker analysis (see Table 2). If the collection of the BM sample is not clinically feasible and/or results in a dry tap, a peripheral blood sample for storage and a BM core (eg, trephine) biopsy must be collected and submitted. Refer to the Laboratory Manual for details regarding submission of BM core FFPE block or FFPE slides.
d. Peripheral blood for study-related biomarker analysis of leukemia cells and pharmacodynamic analysis should be collected at each timepoint.
e. In the case consolidation or maintenance treatment is initiated <4 weeks after a response assessment, a repeated “Day -1” (“D-1”) assessment before the start of consolidation or maintenance is not required.

Table 7 Ziftomenib Maintenance Schedule of Activities

Ziftomenib Maintenance Schedule of Activities		Maintenance [Post-HSCT/ziftomenib monotherapy] (up to 2 years)		EOT[b]	Safety Follow-up	Survival Follow-up
	D-1	Q28d[a]	Q3 Cycles/q84d		28 days after EOT	Monthly
Protocol Activity	**+1d**	**±5d**	**±7d**	**±7d**	**±7d**	**±14d**
Physical Exam[c]	(X)	(X)		X		
Weight	X	X		X		
Vital Signs[d]	X	X		X		
ECOG PS[e]	(X)	(X)		X		
12-Lead ECG[f]	(X)	(X)		X		
Hematology, Chemistry, and Safety Labs[g]	X	X		X		
Urinalysis[h]	X	X		X		
Pregnancy Test (WOCBP)[i]	X		X	X		
Evaluate Extent of Disease and Response to Treatment[j]	X		X	X		
Biomarker Sampling (BMA and Blood)[k]	X		X	X		
Ziftomenib Administration (Continuous)[l]		Daily as 28-day cycles for up to 2 years				
Gilteritinib (Cohort A-3 only)[m]		Daily as 28-day cycles for up to 2 years				
Dispense Patient Diary	X	X				

Collect Ziftomenib Patient Diary	X		X	X		
AEs[n]	Every Visit			X	X	
Con Meds/Procedures[o]	Every Visit			X	X	
Transfusion Dependence[p]	Every Visit			X	X	
New Antineoplastic Therapy[q]				X	X	X
Survival Assessment						X

Abbreviations: AE=adverse event; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=end of treatment; HSCT=hematopoietic stem cell transplant; RBC=red blood cell; SAE=serious adverse event; WOCBP=women of childbearing potential.

(X)= if clinically indicated

a. Q28d is D1 of the next cycle.
b. For patients permanently discontinuing all study treatments.
c. See Section 8.2.2. for further details.
d. See Section 8.2.3. for further details.
e. ECOG status should be recorded as listed and if a change in ECOG status occurs. See Section 8.2.5.
f. Additional 12-lead ECGs may be performed as clinically indicated, and triplicate 12-lead ECGs should be performed at EOT. See Section 8.2.4 for further details.
g. See Table 23 for respective analytes/laboratory parameters.
h. See Section 8.2.1.1 for further details.
i. See Section 8.2.1.2 for further details.
j. Refer to Table 2 and Table 4 for response assessments.
k. Refer to Table 5 and Table 6 for biomarker sampling procedures based on cohort assignment.
l. After completion of all required procedures for Day -1, patients can begin therapy on the same day (ie, Day 1).
m. Per investigator decision, patients enrolled into Cohort A-3, may continue gilteritinib in the maintenance/post-HSCT setting.
n. AEs/SAEs should continue to be recorded and monitored. The site should contact the patients regarding any AEs/SAEs until 28 calendar days after the last dose of study treatment. If possible, after treatment discontinuation, SAEs should be followed until considered resolved or stable (unchanging) or confirmed to be “lost to follow-up” by the treating investigator. Refer to Appendix 6 for additional information.
o. Information on RBC and platelet transfusions (eg, dates and units administered) and associated hemoglobin, RBC, and/or platelet levels should be collected through the safety follow-up period.
p. Continue to collect information on RBC and platelet transfusions (eg, dates and units administered) and associated hemoglobin, RBC, and/or platelet levels through the Safety Follow-up period.
q. Documentation of new antineoplastic therapies, including HSCT and associated conditioning therapies.

2 INTRODUCTION

2.1 Background

2.1.1 Acute Myeloid Leukemia

Acute myeloid leukemia (AML) is the most common form of acute leukemia in adults, with an estimated worldwide incidence of approximately 120,000 new cases per year (Yi et al, 2020). In the United States, the estimated incidence of AML is 20,800 diagnoses and 11,200 deaths per year. The median age at diagnosis is 68 years, with approximately one-third of patients diagnosed over the age of 75 (Seer Cancer, 2024). AML is characterized by the clonal expansion of myeloid blasts in the bone marrow (BM), peripheral blood, and extra medullary tissues, and is defined by World Health Organization as a myeloid neoplasm with 20% or more blasts in the peripheral blood or BM. This heterogeneous disease encompasses a large number of distinct subtypes that have different clinical presentations and responses to treatment.

These differences in clinical presentation and treatment response are due, at least in part, to the high degree of genetic and epigenetic dysregulation in hematopoietic precursor cells that give rise to AML. Genetic abnormalities include chromosomal alterations, such as nonrandom translocations, gain or loss of entire (or portions of) chromosomes, and other karyotypic abnormalities as well as other gene-specific mutations. While the development of targeted agents against certain driver mutations, such as isocitrate dehydrogenase-1 and 2 (IDH1 and IDH2, respectively) and FMS-like tyrosine kinase 3 (FLT3), have led to the Food and Drug Administration (FDA) approval of therapies for patients with these mutations, the broader AML population is not eligible to receive these medicines and responses for those who are eligible are often short-lived. As such, more must be done to develop meaningful therapies to address this unmet need.

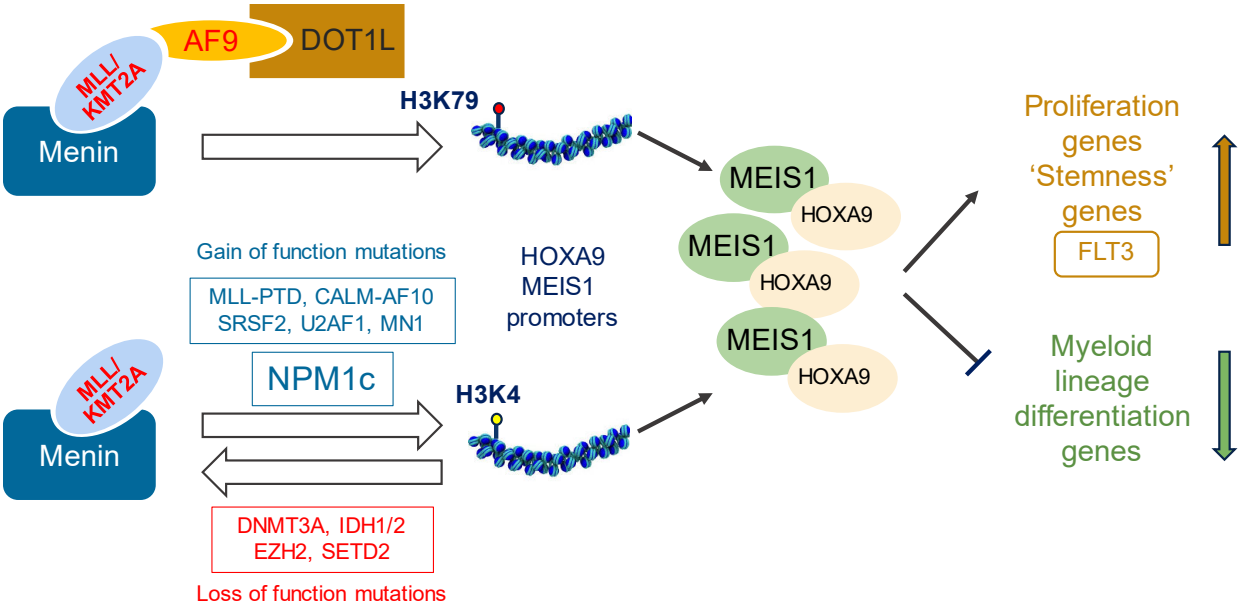
In addition to mutation of individual genes, chromosomal translocations can generate chimeric fusion genes that drive the development of malignant blast cells, and often portend poor prognosis. Important examples of this are translocations of the former mixed-lineage leukemia (MLL) gene *11q23* (recently renamed lysine [K]-specific methyltransferase 2A or *KMT2A*) that underpin an aggressive group of blood cancers known as *KMT2A*-rearranged (*KMT2A*-r) leukemias that include AML and acute lymphocytic leukemia. Rearrangements of *KMT2A,* a histone methyltransferase responsible for transcriptional coregulation of genes during normal hematopoiesis, results in fusion of the first 8 to 13 exons of *KMT2A* with a variable number of exons from any 1 of more than 100 partner genes leading to expression of chimeric MLL(KMT2A) fusion proteins. The resulting fusion proteins retain the approximately 1400 amino acid fragment from the N-terminus of MLL(KMT2A) that contains the menin binding domain, which is a key scaffolding protein required for the activity of the rearranged form of MLL(KMT2A) (Krivtsov et al, 2019; Krivtsov and Armstrong, 2007; Slany, 2009; Hess, 2004; Matkar et al, 2013). Numerous studies demonstrated the critical role of menin as an oncogenic cofactor in leukemic transformations mediated by MLL(KMT2A) fusion proteins (Figure 1; Caslini et al, 2007; Klossowski et al, 2020; Krivtsov et al, 2019; Yokoyama and Cleary, 2008; Yokoyama et al, 2005), suggesting that targeting this menin dependency could be a rational therapeutic strategy for *KMT2A*-r AML. Given the recent naming conversion from MLL to *KMT2A*, the literature contains a mix of naming conventions most predominately used

for the resulting protein and fusion proteins; therefore, for clarity, the gene will be referred to as *KMT2A* and the protein as MLL(KMT2A).

However, menin dependency is also found in other AML subsets, including those expressing wild-type *KMT2A* (*KMT2A*-wt) that have mutations in other key epigenetic regulators (eg, *NPM1*, DNA methyltransferase 3 alpha [DNMT3A], and IDH 1/2). Of these, nucleophosmin 1 (*NPM1*) mutation is one of the most commonly mutated genes in AML, found in 25% to 30% of patients. How the mutant form of *NPM1* causes transformation is not completely understood. Nonetheless, several studies have demonstrated a critical role of the menin/MLL(KMT2A) complex in the leukemogenesis mediated by *NPM1* mutations (Klossowski et al, 2020; Kühn et al, 2016; Tibsovo® USPI, 2021). Thus, there is strong rationale for targeting additional acute leukemia genetic subsets that require menin-MLL(KMT2A) interaction, such as in *NPM1*-mutant (*NPM1*-m) AML.

Ziftomenib is a highly potent compound targeting the menin-MLL(KMT2A) interaction and is under clinical investigation for treatment of genetically defined AML subgroups with high unmet need that are menin-dependent, such as *KMT2A*-r and *NPM1*-m disease (Grembecka et al, 2012; Klossowski et al, 2020; Shi et al, 2012). Ziftomenib showed antitumor activity in *KMT2A*-r and *KMT2A*-wt/*NPM1*-m AML nonclinical models and evidence of clinical activity has been demonstrated in patients with relapsed/refractory (R/R) AML receiving single-agent ziftomenib in an ongoing clinical study (KO-MEN-001; NCT04067336) targeting *KMT2A*-r and *KMT2A*-wt/*NPM1*-m AML. Therefore, this study is designed to further characterize the safety and efficacy of ziftomenib in combination with standard-of-care (SOC) chemotherapy regimens or targeted agents in R/R *KMT2A*-r and *NPM1*-m AML.

Figure 1 Menin-MLL(KMT2A): A Central Role in Epigenetic Dysregulation in Acute Myeloid Leukemia



Abbreviations: AF9=MLLT3 super elongation complex subunit; CALM-AF10=fusion gene; DNMT3A=DNA methyltransferase 3 alpha; DOT1L=disruptor of telomeric silencing 1-like; EZH2=enhancer of zeste homolog 2; FLT3=FMS-like tyrosine kinase 3; HOXA9=homeobox protein Hox-A9; IDH1/2=isocitrate dehydrogenase 1/2; *KMT2A*=lysine-specific *N*-methyltransferase 2A; MEIS1=homeobox protein Meis1; MLL=mixed-lineage leukemia; MLL-PTD=MLL partial tandem duplications; MN1=meningioma (disrupted in balanced translocation) 1; *NPM1*c=nucleolar phosphoprotein B23; SETD2=SET domain containing 2; SRSF2=serine/arginine-rich splicing factor 2; U2AF1=U2 small nuclear RNA auxiliary factor 1.

2.2 Study Rationale

Standard treatment for newly diagnosed AML is dependent upon several factors, including age, presence of comorbidities, and the mutational and/or karyotypic profile of the AML. Those who are young (ie, <60 years of age) and/or medically fit often receive an induction therapy of cytarabine and anthracycline-based (eg, daunorubicin or idarubicin) chemotherapy regimen known as 7+3, followed by consolidation therapy. While some older patients are able to receive standard induction therapy, most patients 75 years or older, or younger patients with comorbidities that preclude use of intensive induction therapy, receive venetoclax in combination with a hypomethylating agent (eg, azacytidine or decitabine) or low-dose cytarabine (LDAC) as SOC, based on increased tolerability and their ability to still have a clinically meaningful impact on response rate and overall survival.

While some patients achieve a complete and durable response from first-line treatment, with or without a hematopoietic stem cell transplant (HSCT), many patients relapse or are outright refractory to treatment – particularly those unable to receive intensive chemotherapy. Once AML has become R/R, the available SOC consists of the same front-line chemotherapies and/or targeted agents that were not used in the front line. In this setting, these agents have been generally shown to have decreased efficacy compared to front-line options. For those R/R patients still fit enough to receive intensive chemotherapy, use of the fludarabine + cytarabine + granulocyte colony-stimulating factor (G-CSF) + idarubicin (FLAG-IDA) regimen is associated

with a 56% overall complete remission (CR) rate and a median overall survival of 15 months (Westhus et al, 2019). However, most R/R patients are not eligible to receive intensive chemotherapy and instead receive agents such as LDAC, or azacytidine, which are associated with suboptimal response rates of less than 15% (Kantarjian et al, 2012) and 17% (Itzykson et al, 2014), respectively. Although not an approved therapy for AML patients with R/R disease, venetoclax/azacytidine has demonstrated encouraging activity particularly in R/R patients with *NPM1*-m AML. However, given the broad use of this regimen in the front line, this is often not a viable treatment option in the R/R setting. For patients with *FLT3*-mutated (*FLT3*-m) AML, gilteritinib, a *FLT3*-targeted agent associated with a 21% CR/CR with partial hematologic recovery (CRh) rate and a 4.6-month duration of remission, is approved for use in the R/R setting (XOSPATA® USPI, 2022). Of note, *FLT3* is a downstream effector of the menin-MLL(KMT2A) pathway (Figure 1), suggesting that combination with a menin inhibitor could more completely abrogate this oncogenic pathway in patients with co-occurring *NPM1*-m or *KMT2A*-r to increase the proportion of patients able to derive benefit. Therefore, the development of agents, such as ziftomenib, in rational combinations able to broadly disrupt key drivers of AML pathogenesis in genetically defined subgroups, like the menin-dependent *NPM1*-m and *KMT2A*-r subtypes, are of significant interest.

As described above, ziftomenib is a highly potent inhibitor of the menin-MLL(KMT2A) interaction that is currently under clinical investigation for treatment of *KMT2A*-r or *NPM1*-m AML. In a first-in-human dose escalation and expansion study (NCT04067336), ziftomenib has shown clear evidence of single-agent activity in a heavily pretreated R/R AML population (Wang, 2024), which was amended to become a pivotal study with registrational intent in *NPM1*-m AML. Whether combining ziftomenib with other SOC regimens in R/R *KMT2A*-r or *NPM1*-m AML can improve response rates and survival outcomes has not been tested. Therefore, the purpose of this Phase 1 study in R/R K*MT2A*-r or *NPM1*-m AML is to assess the safety, tolerability, and preliminary therapeutic activity of ziftomenib in combination with intensive chemotherapy (FLAG-IDA), nonintensive chemotherapy (LDAC), or the *FLT3*-targeted agent gilteritinib (Note: Cohort A-3 investigating ziftomenib plus gilteritinib is only for patients with *NPM1*-m disease and concurrent *FLT3*-m). Along with the encouraging signs of clinical activity seen with use of ziftomenib monotherapy, the development of ziftomenib combination therapies may represent a significant advancement in the targeted treatment of menin-dependent AML.

A summary of ziftomenib nonclinical and clinical studies is provided below. Refer to the Investigator's Brochure (IB) for the most recent information on the clinical development status and safety information for ziftomenib.

2.2.1 Ziftomenib Nonclinical Studies

2.2.1.1 Ziftomenib In Vitro Activity

In vitro ziftomenib displays potent and selective biochemical and cellular activity against the menin-MLL(KMT2A) interaction (Table 8). Ziftomenib has comparable potency independent of fusion partner, but limited activity was observed in cell lines without MLL(KMT2A) fusion.

Table 8 IC50 Cell Lines With and Without MLL(KMT2A) Fusions

Cell Lines With KMT2A Fusions as Drivers (GI_{50})		Biochemical Assay (IC_{50})	
Murine BM Cell line (r*KMT2A*-AF9)	7 nM	MLL (4-43)/Menin Binding	22 nM
MV4;11 (MLL-AF4 AML)	15 nM	Control cell lines without MLL fusion (GI_{50})	
MOLM13 (MLL-AF9 AML)	16 nM	REH	1500 nM
KOPN8 (MLL-ENL AML)	20 nM	U937	>6000 nM
RS4;11 (MLL-AF4 ALL)	23 nM	K562	>6000 nM
SEM (MLL-AF4 ALL)	17 nM	KG-1	>4500 nM

Abbreviations: ALL=acute lymphoid leukemia; AML=acute myeloid leukemia; BM=bone marrow; GI_{50}=50% growth inhibition; IC_{50}=half maximal inhibitor concentration; *KMT2A*=lysine[K]-specific methyltransferase 2A; MLL=mixed-lineage leukemia.

2.2.1.2 Ziftomenib In Vivo Activity

2.2.1.2.1 Antitumor Activity in *KMT2A*-r Mouse Models

The pharmacodynamic (PDn) activity and antitumor activity of ziftomenib were tested in 2 widely used mouse xenograft models of *KMT2A*-r AML, MV4;11 and the more aggressive MOLM13. In the disseminated MV4;11 xenograft model, treatment with ziftomenib at 50 mg/kg twice daily (BID) and 100 mg/kg once daily (QD) doses from Day 16 to 25 after implantation yielded a median overall survival increase of 25.5 and 24.5 days, respectively as compared with vehicle. Ziftomenib was well tolerated with all treated animals maintaining or gaining weight during therapy. Ziftomenib also demonstrated antitumor activity in the disseminated MOLM13 xenograft model, significantly prolonging median survival from 17 days in vehicle group to 20, 26, and 48 days in mice treated with ziftomenib at 25, 50, and 100 mg/kg/day QD, respectively ($p < 0.0001$).

2.2.1.2.2 Antitumor Activity in *KMT2A*-wt/*NPM1*-m Mouse Models

Ziftomenib reversed the leukemic progression and induced robust myeloid differentiation in vitro in *KMT2A*-wild-type (*KMT2A*-wt)/*NPM1*-m OCI-AML3 cells and induced CRs in vivo in models of *KMT2A*-wt AM7577 *NPM1/DNMT3A/FLT3/IDH2*-mutant and LEXFAM2734 *NPM1/FLT3/IDH1*-mutant patient-derived xenograft AML models.

In the AM7577 model, ziftomenib at 100 mg/kg QD, ziftomenib at 150 mg/kg QD, a *FLT3* inhibitor (AC220/quizartinib) and a vehicle control were each administered for 42 days. Ziftomenib produced durable CRs at both dose groups, whereas the *FLT*3 inhibitor did not. In this model, there was a >80% induction of the differentiation marker, CD11b, that peaked 1 to 2 weeks prior to disappearance of human cells from the ziftomenib-treated animals, suggesting that the dominant mechanism of leukemic cell death is natural apoptosis of terminally differentiated cells at the end of their natural lifespan. Notably, although the complete eradication of CD45+ blasts was delayed with ziftomenib compared to treatment with the *FLT3* inhibitor, tumor regrowth was evident in the *FLT*3 inhibitor alone arm. Tolerability as measured by body weight change, was no different than in the vehicle group. Taken together, these observations indicate that ziftomenib drives robust terminal differentiation and subsequent natural apoptosis that is not reversed upon drug discontinuation. In the *NPM1/FLT3/IDH1*-mutant AML LEXFAM2734 model that was initially sensitive to

ARA-C-dex but resistant to decitabine, ziftomenib tested at doses of 150 mg/kg QD produced lasting CR out to 84 days (the time of study completion) with evidence that only differentiated myeloid cells remained in the BM of the ziftomenib-treated animals.

In summary, in multiple complex phenotype murine patient-derived xenograft models, including disseminated models of both *KMT2A*-r and non-*KMT2A*-wt *NPM1*-m AML, ziftomenib reverses leukemic progression, induced robust myeloid differentiation, achieved durable CRs, and increased survival suggesting that ziftomenib may be active in subsets of both complex and normal karyotype AML. Discussion of additional mechanisms of action and nonclinical pharmacology details can be found in Section 4.2 of the ziftomenib IB.

2.2.2 Ziftomenib Pharmacology and Metabolism

Full details of ziftomenib nonclinical pharmacology and toxicology are provided in the Investigator's Brochure (IB). A summary is provided below.

Ziftomenib has been characterized in cell line-derived xenograft (CDX) and patient-derived xenograft (PDX) tumor models and has demonstrated potent, selective, and well-tolerated inhibition of the menin-MLL(KMT2A) interaction. Ziftomenib metabolizes to active metabolites KO-516 and KO-739, both minor in humans (see Section 2.2.3).

The nonclinical safety profile of ziftomenib was characterized in mice and dogs in studies up to 13 weeks in duration; as in vitro metabolism studies indicated the metabolism of ziftomenib in mouse and dog microsomes is qualitatively comparable to that in humans, these nonclinical test species were considered appropriate for human risk assessment. Target organ effects in ziftomenib-treated animals were noted in the hepatobiliary system (mice and dogs), kidney (mice and dogs), lymphoid tissues (mice and dogs), lung (mice only), and adrenal glands (mice and dogs).

In vitro and in vivo genotoxicity assays demonstrated that ziftomenib was neither mutagenic nor clastogenic/aneugenic. Reproductive and developmental toxicity studies in mice demonstrated adverse effects on intrauterine growth and survival, as well as fetal external and skeletal malformations and thus was positive for teratogenicity in mice.

2.2.3 Ziftomenib Clinical Studies

KO-MEN-001 is an open-label, multinational, first-in-human Phase 1/2 study designed to determine the safety, tolerability, and clinical activity of ziftomenib in R/R AML. The Phase 1 portion included a dose escalation and expansion design that established 600 mg QD as the Recommended Phase 2 Dose (RP2D) for ziftomenib monotherapy (Lancet, 2024). In the Part 1b portion of the study, patients with R/R *KMT2A*-r and *NPM1*-m AML were randomized to 2 parallel cohorts to further assess the 200 mg QD and 600 mg QD dose levels for RP2D selection. As of 30 August 2023, for *KMT2A*-r and *NPM1*-m patients from Part 1a and Part 1b, who were treated at 200 mg QD or 600 mg QD, the CR/CRh rate for those treated at 600 mg QD was 23.7 (versus 5.6% for 200 mg QD) with an overall response rate (CR, CRh, complete remission with incomplete hematologic recovery [CRi], and a morphologic leukemia-free state [MLFS]) of 31.6% (versus 11.3% for 200 mg QD) (Lancet, 2024). These findings clearly supported selection of the 600 mg ziftomenib dose as the RP2D and were achieved in patients who were heavily pretreated with a median of 3 prior lines of therapy (range: 1 to 11). The registration-directed

Phase 2 portion of KO-MEN-001 evaluating ziftomenib monotherapy (600mg QD) in *NPM1*-m R/R AML is ongoing.

Median peak ziftomenib concentration in KO-MEN-001 was 3.5 hours after daily po dosing, with a half-life of 61.5 hours (KO-MEN-005). Ziftomenib exhibited an approximate dose-dependent increase in exposure up to 600 mg.

In KO-MEN-005, a human absorption, distribution, metabolism, excretion, and absolute bioavailability study conducted with radiolabeled ziftomenib, 0.525% of the ziftomenib dose was recovered in urine, suggesting minimal ziftomenib renal elimination. Additionally, population PK analysis of KO-MEN-001 data demonstrated that mild or moderate renal impairment was not a significant covariate of ziftomenib clearance, indicating that renal impairment is unlikely to have meaningful clinical impact on ziftomenib exposure and supportive of the creatinine clearance (CLcr) ≥ 30 mL/min inclusion criterion. Based on these data, an inclusion criterion for (CLcr) ≥ 30 mL/min (see Section 5.1) is used for this study. Nonetheless, in addition to monitoring renal function with standard analytes (eg, BUN, creatinine, etc; see Appendix 1), we will also monitor cystatin C throughout the study to more closely evaluate any potential effects of the various combinations on the kidneys. Lastly, data from KO-MEN-005 demonstrated that ziftomenib was the major and most abundant plasma and circulating component while all other metabolites (including KO-516 and KO-739) were minor (<10% of total drug-related exposure) in plasma.

Physiologically based PK (PBPK) modeling was conducted to assess the effect of CYP3A4 modulators on ziftomenib PK. The analysis included assessment of ziftomenib fraction metabolized by CYP3A4 based on PK data from KO-MEN-001 study in 10 patients who were not on CYP3A4 inhibitors, 12 who were on moderate CYP3A4 inhibitors (fluconazole, isavuconazole, and isavuconazonium) and 31 who were on strong CYP3A4 inhibitors (posaconazole and voriconazole). Dose-normalized AUC of these patients demonstrated that there was an approximately 2-fold increase in ziftomenib exposure with strong CYP3A4 inhibitor, which is a weak CYP3A4 interaction per the FDA guidance (Clinical Drug Interaction Studies - Cytochrome P450 Enzyme- and Transporter Mediated Drug Interactions Guidance for Industry, 2020) and, therefore, would not necessitate alternative dosing or separate dose escalation cohorts for ziftomenib when coadministered with a strong CYP3A4 inhibitor. Modeling of these data demonstrated that the ziftomenib fraction metabolized by CYP3A4 was 60% with the rest of the metabolism distributed equally to CYP2D6 and CYP1A2. PBPK modeling indicated a moderate interaction of ziftomenib with a strong CYP3A4 inhibitor. However, this is not considered to be clinically relevant as there are no indications of significant increase in adverse events when ziftomenib is coadministered with strong CYP3A4 inhibitors. Additionally, PBPK modeling demonstrated that coadministration of the sensitive CYP3A4 substrates, midazolam and venetoclax, with ziftomenib increasing midazolam and ven AUCs by 3% and 2%, respectively, indicating no interaction between ziftomenib and the CYP3A4 substrates. Table 9 summarizes ziftomenib drug-drug interaction (DDI) predictions based on PBPK modeling.

Table 9 Ziftomenib Drug-drug Interaction Predictions Based on PBPK Modeling

Perpetrator	Mechanism	AUC GMR (90%CI)
CYP Inhibitor		
Itraconazole	Strong CYP3A4 inhibitor	2.86 (2.68-3.04)
Fluconazole	Moderate CYP3A4 inhibitor	1.83 (1.77-1.88)
Bupropion	CYP2D6 inhibitor	1.20 (1.17-1.23)
Fluvoxamine	CYP1A2 inhibitor	1.55 (1.51-1.60)
CYP Inducer		
Rifampin	Strong CYP3A inducer	0.26 (0.24-0.28)
Efavirenz	Moderate CYP3A4 inducer	0.33 (0.31-0.35)
Dexamethasone	Weak CYP3A4 inhibitor	0.65 (0.63-0.66)
CYP Substrate		
Ziftomenib	Midazolam	1.03 (1.02-1.03)
Ziftomenib	Venetoclax	1.02 (1.02-1.03)

Abbreviations: AUC=area under the concentration-time curve; CI=confidence interval; CYP=cytochrome P450; GMR=geometric mean ratio; PBPK=physiologically based pharmacokinetic.
Abbreviations: AUC=area under the concentration-time curve; Cmax=maximum plasma concentration; CYP=cytochrome P450.

Refer to the IB for more information on the clinical development status and safety profile of ziftomenib.

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits, risks and reasonably expected adverse events (AEs) of ziftomenib may be found in the IB.

2.3.1 Known Potential Risks

A summary of known potential risks is provided below. Please refer to the respective IB or locally approved label for more detailed information regarding ziftomenib or the respective combination agents (Fludarabine USPI, 2016, Idamycin® USPI, 2021, Cytarabine USPI, 2020, Azacitidine USPI, 2020, XOSPATA® USPI, 2022).

2.3.1.1 Risks Related to Ziftomenib

Ziftomenib-mediated inhibition of menin activity disrupts gene expression pathways responsible for maintaining the pathologic dedifferentiated stem cell-like phenotype of *KMT2A*-r and *NPM1*-m AML. The resultant terminal differentiation of these leukemic blast cells may contribute to TEAEs of DS, which are not unexpected and have occurred (including 1 fatal event) in patients treated with ziftomenib monotherapy. During the Part 1b portion of KO-MEN-001, the rate of DS was consistent between the 200 mg and 600 mg dose levels, suggesting that the risk of DS does not increase with ziftomenib dose. However, the majority of the DS events (overall and ≥Grade 3) were reported in patients with *KMT2A*-r AML, suggesting that this genetic subset was potentially more susceptible to DS events – perhaps due to the monocytic nature of this AML subtype that has increased propensity for development of diffuse extramedullary disease (EMD). Due to the DS risk, a guidance for the management of

ziftomenib-related DS was developed (see Section 6.5.4.1). Following the implementation of this guidance in KO-MEN-001, DS severity declined, suggesting this TEAE is manageable when monitored appropriately. In the present study, all patients except those in Cohort A-3 subset will start ziftomenib 7 days after initiation of the SOC backbone treatment, which may allow for disease "debulking" prior to ziftomenib administration and may decrease the amount of blast cells available to contribute to a DS event. However, patients in Cohort A-3 (ziftomenib/gilteritinib in *NPM1*-m patients) will start ziftomenib concurrently with gilteritinib on Day 1. This is because single-agent gilteritinib is not expected to provide sufficient single-agent efficacy to allow for "debulking" during a 7-day lead-in to decrease any potential DS risk. Although gilteritinib is associated with some DS risk (3% reported DS rate in gilteritinib clinical studies [XOSPATA® USPI, 2022]), the overall DS risk is expected to be manageable, given the effectiveness of the ziftomenib DS guidance. Additionally, Cohort A-3 is enrolling only *NPM1*-m patients, who have reported fewer and more manageable (majority ≤Grade 2) instances of ziftomenib-related DS (versus *KMT2A*-r).

Tumor lysis syndrome (TLS) is a phenomenon that can occur with or without concurrent DS as a consequence of rapid cell death that releases a flood of potassium, phosphorus, nucleic acids, and cytokines into the bloodstream that overwhelm the body's homeostatic mechanisms for CL (Heuser et al, 2021). Due to the mechanism of action of monotherapy ziftomenib, it is not expected that TLS will occur outside of the setting of DS and/or hyperleukocytosis. Six cases of TLS had been reported in the KO-MEN-001 study as of 29 February 2024; 2 of the TLS events were considered to be related to ziftomenib treatment by the investigator, 2 were considered serious (1 of which was considered related to ziftomenib treatment by the investigator), and all 6 were Grade 3 or higher, including 1 case at 50 mg in Part 1a, and 2 cases at 200 mg and 3 cases at 600 mg in Part 1b. Further details regarding the management of TLS are provided in Section 6.5.4.1. To reduce the risk of potential TLS of ziftomenib combinations, TLS prophylaxis should be administered per institutional practice, and it is recommended to continue TLS prophylaxis (a) through Day 14 (Cohorts A-1, B-1, A-2, and B-2) to account for the first week of ziftomenib monotherapy or (b) through Day 7 (Cohort A-3). DS prophylaxis is not required but should be instituted for patients at higher risk of DS (Section 6.5.4.1.1 #3). Additionally, as discussed above, all ziftomenib combinations (except for Cohort A-3) will begin ziftomenib 7 days after initiation of the SOC treatment.

The other commonly reported (ie, occurring in ≥5% of patients) ziftomenib-related AEs in all patients treated in KO-MEN-001 as of the 29 February 2024 data cut were nausea, diarrhea, increased alanine aminotransferase, increased aspartate aminotransferase, and pruritus. All commonly reported AEs were manageable.

Refer to the IB for additional information related to ziftomenib.

2.3.1.2 Risks Related to SOC AML Therapies

Fludarabine has been associated with dose-dependent neurologic toxicities most commonly when used at doses above the recommended dose (eg, blindness, coma, and death) or when in combination with other agents known to cause neurologic toxicity. BM suppression, transfusion associated graft-versus-host disease (GvHD), and the occurrence of TLS have been reported.

Most common AEs (occurring in ≥10%) include myelosuppression (neutropenia, thrombocytopenia, and anemia), fever and chills, fatigue, weakness, infection, pneumonia,

cough, nausea, vomiting and diarrhea. Other commonly reported events include malaise, mucositis, and anorexia.

Idarubicin is a potent BM suppressant. Therefore, patients are at risk for opportunistic infections and/or bleeding complications. Myocardial toxicity, as manifested by potentially fatal congestive heart failure, acute life-threatening arrhythmias, or other cardiomyopathies, may occur following therapy with idarubicin, as is consistent with other anthracyclines. Gastrointestinal (eg, nausea, vomiting, mucositis, and diarrhea) and dermatologic (eg, alopecia and rash) events are frequently reported in patients receiving idarubicin. Hepatic and/or renal function affect idarubicin metabolism; liver and kidney function should be evaluated per institutional guidelines prior to and during treatment.

Cytarabine is a myelosuppressive agent, which increases the risk of infectious complications (viral, fungal, parasitic, or saprophytic infections) and/or bleeding. Cytarabine syndrome, characterized by fever, myalgia, bone pain, occasional chest pain, maculopapular rash, conjunctivitis, and malaise can occur. The most frequent adverse reactions reported with cytarabine include anorexia, nausea, vomiting, diarrhea, oral and anal inflammation or ulceration, hepatic dysfunction, fever, rash, thrombophlebitis, and bleeding (all sites).

G-CSF, which is given as part of the FLAG-IDA regimen, is a growth factor indicated to accelerate neutrophil recovery in AML patients receiving myelosuppressive chemotherapies. Risks associated with G-CSF administration include splenic rupture, which can be fatal, acute respiratory distress syndrome, serious allergic reactions, glomerulonephritis, alveolar hemorrhage and hemoptysis, cutaneous vasculitis, aortitis, and capillary leak syndrome. Thrombocytopenia and leukocytosis have also been reported and should be monitored per institutional standards.

Treatment with gilteritinib is associated with increased risk of DS, which can be life-threatening or fatal if not properly managed. In addition, patients receiving gilteritinib may be at increased risk of QTc interval elongation, pancreatitis, and posterior reversible encephalopathy syndrome. During gilteritinib clinical studies, the most frequent (≥5%) Grade ≥3 nonhematological adverse reactions reported in patients were increased transaminases (21%), dyspnea (12%), hypotension (7%), mucositis (7%), myalgia/arthralgia (7%), and fatigue/malaise (6%). Consult the most recent gilteritinib locally approved label for additional information on risk and/or management of these events.

2.3.2 Known Potential Benefits

Ziftomenib is a novel investigational drug candidate that potently and selectively disrupts the menin-MLL (KMT2A) protein interaction to arrest leukemogenesis and drive myeloid cells toward terminal differentiation in preclinical models. The inhibitory activity of ziftomenib on the menin-MLL(KMT2A) interaction has been demonstrated in both in vitro and in vivo models of both *KMT2A*-r and *KMT2A*-wt/*NPM1*-m AML, in which the compound disrupts leukemic clones that are dependent upon the menin pathway. Importantly, evidence of clinical activity has been noted in patients with R/R AML receiving single-agent ziftomenib in an ongoing clinical study (KO-MEN-001). As shown in Wang, 2024, the CR/CRh rate in KO-MEN-001 when evaluating

NPM1-m and *KMT2A*-r patients in Part 1a together with the patients in Part 1b who were treated at the 600 mg RP2D for ziftomenib monotherapy was 23.7% (9 of 38) (Lancet, 2024). This

response rate observed for *NPM1*-m and *KMT2A*-r patients is similar to the CR/CRh rate of several targeted agents approved for the treatment of other genetically defined AML subtypes (ivosidenib, 32.8% [Tibsovo® USPI, 2021]; gilteritinib, 21% [XOSPATA® USPI, 2022]; enasidenib, 23% [Idhifa® USPI, 2017]).

In the current study, ziftomenib is being evaluated in combination with SOC treatment regimens that are associated with significant response rates and clinical benefit. Because of ziftomenib's ability to target menin dependency in *KMT2A*-r or *NPM1*-m mediated AML, which is foundational to leukemogenesis in these genetic subtypes, development of ziftomenib in combination with these SOC treatments may provide clinical benefit for this population with high unmet need.

2.3.3 Overall Benefit-Risk Conclusion

Overall, the benefit-risk profile for the evaluation of ziftomenib in combination with SOC treatment regimens in *NPM1*-m or *KMT2A*-r R/R AML is considered to be favorable. In an ongoing Phase 1/2 study (KO-MEN-001), ziftomenib monotherapy has shown encouraging signs of clinical activity in a *KMT2A*-r and *NPM1*-m R/R AML population that was heavily pretreated. The CR/CRh rate for all *NPM1*-m and *KMT2A*-r patients treated with ziftomenib monotherapy at the 600 mg RP2D during Phase 1 was 23.7% (Lancet, 2024), which compares favorably with the CR/CRh rate reported for other targeted agents that are approved for treatment of other genetically defined AML populations. In this study (KO-MEN-008), ziftomenib is being combined with SOC treatments that are associated with significant clinical activity that is well established, but in most cases is not curative. The combination of these SOC treatments with a menin pathway inhibitor in patients whose AML is menin-dependent may provide clinically meaningful antileukemic effect. As a result, these ziftomenib combinations warrant further clinical investigation.

Importantly, data gathered to date suggests that *KMT2A*-r patients treated with ziftomenib monotherapy are at greatest risk for development of severe DS, regardless of dose. All *KMT2A*-r cohorts will begin dosing of ziftomenib 7 days after initiation of the SOC regimen (ie, Day 8) to investigate the potential of this regimen adjustment to mitigate DS risk. In the *NPM1*-m patient population, the safety and tolerability profile of ziftomenib is generally predictable and manageable following implementation of guidance for identification and management of ziftomenib-related DS (see Section 6.5.4.1.1). Nonetheless, to potentially improve tolerability and decrease the DS risk for *NPM1*-m patients, ziftomenib administration will begin on Day 8 for all cohorts (except Cohort A-3). In Cohort A-3, which combines ziftomenib with the *FLT*3-targeted gilteritinib, concurrent dosing will occur on Day 1, given a 7-day lead-in of gilteritinib is not expected to cause sufficient cytoreduction to decrease any potential risk of DS or TLS and that this cohort is only enrolling *NPM1*-m patients – a population who have reported lower incidence and severity of DS in ziftomenib studies to date. Combining ziftomenib with SOC treatments may also lead to increased risk of TLS. Therefore, TLS prophylaxis should be administered per institutional practice, and it is recommended to continue TLS prophylaxis through Day 14 (Cohorts A-1, B-1, A-2, and B-2) to account for the first week of ziftomenib monotherapy or through Day 7 (Cohort A-3). Additionally, this study will investigate the effect of delaying the start of ziftomenib dosing on the risk of DS and TLS associated with ziftomenib combinations.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of ziftomenib may be found in the IB.

3 OBJECTIVES AND ENDPOINTS

Table 10 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To determine the safety and tolerability of each protocol-specified ziftomenib combination in patients with *KMT2A*-r or *NPM1*-m (± co-occurring *FLT3*-m) R/R AML	• Rate of DLT per dose level • Descriptive statistics of AEs per the NCI CTCAE v5.0
Secondary	
• To evaluate the clinical activity for ziftomenib combinations in patients with *KMT2A*-r or *NPM1*-m (± co-occurring *FLT3*-m) R/R AML based on the ELN 2022 (Döhner et al, 2022)	• For Cohorts A-1, A-2, B-1, and B-2: CR rate • For Cohort A-3: CR/CRh rate
• To evaluate survival and disease control outcomes for protocol-specified ziftomenib combinations in patients with *KMT2A*-r or *NPM1*-m (± co-occurring *FLT3*-m) R/R AML	• CRc (CR+CRi+CRh) and MLFS rates per 2022 ELN Criteria (Döhner et al, 2022) • OS • 6-month OS: Proportion of patients alive at 6 months • Median EFS • 6-month EFS • Duration of remission • MRD assessment in the BM by flow cytometry and molecular analysis (PCR, NGS) • Proportion of patients that undergo HSCT • Rate of transfusion independence
• To characterize the PK of ziftomenib and metabolites when administered in combination with SOC treatments in adults with R/R *NPM1*-m or *KMT2A*-r AML	• Multiple dose: C_{max}, T_{max}, $AUC_{(0\text{-}last)}$, $AUC_{(tau)}$
• To evaluate the PK of gilteritinib when administered concurrently with ziftomenib in adults with R/R *NPM1*-m (+ co-occurring *FLT3*-m)	• Multiple dose: C_{max}, T_{max}, $AUC_{(0\text{-}last)}$, $AUC_{(tau)}$
Exploratory	
• To evaluate biomarkers related to the biology of AML and their potential correlation to efficacy and resistance to ziftomenib combined with SOC treatments • To evaluate pharmacodynamic biomarkers potentially related to the activity of ziftomenib combined with SOC treatments in adults with R/R AML with *NPM1*-m (± co-occurring *FLT3* mutation) or *KMT2A*-r	• Prevalence of biochemical, cytogenetic, and molecular biomarkers in blood and BM collected at diagnosis, on-treatment, and at disease progression • Analysis of biomarker expression in samples collected at diagnosis, on-treatment, and at disease progression • Quantitative measurement of leukemia biomarkers and their correlation with PK and efficacy in blood and BM collected before and after administration of each combination

Abbreviations: AE=adverse event, AML=acute myeloid leukemia; $AUC_{(0\text{-}last)}$=area under the concentration-time curve from time 0 to the time of the last quantifiable concentration; $AUC_{(tau)}$=area under the concentration-time curve over a dosing

Objectives	Endpoints

interval; BM=bone marrow; C_{max}=maximum plasma concentration; CR=complete remission; CRc=composite complete remission; CRh=complete remission with partial hematologic recovery; CRi=complete remission with incomplete hematologic recovery; DLT=dose-limiting toxicity; EFS=event-free survival; ELN=European Leukemia Network; *FLT3*-m=FMS-like tyrosine kinase 3-mutated; HSCT=hematopoietic stem cell transplant; *KMT2A*-r=lysine[K]-specific methyltransferase 2A-rearranged; MLFS=morphologic leukemia-free state; MRD=minimum residual disease; NCI CTCAE=National Cancer Institute Common Terminology for Adverse Events; NGS=next-generation sequencing; *NPM1*-m=nucleophosmin 1-mutant; OS=overall survival; PCR=polymerase chain reaction; PK=pharmacokinetics; R/R=relapsed/refractory; SOC=standard-of-care; T_{max}=time to maximum plasma concentration.

4 STUDY DESIGN

4.1 Overall Design

The purpose of this Phase 1 open-label, dose escalation and expansion study is to determine the safety, tolerability, and preliminary clinical activity of ziftomenib when combined with SOC regimens for the treatment of either *NPM1*-m (Arm A) or *KMT2A*-r (Arm B) R/R AML. Each genetically defined arm will evaluate ziftomenib in combination with various SOC treatments in separate and independent cohorts, as outlined below:

- **Arm A:** *NPM1*-m R/R AML
  - **Cohort A-1** (US only)**:** Ziftomenib plus FLAG-IDA (intensive chemotherapy)
  - **Cohort A-2:** Ziftomenib plus LDAC (nonintensive chemotherapy)
  - **Cohort A-3:** Ziftomenib plus gilteritinib (*FLT3-m* targeted therapy for *NPM1*-m + *FLT3*-m R/R AML)
- **Arm B:** *KMT2A*-r R/R AML
  - **Cohort B-1** (US only)**:** Ziftomenib plus FLAG-IDA (intensive chemotherapy)
  - **Cohort B-2:** Ziftomenib plus LDAC (nonintensive chemotherapy)

Each individual cohort within each genetically defined arm may start, progress, and/or close independently of the outcome or status of the other cohorts.

Study Population

Up to 96 evaluable patients in Part 1a depending on the number of DLTs that will be observed and up to 75 patients in Part 1b will be enrolled in this study.

Note: *Enrolled* refers to patients or their legally authorized representatives who agree to participate in a clinical study following completion of the informed consent process and screening and who receive at least 1 dose of study treatment.

In any cohort, there is an option to expand enrollment if needed due to encouraging results and to provide a bridge to a future study.

4.2 Dose Escalation (Part 1a)

The evaluation of up to 4 dose levels (Dose Levels [DLs] 1, 2, 3, and, if needed, DL-1) is planned for Cohorts A-1, A-2, B-1, and B-2. Up to 5 DLs (DLs 1, 2, 3, 4, and, if needed, DL-1) are planned for Cohort A-3. In each ziftomenib combination tested, only the ziftomenib dose will be escalated in combination with the labeled dose of the approved agent(s), as shown in Table 11.

Dose finding for each of the 5 cohorts will occur separately and in parallel. Each respective dose escalation cohort within a genetically defined arm is independent and may start, progress, and/or close independently of each other. Initially, 6 patients will be treated at DL1 within the respective cohort. However, additional patients may be enrolled at a given dose level to ensure at least 6 patients are DLT evaluable. Dose escalation within each cohort will occur following a rule-based approach based on a i3+3 design (Lancet, 2024), with a target DLT probability of

0.25 and an equivalence interval (EI) of 0.20 to 0.30, meaning that the DLT rate must not exceed the upper bound of the EI in order to escalate to the next higher dose or for a dose to be selected for dose validation/expansion in Part 1b (if already at the highest dose level). Given that variability in the data can be large in a small cohort, the i3+3 design requires 2 criteria are met when determining whether to stay at the current dose or to de-escalate. First, the DLT rate must exceed the upper bound of the EI (ie, ≥2 DLTs occur in 6 patients). Next, if subtracting 1 from the number of DLTs results in a DLT rate within the EI, then the i3+3 rules state to stay at the current dose and enroll 6 additional patients (Note: if a cohort in Part 1a is expanded to 12 patients and the adjusted DLT rate remains within the EI, this dose may be further expanded/validated in Part 1b following discussion with the Independent Data Monitoring Committee [IDMC]/Safety Monitoring Committee [SMC]). However, if the adjusted DLT rate still exceeds the EI, the rules state to enroll 6 patients at the next lower dose.

Based on this design, the rules in Table 12 will be applied, starting with DL1 for each cohort. Following consultation and alignment with the IDMC/SMC, dose escalation of ziftomenib may continue beyond the 600 mg dose level within the respective cohorts in order to achieve adequate certainty about the candidate RP2D for expansion in Part 1b. If the DLT rate for the lowest dose level is such that the rules state that further dose de-escalation is required, the ziftomenib dose and/or the dose of the SOC combination agent(s) may be lowered following consultation with the SMC and/or IDMC.

Table 11 Dose Levels for Cohorts Evaluating Ziftomenib Plus Chemotherapy or Targeted Therapy (Cohorts A-1, A-2, A-3, B-1, and B-2)

Dose Level	Ziftomenib Dose[a]
Cohorts A-1, A-2, B-1, and B-2	
DL3: RP2D from Phase 1/2 monotherapy study	Proposed dose: 600 mg administered QD with continuous 28-day cycles
DL2: 1 dose level below the RP2D from Phase 1/2 monotherapy study	Proposed dose: 400 mg administered QD with continuous 28-day cycles
DL1 (Starting Dose): 2 dose levels below the RP2D from Phase 1/2 monotherapy study	Proposed dose: 200 mg administered QD with continuous 28-day cycles **The 200 mg dose is the starting dose for all chemotherapy combinations.**
DL-1: 3 dose levels below the RP2D from Phase 1/2 monotherapy study	Proposed dose: 100 mg administered QD with continuous 28-day cycles **NOTE:** In the event DL-1 is opened for any cohort, the dose of the SOC combination agent(s) may be lowered with a ziftomenib dose of either 200 mg or 100 mg following consultation with the SMC and/or IDMC.
Cohort A-3	
DL4: RP2D from Phase 1/2 monotherapy study	Proposed dose: 600 mg administered once daily with continuous 28-day cycles
DL3: 1 dose level below the RP2D from Phase 1/2 monotherapy study	Proposed dose: 400 mg administered once daily with continuous 28-day cycles

Dose Level	Ziftomenib Dose[a]
DL2: 2 dose levels below the RP2D from Phase 1/2 monotherapy study	Proposed dose: 200 mg administered once daily with continuous 28-day cycles
DL1 (Starting Dose): 3 dose levels below the RP2D from Phase 1/2 monotherapy study	Proposed dose: 100 mg administered once daily with continuous 28-day cycles **The 100 mg dose is the starting dose for ziftomenib and gilteritinib combination.**
DL-1: 4 dose levels below the RP2D from Phase 1/2 monotherapy study	Proposed dose: 50 mg administered once daily with continuous 28-day cycles. **NOTE:** In the event DL-1 is opened for Cohort A-3, the dose of gilteritinib may be lowered with a ziftomenib dose of either 100 mg or 50 mg following consultation with the SMC and/or IDMC.

Abbreviations: DL=Dose Level; IDMC=Independent Data Monitoring Committee; QD=once daily; RP2D=recommended Phase 2 dose; SMC=Safety Monitoring Committee; SOC=standard-of-care.
a. Ziftomenib dosing should begin on Cycle 1 Day 8 and on Day 1 of Cycle 2 and every cycle thereafter (for all cohorts except Cohort A-3 which should begin ziftomenib dosing on Cycle 1 Day 1).

Table 12 Decision Rule Table

Number of DLTs for Cohorts of n=6	Number of DLTs for Cohorts of n=12[a]	Decision Rule
≤1	≤2	• Enroll 6 patients and treat with the next higher dose o If already at the highest protocol-specified dose, move to dose validation and expansion (Part 1b)
2	3 to 4	• If cohort size is n=6, enroll 6 patients at the same dose • If cohort size is n=12, move to dose validation and expansion (Part 1b) following IDMC/SMC review
≥3	≥5	• Enroll 6 patients and treat with the next lower dose

Abbreviations: DLT=dose-limiting toxicity; IDMC=Independent Data Monitoring Committee; SMC=Safety Monitoring Committee.
a. Note: This column applies to cohorts of n=6 that previously observed 2 DLTs and were expanded to n=12. The number of DLTs shown in this column reflects the total number observed at a given dose level in Part 1a since study start.

4.2.1 Dose-Limiting Toxicity Definition

The DLT evaluation period will begin upon the concurrent administration of ziftomenib with the respective combination therapy and will close 28 days later. Therefore, for Cohorts A-1, A-2, B-1, and B-2, the DLT evaluation period starts on Cycle 1 Day 8 and closes on Study Day 35 for patients achieving leukemic clearance. Otherwise, the DLT period will end at the start of Cycle 2 for any patients with residual disease after Cycle 1 who are continuing treatment. For Cohort A-3, the DLT evaluation period begins on Cycle 1 Day 1 and closes on Cycle 1 Day 28. A TEAE considered at least possibly related to ziftomenib will be considered a DLT based on the following criteria:

- Nonhematologic DLT will be determined based on nonhematologic Grade 3 toxicity with exceptions (see below) or any Grade ≥4 toxicity at least possibly related to ziftomenib that occurs during the first 28 days of ziftomenib administration. Severity of AEs will be

graded according to National Cancer Institute Common Terminology for Adverse Events (NCI CTCAE) v5.0.

- Grade 3 exceptions:
  - Alopecia
  - Grade 3 fatigue ≤14 days
  - Correctable electrolyte abnormalities within 72 hours
  - Isolated, asymptomatic aspartate aminotransferase (AST), alanine aminotransferase (ALT), lipase, and/or amylase that resolves to ≤ Grade 1 within 7 days of drug discontinuation
  - Grade 3 nausea, vomiting, or diarrhea not requiring total parenteral nutrition, tube feeding or hospitalization that resolved to ≤ Grade 1 or baseline in 2 weeks after receiving the maximal supportive therapy and use of optimal antiemetic regimen based on standard practice
  - Grade 3 DS that can be managed to ≤ Grade 3 per the protocol specified DS guidance (see Section 6.5.4.1.1) within 7 days without end-organ damage
  - Transient asymptomatic Grade 3 laboratory abnormalities considered not clinically significant following agreement between investigators and the Sponsor's medical monitor and/or starting to recover after <72 hours with standard supportive care
  - Grade 3 rash that resolves to Grade ≤2 within 14 days.

- For Cohorts A-1 and B-1, a hematologic DLT will be defined as prolonged Grade ≥4 neutropenia, or thrombocytopenia in the absence of residual leukemia lasting for 42 days or more from the start of the cycle and with confirmation of no residual leukemia at least twice during the period of Grade ≥4 cytopenias.
- For Cohorts A-2, B-2, and A-3, a hematologic DLT will be defined as a Grade ≥4 neutropenia, or thrombocytopenia lasting more than 7 days in the absence of residual leukemia and with confirmation of no residual leukemia at least twice during the period of Grade ≥4 cytopenias.
- Any treatment-related death
- Any confirmed Hy's law cases
- Any AEs that lead to a permanent dose reduction or withdrawal.
- Grade ≥3 TLS
  - Exceptions: Grade 3 or 4 TLS will not be considered a DLT if it is successfully managed clinically and resolves within 7 days without end-organ damage

4.3 Dose Validation and Expansion (Part 1b)

The toxicity and preliminary clinical activity profile of at least 1 dose level for each combination from the dose escalation (Part 1a) phase will be examined in the dose validation and expansion phase (Part 1b) to determine the RP2D for each combination. Up to 15 patients will be enrolled per cohort at the dose level chosen for validation.

A review of the safety data from the dose validation/expansion cohorts will be performed continuously by the SMC and IDMC with formal meetings scheduled as deemed necessary and

per the respective SMC and IDMC charters. As described in Section 9.5, a Bayesian toxicity stopping rule will be employed in each expansion cohort to assess the overall DLT rate. The stopping rule will be met in a cohort if the probability of excessive toxicity (ie, the DLT rate is greater than 25%) exceeds 80%. This posterior probability will be computed using a noninformative prior beta (1,1) for the underlying DLT rate. See Section 9.5.1 for additional details on DLT monitoring during dose validation.

Likewise, the efficacy of each cohort will also be evaluated using a Bayesian approach to determine whether the respective combinations demonstrate clinical activity that is not less than the expected clinical activity of the SOC agent(s) in each combination. The defined alerts for data evaluation will be set for the potential to approach a suboptimal response rate for each of the cohorts in the study (see Section 9.5.2). These alerts will be met in each cohort if the probability of a suboptimal response rate, relative to the target response rate, exceeds 80%. Therefore, if the efficacy assessment outcome is the "alert rule is met," there is a >80% probability of a suboptimal response within a given cohort (see Table 22), and the Sponsor will consult with the SMC and/or the IDMC to determine if further investigation of the respective combination should stop. If the efficacy assessment outcome is the "alert rule is not met," there is <80% probability of a suboptimal response and further clinical investigation of the combination may proceed. Refer to Section 9.5.2 for additional details, including target response rates for each cohort.

Following completion of the dose validation/expansion phase and in consultation with the SMC and IDMC, a safe and biologically effective combination RP2D for ziftomenib with each combination regimen for the respective genotypes will be selected from the doses expanded based on the safety and tolerability data (beyond DLT and including dose modifications), clinical activity, exposure, and other PK and PD effects.

4.4 Criteria for Selection of RP2D of Ziftomenib Combinations

The ziftomenib monotherapy RP2D was determined in KO-MEN-001, based on the data cut from 04 July 2022. The dose-validation portion evaluated the randomized comparison of 2 monotherapy dose levels: 200 mg and 600 mg. As of the 04 July 2022 data cut used to determine the RP2D, the 600 mg dose showed clear evidence of clinical activity. No responses were observed in the first 12 patients randomized to the 200 mg dose level in Part 1b, which resulted in closure of future enrollment to the 200 mg cohort following a protocol-specified futility analysis. PK analyses showed evidence of increased ziftomenib exposure with increasing dose, and the safety profile of the 600 mg dose level was tolerable and largely consistent with the safety profile observed at the 200 mg dose level, suggesting ziftomenib has a wide therapeutic window. Taken together, these data supported the selection of the 600 mg ziftomenib dose as the minimal biologically effective and safe dose for continued clinical development of ziftomenib monotherapy in this genetically defined subset of AML patients in Phase 2 and beyond.

The determination of the RP2D for ziftomenib in combination with the respective SOC treatments will follow a similar approach and will be based on the available PK, safety, and efficacy data gathered during the dose escalation and expansion phases. The PK of ziftomenib will be evaluated in each combination to establish the dose/exposure relationship of ziftomenib when given concurrently with other anticancer agents and to ensure the concurrent administration with other anticancer agents does not result in a ziftomenib exposure exceeding a

level known to be safe based on the data from the Phase 1 monotherapy study (KO-MEN-001). With respect to safety, each ziftomenib dose identified during the dose escalation portion for evaluation in the dose validation/expansion should have a safety profile that supports a positive benefit-risk profile for the combination when considered together with the PK and efficacy data.

Lastly, the dose selected during the escalation portion for evaluation in the dose validation/expansion phase should demonstrate sufficient clinical activity to suggest a reasonable likelihood that the combination is more active than either the SOC regimen alone or ziftomenib monotherapy through the application of a futility analysis (see Section 9.5.1). As a CR requires hematologic recovery, which can take time following leukemic clearance of blast cells from the BM, secondary efficacy endpoints known to occur earlier in treatment (eg, CRi, CRh, etc.) may be considered as support for the RP2D to facilitate expedient and efficient selection of the RP2D during the expansion phase. Baseline statistical assumptions for each combination, along with criteria for the respective futility stopping rules, are described in Section 9.5.2.

4.5 Treatment Group Assignment and Study Treatment Overview

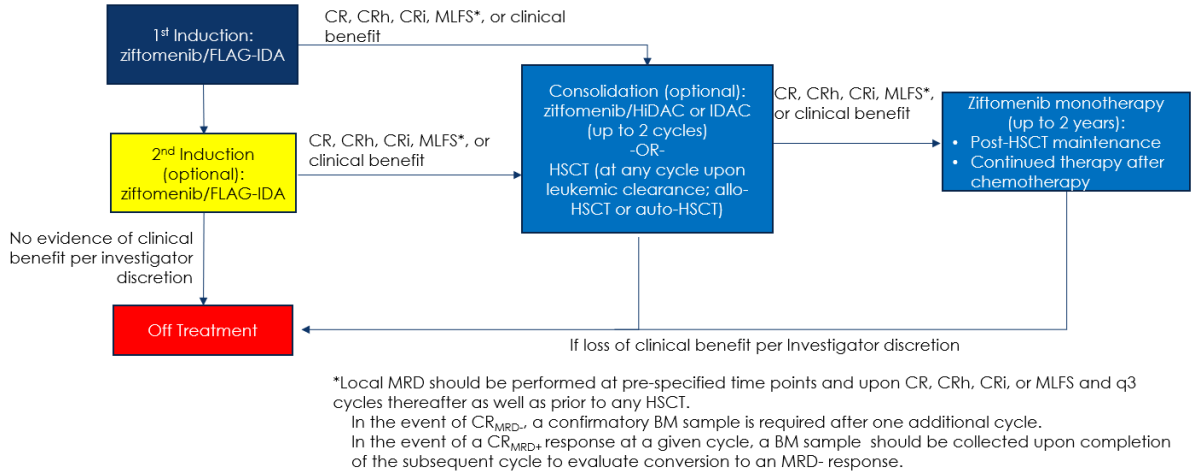
As discussed above, patient assignment to a given arm and cohort is based on investigator discretion, confirmation of eligibility criteria for the arm and cohort (eg, fitness status, *FLT3*-m status for Cohort A-3 enrollment), and slot availability. Patients may receive TLS prophylaxis per institutional practice, and it is recommended to continue TLS prophylaxis through Day 14 (Cohorts A-1, B-1, A-2, and B-2) to account for the first week of ziftomenib monotherapy or through Day 7 (Cohort A-3). DS prophylaxis is recommended in certain patients as per Section.6.5.4.1.1, #3 DS guidance. Thereafter, patients may receive TLS and DS prophylaxis and management if clinically warranted. While *KMT2A*-r patients are at the highest risk of developing DS and/or hyperleukocytosis with concurrent TLS, disseminated intravascular coagulation (DIC), and other associated events, all patients are potentially at risk. Hospitalization may be considered for initial dosing and at the time of any concerning signs/symptoms. See Section 6.5.4, Appendix 4, and Appendix 5 for more information.

The use of proton pump inhibitors should be avoided while on treatment, and if acid-reducing agents are required, it is recommended that an H2 antagonist be used (eg, famotidine, cimetidine, ranitidine) on a staggered schedule (eg, 10 hours prior to ziftomenib dosing and/or 2 hours after ziftomenib dosing). See Section 6.8.

4.5.1 *NPM1*-m Patients (Cohort A-1) and *KMT2A*-r Patients (Cohort B-1) Receiving Ziftomenib Plus FLAG-IDA

Cohorts A-1 and B-1 of this Phase 1 clinical study will assess the safety, tolerability, and preliminary clinical activity of ziftomenib in combination with FLAG-IDA induction therapy in patients with *NPM1*-m or *KMT2A*-r R/R AML. Patients eligible to enroll under this arm must be ≤75 years of age and should meet the fitness criteria for receipt of intensive chemotherapy as defined per institutional standards. An overview of the screening and treatment phases of the study, including decision points determining whether patients continue treatment, is outlined below and in Figure 2. Patients with *FLT3*-m co-mutations may be allowed to enroll in these cohorts provided that they have previously failed or been intolerant to a *FLT*3-inhibtor.

Figure 2 Patient Flow Diagram for Cohorts A-1 and B-1: Ziftomenib Plus FLAG-IDA



Abbreviations: allo-HSCT=allogeneic hematopoietic stem cell transplant; auto-HSCT=autologous hematopoietic stem cell transplant; BM=bone marrow; CR=complete remission; CRh=complete remission with partial hematologic recovery; CRi=complete remission with incomplete hematologic recovery; FLAG-IDA=fludarabine + cytarabine + granulocyte colony-stimulating factor + idarubicin; HSCT= hematopoietic stem cell transplant; HiDAC=high-dose cytarabine; HSCT=hematopoietic stem cell transplant; IDAC=intermediate-dose cytarabine; MLFS=morphologic leukemia-free state; MRD=measurable residual disease.

4.5.1.1 Screening Period

Patients, or their legally authorized representative, must sign the informed consent prior to the initiation of screening evaluations. Clinical and molecular screening evaluations should be completed up to 4 weeks (28 days) prior to Cycle 1 Day 1. Patients should be enrolled based on local testing and must submit a portion of the BM aspirate for study-related biomarker testing. However, patients who have started their SOC backbone treatment outside of the study may be allowed to enroll provided they have completed biomarker testing and all other screening activities within 7 days of starting their SOC therapy. For these patients, archival samples collected prior to SOC backbone treatment should be submitted for study-related biomarker testing. Any screening evaluation, including disease status, will need to be repeated if performed >4 weeks from Cycle 1 Day 1.

During the screening period, hydroxyurea and/or leukapheresis are allowed for the control of peripheral leukemic blasts in patients with leukocytosis (eg, white blood cell [WBC] counts $>25\times10^9$/L).

BM aspirate samples and/or core biopsy should be collected for all patients at Screening to establish baseline BM blast counts, local cytogenetics, local *NPM1*-m or *KMT2A*-r molecular screening results, collect mandatory biomarker assessments, and for retrospective central confirmation of *NPM1*-m and *KMT2A*-r. BM aspirates performed prior to the Screening period as SOC will be accepted for baseline disease assessment if within 28 days prior to C1D1 if it is not clinically feasible or within institutional standards to repeat. If a repeat aspirate is not obtained due to this, a fresh peripheral blood sample and an archival marrow sample (if available) are required as per Table 5.

4.5.1.2 Treatment Period

4.5.1.2.1 Induction Cycle 1

FLAG-IDA plus ziftomenib should be administered to patients in Cohort A-1 or B-1 in both the dose escalation and dose validation/expansion portions of the study as described in Section 6.1.2 and in Table 13. FLAG-IDA may be administered per institutional SOC with approval of the medical monitor.

Ziftomenib administration starts at Cycle 1 Day 8 and is administered continuously throughout the duration of study treatment, irrespective of the cycle of backbone combination. In the event of persistent WBC >25×10^9/L prior to Cycle 1 Day 8, please consult with the medical monitor before using additional cytoreductive agents or initiating ziftomenib.

The first BM assessment of treatment response should be performed on Day 28 (±7d) as shown in Table 2 with the recommendation to repeat per SOC if results are equivocal. As shown in Figure 2 patients who achieve leukemic clearance (eg, CR, CRh, CRi, or MLFS) may proceed immediately to single-agent ziftomenib maintenance therapy or to consolidation chemotherapy (only if CR, CRh, or CRi) or HSCT per the investigator's discretion.

As the mechanism of ziftomenib is driven mainly by differentiation of leukemic blast cells and subsequent natural apoptosis, response to treatment may require continued exposure. Patients with residual disease who experience clinical benefit, as determined by the investigator's assessment at the end of Cycle 1, and who have the potential to benefit from additional therapy may continue on study as shown in Figure 2 (see Section 4.5.1.2.2). A patient can be deemed by the investigator's assessment to have derived clinical benefit and remain on treatment at the protocol-specified timepoints if the patient has had BM blast stabilization or reduction from pretreatment assessment, peripheral blood blast stabilization or reduction from pretreatment assessment, decreased requirement for cytoreduction with hydroxyurea, improvement in cytopenias, or improvement in extra medullary disease (see Section 8.1.1).

Patients may receive TLS prophylaxis prior to administration with FLAG-IDA per institutional standards, however it is strongly recommended that all patients receive TLS prophylaxis during the first week of concomitant administration of ziftomenib (through Cycle 1 Day 14) as shown in Table 1. DS prophylaxis is recommended in certain patients as per Section 6.5.4.1.1, #3 DS guidance. Thereafter, patients may receive prophylaxis and management, if clinically necessary.

4.5.1.2.2 Induction Cycle 2 (Optional)

One additional round of induction is allowed for patients. If a patient has achieved CR/CRh/CRi/PR, Cycle 2 may start upon recovery of neutrophils and platelets in the peripheral blood (absolute neutrophil count [ANC] ≥1.0×10^9/L and/or platelets ≥50×10^9/L, but preferably ≥100×10^9/L) in combination with signs of a cellular BM. If the marrow is acellular, then BM assessments may be repeated per SOC until the ANC ≥1.0×10^9/L and/or platelets ≥50×10^9/L. If the BM shows evidence of persistent disease, Induction Cycle 2 may be started without waiting for count recovery.

Upon completion of a second induction cycle, patients achieving leukemic clearance (eg, CR, CRh, CRi, or MLFS) or those continuing to receive clinical benefit per the investigator's

discretion (Section 8.1.1) may proceed to ziftomenib single-agent maintenance or to consolidation ziftomenib/chemotherapy (only if CR, CRh, or CRi) or hematopoietic stem cell transplant (HSCT), as appropriate.

Patients who have not attained an ELN 2022-defined response (Table 17) after 2 induction cycles should be taken off treatment unless the investigator believes it is in the patient's best interest to continue to ziftomenib monotherapy.

4.5.1.2.3 Consolidation (Optional)

Depending on the outcome of a risk assessment performed according to the local institutional prognostic algorithm that involves clinical, hematological, cytogenetic, molecular, and measurable residual disease (MRD) data, patients with leukemic clearance (eg, CR/CRh/CRi/MLFS, etc.) after induction have the option to proceed to either:

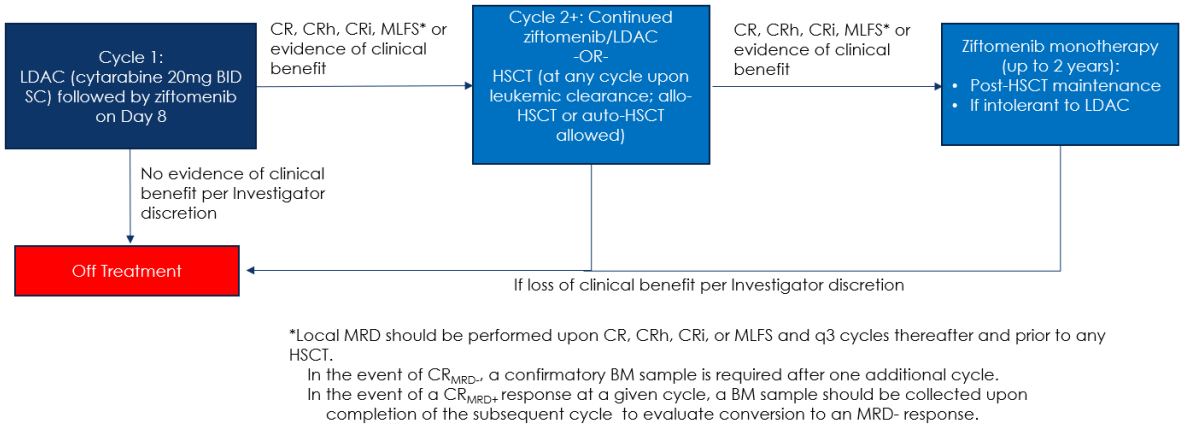
- If CR, CRh, or CRi post-induction, ziftomenib in combination with high-dose cytarabine (HiDAC) or intermediate-dose cytarabine (IDAC) consolidation (Section 6.1.3; NOTE: consolidation with LDAC plus ziftomenib is not allowed), or
- Autologous-HSCT followed by ziftomenib maintenance therapy as applicable (Sections 6.1.5.1 and 6.1.6, respectively), or
- Allogeneic-HSCT followed by ziftomenib maintenance therapy as applicable (Sections 6.1.5.2 and 6.1.6, respectively).

Generally, patients will receive only 1 of the consolidation treatment options above. However, consolidation with ziftomenib in combination with HiDAC or IDAC followed by HSCT is allowed. Patients may receive ziftomenib single-agent maintenance post-chemotherapy consolidation (if the patient did not have HSCT) or post-HSCT as a continued therapy. Those not eligible for either consolidative option who are otherwise deriving clinical benefit, per investigator discretion, may continue on to receive ziftomenib monotherapy.

4.5.2 *NPM1*-m Patients (Cohort A-2) and *KMT2A*-r Patients (Cohort B-2) Receiving Ziftomenib Plus LDAC

Cohorts A-2 and B-2 of this Phase 1 clinical study will assess the safety, tolerability, and preliminary clinical activity of ziftomenib in combination with an LDAC regimen in patients with *NPM1*-m or *KMT2A*-r R/R AML. Patients should be assigned to this arm based on their fitness as defined per institutional standards. An overview of the screening and treatment phases of the study, including decision points determining whether patients continue treatment, is outlined below and in Figure 3. Patients with *FLT3-m* co-mutations may be allowed to enroll in these cohorts provided that they have previously failed or been intolerant to an *FLT*3-inhibitor.

Figure 3 Patient Flow Diagram for Cohorts A-2 and B-2: Ziftomenib Plus LDAC



Abbreviations: allo-HSCT=allogeneic hematopoietic stem cell transplant; auto-HSCT=autologous hematopoietic stem cell transplant; BM=bone marrow; CR=complete remission; CRh= complete remission with partial hematologic recovery; CRi=complete remission with incomplete hematologic recovery; HSCT=hematopoietic stem cell transplant; LDAC=low-dose cytarabine; MLFS=morphologic leukemia-free state; MRD=measurable residual disease.

4.5.2.1 Screening Period

Patients, or their legally authorized representative, must sign the informed consent prior to the initiation of screening evaluations. Clinical and molecular screening evaluations should be completed up to 4 weeks (28 days) prior to Cycle 1 Day 1. Patients should be enrolled based on local testing and must submit a portion of the BM aspirate for study-related biomarker testing. However, patients who may have started receiving LDAC (per Section 6.1.3) as part of SOC may be allowed to enroll, provided they have appropriate archival samples for study-related biomarker testing and have completed all other screening activities prior to Cycle 1 Day 8 when treatment with ziftomenib should begin. For these patients, archival samples collected prior to SOC backbone treatment should be submitted for study-related biomarker testing. Any screening evaluation, including disease status, will need to be repeated if performed >4 weeks from Cycle 1 Day 1.

During the screening period, hydroxyurea and/or leukapheresis, are allowed for the control of peripheral leukemic blasts in patients with leukocytosis (eg, WBC counts >25×10^9/L).

BM aspirate samples and/or core biopsy should be collected for all patients at Screening to establish baseline BM blast counts, local cytogenetics, local *NPM1*-m or *KMT2A*-r molecular screening results, collect mandatory biomarker assessments, and for retrospective central confirmation of *NPM1*-m and *KMT2A*-r. BM aspirates performed prior to the Screening period as SOC will be accepted for baseline disease assessment if within 28 days prior to C1D1 if it is not clinically feasible or within institutional standards to repeat. If a repeat aspirate is not obtained due to this, a fresh peripheral blood sample and an archival marrow sample (if available) are required as per Table 6.

4.5.2.2 Treatment Period

4.5.2.2.1 Cycle 1

During Cycle 1, LDAC should be administered on Days 1 to 10 (20 mg given SC, BID per Section 6.1.3), followed by ziftomenib continuously starting on Day 8 for patients in Cohort A-2 or B-2 in both the dose escalation and dose validation/expansion portions of the study, as described in Sections 6.1.1, 6.1.3, and in Table 13. LDAC may be administered per institutional SOC with approval of the medial monitor.

In the event of persistent WBC > 25×10^9/L prior to Cycle 1 Day 8, please consult with the medical monitor before using additional cytoreductive agents or initiating ziftomenib. Patients who achieve leukemic clearance (eg, CR, CRi, CRh, or MLFS) during study participation may proceed to HSCT or ziftomenib monotherapy or continue ziftomenib in combination with LDAC for up to 6 total cycles, per the investigator's discretion. Otherwise, patients who experience clinical benefit (see Section 8.1.1) during Cycle 1 may receive additional treatment cycles of ziftomenib plus LDAC (up to 6 cycles total), followed by ziftomenib monotherapy. Ziftomenib administration starts Cycle 1 Day 8 and then is administered continuously throughout the duration of study treatment, irrespective of the cycle and backbone combination (see Table 13).

Patients may receive TLS prophylaxis in the first week of Cycle 1 per institutional practice, however it is strongly recommended that patients receive TLS prophylaxis during the first week of concomitant administration of ziftomenib (through Cycle 1 Day 14) as shown in Table 3. DS prophylaxis is recommended in certain patients as per Section.6.5.4.1.1, #3 DS guidance. Thereafter, patients may receive prophylaxis and management if clinically necessary. TLS and DS prophylaxis and management are described in Section 6.5.4.1.1 and Appendix 5.

4.5.2.2.2 Cycle 2 and Beyond

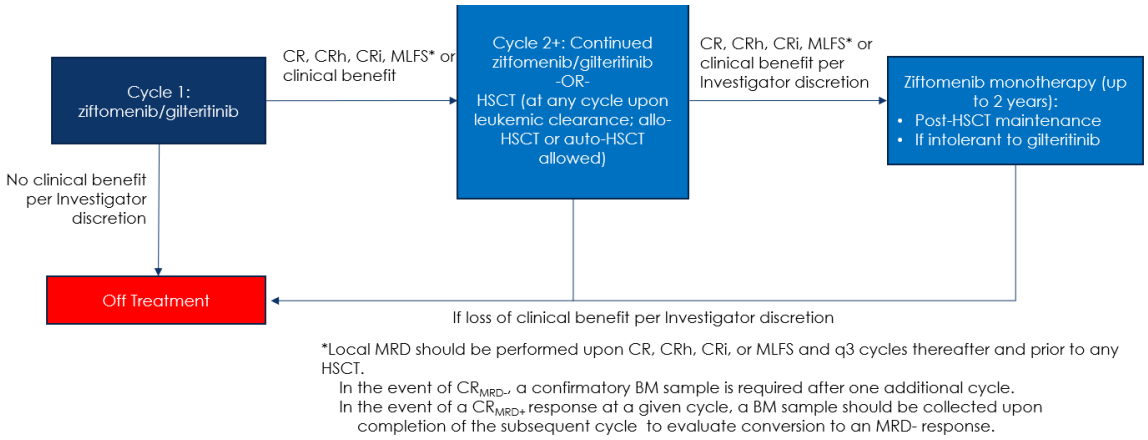
Patients who have leukemic clearance or clinical benefit may continue therapy (see Section 6.1.3) until relapse or loss of benefit. In Cycle 2 and beyond, ziftomenib is administered continuously unless dose interruptions are required per Section 6.4. Those who achieve leukemic clearance (eg, CR, CRi, CRh, or MLFS) during any treatment cycle may proceed to HSCT or ziftomenib monotherapy, per the investigator's discretion. Otherwise, patients should continue ziftomenib in combination with LDAC for up to 6 total cycles, followed by ziftomenib monotherapy in Cycle 7 and beyond. Patients who develop intolerance to LDAC may be either discontinued from combination therapy while maintaining ziftomenib and/or the schedule and dose may be adjusted based on tolerability and safety. Patients may continue to receive ziftomenib following discontinuation of LDAC provided that they have not met the definition of relapse, or treatment failure (ie, received 6 cycles without clinical benefit).

4.5.3 *NPM1*-m Patients (Cohort A-3) Receiving Ziftomenib Plus Gilteritinib

Cohort A-3 of this Phase 1 clinical study will assess the safety, tolerability, and preliminary efficacy of ziftomenib in combination with gilteritinib in patients with *NPM1*-m R/R AML with a concurrent *FLT*3 mutation indicated for treatment with *FLT*3-targeted therapy per the gilteritinib prescribing information. Ziftomenib was shown to inhibit CYP3A4 in an in vitro assay but PBPK modeling has demonstrated that ziftomenib is a weak inhibitor of CYP3A4

(using midazolam as a CYP3A4 substrate). However, because gilteritinib is a sensitive CYP3A4 substrate and CYP3A4 inhibitors increase gilteritinib exposure, which can lead to serious or life threatening AEs, the Part 1a dose escalation for Cohort A-3 will begin at the 100 mg dose level as shown in Table 11. An overview of the screening and treatment phases of the study, including decision points determining whether patients continue treatment, is outlined below and in Figure 4.

Figure 4 Patient Flow Diagram for Cohort A-3: Ziftomenib Plus Gilteritinib



Abbreviations: allo-HSCT=allogeneic hematopoietic stem cell transplant; auto-HSCT=autologous hematopoietic stem cell transplant; BM=bone marrow; CR=complete remission; CRh= complete remission with partial hematologic recovery; CRi=complete remission with incomplete hematologic recovery; HSCT=hematopoietic stem cell transplant; MLFS=morphologic leukemia-free state; MRD=measurable residual disease.

4.5.3.1 Screening Period

Patients, or their legally authorized representative, must sign the informed consent prior to the initiation of screening evaluations. Clinical and molecular screening evaluations, including confirmation of current *FLT*3 status following completion/discontinuation of the immediate prior therapy to study entry, should be completed up to 4 weeks (28 days) prior to Cycle 1 Day 1. Patients should be enrolled based on local testing and must submit a portion of the BM aspirate for study-related biomarker testing. However, patients who may have started gilteritinib as part of SOC may be allowed to enroll provided they have appropriate archival samples for study-related biomarker testing and have completed all other screening activities prior to Cycle 1 Day 1. For these patients, archival samples collected prior to SOC backbone treatment should be submitted for study-related biomarker testing (Table 6). Any screening evaluations, including disease status, will need to be repeated if performed >4 weeks from Cycle 1 Day 1.

During the screening period, hydroxyurea and/or leukapheresis, are allowed for the control of peripheral leukemic blasts in patients with leukocytosis (eg, WBC counts >25×10^9/L).

BM aspirate samples and/or core biopsy should be collected for all patients at Screening to establish baseline BM blast counts, local cytogenetics, local *NPM1*-m and *FLT3*-ITD molecular screening results, collect mandatory biomarker assessments, and for retrospective central confirmation of *NPM1*-m and *FLT3*-ITD. BM aspirates performed prior to the Screening period as SOC will be accepted for baseline disease assessment if within 28 days prior to Cycle 1 Day 1

if it is not clinically feasible or within institutional standards to repeat. If a repeat aspirate is not obtained due to this, a fresh peripheral blood sample and an archival marrow sample (if available) are required as per Table 6.

4.5.3.2 Treatment Period

The ziftomenib/gilteritinib combination should be administered continuously (oral QD) to patients in Cohort A-3 in both the dose escalation and dose validation/expansion portions of the study as described in Section 6.1 and in Table 13.

Hydroxyurea is permitted from Screening through completion of Cycle 1 and beyond for control of peripheral leukemic blasts. Patients who experience clinical benefit (see Section 8.1.1), as determined by the investigator's assessment from Cycle 1, may continue ziftomenib/gilteritinib until relapse or loss of benefit. Patients should be treated for a minimum of six 28-day cycles of combination therapy unless there is evidence of relapse or no response to therapy.

Patients may receive TLS prophylaxis on the day prior to study drug administration (D-1) per institutional practice, however it is strongly recommended that patients receive TLS prophylaxis during the first week of concomitant administration of ziftomenib (through Cycle 1 Day 7) as shown in Table 3. DS prophylaxis is recommended in certain patients as per Section 6.5.4.1.1, # 3. DS guidance. Thereafter, patients may receive prophylaxis and management if clinically necessary. TLS and DS prophylaxis management are described in Section 6.5.4.1.1 and Appendix 5.

Patients achieving leukemic CL (eg, CR, CRi, CRh, or MLFS) may proceed to HSCT or continue ziftomenib in combination with gilteritinib until relapse per the investigator's discretion. Patients achieving clinical benefit may continue ziftomenib in combination with gilteritinib until relapse per the investigator's discretion. Patients who develop intolerance to either agent may be either discontinued from 1 agent while continuing the other as monotherapy and/or the schedule and dose may be adjusted based on tolerability and safety.

4.6 Scientific Rationale for Study Design

A 2-part, Phase 1 study design with a dose escalation (Part 1a) and a dose validation/expansion (Part 1b) was selected to facilitate optimal combination dose selection. Dose escalation occurs in Part 1a, and a more extensive evaluation and selection of the RP2D combination dose of ziftomenib with the FLAG-IDA, LDAC, or gilteritinib regimens occurs in Part 1b. A rule-based approach based on observations of DLTs during the first 28 days of concurrent dosing of ziftomenib with the respective combination partner was chosen for the Part 1a dose escalation to preliminarily evaluate and select a combination dose for more extensive evaluation in the dose validation/expansion. A Bayesian approach using tolerability and safety assessment rules was chosen for Part 1b to more extensively evaluate the selected doses using allocation of patients to select an optimal RP2D for each respective combination based on safety and tolerability data (beyond DLT and including dose modifications), clinical activity, exposure, and other PK and PDn effects.

4.7 Justification for Dose

As discussed in Section 4.4, the RP2D for ziftomenib monotherapy in AML patients was determined to be 600 mg QD based on a data cut from 04 July 2022 of the ongoing KO-MEN-001 study. Therefore, the monotherapy RP2D serves as the top level of the ziftomenib dose range selected (Table 11) for investigation in combination with the established doses of SOC treatments in the dose escalation portion of this study.

Ziftomenib therapy was administered at doses ranging from 50 to 1000 mg in the KO-MEN-001 study. Signs of clinical activity were evident across a range of doses and the drug was safely administered through the MTD of 800 mg, suggesting a wide therapeutic window. Following the dose escalation portion, 2 doses were selected for randomized comparison in the dose validation/expansion portion to facilitate selection of the RP2D. A Bayesian approach was used per protocol to assess the first 24 patients randomized to Part 1b in support of analyses for the RP2D determination. While subsequent enrollment was then ungated, this planned analysis was the primary basis for RP2D determination as it provided data on the predefined RP2D patient population – a population that had the benefit of treatment refinement from a Part 1a experience and was the most mature at the time of the data cut-off. In Part 1b, while patients enrolled at the 200 mg dose experienced clinical benefit, no CR/CRh responses were attained. The 600 mg dose showed a clear differentiation over the 200 mg dose in CR/CRh rate overall (25% versus 0%) and by genotype, with 33.3% of *NPM1*-m patients responding compared to 16.7% of *KMT2A*-r patients at the 600 mg dose. The CR/CRh rate for all *NPM1*-m and *KMT2A*-r patients treated with ziftomenib monotherapy at the 600 mg RP2D during Phase 1 was 23.7% (Lancet, 2024) compared to 5% in the 200 mg cohort.

Overall, the safety data suggest no apparent association between dose and the rate of non-DS TEAEs, regardless of severity, seriousness or relatedness, or other clinical safety assessments (including laboratory evaluations and electrocardiograms [ECGs]). However, the data suggest that DS represents the most significant AE associated with ziftomenib, and a clear association of DS with *KMT2A*-r versus *NPM1*-m AML. As described in Section 2.3 (Benefit/Risk Assessment), the risk of DS events in the *KMT2A*-r patients treated with ziftomenib may be mitigated if patients are treated with antileukemic agents that may “debulk” disease burden prior to the initiation of ziftomenib treatment. For *NPM1*-m patients, although infrequent, DS has been manageable with the implementation of guidance, and the occurrence of DS often predicts a patient’s CL of leukemia (~75% of *NPM1*-m patients with a DS event attained a CR/CRh/CRi). Because DS in *NPM1*-m patients has been manageable and indicative of response and that a gilteritinib monotherapy lead-in is not expected to provide meaningful cytoreductive effect, ziftomenib and gilteritinib should begin concurrent administration on Cycle 1 Day 1 in Cohort A-3.

Taken together, these data support the approach to ziftomenib in the current study. The starting dose for Cohorts A-1, A-2, B-1, and B-2 in the Part 1a dose escalation portion of 200 mg has been demonstrated to be safe in *KMT2A*-r and *NPM1*-m AML patients, and PK analyses have shown that administration of the 200 mg dose results in an approximate 3-fold decrease in ziftomenib exposure compared to the monotherapy RP2D of 600 mg. Because a potential drug-drug interaction between ziftomenib and gilteritinib exists, the starting dose for Cohort A-3 is 100 mg. In the event of toxicity at the starting dose level when combined with other SOC

treatments, the study allows for de-escalation below 200 mg for chemotherapy combinations and 100 mg for targeted therapy combinations, if required, following consultation with the SMC and/or IDMC. Conversely, the maximum ziftomenib dose of 600 mg corresponds to the monotherapy RP2D, which has been determined as the minimal biologically effective and safe dose for inhibiting menin activity in AML patients.

4.8 End of Study Definition

A patient is considered to have completed the study if he/she dies, withdraws consent, or is lost to follow-up. For administrative and safety reporting purposes, the end of this clinical study is defined as approximately 2 years from initial dosing of the last enrolled study patient and will occur no earlier than the date of the last enrolled patient's end of treatment (EOT) visit or prior to initiation of another anticancer therapy, whichever occurs first. If the last study patient has completed their end of treatment visit and withdraws consent, is lost to follow up, or dies earlier than 2 years, this should be noted as the end of study.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as a protocol waiver or exemption, is not permitted.

5.1 Inclusion Criteria

Patients are eligible to be included in the study only if all of the following criteria apply:

1. Adults, age ≥18 years at study entry, diagnosed with AML per the World Health Organization Classification of Hematolymphoid Tumors (5th Edition) that have relapsed following or were refractory (R/R) to at least 1 prior line of therapy, where R/R is defined as reappearance or persistence of ≥5% blasts in the BM or reappearance of blasts in the blood in ≥2 peripheral blood samples ≥1 week apart; or development of new extramedullary disease.
   a. Note: Patients must be ≤75 years of age to be eligible to participate in combinations within intensive chemotherapy.
   b. Note: For Cohort A-3, prior gilteritinib exposure is allowed.
2. Documented *NPM1* mutation or *KMT2A* rearrangement (excluding partial tandem duplications [PTD]).
   a. For Cohort A-3 only: Documented *FLT3* mutation (internal tandem duplications [ITD] or tyrosine kinase domain) in BM or peripheral blood following completion of immediate prior therapy
   b. For all other cohorts (ie, A-1, A-2, B-1, and B-2): *FLT3*-m AML patients must have previously been exposed to/failed/refused/ineligible for a FLT3 inhibitor.
3. Eastern Cooperative Oncology Group (ECOG) Performance Status ≤2.
4. Life expectancy attributed to AML of ≥3 months. Life expectancy from any comorbid illness or non-AML malignancy must be ≥2 years.
5. Adequate hepatic function including AST <3× upper limit of normal (ULN), ALT <3× ULN, and total bilirubin <1.5× ULN (except for patients with known Gilbert's syndrome for which the total bilirubin must be < 5 x ULN). If due to disease, higher values may be approved after discussion with the medical monitor.
6. Adequate renal function calculated by creatinine CL ≥30 mL/min according to one of the following (as medically appropriate): Cockcroft-Gault equation, 2021 CKD-EPI creatinine equation, or 2021 CKD-EPI creatinine-cystatin C equation.
7. Ejection fraction by transthoracic echocardiogram or multi-gated acquisition scan
   a. Patients in Cohorts A-1 and B-1 (ie, ziftomenib/FLAG-IDA): ≥50 %
   b. Patients in Cohorts A-2, B-2, and A-3 (ie, ziftomenib/LDAC and ziftomenib/gilteritinib): ≥40%
8. Patient, or legally authorized representative, must be able to understand and provide written informed consent prior to the first screening procedure.
9. Female patients of childbearing potential must agree to use a highly effective method of contraception as well as a double-barrier method (eg, condom) and refrain from egg donation from screening visit until 180 days following the last dose of study intervention. Male patients capable of having intercourse with females of childbearing potential must agree to abstain from heterosexual intercourse or use a double-barrier method of contraception and have their partner use a highly effective method of contraception from

the screening visit until 120 days following the last dose of study intervention. They must also refrain from sperm donation from the screening visit until 90 days following the last dose of study intervention. See Appendix 2 for further details.

5.2 Exclusion Criteria

Patients are excluded from the study if any of the following criteria apply:

1. Diagnosis of acute promyelocytic leukemia or blast phase chronic myeloid leukemia.
2. Clinically active central nervous system (CNS) leukemia. A patient may be considered eligible if the prior CNS leukemia is controlled (defined as clearance of CSF blasts and other evidence of CNS disease per the investigator) at enrollment and should continue to receive intrathecal therapy (or cranial radiation) as clinically indicated.
3. Active and uncontrolled infection. Once treated and under control, as per the investigator, patients with ongoing infections may be allowed to enroll.
   a. Patients with known uncontrolled human immunodeficiency virus (HIV) infection (HIV testing is not required) are excluded.
   b. Patients with known active hepatitis B (HBV) or C (HCV) infection are excluded. HBV and HCV testing is not required except for those patients with a detectable viral load within 3 months of enrollment. Patients with serologic evidence of prior vaccination to HBV (HBV surface antigen negative and anti-HBV surface antibody positive) or those with previously treated and eradicated Hepatitis C may participate.
4. Mean corrected QT interval by Fredericia's formula (QTcF) >480 ms on triplicate 12-lead ECGs all collected within a 10-minute period.
5. Clinical signs/symptoms of leukostasis or WBC $>25\times10^9$/L.
   a. Note: Hydroxyurea and/or leukapheresis are permitted to meet this criterion. Hydroxyurea may continue beyond Cycle 1 Day 1 at the discretion of the investigator.
6. Diagnosis with any of the following per investigator opinion: uncontrolled intercurrent illness including but not limited to:
   - Symptomatic congestive heart failure (CHF)
   - Unstable angina pectoris
   - Serious cardiac arrhythmia
   - Myocardial infarction with evidence of residual abnormalities within 6 months prior to enrollment (troponin leak alone not included if no residual dysfunction)
   - New York Heart Association Class III or IV heart failure
   - Severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia
7. Has received radiation, chemotherapy, immunotherapy, or any other anticancer therapy including investigational therapy <14 days prior to or within 5 drug half-lives of the first day of study participation, whichever is shorter, with the following exceptions:
   i. Use of hydroxyurea and/or leukapheresis to control rapidly proliferative disease.
   ii. *FLT3*m patients receiving gilteritinib intending enrollment in Cohort A-3.
   iii. Patients with CNS involvement receiving intrathecal therapy or radiation or those at high risk of developing CNS disease receiving intrathecal therapy as prophylaxis.

8. Has had major surgery within 4 weeks prior to the first dose of study intervention. Surgery requiring local/epidural anesthesia must be completed at least 72 hours before study drug administration and patients should be recovered.
9. Has received a HSCT and has not previously had adequate recovery (ie, ANC $\geq 1.0\times10^9$/L and platelets at least $\geq 50\times10^9$/L).
10. Patients with active GvHD requiring more than 0.5 mg/kg prednisone (or equivalent) or any new or increase in immunosuppressants in the prior 2 weeks for GvHD treatment (except adjustments of calcineurin or mTOR inhibitors to maintain therapeutic trough levels).
11. Has not recovered to ≤Grade 1 or baseline from all nonhematological toxicities from prior AML therapies except alopecia.
12. Has psychological, familial, social, or geographic factors that otherwise preclude them from giving informed consent, following the protocol, or potentially hamper compliance with study intervention and follow-up.
13. Has any other significant medical condition, including psychiatric illness or laboratory abnormality, that would preclude the patient participating in the study or would confound the interpretation of the results of the study.
14. Has known allergy or hypersensitivity to gilteritinib, cytarabine, fludarabine, idarubicin, and G-CSF or any of their components, as appropriate to cohort assignment.
15. Women who are pregnant or lactating. All female patients of childbearing potential must have a negative serum pregnancy test within 72 hours prior to start of study intervention.

5.3 Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently entered in the study because of not having met inclusion/exclusion criteria.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE. Once a patient has signed consent and screened for the study, the assigned Patient Number will not be reused if the patient is a screen failure.

Serious AEs that occur during the screening phase of the study need to be reported per the electronic case report form (eCRF) Completion Guidelines.

Patients who do not initially meet inclusion or exclusion criteria are permitted to rescreen for the study once.

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

6.1 Study Drug

Dosing regimens for each of the combinations are outlined below. The respective backbone combination agents within each cohort, in addition to any associated premedication, should be administered per institutional SOC and according to the respective manufacturer's prescribing information. Site protocols for administration of backbone regimens can be shared in advance for Sponsor review to ensure that it remains in general alignment with the dosing regimens outlined below.

6.1.1 Ziftomenib

Ziftomenib is formulated as a capsule in varying strengths, including but not limited to 50 mg and 200 mg, for oral administration and is supplied in high density polyethylene bottles. Each dose strength of ziftomenib contains a matching quantity of active substance. In addition to the active substance, each dose strength of ziftomenib contains the same qualitative composition of the following inactive ingredients: mannitol, microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulphate, and magnesium stearate.

Detailed technical information regarding ziftomenib can be found in the Pharmacy Manual.

Oral administration of 50 mg and/or 200 mg dose strengths of study drug should be given QD according to the patient's cohort schedule. Patients can self-administer treatment. Ziftomenib should be taken at least 1 hour before or 2 hours after a meal with 8 oz of water. Written instructions for administration of ziftomenib should be provided to patients. On days when an in-clinic study visit is scheduled, patients should be instructed to hold their dose of ziftomenib to be administered at the clinic under direct supervision of study personnel after predose PK samples have been collected.

Doses of ziftomenib must be taken within ±12 hours of the scheduled dosage. Missed doses outside this window or vomited doses should not be taken or repeated.

For all cohorts except for Cohort A-3, ziftomenib should be administered continuously starting on Cycle 1 Day 8. Cohort A-3 should receive ziftomenib starting on Cycle 1 Day 1. Ziftomenib is administered continuously throughout treatment unless held for toxicities (Section 6.4). Note: Although dispensed every 28 days, all cycles are defined by backbone combination therapy, not ziftomenib dispensation. All cohorts should administer ziftomenib on Days 1 to 28 of Cycle 2 and beyond, as described.

Evaluation and assessments will occur as 28-day cycles.

6.1.2 FLAG-IDA

The components of FLAG-IDA (fludarabine + cytarabine + G-CSF + idarubicin) should be administered according to the details outlined in their respective prescribing information. The preferred dosing is detailed below but institutional SOC regimen may be used after approval by the medical monitor.

- Fludarabine should be administered 30 mg/m^2/day IV on Days 1 to 4, idarubicin should be administered 6 to 10 mg/m^2/day IV on Days 1 to 3, cytarabine should be administered 1500 to 2000 mg/m^2/day IV on Days 1 to 5, and G-CSF should be administered 300 mcg/m^2/day SC from Days -1 to 5. Additional G-CSF may be administered starting Day 6 following completion of chemotherapy until ANC > 1000/µL. G-CSF should be discontinued for at least 7 days prior to obtaining bone marrow to document remission.
- Ziftomenib should be administered starting on Day 8 of Cycle 1, with continuous QD oral dosing.
  - Ziftomenib should be administered continuously throughout the study (eg, during induction, consolidation, and/or maintenance) except for the following:
    - during the interval immediately prior to autologous-HSCT or allogeneic-HSCT conditioning and for at least 30 days post-HSCT
    - in case of temporary interruption of treatment because of suspected toxicity
    - other dose interruptions as specified in the protocol.

In case thrombocytopenia Grade 4 (platelet count <25×10^9/L) persists until Day 42 of the respective induction cycle or consolidation cycle and BM shows signs of blast CL (<5%), treatment with ziftomenib should be interrupted ("drug holiday"). Ziftomenib should be restarted upon recovery of platelet counts ≥25×10^9/L.

6.1.3 Cytarabine: HiDAC, IDAC, and LDAC

Cytarabine should be administered per the manufacturer's prescribing information and according to institutional standards.

HiDAC: patients indicated to receive HiDAC for treatment consolidation in combination with ziftomenib should receive a 3000 mg/m^2 dose of cytarabine by IV over 3 hours every 12 hours on Days 1, 3, and 5 (total dose 18,000 mg/m^2) per cycle. Ziftomenib should be administered on Days 1 to 28 of each consolidation cycle (see Table 13). The dose and/or schedule may be modified accordingly based on institutional practice and/or myelosuppression, per investigator discretion.

IDAC: patients indicated to receive IDAC for treatment consolidation in combination with ziftomenib should receive a 1500 mg/m^2 dose of cytarabine by IV over 3 hours every 12 hours on Days 1, 3, and 5 (total dose 9000 mg/m^2) per cycle. Ziftomenib should be administered on Days 1 to 28 of each consolidation cycle (see Table 13). The dose and/or schedule may be modified accordingly based on institutional practice and/or myelosuppression, per investigator discretion.

The use of G-CSF with HiDAC or IDAC is allowed per institutional practice guidelines or the preference of the attending physician. Patients should be discontinued from growth factors (i.e., G-CSF) for at least 7 days prior to obtaining bone marrow to document remission.

LDAC: patients indicated to receive LDAC in combination with ziftomenib (Cohorts A-2 and B-2) should be administered a 20 mg dose of cytarabine BID SC on Days 1 to 10 of the 28-day cycle. Ziftomenib should begin on Day 8 of Cycle 1 and should be administered continuously throughout treatment unless held for toxicities (Section 6.4). The dose and/or schedule may be

modified accordingly based on institutional practice and/or myelosuppression, per investigator discretion.

NOTE: LDAC is not a consolidative option for patients in Cohorts A-1 or B-1.

6.1.3.1 Considerations for Chemotherapy Consolidation with Cytarabine (HiDAC or IDAC) and Ziftomenib (Cohorts A-1 and B-1)

Patients who achieve a CR, CRh, or CRi, and who fulfill the relevant criteria, per institutional standards, for start of the appropriate consolidation treatment (HiDAC or IDAC) after remission induction may receive up to 2 cycles of consolidation therapy. Each consolidation cycle is 28 days in duration (with continuously administered ziftomenib) and should begin within 2 weeks following the partial hematologic recovery (ANC $\geq 1.0\times10^9$/L and platelets at least $\geq 50\times10^9$/L but preferably $\geq 100\times10^9$/L) but not sooner than 4 weeks from the beginning of the previous cycle. If the remission consolidation cycle is delayed >8 weeks from the start of the previous cycle due to slow resolution of toxicity or slow recovery of complete blood counts, please contact the medical monitor. Remission consolidation can be given inpatient or outpatient per institutional standards. BM and peripheral blood analysis for response assessment after consolidation should be performed preferably at hematologic recovery. Response assessment should include assessment of MRD and should be performed after completion of Cycles 1 and 2 of consolidation (or sooner if chemotherapy is discontinued prior to 2 cycles due to intolerance or other reasons).

Serial neurological evaluations should be performed before and following the infusion of HiDAC as per site SOC to assess for cytarabine neurotoxicity.

Dexamethasone 0.1% or other corticosteroid ophthalmic solution should be administered as 2 drops to each eye 4 times daily beginning 6 to 12 hours prior to the initiation of the cytarabine infusion and should continue for at least 24 hours after the last cytarabine dose as per site SOC to minimize cytarabine ocular toxicities.

Patients may receive TLS prophylaxis and management during consolidation, if clinically necessary.

6.1.4 Gilteritinib

Gilteritinib should be administered according to the details outlined in its respective prescribing information.

Ziftomenib was shown to inhibit CYP3A4 in an in vitro assay. PBPK modeling, as described in Section 2.2.3, demonstrated that ziftomenib does not increase exposure of sensitive CYP3A4 substrates (midazolam and venetoclax). However, the interaction between ziftomenib and gilteritinib is unknown. To account for potential DDI between ziftomenib and gilteritinib, patients in Cohort A-3 should be monitored according to the manufacturer's prescribing information for use with a CYP3A4 inhibitor. Depending on the progress and/or outcomes of the dose escalation portion of the study, the gilteritinib and/or ziftomenib dose may be adjusted based on emergence of new clinically meaningful data.

Ziftomenib should be administered concurrently with gilteritinib starting on Cycle 1 Day 1 with continuous QD oral dosing in 28-day cycles.

6.1.5 Hematopoietic Stem Cell Transplantation

6.1.5.1 Autologous Hematopoietic Stem Cell Transplantation

Patients with favorable or intermediate disease risk, according to institutional/cooperative group prognostic model, may undergo peripheral blood stem cell mobilization according to local practice and guidelines after remission, except in patients who will certainly proceed to an allogeneic-HSCT. Procedures for hematopoietic cell collection, cryopreservation and conditioning should be performed according to institutional guidelines and local procedures.

Patients who undergo autologous-HSCT should not receive ziftomenib during the conditioning regimen preceding autologous-HSCT, engraftment, or hematologic recovery phases. Ziftomenib should be last dosed on the day preceding start of conditioning. Treatment with ziftomenib may resume following autologous-HSCT (during maintenance) after hematologic count recovery as detailed below in the maintenance section.

6.1.5.2 Allogeneic Hematopoietic Stem Cell Transplantation

Conditioning should take place according to institutional guidelines. GvHD prophylaxis should be administered according to local practice. Haploidentical donor transplants are permitted.

Prophylaxis against bacterial and fungal infections and *Pneumocystis jirovecii* pneumonia should be performed according to local practice. Monitoring of cytomegalovirus and Epstein Barr virus should be performed following standard procedures and pre-emptive therapeutic intervention should be initiated when appropriate.

Patients who undergo allogeneic-HSCT should not receive ziftomenib during conditioning, engraftment, or hematologic recovery phases. Ziftomenib should be last dosed the day prior to start of conditioning. Treatment with ziftomenib may resume following allogeneic-HSCT (during maintenance) after hematologic count recovery as detailed below in the maintenance section (Section 6.1.6).

6.1.5.3 Adverse Event Reporting During the Stem Cell Transplant Period

For patients who undergo HSCT, AEs and SAEs should continue to be collected for 28 days following the last dose of ziftomenib at the start of conditioning, ***excluding any common transplant-related events***. Any ziftomenib related SAEs should continue to be reported regardless of timing. Following the start of conditioning, only the following AESIs should be collected until ziftomenib is restarted post HSCT: veno-occlusive disease (VOD)/sinusoidal obstruction syndrome (SOS), acute graft vs host disease (GvHD) (Grade II-IV per MAGIC Criteria, Appendix 7), and chronic GvHD (NIH Consensus Criteria Jagasia et al, 2015).

6.1.6 Ziftomenib Maintenance Therapy

Based on an analysis performed as of 24 October 2022, following the full enrollment of the Phase 1 portion of KO-MEN-001, 20 out of the 83 R/R AML patients (24.1%) enrolled had a history of prior HSCT before receiving ziftomenib monotherapy. This includes 4 patients who had HSCT as their immediate prior therapy, 1 of whom was ongoing at the time of analysis with a duration of time on study of 26 months. Of the 20 with prior HSCT, 13 (65.0%) were *KMT2A*-r

patients who received doses at 200 mg [n=5 (38.5%)], 600 mg [n=6 (46.2%)], 800 mg [n=2 (15.4%)] and 3 patients (16.7%) were *NPM1*-m and received doses of 200 mg [n=1(33.3%)], 600 mg [n=2 (66.7%)]. Four of the 20 patients (22.2%) had off-target mutations (ie, *KMT2A*-r and *NPM1*-m wild-type) and received doses of 100 mg, 200 mg, 600 mg, or 800 mg [1 each (25.0%)]. Overall, there were no appreciable differences in safety in these patients when compared to the larger, modified intent-to-treat (mITT) set. All 20 prior HSCT patients experienced at least 1 TEAE and 19 patients (95.0%) reported serious TEAEs, with 6 patients (30.0%) reporting serious TEAEs considered by the investigator to be related to ziftomenib. Treatment-related serious TEAEs occurred across a range of dose levels [1 patient [100%] at 100 mg, 3 patients [42.9%] at 200 mg, and 2 patients [22.2%] at 600 mg], suggesting no apparent association between ziftomenib dose and risk of treatment-related SAEs in these patients. Additionally, for the 20 prior HSCT patients, none reported a TEAE requiring a dose reduction, and the rate of patients requiring dose interruptions or treatment discontinuations was similar to the overall mITT population enrolled in Part 1a and Part 1b (40.0% vs 20.0% and 35.8% in Parts 1a and 1b for dose interruptions, respectively and 20.0% vs 26.7% and 15.1% in Parts 1a and 1b for treatment discontinuations, respectively). Two post-HSCT patients (10.0%) experienced a DLT vs 8.0% and 13.2% in the mITT populations in Parts 1a and Parts 1b, respectively. The frequency of TEAEs leading to death was also similar to the broader population, and these events were observed in 5 patients (25.0%) in the post -HSCT group compared to 20.0% and 32.1% in the mITT populations in Part 1a and Part 1b, respectively. The rate and severity of DS observed in patients post-HSCT was also comparable; 5 DS events (25.0%) were reported overall, with 4 of those patients (20.0%) experiencing ≥Grade 3 events. In Part 1b, 14 patients in the overall population (26.4%) had DS events, with 9 patients (17.0%) reporting ≥Grade 3 events, and in Part 1a, 1 DS event ≥Grade 3 was reported in 1 patient (3.3%). Lastly, only 1 patient (5.0%) experienced a GvHD exacerbation which was <Grade 3 in severity and unrelated to ziftomenib.

Since 24 October 2022, 1 patient was treated with ziftomenib maintenance post-HSCT in KO MEN-001. This patient was treated with ziftomenib monotherapy at the RP2D of 600 mg QD from 18 August 2022 through 30 December 2022, at which point study treatment was stopped to prepare the patient for HSCT on 21 December 2022. The patient-initiated tacrolimus 2.5 mg BID PO on 21 December 2022 and restarted ziftomenib monotherapy as maintenance therapy with concurrent tacrolimus administration on 02 March 2023. As of 07 December 2023, the patient was still receiving ziftomenib and tacrolimus was discontinued on 13 November 2023. Although multiple AEs (eg, Grade 1 muscle weakness, abdominal pain, Grade 2 hypertension) have been reported since the HSCT, no TEAEs related to ziftomenib have been reported.

Given the consistency of the data in the subset of patients who have received prior HSCT with the overall mITT population enrolled in KO-MEN-001, there appears to be no evidence of additional risk to patients receiving ziftomenib following HSCT transplant versus those without prior HSCT. This includes no evidence of exacerbation of GvHD in transplanted patients. Therefore, the continued use of ziftomenib monotherapy in the post-transplantation setting is allowed.

Patients who have completed consolidation (either chemotherapy, autologous-HSCT or allogeneic-HSCT) and are in CR, CRh, CRi, MLFS, or continuing to receive clinical benefit (see Section 8.1.1) as determined by the investigator may continue onto maintenance and receive the

ziftomenib combination RP2D for up to 2 years from Day 1 of the start of maintenance treatment, until relapse or development of an unacceptable toxicity based on investigator decision. Patients during the dose escalation phase that proceed to HSCT and ziftomenib maintenance will receive 600 mg (ie, the RP2D of ziftomenib monotherapy) with flexibility to de-escalate as needed.

Patients who received an HSCT, can begin ziftomenib concurrently with immunosuppressive drugs (eg, calcineurin inhibitors, CNIs). While, the commonly used calcineurin inhibitors such as tacrolimus and cyclosporine A are metabolized by CYP3A (Iwasaki et al, 2007; Hebert et al, 1997) and are known CYP3A4 inhibitors (Amundsen et al, 2012), a clinical study has demonstrated that tacrolimus does not alter the exposure of midazolam, a sensitive CYP3A4 substrate (Huppertz et al, 2021). Since strong CYP3A4 inhibitors did not affect ziftomenib exposure in a clinically meaningful manner (described in Section 2.2.3), it is unlikely that coadministration of calcineurin inhibitors will have significant effect on ziftomenib PK. Although a formal drug-drug interaction study has not been conducted, available information indicates minimal PK interaction between ziftomenib and immunosuppressive drugs. Therefore, ziftomenib maintenance in post-HSCT patients on immunosuppressive drugs is allowed.

Maintenance after allo-HSCT or auto-HSCT may begin upon:

- Early hematologic recovery (defined as ANC $\geq 0.5\times10^9$/L and platelets $\geq 20\times10^9$/L),
- Maintenance should not start before day +30 counted from cell infusion/transplant. If the start of maintenance is delayed by more than 4 months after stem cell infusion, this should be discussed with the medical monitor, and the outcome of the discussion must be documented.
- All non-hematologic toxicities should be resolved to <Grade 2 per the National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE) v5.0.
- For patients receiving an allo-HSCT, any GvHD should have resolved to <Grade 1 (ie, no active GvHD; Appendix 7) and the patient should not have had an increase in immune suppression in the past 2 weeks (except adjustments in CNI to maintain therapeutic trough), and prednisone (or equivalent) is <0.5 mg/kg/day.

6.1.7 Stopping Rules for Toxicity Associated with Post-HSCT Ziftomenib Maintenance

Patients receiving ziftomenib after HSCT should discontinue ziftomenib permanently if any of the following conditions are met:

- Any Grade 4 nonhematologic event unless the event is clearly and incontrovertibly due to extraneous causes of disease progression
- Persistent Grade 4 neutropenia and/or thrombocytopenia unless the event is clearly and incontrovertibly due to extraneous causes or disease progression

6.1.8 Dosing Administration for All Combination Regimens

Table 13 Dosing Administration (All Combination Regimens)

Nonintensive Chemotherapy: LDAC + Ziftomenib														
Combination Agent	**Induction Cycle 1**											**Continued Therapy**		**Ziftomenib Monotherapy (including Post-HSCT Maintenance)**
	D1	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D9**	**D10**	**D11-28**	**D1-10**	**D11-28**	**D1-D28**
Cytarabine[a]	X	X	X	X	X	X	X	X	X	X		X		
Ziftomenib[d]								X	X	X	X	X	X	X
***FLT3*-m Targeted Therapy: Gilteritinib + Ziftomenib**														
Combination Agent	**All Treatment Cycles**											**Post-HSCT Maintenance**		
	D1-D28											**D1-D28**		
Gilteritinib	X											X[b]		
Ziftomenib[d]	X											X		
High-intensity Chemotherapy: FLAG-IDA + Ziftomenib														
Combination Agent	**Induction Cycles 1-2 (as applicable)**								**Consolidation Treatment (as applicable)**					**Ziftomenib Monotherapy (including Post-HSCT Maintenance)**
	D-1	**D1**	**D2**	**D3**	**D4**	**D5**	**D6-7**	**D8-D28**	**D1**	**D2**	**D3**	**D4**	**D5**	**D6-28**	**D1-D28**
Fludarabine		X	X	X	X										
Idarubicin		X	X	X											
Cytarabine		X	X	X	X	X			X[c]		X[c]		X[c]		
G-CSF	X	X	X	X	X	X									
Ziftomenib[d]								X	X	X	X	X	X	X	X

Abbreviations: BID=twice daily; D=day; FLT3-m=FMS-like tyrosine kinase 3-mutated; G-CSF=granulocyte colony-stimulating factor; HiDAC=high-dose cytarabine; HSCT= hematopoietic stem cell transplant IDAC=intermediate-dose cytarabine; IV=intravenous; LDAC=low-dose cytarabine; SC=subcutaneous

Note: Dosing regimens for each of the combinations are outlined in the footnotes below. All SOC backbone agents within the respective cohorts should be administered per institutional SOC and according to the respective manufacturer's prescribing information. Site protocols for the administration of backbone regimens can be shared in advance for Sponsor review to ensure it remains in general alignment with the dosing regimens described in the footnotes below.

a. Patients indicated to receive LDAC in combination with ziftomenib should be administered a 20 mg dose of cytarabine BID SC on Days 1 to 10 of each 28-day cycle.
b. Based on PI decision, patients may restart gilteritinib in combination with ziftomenib or continue to ziftomenib monotherapy in the post HSCT maintenance period.

c. Patients indicated to receive chemotherapy consolidation are allowed to receive ziftomenib in combination with HiDAC or IDAC per investigator discretion. Those administered HiDAC in combination with ziftomenib should receive a 3000 mg/m^2 dose of cytarabine by IV over 3 hours every 12 hours on Days 1, 3, and 5 (total dose 18,000 mg/m^2) per cycle. Those administered IDAC in combination with ziftomenib should receive a 1500 mg/m^2 dose of cytarabine by IV over 3 hours twice daily on Days 1, 3, and 5 (total dose 9000 mg/m^2). Ziftomenib is administered on Day 1 to 28 of each consolidation cycle.

d. Ziftomenib should be administered starting on C1D8 (with the exception of the zifto/gilt combo (Cohort A-3) in which ziftomenib will begin on C1D1) with continuous once daily oral dosing throughout the study. Dose interruption and dose de-escalation are allowed as described in Section 6.4. As ziftomenib dosing is continuous, all cycles are defined by backbone combination therapy and not ziftomenib dispenses from Interactive Response Technology (IRT).

6.2 Preparation, Handling, Storage, and Accountability

6.2.1 Ziftomenib

Ziftomenib should be stored below 25ºC (68ºF). All study supplies must be kept in a restricted access area. At a minimum, the label of each bottle of ziftomenib shipped to the study sites will provide the following information: batch number/lot number, expiry date (if applicable), required storage conditions, directions for use, and country-specific required caution statements (eg, in the US, "New Drug – Limited by United States federal law to investigational use").

Ziftomenib accountability records should be maintained by the pharmacy or designated drug preparation area at the study sites. Upon receipt of ziftomenib supplies, the pharmacist or designee should inventory ziftomenib (separately for each strength) and complete the designated section of the shipping form. The shipping/inventory form must be sent to the Sponsor or its designee, as instructed.

Additional guidance regarding storage and handling of ziftomenib will be provided within the Pharmacy Manual.

6.2.2 FLAG-IDA

The components of FLAG-IDA (fludarabine + cytarabine + G-CSF + idarubicin) should be prepared, handled, and stored in accordance with their respective prescribing information.

6.2.3 Cytarabine

Cytarabine should be prepared, handled, and stored in accordance with its respective prescribing information.

6.2.4 Gilteritinib

Gilteritinib should be prepared, handled, and stored in accordance with its respective prescribing information.

6.3 Study Intervention Compliance

When patients are dosed at the site, they should receive study intervention directly from the investigator or designee, under medical supervision. The date, time, and dose administered in the clinic should be recorded in the source documents. The dose of study intervention and study patient identification should be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

The importance of treatment compliance should be emphasized to the patient. Patients should be given detailed instructions on how to take the study intervention at home. Patients should be instructed to return all used and unused study intervention containers at each study visit. Patient compliance with the dosing schedule should be assessed by reconciliation of the used and unused study intervention at each clinic visit and by review of the dosing diaries. The quantity dispensed, returned, used, lost, etc., must be recorded on the dispensing log provided. In addition, it should be recorded whether the dose was taken with food.

Compliance should be monitored and documented by site personnel on the appropriate form. The site personnel will question the patient regarding adherence to the dosing schedule by reviewing the dosing diaries, recording the number of capsules (and strengths, if applicable) returned, the date returned, and determining treatment compliance before dispensing new study intervention to the patient.

During the DLT period, patients who do not complete at least 75% of dosing due to cause other than a DLT will be replaced and deemed not DLT evaluable; following discussion with the medical monitor, the patient may continue in the study, but the patient's data will not contribute to the evaluation of DLTs and/or dose escalation decisions in Part 1a. Beyond the DLT period, patients who do not complete at least 75% of dosing, may be re-educated on dosing with confirmation that the patient can continue to meet the dosing requirements of the protocol at the discretion of the investigator.

6.4 Dose Modification

6.5 Measures to Minimize Bias: Randomization and Blinding

Not applicable.

6.5.1 DLT Management

All potential DLTs should be reported to the Sponsor (or designee) within 24 hours of the site's awareness of the occurrence of the event.

The treating investigator has the discretion to discontinue treatment with the study drug if any of the DLT criteria occurred in the treated patient. However, in cases where the event has resolved, and in the opinion of the treating investigator, if the patient has experienced clinical benefit (see Section 8.1.1) from therapy and continued therapy is thought to be associated with an acceptable risk, the patient may continue therapy at the next lower dose level upon discussion with and approval by the medical monitor.

If a DLT results in an SAE (see Appendix 6), this must be reported on the eCRF.

6.5.2 Dose Modifications Due to SMC/IDMC Recommendations

Based on SMC and/or IDMC recommendations, doses of ziftomenib in combination with any respective combination agent (FLAG-IDA, LDAC, or gilteritinib) may be escalated or de-escalated; all changes in dose should be based on safety and efficacy rules and clinical data recommendations.

6.5.3 Dose Modifications Due to Adverse Events and Laboratory Abnormalities

At any time, the doses of ziftomenib and each respective combination agent may be modified due to clinically meaningful safety events, as outlined in, Table 14, Table 15, or Table 16 and according to appropriate adjustments outlined in the label instructions. After the DLT period, in exceptional circumstances, dosing delays or skipping of doses for reasons other than management of toxicity will be allowed at the judgment of the investigator (and in agreement with the Sponsor).

Each drug can be dose adjusted for toxicity independently as appropriate based upon the nature of the event; however, during the DLT period if there is a significant deviation from the intended dose due to nonsafety related issues (eg, general noncompliance), patients will not be considered evaluable for DLT assessment and will be replaced. Following the DLT period, patients may be discontinued from 1 (or more) of the combination agent(s) if deemed intolerable while maintaining ziftomenib.

Dose interruptions for ≥Grade 3 TEAEs are not required for toxicities that have clear attribution to the patient's underlying disease or condition. Such events can be managed with supportive care at the discretion of the investigator.

Unless otherwise indicated in Table 14, Table 15, or Table 16, ziftomenib may be re-escalated to the original dose, at the judgment of the investigator. Patients who experience a recurrence of a ziftomenib-related ≥ Grade 3 toxicity, or patients who experience more than 1 dose delay ≥14 days, the ziftomenib dose should be reduced to the next lower dose level. Up to 2 dose reductions may be allowed, provided the starting dose of ziftomenib was 600 mg.

Asymptomatic laboratory findings (eg, those not requiring corrective actions/therapies) not covered in this section will not be considered dose-limiting, unless otherwise determined by the investigator. Summary of dose modifications for all study treatment combinations are presented in recommendations Table 14, Table 15, or Table 16.

Asymptomatic laboratory findings (eg, those not requiring corrective actions/therapies) not covered in this section will not be considered dose-limiting, unless otherwise determined by the investigator.

Toxicity assessments and attributions should consider the different start dates for treatments in cohorts A-1, B-1, A-2, and B-2. Summary of dose modifications for all study treatment combinations are presented in recommendations Table 14, Table 15, or Table 16.

Table 14 Summary of Dose Modifications for Treatment-Related Toxicities in Cohorts A-1 and B-1: Ziftomenib and FLAG-IDA

Note: Dose reductions for FLAG-IDA beyond those mentioned or specified in Table 14 should be discussed with the investigator and documentation of the justification should be recorded in the medical record.

Adverse Event	Grade or Result	Ziftomenib Management and Dosing Recommendation	Fludarabine	Cytarabine	Idarubicin	G-CSF
Nonhematological	≥ Grade 3	Interrupt ziftomenib if not resolved with supportive care and toxicity is deemed related to ziftomenib. Upon resolution to Grade 1 or baseline level, resume at same or the next lower dose level at the judgment of the investigator. For Grade 4 events considered related to ziftomenib: permanently discontinue ziftomenib unless the patient is experiencing clinical benefit and following consultation with the medical monitor. If deemed reasonable to restart ziftomenib, the dose should be reduced.	Follow institutional standards of care.			
Hematological	≥ Grade 3	In the case of Grade 4 thrombocytopenia (platelet count $<25\times10^9$/L) that persists until Day 42 of the respective induction cycle or consolidation cycle and BM shows signs of blast clearance (<5%), then treatment with ziftomenib should be interrupted ("drug holiday"). Ziftomenib should be restarted upon recovery of platelet counts $\geq25\times10^9$/L. In case of Grade 4 thrombocytopenia or neutropenia at any time during maintenance treatment, ziftomenib should be interrupted and/or dose reduced until thrombocytopenia or neutropenia has resolved.	Follow institutional standards of care.			

Adverse Event	Grade or Result	Ziftomenib Management and Dosing Recommendation	Fludarabine	Cytarabine	Idarubicin	G-CSF
Cardiac	≥ Grade 3	If considered related to ziftomenib: interrupt ziftomenib if not resolved with supportive care. Upon resolution to Grade 1 or baseline level, resume at same or the next lower dose level at the judgment of the investigator. For Grade 4 events considered related to ziftomenib: permanently discontinue ziftomenib unless the patient is experiencing clinical benefit and following consultation with the medical monitor. If deemed reasonable to restart ziftomenib, the dose should be reduced.	Follow institutional standards of care.			
Hepatic	Mild (CPC A), Moderate (CPC B), or Severe (CPC-C) hepatic impairment	See Section 6.5.4.2 (Drug-Induced Liver Injury) for further guidance/details.	Follow institutional standards of care.			
	Bilirubin >2 mg/dL	No dose adjustments recommended.	Follow institutional standards of care.			
Renal	Serum creatinine >3.0 mg/dL	If considered related to ziftomenib: interrupt ziftomenib if not resolved with supportive care. Upon resolution to Grade 1 or baseline level, resume at same of the next lower dose level at the judgment of the investigator. For Grade 4 events considered related to ziftomenib: permanently discontinue ziftomenib unless the patient is experiencing clinical benefit and following consultation with the medical monitor. If deemed reasonable to restart ziftomenib, the dose should be reduced.	Follow institutional standards of care.			

Adverse Event	Grade or Result	Ziftomenib Management and Dosing Recommendation	Fludarabine	Cytarabine	Idarubicin	G-CSF
	Unexplained elevations of blood urea nitrogen or serum creatinine	No dose adjustments recommended.	Follow institutional standards of care.			
Bone pain (if attributed to G-CSF and uncontrolled with pain medications)	N/A	No dose adjustments recommended.	Follow institutional standards of care.			
N/A	All other Grade 1 or Grade 2 events not previously described	Maintain dose levels.	Follow institutional standards of care.			
TLS	Patients may receive TLS prophylaxis prior to administration with FLAG-IDA per institutional practice, however it is strongly recommended that all patients receive TLS prophylaxis during the first week of concomitant administration of ziftomenib (through Cycle 1 Day 14). Thereafter, patients may receive TLS prophylaxis and management if clinically warranted. *KMT2A*-r patients are at the highest risk of developing differentiation syndrome and/or hyperleukocytosis. Consider hospitalization for initial dosing and at the time of any concerning signs/symptoms. Consider prophylactic steroids at the time of study drug initiation. If a patient meets criteria for clinically significant laboratory or clinical TLS (see Appendix 4), no additional study treatment should be administered until resolution.				

Abbreviations: BM=bone marrow; CPC=Child-Pugh Classification; FLAG-IDA=fludarabine + cytarabine + granulocyte colony-stimulating factor + idarubicin; G-CSF=granulocyte colony-stimulating factor; *KMT2A*-r=lysine[K]-specific methyltransferase 2A-rearranged; N/A=not applicable; TLS=tumor lysis syndrome.

Table 15 Summary of Dose Modifications for Treatment-Related Toxicities for Cohorts A-2 and B-2: LDAC plus Ziftomenib

Adverse Event	Grade or Result	Ziftomenib Management and Dosing Recommendation	Cytarabine Management and Dosing Recommendation
Nonhematological	≥ Grade 3	Interrupt ziftomenib if not resolved with supportive care and toxicity is deemed related to ziftomenib. Upon resolution to Grade 1 or baseline level, resume at same or the next lower dose level at the judgment of the investigator. For Grade 4 events considered related to ziftomenib: permanently discontinue ziftomenib unless the patient is experiencing clinical benefit and following consultation with the medical monitor. If deemed reasonable to restart ziftomenib, the dose should be reduced.	Follow institutional standards of care and/or manufacturer's prescribing information.
Hematological	≥ Grade 3	In case of Grade 4 thrombocytopenia (platelet count $<25\times10^9$/L) persists until Day 42 of the respective induction cycle or consolidation cycle and BM shows signs of blast clearance (<5%), treatment with ziftomenib should be interrupted ("drug holiday"). Ziftomenib should be restarted upon recovery of platelet counts $\geq25\times10^9$/L. In case of Grade 4 thrombocytopenia or neutropenia at any time during maintenance treatment, ziftomenib should be interrupted until thrombocytopenia or neutropenia has resolved.	Follow institutional standards of care and/or manufacturer's prescribing information.
Cardiac	≥ Grade 3	If considered related to ziftomenib: interrupt ziftomenib if not resolved with supportive care. Upon resolution to Grade 1 or baseline level, resume at same or the next lower dose level at the judgment of the investigator. For Grade 4 events considered related to ziftomenib: permanently discontinue ziftomenib unless the patient is experiencing clinical benefit and following consultation with the medical monitor. If deemed reasonable to restart ziftomenib, the dose should be reduced.	Follow institutional standards of care and/or manufacturer's prescribing information.
Hepatic	Mild (CPC A), or Moderate (CPC B), or Severe (CPC-C) hepatic impairment	See Section 6.5.4.2 (Drug-Induced Liver Injury) for further guidance/details.	Follow institutional standards of care and/or manufacturer's prescribing information.

Adverse Event	Grade or Result	Ziftomenib Management and Dosing Recommendation	Cytarabine Management and Dosing Recommendation
Renal	Serum creatinine levels >3.0 mg/dL	If considered related to ziftomenib: interrupt ziftomenib if not resolved with supportive care. Upon resolution to Grade 1 or baseline level, resume at same of the next lower dose level at the judgment of the investigator. For Grade 4 events considered related to ziftomenib: permanently discontinue ziftomenib unless the patient is experiencing clinical benefit and following consultation with the medical monitor. If deemed reasonable to restart ziftomenib, the dose should be reduced.	Follow institutional standards of care and/or manufacturer's prescribing information.
TLS	Patients may receive TLS prophylaxis prior to LDAC administration per institutional practice, however it is strongly recommended that patients receive TLS prophylaxis during the first week of concomitant administration of ziftomenib (through Cycle 1 Day 14). Thereafter, patients may receive TLS prophylaxis and management if clinically warranted. *KMT2A*-r patients are at the highest risk of developing differentiation syndrome and/or hyperleukocytosis. Consider hospitalization for initial dosing and at the time of any concerning signs/symptoms. Consider prophylactic steroids at the time of study drug initiation. If a patient meets criteria for clinically significant laboratory or clinical TLS (see Appendix 4), no additional study treatment should be administered until resolution.		
N/A	All other Grade 1 or 2 events not previously described	Maintain dose levels.	Maintain dose levels.

Abbreviations: BM=bone marrow; CPC=Child-Pugh Classification; *KMT2A*-r=lysine[K]-specific methyltransferase 2A-rearranged; LDAC=low-dose cytarabine; N/A=not applicable; TLS=tumor lysis syndrome.
Source: Cytarabine USPI, 2020

Table 16 Summary of Dose Modifications for Treatment-Related Toxicities for Cohort A-3: Ziftomenib and Gilteritinib

Adverse Event	Grade or Result	Ziftomenib Management and Dosing Recommendation	Gilteritinib Management and Dosing Recommendation
Nonhematological	≥ Grade 3	Interrupt ziftomenib if not resolved with supportive care and toxicity is deemed related to ziftomenib. Upon resolution to Grade 1 or baseline level, resume at same or the next lower dose level at the judgment of the investigator. For Grade 4 events considered related to ziftomenib: permanently discontinue ziftomenib unless the patient is experiencing clinical benefit and following consultation with the medical monitor. If deemed reasonable to restart ziftomenib, the dose should be reduced.	Follow institutional standards of care and/or manufacturer's prescribing information.
Hematological	≥ Grade 3	In case of thrombocytopenia Grade 4 (platelet count<25×10^9/L) persists until Day 42 of the respective induction cycle or consolidation cycle and BM shows signs of blast clearance (<5%), treatment with ziftomenib should be interrupted ("drug holiday"). Ziftomenib should be restarted upon recovery of platelet counts ≥25×10^9/L. In case of Grade 4 thrombocytopenia or neutropenia at any time during maintenance treatment, ziftomenib should be interrupted until thrombocytopenia or neutropenia has resolved.	Follow institutional standards of care and/or manufacturer's prescribing information.
	Hematologic recovery (ANC OR PLT) with more than 25% increase above the nadir (midcycle) is not seen by Day 28 (after Cycle 4)	No dose adjustments recommended.	Follow institutional standards of care and/or manufacturer's prescribing information.
	If a 25% increase in nadir (midcycle) has not been achieved within 14 days after the completion of a cycle	No dose adjustments recommended.	Follow institutional standards of care and/or manufacturer's prescribing information.

Adverse Event	Grade or Result	Ziftomenib Management and Dosing Recommendation	Gilteritinib Management and Dosing Recommendation
Hepatic	Mild (CPC A), Moderate (CPC B), or Severe (CPC-C) hepatic impairment	See Section 6.5.4.2 (Drug-Induced Liver Injury) for further guidance/details.	Follow institutional standards of care and/or manufacturer's prescribing information.
Cardiac	QTcF interval >500 msec	Refer to recommendations for ≥ Grade 3 cardiac toxicity below.	Interrupt gilteritinib administration and resume at 80 mg dose when QTcF interval returns to within 30 msec of baseline or ≤480 msec.
	QTcF interval increased by >30 msec on ECG from Cycle 1 Day 8	If QTcF interval increased >60 msec on ECG from Cycle 1 Day 8, refer to recommendations for ≥ Grade 3 cardiac toxicity below; otherwise, no dose adjustments recommended.	Confirm change with ECG on Cycle 1 Day 9. If the QTcF interval change is confirmed, consider a dose reduction to 80 mg.
	≥ Grade 3	If considered related to ziftomenib: interrupt ziftomenib if not resolved with supportive care. Upon resolution to Grade 1 or baseline level, resume at same or the next lower dose level at the judgment of the investigator. For Grade 4 events considered related to ziftomenib: permanently discontinue ziftomenib unless the patient is experiencing clinical benefit and following consultation with the medical monitor. If deemed reasonable to restart ziftomenib, the dose should be reduced.	Interrupt gilteritinib until recovery to ≤ Grade 1 if toxicity is deemed related to gilteritinib, then resume at 80 mg dose.
Posterior Reversible Encephalopathy Syndrome	N/A	No dose adjustments recommended.	Discontinue gilteritinib.
Hypokalemia and Hypomagnesemia	N/A	No dose adjustments recommended.	Monitor prior to and during gilteritinib administration. Correct hypokalemia or hypomagnesemia prior to and during gilteritinib administration.
Pancreatitis	N/A	No dose adjustments recommended.	Interrupt gilteritinib until pancreatitis is resolved. Then, resume gilteritinib at 80 mg dose.
TLS	Patients may receive TLS prophylaxis on the day prior to study drug administration (D-1) per institutional practice, however it is strongly recommended that patients receive TLS prophylaxis during the first week of concomitant administration of ziftomenib (through Cycle 1 Day 7). Thereafter, patients may receive TLS prophylaxis and management if clinically warranted. *KMT2A*-r patients are at the highest risk of developing differentiation syndrome and/or hyperleukocytosis. Consider hospitalization for initial dosing and at the time of any concerning signs/symptoms. Consider prophylactic steroids at the time of study drug initiation. If a patient meets criteria for clinically significant laboratory or clinical TLS (see Appendix 4), no additional study treatment should be administered until resolution.		

Adverse Event	Grade or Result	Ziftomenib Management and Dosing Recommendation	Gilteritinib Management and Dosing Recommendation
N/A	All other Grade 1 or 2 events not previously described	Maintain dose levels.	Maintain dose levels.

Abbreviations: ANC=absolute neutrophil count; BM=bone marrow; CPC=Child-Pugh Classification; ECG=electrocardiogram; *KMT2A*-r=lysine[K]-specific methyltransferase 2A-rearranged; N/A=not applicable; PLT=platelet count; QTc=corrected QT interval; TLS=tumor lysis syndrome.
Source: XOSPATA® USPI, 2022

6.5.4 Management of Adverse Events of Special Interest

6.5.4.1 Differentiation Syndrome

In nonclinical studies, ziftomenib drives terminal differentiation and scheduled apoptosis. One potential serious sequela in the clinical setting is DS, which can be life-threatening or fatal if not treated. DS has been noted in patients treated with IDH inhibitors (Norsworthy et al, 2020) and has been reported in patients following administration of ziftomenib, with some fatal outcomes. As noted in the Summary of Product Characteristics (SmPC), DS has also been reported in 3.4% (all grade) of patients treated with gilteritinib. Increased recognition of the signs and symptoms of DS through the framework of the Montesinos criteria may lead to earlier diagnosis and treatment, which may decrease severe complications and mortality.

DS can be observed with or without hyperleukocytosis. An algorithm based on Montesinos criteria (Norsworthy et al, 2020) and learnings with other differentiating agents were used to identify associated etiology of DS symptoms. Section 6.5.4.1.1 below outlines AEs that should be examined and the diagnostic criteria that should be applied for the monitoring and treatment of potential DS in patients who received at least 1 dose of ziftomenib.

6.5.4.1.1 Monitoring and Treatment Recommendations for Differentiation Syndrome and/or Hyperleukocytosis with Ziftomenib Therapy

DS and/or hyperleukocytosis should be monitored and treated according to the latest version of the DS and Hyperleukocytosis Guidance.

Key Considerations

1. Hospitalization for initial dosing and at the time of any concerning signs or symptoms noted above

   NOTE: Safety labs as per study specific SOA are required. It is recommended to continue safety labs per study specific SOA for subsequent cycles until there is no longer persistent leukemia as determined by the investigator. Safety labs include:
   a. Inflammatory markers (ferritin, C-reactive protein)
   b. Assessment of coagulopathy (fibrinogen, D-dimer, international normalized ratio, prothrombin time/prothrombin time test, peripheral blood smear review if concerns for microangiopathic hemolytic anemia
   c. Assessment for TLS (CBC with manual differential, serum electrolytes including calcium and phosphorus, creatinine and blood urea nitrogen (or urea), uric acid, lactate dehydrogenase)

2. Prophylactic steroids (0.5 mg/kg prednisone or equivalent) at time of study drug administration if:

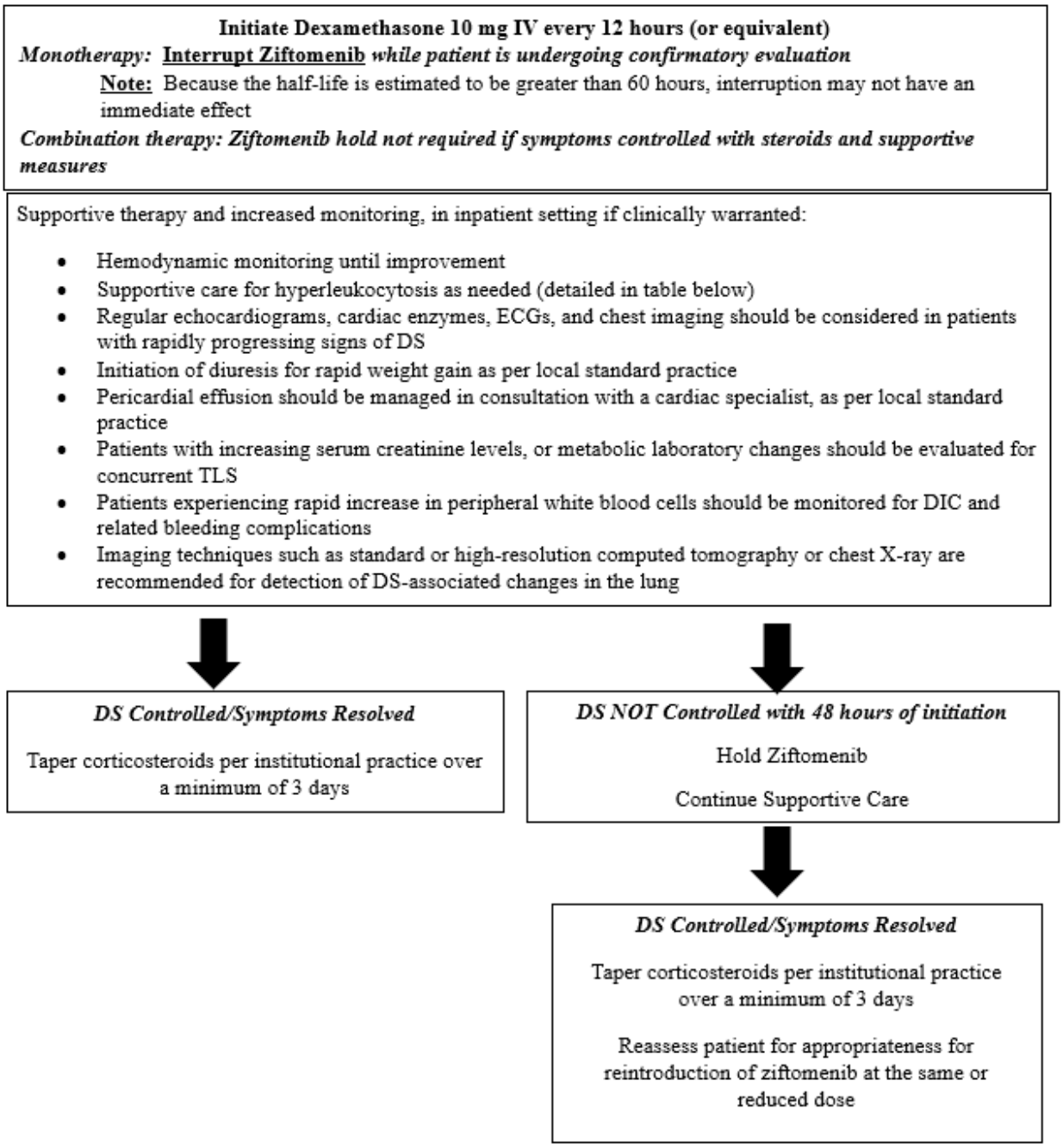
   - Baseline WBC is >5 x 10^9/L
   - Increased creatinine
   - Significant extramedullary disease
   - Known/Suspected proliferative disease

NOTE: prophylactic steroids have not been universally endorsed as a preventative measure for non-APL DS. If prophylactic steroids are initiated, fungal and Pneumocystis Jirovecii Pneumonia prophylaxis are recommended (per institutional guidelines) to ensure appropriate coverage for risk of opportunistic infections due to the combination of underlying AML and prolonged corticosteroid use. In addition, measures to minimize unnecessary exposure to corticosteroids should be taken.

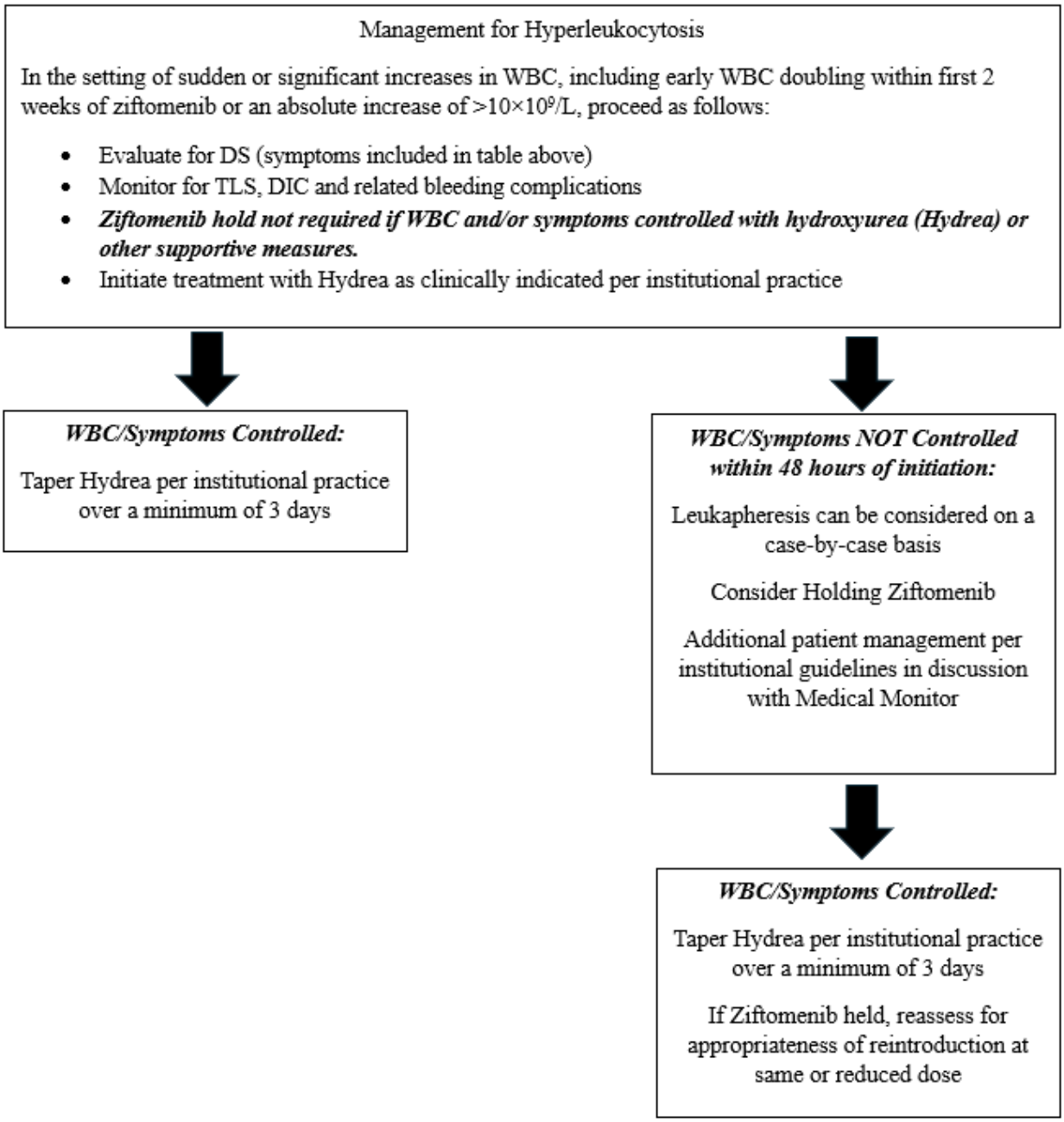
Steroid Taper: Taper according to institutional standards when a) no evidence of DS at the completion of Cycle 1; or b) earlier evidence of DS has improved and marrow blasts are <5% at the completion of Cycle 1.

3. *KMT2A-r* patients are at the highest risk of developing DS and/or hyperleukocytosis; however, *NPM1*-m patients have experienced severe events. The likelihood of DS in other mutations causing *MEIS-1* overexpression is currently unknown.

Treatment of DS or suspected DS:



For the Management of Hyperleukocytosis:



Tumor Lysis Prophylaxis

Prophylaxis should be instituted per the following recommendations (adapted from Cairo et al, 2010) for all patients as per protocol SOA and with regular assessment. Continue TLS prophylaxis while the patient remains at risk.

Low Risk for TLS: Recommend monitoring and IV hydration ± allopurinol

- Patients with WBC <25 x10^9/L and LHD <2x ULN

Intermediate Risk for TLS: Recommend monitoring, IV hydration, and allopurinol

- Patients with WBC between 25 and 100 x10^9/L; or
- Patients with WBC <25 x10^9/L and LDH ≥ 2x ULN; or

High Risk for TLS: Recommend monitoring, IV hydration and rasburicase

- Patients with WBC ≥ 100 x10^9/L
- Patients with intermediate risk *plus* evidence of renal dysfunction
- Patients with intermediate risk *plus* evidence of uric acid, potassium, and/or phosphate > ULN

Dosing of allopurinol and rasburicase is per institutional standards and/or approved labeling. For reference, prophylactic doses are:

- Allopurinol 200 – 400 mg/m^2/day in 1 to 3 divided doses for adults, maximum 800 mg daily
- Rasburicase 0.2 mg/kg IV infusion over 30 minutes daily for up to 5 days

Note: when rasburicase is being used, the addition of allopurinol is unnecessary and has the potential to reduce the effectiveness of rasburicase

Management of electrolyte abnormalities is per institutional standards. Suggested management is shown in the tables below.

Abnormality	Management Recommendations
Hyperkalemia (including rapidly rising potassium)	
Potassium ≥ 0.5 mmol/L increase from prior value (even if potassium within normal limits [WNL])	• Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour STAT. If further ≥ 0.2 mmol/L increase in potassium, but still < upper limit of normal (ULN), manage per potassium ≥ ULN. Otherwise recheck in 1 hour. • Resume per protocol testing if change in potassium is < 0.2 mmol/L, and potassium < ULN, and no other evidence of tumor lysis. • At discretion of investigator, may recheck prior to hospitalization. If stable or decreased, and still WNL, hospitalization is at the discretion of the investigator. Potassium, phosphorus, uric acid, calcium, and creatinine must be rechecked within 24 hours.

Potassium > upper limit of normal	• Perform STAT ECG and commence telemetry. • Nephrology (or other acute dialysis service) notification with consideration of initiating dialysis. • Administer Kayexalate 60 g (or Resonium A 60 g). • Administer furosemide 20 mg IV × 1. • Administer calcium gluconate 100 – 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour STAT. • If potassium < ULN 1 hour later, repeat potassium, phosphorus, uric acid, calcium.
Potassium ≥ 6.0 mmol/L (6.0 mEq/L) and/or symptomatic (eg, muscle cramps, weakness, paresthesias, nausea, vomiting, diarrhea)	• Perform STAT ECG and commence telemetry. • Nephrology (or other acute dialysis service) assessment with consideration of initiating dialysis. • Administer Kayexalate 60 g (or Resonium A 60 g). • Administer furosemide 20 mg IV × 1. • Administer insulin 0.1 U/kg IV + D25 2 mL/kg IV. • Administer sodium bicarbonate 1 – 2 mEq/kg IV push. • If sodium bicarbonate is used, rasburicase should not be used as this may exacerbate calcium phosphate precipitation. • Administer calcium gluconate 100 – 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. Do not administer in same IV line as sodium bicarbonate. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine every hour STAT.
Abnormality	**Management Recommendations**
Hyperuricemia	
Uric acid ≥ 8.0 mg/dL (476 µmol/L)	• Consider rasburicase (prior to rasburicase administration please refer to local label for tests to be performed, contraindications and precautions. Dosing is per institutional guidelines). • If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour STAT.
Uric acid ≥ 10 mg/dL (595 µmol/L) OR Uric acid ≥ 8.0 mg/dL (476 µmol/L) with 25% increase and creatinine increase ≥ 0.3 mg/dL (≥ 0.027 mmol/L) from pre-dose level	• Administer rasburicase (prior to rasburicase administration please refer to local label for tests to be performed, contraindications and precautions. Dosing is per institutional guidelines). • If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Notify nephrology (or other acute dialysis service). • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour STAT. • If uric acid < 8.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 2 and 4 hours later if no other evidence of tumor lysis.

Hypocalcemia	
Calcium ≤ 7.0 mg/dL (1.75 mmol/L) AND Patient symptomatic eg, muscle cramps, hypotension, tetany, cardiac arrhythmias)	• Administer calcium gluconate 50 – 100 mg/kg IV slowly with ECG monitoring. • Telemetry. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour STAT. • If calcium normalized 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 2 and 4 hours later if no other evidence of tumor lysis. • Calculate corrected calcium and check ionized calcium if albumin low.
Hyperphosphatemia	
Phosphorus ≥ 5.0 mg/dL (1.615 mmol/L) with ≥ 0.5 mg/dL (0.16 mmol/L) increase	• Administer a phosphate binder (eg, aluminum hydroxide, calcium carbonate, sevelamer hydroxide, or lanthanum carbonate). • Nephrology (or other acute dialysis service) notification (dialysis required for phosphorus ≥ 10 mg/dL). • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour STAT. • If phosphorus < 5.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 2 and 4 hours later if no other evidence of tumor lysis.
Creatinine	
Increase ≥ 25% from baseline	• Start or increase rate of IV fluids. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 – 2 hours STAT.

6.5.4.2 Drug-induced Liver Injury

If patients with abnormal baseline liver indices develop elevations of AST or ALT >2× baseline or total bilirubin >1.5× baseline values during the study, repeat testing should be performed within 48 to 72 hours. If there are persistent elevations (ALT or AST >2× baseline or total bilirubin 1.5× baseline values) upon repeat testing, then close observation (testing and physical examination 2 to 3 times per week) should be implemented, and discontinuation of drug should be considered.

A decision to discontinue or temporarily interrupt the study drug should be considered based on factors that include how much higher than baseline ALT and AST levels were relative to the ULN and how much the on-study ALT and AST levels have increased relative to baseline, in addition to whether there is concomitant elevation of bilirubin. You need to discontinue or temporarily interrupt the study drug:

- If baseline measurements were <2.5× ULN, discontinue if ALT or AST increases to >5× baseline values.
- Discontinue if ALT or AST increase >2× baseline AND the increase is accompanied by a concomitant increase in total bilirubin to >2× baseline.

- In any patients with signs and symptoms of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%) that is not attributable to any other underlying condition.

6.6 Continued Access to Study Intervention After the End of the Study

On-study treatment will continue until disease progression, intolerable toxicity, or other criteria for treatment discontinuation are met. If the End of Study occurs while patients continue treatment, provisions should be made to continue to treat those remaining patients who are experiencing clinical benefit (see Section 8.1.1) with study intervention, with appropriate safety monitoring. Patients may continue to receive drug on a case-by-case basis via compassionate use or similar mechanisms. Additional guidance will be provided for patients that transition to compassionate use.

Patients who are continuing to benefit after 6 months from treatment may be allowed to continue on study drug. Treatment benefit in patients is considered any 1 of the following:

1. Transfusion-independence while on study treatment
2. >30% reduction in BM blast count percentage from baseline BM blast count that persists for at least 2 BM assessments separated by at least 4 weeks (28 days)
3. ANC >500 μL
4. Platelets >50,000/μL

6.7 Treatment of Overdose

Any overdose must be recorded in the study intervention section of the eCRF, as well as in the AE section if the overdose is associated with an AE.

For this study, a dose of ziftomenib greater than 20% of the daily intended dosage should be considered an overdose. There is no known antidote for ziftomenib. In the event of overdose of ziftomenib, patients should receive appropriate advice and supportive medical care by the investigator or his/her designee and be followed accordingly.

Overdose of FLAG-IDA, cytarabine, or gilteritinib should be defined per the respective package inserts.

For monitoring purposes, any case of overdose of either agent – whether associated with an AE (serious or nonserious) – must be reported in an expedited manner.

In the event of an overdose, the investigator should:

- Contact the medical monitor immediately.
- Evaluate the patient to determine, in consultation with the medical monitor, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the patient for any AE/SAE and laboratory abnormalities. Refer to Appendix 6 for further information on AE reporting requirements.

Document the quantity of the excess dose as well as the duration of the overdose.

6.8 Concomitant Therapy

There is no clinical data currently available describing the effect of ziftomenib on the PK of other drugs. Please refer to the ziftomenib IB for further information.

The use of proton pump inhibitors (eg, lansoprazole [Prevacid], omeprazole [Prilosec], pantoprazole [Protonix], rabeprazole [AcipHex], and esomeprazole [Nexium]) should be avoided while being treated with ziftomenib; these drugs increase the pH of the stomach, resulting in a decrease in absorption of ziftomenib. If acid-reducing agents are required, it is recommended that an H2 antagonist be used (eg, famotidine, cimetidine, ranitidine) on a staggered schedule. The H2 antagonist should be administered at least 10 hours prior to and/or at least 2 hours after the administration of ziftomenib. For BID regimens, administer the H2 antagonist in the evening and in the morning at least 2 hours after ziftomenib.

Patients may continue to use any ongoing medications not prohibited by the inclusion/exclusion criteria, per investigator discretion. However, efforts should be made to maintain stable dosing of required concomitant medications during the course of study treatment. Prior exposure to gilteritinib is permitted.

While on study, when clinically appropriate, patients should strictly follow the study-prescribed treatment regimen in accordance with the following guidance.

- Concurrent administration of any systemic anticancer therapies and/or other investigational agents are prohibited throughout the treatment period, except for brief periods required for the management of hyperleukocytosis and/or DS (See Section 6.5.4).
- The concurrent administration of strong CYP3A4 inhibitors is allowed, however the concurrent administration of strong CYP3A4 inducers should be avoided if possible while receiving ziftomenib or alternative therapies, ie, therapies that do not strongly induce CYP3A4. See the US FDA website for Drug Development and Drug Interactions for additional information (US FDA, 2020). Patients who require strong CYP3A4 inducers should discuss with the medical monitor.
- Any vaccination containing live, attenuated, or inactivated virus may be permitted if clinically indicated. However, this must be discussed with the medical monitor prior to administration. Inactivated influenza and coronavirus disease-2019 (COVID-19) vaccination is permitted on study without restriction.
  - If a vaccine that is recommended is still considered experimental/has received Emergency Use Authorization (except for Emergency Use Authorization-approved COVID-19 vaccines), discussion with the medical monitor is required.
- During study treatment, patients may receive supportive care to include bisphosphonates, antiemetics or hydration, blood product and growth factor anti-infectious support, and pain management.
- Concurrent administration of strong CYP3A4 inhibitors with daunorubicin may have the potential for severe mucositis and patients may require additional monitoring.

All concomitant medication, including over-the-counter medications such as proton pump inhibitors and H2 blockers, should be documented in the case report form (CRF) at each study

visit. In addition, all anticancer surgeries or treatments, and response to those treatments, should be recorded throughout the duration of study follow-up.

6.8.1 Drug-Drug Interactions

The effect of ziftomenib on the absorption, metabolism, or excretion of other drugs has not been studied in humans. In in vitro models, ziftomenib displays potential mild, time-dependent CYP3A4 inhibition. Ziftomenib metabolism is also mainly mediated by CYP3A4 in recombinant human P450 enzyme assays. In hepatocytes, ziftomenib displayed weak CYP1A2 induction potential and no induction effects were observed on CYP3A4.

CYP3A4 Substrates: As described in Section 2.2.3, PBPK modeling demonstrated that coadministration of sensitive CYP3A4 substrates with ziftomenib increased midazolam AUC and C_{max} by 5% and 3%, respectively, and increased venetoclax AUC and C_{max} by 6% and 3%, respectively. These levels of CYP3A4 substrate exposure increase indicated no interaction between ziftomenib and CYP3A4 substrates.

CYP3A4 Inhibitors: As described in Section 2.2.3, PBPK modeling demonstrated that the PK of ziftomenib does not appear to be affected in a clinically relevant manner by coadministration of moderate or strong CYP3A4 inhibitors. These data support allowing the concomitant use of ziftomenib with CYP3A4 inhibitors. Recognizing that the use of antifungals, antibiotics, and antivirals (commonly strong CYP3A4 inhibitors) are important for the management of patients with AML, if such treatment is needed during study participation, ziftomenib treatment should continue and vigilance should be exercised in patient safety monitoring. If a patient comes onto study already on prophylactic care with a strong CYP3A4 inhibitor, the medication may be continued concomitantly with the start of ziftomenib dosing. For candida species coverage, fluconazole or posaconazole are the preferred treatments (Bruggeman et al, 2009). However, since the effects of CYP3A4 inhibitors on ziftomenib PK have not been investigated in a dedicated DDI trial, additional assessments or supportive care to aid in the management of AEs may be performed at the discretion of the investigators and study staff.

CYP3A4 Inducers: Whenever possible, concurrent administration of strong CYP3A4 inducers should be avoided while receiving ziftomenib or alternative therapies should be selected (ie, therapies that do not strongly induce CYP3A4). See the US FDA website for Drug Development and Drug Interactions for additional information (US FDA, 2020).

Immunosuppressive Agents: While the commonly used (CNIs) such as tacrolimus are metabolized by CYP3A (Iwasaki et al, 2007; Hebert et al, 1997) and are known CYP3A4 inhibitors (Amundsen et al, 2012), a clinical study has demonstrated that tacrolimus does not alter midazolam exposure (Huppertz et al, 2021). Because strong CYP3A4 inhibitors did not affect ziftomenib exposure in a clinically meaningful manner (see Section 2.2.3), it is unlikely that coadministration of calcineurin inhibitors will significantly affect ziftomenib PK. Although a formal drug-drug interaction study has not been conducted, available information indicates minimal PK interaction between ziftomenib and immunosuppressive drugs. Therefore, the concurrent use of CNIs (eg tacrolimus and cyclosporine A) with ziftomenib is allowed.

Proton Pump Inhibitors: The absorption of ziftomenib is decreased significantly (53% to 80% reduction in absorbed dose) when coadministered with proton pump inhibitors. Proton pump inhibitors should be avoided while receiving ziftomenib; it is recommended that patients requiring acid reducing agents receive H2 antagonists on a staggered schedule (eg, 10 hours prior

to ziftomenib dosing and/or 2 hours after ziftomenib dosing). Additional antacids may be used if an H2 antagonist is insufficient following the same staggered schedule as H2 antagonists.

7 DISCONTINUATION OF STUDY INTERVENTION AND PATIENT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

Patients may withdraw their consent to participate in this study at any time without prejudice. The investigator must withdraw from the study anyone who requests to be withdrawn. If a patient withdraws from the study, the patient may request destruction of any remaining samples collected as part of this study that have not already been tested. The investigator must document the request to destroy the remaining samples and notify the Sponsor of this request immediately. A patient's participation in the study may also be discontinued at any time at the discretion of the investigator and in accordance with his/her clinical judgment. Every effort should be made to complete, whenever possible, the tests and evaluations listed for the EOT visit. The Sponsor must be notified of all patient withdrawals as soon as possible. The Sponsor also reserves the right to discontinue the study at any time for either clinical research or administrative reasons and to discontinue participation by an individual investigator or site for poor enrollment or noncompliance.

Reasons for which the investigator or Sponsor may withdraw a patient from study intervention include, but are not limited to, the following:

- Patient experiences disease progression
- Patient experiences an unacceptable toxicity/AE
- Patient requests to withdraw from the study intervention
- Patient requires medication prohibited by the protocol
- Patient is unwilling or unable to comply with the study requirements
- Patient withdraws consent to collect health information
- Patient was erroneously admitted into the study or does not meet entry criteria
- Patient is lost to follow-up
- Patient becomes pregnant

Patients enrolled in the study will return for a Safety Follow-up visit approximately 28 days after the last administration of the study intervention (or sooner if another anticancer therapy is to be initiated).

7.2 Premature Study Termination

This study may be discontinued prematurely in the event of any of the following:

- SMC and/or IDMC recommendation based on observed safety leading to an unfavorable risk-benefit of the ziftomenib combination investigated in a specific cohort
- Development of new information leading to a judgment by the Sponsor and/or SMC/IDMC of unfavorable risk-benefit of a respective ziftomenib combination (eg, occurrence of significant previously unknown adverse reactions or unexpectedly high intensity or incidence of previously known adverse reactions, or other unfavorable safety findings with use of either individual agent or the combination)
- Sponsor decision
- Poor enrollment of patients, making timely completion of the study unlikely
- Discontinuation of development of an individual agent

- Request by a Health Authority

Health Authorities and Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) will be informed about the discontinuation of the study in accordance with applicable regulations. In the case of premature discontinuation of the study, the investigations scheduled for the EOT visit should be performed and the appropriate eCRF section completed.

7.3 Lost to Follow-up

A patient should be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether the patient wishes to and/or should continue in the study.
- Before a patient is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, he/she should be considered to have withdrawn from the study.
- Site personnel, or an independent third party, should attempt to collect the vital status of the patient within legal and ethical boundaries for all patients treated with study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this should be documented, and the patient should not be considered lost to follow-up. Sponsor personnel should not be involved in any attempts to collect vital status information.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Table 1, Table 3, and Table 7).

- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the patient's routine clinical management (eg, blood count) and obtained before signing of the informed consent form (ICF) may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA.

8.1 Efficacy Assessments

Planned timepoints for all efficacy assessments are provided in the Disease Response Assessment tables (Table 2 and Table 4). Unscheduled assessments should be considered, if clinically indicated, with results collected in the eCRF. Treatment response should be assessed per the 2022 ELN response criteria (Döhner et al, 2022), which is summarized in Table 17. Assessment of MRD should be determined as described in the MRD consensus document published by the ELN (Heuser et al, 2021).

Long-term Follow-up: For patients who discontinue for reasons other than disease progression or death, study personnel should obtain survival information and disease response evaluations performed per SOC during the follow-up period. Personnel should collect this information (including poststudy anticancer therapies) during routine clinic visits, review of the local medical records, by communicating with referring healthcare providers for the patients who do not return to the study site for subsequent care, or review of the Social Security Death Index.

Table 17 2022 ELN Response Criteria

Response Criteria	Bone Marrow Blasts (%)	Neutrophils (µL)	Platelets (µL)	Peripheral Blasts	Other
CR[a]	<5	≥1,000	≥100,000	Absence of circulating blasts	No EMD
CRh[a,b]	<5	≥500	≥50,000	Absence of circulating blasts	No EMD
CRi[a,c]	<5	All CR criteria except for residual neutropenia (ANC <1,000) **OR** thrombocytopenia (platelets <100,000) and not meeting criteria for CRh		Absence of circulating blasts	No EMD
CR, CRh, or CRi without MRD[d] (CR_{MRD-}, CRh_{MRD-}, or CRi_{MRD-}) CR_{MRD-LL}	<5	Counts as per CR/CRi/CRh criteria above	Counts as per CR/CRi/CRh criteria above	Absence of circulating blasts	CR, CRh, or CRi with MRD per ELN 2022 guidance with response confirmed from the **same sample source** via subsequent assessment at least 4 weeks apart
MLFS	<5	Counts not meeting threshold for CR, CRi, CRh	Counts not meeting threshold for CR, CRi, CRh	Absence of circulating blasts	No EMD; BM should not be merely aplastic; BM spicules should be present; at least 200 cells in the aspirate or cellularity at least 10% in the biopsy
PR	Decreased pretreatment BM blast by at least 50%; decreased BM blast percentage to 5 to 25%	≥1,000	≥100,000	Absence of circulating blasts	N/A
Refractory Disease	N/A	N/A	N/A	N/A	No CR, CRh, or CRi at the response landmark (eg,

Response Criteria	Bone Marrow Blasts (%)	Neutrophils (µL)	Platelets (µL)	Peripheral Blasts	Other
					after 2 induction cycles of IC or No CR,CRi,CRh, or, MLFS after **6 cycles of Non-IC**)
Relapsed Disease (After CR, CRh, or CRi)	≥5	N/A	N/A	Or reappearance of blasts in the blood in at least 2 peripheral blood samples at least 1 week apart	Or New EMD
MRD[d] relapse (After CR, CRh, or CRi without MRD)	N/A	N/A	N/A	N/A	Conversion from MRD negativity to MRD positivity per ELN 2022 guidance
No response	N/A	N/A	N/A	N/A	Failure to achieve CR, CRh, CRi, MLFS, or PR prior to the response Landmark
Nonevaluable for response	N/A	N/A	N/A	N/A	Patients lacking an adequate BM response evaluation, including patients with early death, withdrawal prior to response assessment, or a technically suboptimal bone marrow sample precluding assessment

Abbreviations: BM=bone marrow; CR=complete remission; CRh=complete remission with partial hematological recovery; CRi=complete remission with incomplete recovery; CR_{MRD-}=complete remission without measurable residual disease; CRh_{MRD-}=complete remission with partial hematologic recovery without measurable residual disease; CRi_{MRD-}=complete remission with incomplete recovery without measurable residual disease; CR_{MRD-LL}=complete response with MRD detection at low level; CRh_{MRD-LL}=complete remission with partial hematological recovery with MRD detection at low level; CRi_{MRD-LL}=complete remission with incomplete recovery with MRD detection at low level; C_t=cycling threshold;

Response Criteria	Bone Marrow Blasts (%)	Neutrophils (µL)	Platelets (µL)	Peripheral Blasts	Other

EMD=extramedullary disease; IC=intensive chemotherapy; log_{10}=log base 10; MFC=multiparameter flow cytometry; MLFS=morphologic leukemia-free state; MRD=measurable residual disease; N/A=not applicable; Non-IC=nonintensive chemotherapy; PR=partial remission; qPCR=quantitative polymerase chain reaction.

NOTE: Per ELN 2022, response definitions for patients with marrow blast clearance (<5%) may be adjusted to reflect the best hematologic response achieved prior to starting the next cycle of backbone therapy.

a. For patients with CR, CRh, or CRi, the presence of a low percentage of circulating blasts in the blood may represent a regenerating marrow and should not be interpreted as persistent disease. In such cases the blasts generally disappear within a week and CBC should be repeated and reported in the EDC for confirmation of resolution of circulating blasts.
b. CRh: All CR criteria but the count recovery criteria for CR are not met and patient has both an ANC 500-999/µL and platelet count 50,000–99,999/µL.
c. CRi: All CR criteria except for either residual neutropenia (<1000/µL) or thrombocytopenia (<100,000/µL). A patient with CR criteria and an ANC ≥1000/µL and platelet count <50,000/µL or an ANC <500/µL and platelet count ≥100,000/µL meets CRi. If criteria for CRh are met (footnote b), subject should be considered CRh even if one of the following is present: ANC ≥1000/µL or platelet count ≥100,000/µL
d. Local MRD Assessments: Per institutional practice. Either result should be rapidly confirmed in a second consecutive sample from the same tissue source.

8.1.1 Definition of Clinical Benefit

A patient can be deemed by the investigator's assessment to have derived clinical benefit and remain on treatment at the protocol-specified timepoints if the patient has had BM blast stabilization or reduction from pretreatment assessment, peripheral blood blast stabilization or reduction from pretreatment assessment, decreased requirement for cytoreduction with hydroxyurea, or improvement in cytopenias or improvement in extra medullary disease.

8.2 Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Table 1, Table 3, and Table 7). For a full definition and reporting guidelines please refer to Appendix 6.

SAEs, pregnancy, and/or overdose should be reported to the Sponsor.

This timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports. The investigator is obligated to pursue additional information required for thorough evaluation of each SAE as may be requested by the Sponsor (or designee).

SAE reporting to regulatory authorities and all participating investigators should be conducted by the Sponsor (or designee) in accordance with 21 Code of Federal Regulations (CFR) 312.32 and international regulations, as appropriate.

Suspected unexpected serious adverse reactions (SUSARs) should be collected and reported. In the EU, it is the Sponsor's (or its designee's) responsibility to notify Eudravigilance database of these reports [SUSAR], if applicable, in line with Regulation 536/2014.

8.2.1 Clinical Laboratory Assessments

All protocol-required laboratory tests, as defined in Appendix 1, must be conducted in accordance with the Laboratory Manual and the SoA (Table 1, Table 3, and Table 7) and may be performed by a central or local laboratory.

- Screening and baseline results are required to determine patient eligibility.

- Asymptomatic laboratory findings (eg, those not requiring corrective actions/therapies) not covered in this section will not be considered dose-limiting, unless otherwise determined by the investigator.
- Toxicity assessments and attributions should consider the different start dates for treatments in cohorts A-1, B-1, A-2, and B-2. Summary of dose modifications for all study treatment combinations are presented in recommendations Table 14, Table 15, and Table 16.
- The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents. Relevant results essential for patient management decisions (serum chemistry and hematology) must be available and reviewed before administration of study intervention at Day 1 visits.
- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the patient's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
  - If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in patient management or are considered clinically significant by the investigator (eg, SAE or AE, require study intervention or dose modification), then the results must be recorded in the eCRF.

8.2.1.1 Urinalysis

Macroscopic assessment of the amount of protein, glucose, WBCs and blood should be conducted in accordance with the SoA (Table 1, Table 3, and Table 7). If abnormalities are noted, these should be recorded, and a microscopic analysis conducted and recorded (Appendix 1).

8.2.1.2 Pregnancy Testing

Pregnancy testing should be performed in females of childbearing potential. Testing should be performed in serum at screening (within 72 hours of Cycle 1 Day 1) and may be performed on urine or serum thereafter. If a positive urine pregnancy test is obtained, a confirmatory serum pregnancy test should be conducted. If confirmatory test is positive during study participation, the patient must terminate study treatment immediately and follow pregnancy reporting guidelines outlined in the protocol. Pregnancy testing should be performed locally at the clinical site or its reference laboratory.

8.2.2 Physical Examinations

A complete physical examination of the major body systems should be performed at Screening and EOT visit and include examination of eyes, ears, nose, throat, heart, lungs, abdomen, extremities, nervous system, musculoskeletal systems, and integumentary system. Height (at Screening) and weight will also be measured and recorded.

Otherwise, a limited (ie, symptom-based/focused and history-directed) physical examination should be performed and/or as shown in the applicable SoA (Table 1, Table 3, and Table 7).

Investigators should pay special attention to clinical signs related to previous serious illnesses.

Significant findings are to be reported in electronic data capture on the Medical History or AE pages.

8.2.3 Vital Signs

Temperature, pulse rate, respiratory rate, and blood pressure should be assessed as presented in the SoA (Table 1, Table 3, and Table 7).

Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 1 blood pressure measurement. Additional readings may be taken if clinically indicated. If vital signs are performed after blood collection for laboratory tests, there should be at least 30 minutes in between.

8.2.4 12-lead Electrocardiograms

For the FLAG-IDA combination, triplicate 12-lead ECG (all collected within a 10-minute period) should be performed at screening, Cycle 1 Day 8, and Cycle 2 Day 1 as well as at EOT. On Cycle 1 Day 8 triplicate 12-lead ECG should be collected at pre-dose (relative to ziftomenib), and at 2 hours (± 15 minutes) following study drug administration.

For the LDAC combination, triplicate 12-lead ECG (all collected within a 10-minute period) should be performed at screening, Cycle 1 Day 8, Cycle 2 Day 1, as well as at EOT. On Cycle 1 Day 8, triplicate 12-lead ECG should be collected at pre-dose (relative to ziftomenib), and at 2 hours (± 15 minutes) following study drug administration.

After Cycle 2 Day 1 (Cohorts A-1, B-1, A-2, and B-2), ECGs should be performed as clinically indicated (with the exception of the EOT ECG).

For the gilteritinib combination, triplicate 12-lead ECG (all collected within a 10-minute period) should be performed at screening, Cycle 1 Day 1, Cycle 1 Day 8, Cycle 1 Day 15, Cycle 2 Day 1, Cycle 3 Day 1, and at EOT. On Cycle 1 Day 1, triplicate 12-lead ECG should be collected at pre-dose (relative to ziftomenib), and at 2 hours (± 15 minutes) following study drug administration.

After Cycle 3 Day 1 (Cohort A-3), ECGs should be performed as clinically indicated (with the exception of the EOT ECG).

Screening results are required to determine patient eligibility.

Sites should use an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. The 12-lead ECGs should be conducted after a patient has been in the supine position for 5 minutes.

12-lead ECGs (either triplicate or single, per judgment of the investigator) should be repeated if clinically indicated at any time during the study.

8.2.5 ECOG Performance Assessment

The ECOG performance assessment (Appendix 3) should be conducted as indicated in Table 1, Table 3, and Table 7. Any change in ECOG status should be recorded. Patients are required to have an ECOG performance status of 0 to 2 at screening to be eligible for enrollment.

8.3 Pharmacokinetics

The PK of ziftomenib and metabolites will be measured to determine whether combination therapy affects the PK of ziftomenib and to aid in correlating drug exposure to response and adverse effects. The PK of the other antileukemic drugs administered as part of the respective ziftomenib combinations may also be evaluated as part of these analyses.

Full PK sampling occurs during Cycle 1 and subsequent cycles have sparse PK for all cohorts. Blood samples will be collected for measurement of plasma concentrations of ziftomenib, its metabolites, and gilteritinib as specified in Table 18. Thereafter, patients will have sparse PK sampling for ziftomenib (all cohorts) and gilteritinib (Cohort A-3 only) throughout the length of the study as specified in Table 19. PK samples will also be collected from the first 3 patients in any cohort who receive ziftomenib maintenance post-HSCT and are on oral tacrolimus for measurement of plasma concentrations of tacrolimus, ziftomenib, and ziftomenib metabolites as specified in Table 20.

Determination of ziftomenib, its metabolites, gilteritinib and tacrolimus, plasma concentrations from collected blood samples will be performed by a validated high-performance liquid chromatography with mass spectrometric detection method.

Additional samples may be collected at additional timepoints during the study, if warranted, and agreed upon between the investigator and the Sponsor. The timing of sampling may be altered during the study based on newly available data (eg, to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

On PK sample collection days, patients should not have blood or blood product (eg, whole blood, fresh frozen plasma, packed red blood cells and platelets) transfusions administered within 1 day prior to a scheduled on-study PK collection day until all PK timepoint samples have been successfully collected. If there is a clinical urgency to ensure patient safety by administering the transfusion within this time frame, it is recommended to have the transfusion completed no less than 6 hours before the PK sampling.

Refer to the Laboratory Manual for additional instructions on the collection, handling, storage, and shipment of samples.

Table 18 Full PK Sampling Timepoints – All Cohorts

Time (hour), Relative to Ziftomenib and Gilteritinib Dosing	Allowable Time Window[a]	Ziftomenib[b, c] (All Cohorts)	Gilteritinib[b, c] (Cohort A-3 Only)
Blood Samples		**Cycle 1 Day 28 (± 7 days)**	**Cycle 1 Day 28 (± 7 days)**
Predose	Any time before dosing	X	X
0.5	±5 min	X	X
1	±5 min	X	X
2	±10 min	X	X
3	±10 min	X	X
4	±10 min	X	X
6	±15 min	X	X
8	±15 min	X	X
24	±1 hour	X	X

Abbreviations: PK=pharmacokinetic(s).

Note: On PK sample collection days, patients should not have blood or blood product (eg, whole blood, fresh frozen plasma, packed red blood cells, and platelets) transfusions administered prior to or until all PK timepoint samples have been successfully collected. Furthermore, blood or blood products should not be administered within 1 day prior to a scheduled on-study PK collection day. If clinically urgent for patient safety to transfuse within this window, please have transfusion completed at least 6 hours prior to the PK sampling.

a. Actual time of sample collection should be recorded.
b. Separate blood samples should be collected at each timepoint for the measurement of plasma concentrations of ziftomenib, its metabolites, and gilteritinib (Cohort A-3 only).
c. Patients in Cohort A-3 must have the ziftomenib and gilteritinib PK draws performed on the same day.

Table 19 Sparse PK Blood Sampling Timepoints – All Cohorts

Time (hour), Relative to Ziftomenib or Gilteritinib Dosing	Allowable Time Window	Ziftomenib (All Cohorts)[a]	Gilteritinib (Cohort A-3 only)[a]	Ziftomenib (All Cohorts only)[a]	Gilteritinib (Cohort A-3 only)[a]
		Cycle 2 Day 28 (± 7days)	**Cycle 2 Day 28 (± 7days)**	**Cycle 3+ Day 28 (± 7 days)**	**Cycle 3+ Day 28 (± 7days)**
Blood Sample					
Predose	Any time before dosing	X	X	X	X
1-2	±5 min	X	X		
3-4	±10 min	X	X		
5-8	±15 mins	X	X		

Abbreviations: PK=pharmacokinetic(s).

Note: On PK sample collection days, patients should not have blood or blood product (eg, whole blood, fresh frozen plasma, packed red blood cells, and platelets) transfusions administered prior to or until all PK timepoint samples have been successfully collected. Furthermore, blood or blood products should not be administered within 1 day prior to a

scheduled on-study PK collection day. If clinically urgent for patient safety to transfuse within this window, please have transfusion completed at least 6 hours prior to the PK sampling.

a. Separate blood samples should be collected at each timepoint for the measurement of plasma concentrations of ziftomenib, its metabolites, and gilteritinib (Cohort A-3 only).

Table 20 Blood Sampling Timepoints for Tacrolimus and Ziftomenib

Time (hour), Relative to Tacrolimus or Ziftomenib Dosing	Allowable Time Window	Anytime During Prophylactic Tacrolimus Dosing and Prior to Administration of Ziftomenib[a,b,d]	Day 1 of Coadministration of Tacrolimus and Ziftomenib[a,c,d]	Day 15 (+5 Days) of Coadministration of Tacrolimus and Ziftomenib[a,c,d]
Predose	Any time before dosing	X	X	X
1	±5 mins	X	X	X
2	±10 mins	X	X	X
4	±10 mins	X	X	X
6	±15 mins	X	X	X
8	±15 mins	X	X	X

Abbreviations: PK=pharmacokinetic(s).

Note: On PK sample collection days, patients should not have blood or blood product (eg, whole blood, fresh frozen plasma, packed red blood cells, and platelets) transfusions administered prior to or until all PK timepoint samples have been successfully collected. Furthermore, blood or blood products should not be administered within 1 day prior to a scheduled on-study PK collection day. If clinically urgent for patient safety to transfuse within this window, please have transfusion completed at least 6 hours prior to the PK sampling.

a. Blood samples to be collected from 3 patients on oral tacrolimus.
b. Blood samples for analysis of tacrolimus.
c. Blood samples for analysis or tacrolimus, ziftomenib, and ziftomenib metabolites.
d. Separate blood samples should be collected at each timepoint for the measurement of plasma concentrations of ziftomenib, its metabolites, and tacrolimus

8.4 Biomarkers

8.4.1 *NPM1, KMT2A*, and *FLT3* Testing for Eligibility Determination

All enrolled patients must have documented status of an *NPM1* mutation or *KMT2A* rearrangement (and/or *FLT3* mutation) as determined by an appropriate test. In the US, testing may be performed locally by the site by a Sponsor-approved CLIA-certified local laboratory. Outside the US, the local test must comply with all country-specific regulations for "in-house" tests. The investigator must submit all pages of the local *KMT2A*-r or *NPM1*-m test report for the Sponsor to review prior to enrollment. Local tests should be validated for qualitative detection of *NPM1*-m, *KMT2A*-r, and *FLT3*-m that are typical of screening tests. These qualitative screening tests should be of similar types and sensitivities as the Sponsor's assays used for retrospective central confirmation.

KMT2A rearrangements should be determined using fluorescent in situ hybridization (FISH), next-generation sequencing (NGS), reverse transcriptase polymerase chain reaction (RT-PCR), or another molecular method. Eligible *KMT2A*-r should have a breakpoint occurring in the common break point cluster region (bcr) that results in fusion of the 5′ end of the *KMT2A* gene with another gene. *KMT2A* PTD involving exons 5-12 are not considered an eligible *KMT2A* rearrangement. The Sponsor may request further evidence that the *KMT2A*-r has the correct rearrangement structure for complex cases.

NPM1 mutations should be determined using molecular tests (eg, NGS, PCR, RT-PCR) on nucleic acid extracted from BM (preferred) or peripheral blood. Immunohistochemistry that can detect cytoplasmic localization of the NPM1 protein is not permitted. Eligible *NPM1* mutations include Type A, B, and D mutations caused by a 4-nucleotide insertion in exon 12. Other *NPM1* mutations in the same region that are known or likely to have the same effect on *NPM1* function may be eligible based on Sponsor approval.

Patients who intend to enroll in Cohort A-3 must also have confirmation of their *FLT3*-m status determined by a local (in-house) test following discontinuation of the treatment regimen immediately preceding study participation. *FLT3* mutations should be determined using molecular tests on nucleic acid extracted from BM (preferred) or peripheral blood. Eligible *FLT3* mutations include ITD and/or pathogenic kinase domain mutations (D835 and I836) with a mutant-to-nonmutant allelic ratio of at least 0.05.

Collection of BM aspirate during screening is mandatory for all enrolled AML patients (dose escalation and dose validation/expansion) for retrospective analysis of the local test result for *NPM1*-m (±*FLT3*-m) or *KMT2A*-r status (as applicable), by the Sponsor's central laboratory. A fresh bone marrow aspirate sample is preferred. However, to avoid repeating the BM procedure for subjects whose SOC diagnostic BM has already been collected at the time of screening (within 28 days of C1D1) or a fresh BM aspirate is not clinically feasible, an archival diagnostic sample (frozen DNA from BM or PB, or BM aspirate or peripheral blood) obtained within 28 days prior to the start of SOC backbone treatment (Cycle 1 Day 1) can be submitted along with a fresh PB sample. Other archival samples (eg, frozen mononuclear cells, fixed cell pellet, frozen nucleic acid) may be submitted with preapproval of the Sponsor. Refer to the Laboratory Manual for details including instructions for submitting PB, BM, and archival samples. Leftover or newly collected BM aspirate or tissue sample will be used to validate a companion diagnostic(s) and perform analyses as part of the study-related biomarker objectives. For Part 1b, patients whose NPM1, *KMT2A*, or *FLT3* (for Cohort A-3 only) status is not confirmed by the central laboratory may be replaced to ensure a sufficient sample size of patients with retrospective, centrally confirmed *NPM1*, *KMT2A*, or *FLT3* status for key safety and efficacy analyses.

In addition to *KMT2A*, *NPM1* and *FLT3* status, the Sponsor will collect available data from any hematopathology, cytogenetic, and molecular tests that were performed as part of routine clinical care while on study. These data will be used in correlative analysis to identify clinical factors and biomarkers related to response, resistance, and populations that are likely to benefit from ziftomenib combined with SOC treatments.

8.4.2 Correlative Biomarker Studies

Mandatory blood and BM sampling will be required from all patients to support correlative biomarker studies that drive toward a better understanding of the biology of response predictors, mechanisms of resistance, and populations who benefit from experimental treatments in acute leukemia. In addition, the Sponsor may store blood and BM collected during the study to develop a companion diagnostic for the detection of *NPM1*-m and/or *KMT2A*-r and/or *FLT3*-m.

NPM1-m, *KMT2A*-r, and *FLT3*-m status may be analyzed in pre-treatment samples by retrospective batch analysis in a Sponsor-designated central laboratory and will not be used to determine eligibility at the time of enrollment.

The BM and blood samples should be collected at timepoints described in Table 5 and Table 6. These correlative biomarker studies may include but are not limited to studies aiming to:

1. Investigate the mechanisms of response or resistance to the drug combination through genomic (eg, cytogenetic, molecular, whole transcriptome whole exome/genome sequencing, and epigenome), protein (eg, peptide, proteome), and cellular (eg, multiparameter flow cytometry [MFC]) analysis of leukemia cells
2. Evaluate the pharmacodynamic biomarkers potentially related to activity of the combination
3. Investigate the novel mechanisms of disease resistance using sensitive methods for MRD detection including MFC and/or an NGS gene panel performed by a central laboratory selected by the Sponsor

Sponsor-designated laboratory(ies) will be used for processing of all BM and blood samples collected. The Sponsor will provide kits to collect and ship these samples to Sponsor-designated laboratory(ies) for analysis. Refer to the Laboratory Manual for additional instructions on the collection, handling, storage, and shipment of samples. Sample collection must be captured on the appropriate eCRF and requisition page(s). The samples may be stored under the control of the Sponsor or its authorized agents. Samples may be stored longer if the Sponsor is required to answer questions from a regulatory or governmental agency. The data may be shared with Health Authorities worldwide, at medical meetings, or in medical publications.

While the goal of the study-related biomarker analyses is to provide supportive data for the clinical field and advance research for acute leukemia, there may be circumstances when a decision is made to stop a collection, or not perform or discontinue an analysis due to either practical or strategic reasons (eg, inadequate sample number, issues related to the quality of the sample or issues related to the assay that preclude analysis, impossibility to perform correlative analysis, etc). Therefore, depending on the results obtained during the study, sample collection and/or analysis may be omitted at the discretion of the Sponsor.

Patients will have an opportunity to consent to use of their remaining blood and/or BM from the mandatory study-related biomarker analyses for additional future research. A decision to perform such future research studies would be based on outcome data or from new scientific findings related to the drug class or disease, as well as reagent and assay availability in which case will be outlined in the protocol. A patient's consent to the use of any remaining samples for such additional future research shall be optional and shall not affect participation in the current study. Analysis of germline DNA for the purposes of detecting heritable variants is not planned for this study and will not be performed unless informed consent for the patient is obtained. Patient confidentiality will be maintained.

9 STATISTICAL CONSIDERATIONS

The statistical analysis plan (SAP) will be finalized prior to database lock, and it will include a more technical and detailed description of the statistical analyses described in this section. The statistical approach described in the SAP will supersede the statistical approach described here, in the event of discrepancy. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints. More details will be provided in the SAP. If there are deviations in the analysis methods used for the final analysis from those described in the SAP, such deviations will be described in the clinical study report (CSR).

9.1 Statistical Hypotheses

There is no formal statistical hypothesis testing in this study. The safety and efficacy analyses are descriptive in nature.

9.2 Sample Size Determination

The sample sizes for Part 1a of the study will be determined by the dose escalation rule (Table 12) and the number of DLTs that will be observed. It is estimated that approximately 96 to 156 patients will be enrolled in Part 1a. The sample sizes for each cohort for Part 1b are based on practical reasoning and aligned with the FDA recommendation on the sample sizes for a dose expansion study in AML patients. Approximately 15 patients will be enrolled per cohort at the DL chosen for validation and it is estimated 75 patients will be enrolled in Part 1b.

9.3 Populations for Analysis

The following analysis populations may be used in the study:

- mITT: The mITT set will consist of all patients who were administered any agent (FLAG-IDA, LDAC, gilteritinib, or ziftomenib). The mITT set will also be the safety analysis population.
- Efficacy set: The efficacy set will consist of mITT patients who have locally/centrally confirmed target genotypes (*KMT2A*-r, *NPM1*-m, or *FLT3* [Cohort A-3 only]).
- Dose-Determining Analysis set: The dose-determining analysis set will consist of mITT patients who have experienced a DLT during the DLT observation period or completed the DLT observation period without experiencing such an event and received at least 75% of planned ziftomenib dose for the DLT observation period. See Section 4.2.1 for the DLT definition.
- Pharmacokinetic Analysis set: The PK analysis set (PKAS) will consist of mITT patients who provide at least 1 valid concentration value of ziftomenib and/or gilteritinib (Cohort A-3 only). The PKAS should be used for the analysis of PK data.

Refer to the SAP for additional information regarding analysis populations.

9.4 Statistical Analyses

9.4.1 General Considerations

As a general strategy, data will be analyzed by dose level and combined across all doses for each cohort. Analyses are descriptive in nature. Continuous variables will be summarized by the nonmissing sample size (n), mean, standard deviation, median, first and third quartiles, minimum, and maximum. Proportions of binary endpoints will be provided along with exact 95% confidence interval (CI). Categorical variables will be summarized by the n and percentage in each category. Time to event endpoints will be summarized with Kaplan-Meier (KM) curves, KM proportions at select timepoints, KM quartiles (when estimable), the number of patients with events, the number of patients censored, and the pattern of censoring. Point estimates for efficacy endpoints will be accompanied by 2-sided 95% CIs including estimates of KM quartiles, KM proportions, and binomial proportions.

Part 1a

As a general strategy, data will be analyzed by dose level and combined across all doses within each arm.

Part 1b

Efficacy and safety data will be analyzed for each arm in Part 1b.

9.4.2 Safety Analysis

9.4.2.1 Adverse Events

The patient incidence of AEs will be summarized for all treatment-emergent AEs, serious AEs, AEs leading to withdrawal and interruption of protocol-specified therapy, fatal AEs, and DLTs.

Patient incidence of all treatment-emergent AEs, SAEs, AEs leading to withdrawal and interruption of investigational product, DLTs, and fatal AEs will be tabulated by system organ class and preferred term in descending order of frequency. Similar summaries will be repeated for events of interest (EOIs). Time to onset and duration of selected EOIs may also be summarized. Patient incidence of all treatment-emergent AEs, Grade 3, 4 and 5 AEs will also be tabulated by preferred term in descending order of frequency.

9.4.2.2 Laboratory Test Results or Other Clinical Assessments

Summary statistics over scheduled visits for actual values, changes from baseline of selected laboratory parameters will be presented for patients in the mITT set. In addition, shift tables will be summarized with toxicity grades using NCI CTCAE v5.0 by worst increase and decrease between study baseline and any visit up to the end of the study for selected laboratory parameters.

The number and percentage of patients with abnormal changes in systolic blood pressure, diastolic blood pressure and heart rate will be summarized for the mITT set.

9.4.3 Efficacy Analysis

Summaries will be produced that present the number and percentage of patients with a CR during the induction period for each cohort and overall based on the mITT set and per protocol set. In addition, CR rate in each cohort will be summarized with an exact binomial 95% CI. Patients missing postbaseline disease assessments will be considered not evaluable at the missing timepoint(s).

Similar summaries will be provided for patient incidence of response (ie, CR, CRi, CRh, or MLFS), MRD-, and HSCT.

For each cohort, best overall response (BOR) will be summarized by n (%) for each category (CR, CRh, CRi, MLFS, PR, refractory /no response, and nonevaluable). The details of the category will be described in the Statistical Analysis Plan.

Duration of response (DoR) is defined as time from first response to relapse or death. For patients who did not have relapse/death after achieving response, DoR will be censored at the time of last evaluable response assessment.

KM plots of DoR will be presented. Median DoR will also be summarized, calculated from the KM curve. Only patients who have a CR (or response) will be included in this summary table. Swimmer plots that clearly show the profile of each patient will also be produced.

Event-free survival is defined as time from first dose of any study drug to, whichever of the following comes first:

- Day 1, for those who had induction treatment failure, or
- Relapse for those who had induction treatment success (eg, CR/CRi/CRh), or
- Death from any cause

Overall survival (OS) is defined as time from the first dose of any study drug until death from any cause.

The medians for event-free survival and overall survival at 6 months will be summarized (using the KM curve) and presented for each cohort. More details will be specified in the SAP.

9.4.4 Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to investigational product in the mITT set. The number of cycles administered will be summarized with an additional breakdown of the number of cycles completed and discontinued. In addition, the duration of therapy, the relative treatment duration, the cumulative dose, and the percentage of intended dose will be summarized by cycle and overall, for the ziftomenib group. The number and percent of patients with dose modifications (eg, dose changes, dose interruptions) and reason for modification will be summarized.

9.4.5 Exposure to Concomitant Medication

The number and proportion of patients receiving concomitant medications from Day 1 through safety follow-up will be summarized by preferred term as coded by World Health Organization Drug dictionary in the mITT set. In addition, the number and proportion of patients receiving

anticancer therapies during long-term follow-up will be summarized by World Health Organization Drug dictionary preferred term in the mITT set.

9.4.6 Pharmacokinetic Analysis

Summary statistics (arithmetic mean, standard deviation, geometric mean, median, min, max, and percent coefficient of variation) will be used to describe the noncompartmental analysis PK parameters for ziftomenib and/or its metabolites and/or gilteritinib (Cohort A-3 only) by treatment group (as applicable). Tables of individual concentration-time data, mean concentration-time data (with summary statistics), and the individual and mean (by treatment group) listings of all noncompartmental analysis parameter estimates (eg, maximum plasma concentration, minimum plasma concentration, time to maximum plasma concentration, area under the concentration-time curve from time zero to the time of the last quantifiable concentration after dosing; area under the concentration-time curve over a dosing interval, accumulation ratio) will be reported.

Plots of the mean concentration-time profiles for ziftomenib and/or its metabolite(s) and/or gilteritinib for each dose level (as applicable) and individual concentration-time plots will be generated. Correlations of plasma concentrations of ziftomenib and other PK parameters with toxicity and outcome will be evaluated.

Additional details of the PK analysis will be described in the SAP.

9.4.7 Biomarker Analyses

Summary statistics (total number of individual and co-mutations and other genetic/cytogenetic changes) will be used to describe the prevalence of different genetic alterations in each cohort. Correlative analysis of biomarkers from blood and BM samples collected at screening, during treatment, and at the EOT with patient demographics, clinical history, and study assessments will be performed. Efficacy analysis in different genetic subpopulations will be evaluated. Correlation of plasma concentrations of ziftomenib and PDn biomarkers will be determined.

9.4.8 Subgroup Analyses

Subgroup analyses will be conducted in the following subgroups of the mITT set:

- Sex (male versus female)
- Age at enrollment (<65 versus ≥65 years of age)
- Race (white, black/African American, Asian, other [Native Hawaiian/Pacific Islander or American Indian/Alaska Native or others])
- Genotype *NPM1*-m ± *FLT3* (plus FLT3 %VAF) vs *KMT2A*-r ± *FLT3* (plus FLT3 %VAF); complex cytogenetics or other known negative prognostic markers (eg, mutant *TP53, ASXL1, RUNX1*)

Further details will be provided in the SAP.

9.5 Interim Analyses

9.5.1 Dose-limiting Toxicity Monitoring During Part 1b Dose Validation

A review of the safety data in the dose validation/expansion cohorts will be performed continuously by the SMC, with formal meetings scheduled as deemed necessary (see charter for details), and by the IDMC, which will meet approximately every 4 months or as needed per the IDMC charter. The respective review committees will review the safety of the study from all treatment cycles to evaluate whether there is a serious safety risk in the study. Specifically, for patients enrolled in dose validation/expansion of the study who have an AE meeting DLT criteria in any treatment cycle will be calculated. If the proportion is greater than 30%, the SMC and/or IDMC (as applicable per the respective charters) will be convened to review the data.

A toxicity stopping rule will be employed in each expansion cohort (combining patients from the dose escalation part) to assess the DLT rate. The stopping rule will be set up using a Bayesian approach. The stopping rule will be met in a cohort if the probability of excessive toxicity (ie, the DLT rate is greater than 25%) exceeds 80%. This posterior probability will be computed using a noninformative prior beta (1,1) for the underlying DLT rate (Table 21).

Table 21 Posterior Probability (DLT Rate >0.25)

Number of DLTs	Number of Patients=10	Number of Patients=15
0	0.04224	0.01002
1	0.19710	0.06348
2	0.45520	0.19711
3	0.71330	0.40499
4	0.88537	0.63019
5	0.96567	0.81035
6	0.99244	0.92044
7	0.99881	0.97287
8	0.99987	0.99253

9.5.2 Efficacy Analyses

The purpose of the efficacy assessment rule is to support selection of a RP2D for each cohort and to ensure that the treatment response in each combination with ziftomenib to be no less than the estimated historical response of respective SOC regimens alone. As noted in Section 4.4, in order to facilitate timely and efficient selection of RP2D, analyses performed to support RP2D selection may differ from those specified in the protocol or in the SAP for analyses of primary and secondary efficacy endpoints.

The estimates for minimal target response rate for each respective cohort based on the combination received is as follows:

- **Cohort A-1** (Ziftomenib + FLAG-IDA in *NPM1*-m R/R AML patients): 40% CR rate
  – Based on results from Westhus et al, 2019 and Delia et al, 2017

- **Cohort B-1** (Ziftomenib + FLAG-IDA in *KMT2A*-r R/R AML patients): 30% CR rate
  - Based on results from Issa et al, 2021
- **Cohort A-2 and B-2** (LDAC + ziftomenib in patients with R/R AML): 15% CR rate
  - Based on results from Kantarjian et al, 2012 and Ravandi et al, 2015
- **Cohort A-3** (Ziftomenib + gilteritinib in patients with R/R AML with a *FLT*3 mutation, as detected by an FDA-approved test): 21% CR/CRh rate
  - Based on gilteritinib prescribing information (XOSPATA® USPI, 2022)

The efficacy profiles will be evaluated using a Bayesian approach for each cohort. The defined alerts for data evaluation will be set for the potential to approach suboptimal CR response rates. These alerts will be met in each cohort if the probability of a suboptimal response rate, relative to the target response rate, exceeds 80%.

If the efficacy assessment outcome is the "alert rule is met," this reflects a >80% probability of a suboptimal response, which will result in consultation with the SMC and/or IDMC to determine if further investigation of this combination should stop. If the efficacy assessment outcome is the "alert rule is not met," this reflects <80% probability of a suboptimal response and further clinical investigation of the respective combination may proceed.

The posterior probability will be computed using a noninformative prior beta (1,1) for the underlying CR response rate.

The details of the efficacy assessment rule for each combination therapy are presented in Table 22, assuming up to 15 patients in each cohort (combining patients from escalation part).

Table 22 Efficacy Assessment Rules (15 Patients Per Cohort)

Cohort	Number of Responses (Response Rate)	Posterior Probability of a Suboptimal Response Rate	Decision Rule
Cohort A-1 (Ziftomenib + FLAG-IDA in *NPM1*-m R/R AML patients)	4 (0.27)	0.83	Alert rule is met
	5 (0.33)	0.67	Alert rule not met
	6 (0.40)	0.47	Alert rule not met
Cohort B-1 (Ziftomenib + FLAG-IDA in *KMT2A*-r R/R AML patients)	2 (0.13)	0.90	Alert rule is met
	3 (0.20)	0.75	Alert rule not met
	4 (0.27)	0.55	Alert rule not met
Cohort A-2 and B-2 (LDAC + ziftomenib in patients with R/R AML)	0	0.93	Alert rule is met
	1 (0.07)	0.72	Alert rule not met
	2(0.13)	0.44	Alert rule not met
Cohort A-3 (Ziftomenib + gilteritinib in patients with R/R AML with a *FLT3* mutation, as detected by an FDA-approved test)	1 (0.07)	0.88	Alert rule is met
	2 (0.13)	0.68	Alert rule not met
	3 (0.20)	0.44	Alert rule not met

Abbreviations: AML=acute myeloid leukemia; FLAG-IDA=fludarabine + cytarabine + granulocyte colony-stimulating factor + idarubicin; FDA=Food and Drug Administration; FLT3=FMS-like tyrosine kinase 3; *KMT2A*-r=lysine[K]-specific methyltransferase 2A-rearranged; *NPM1*-m=nucleophosmin 1-mutant; R/R=relapsed/refractory.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences international ethical guidelines
  - Applicable International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, Investigational Directions for Use, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.
- Protocols and any substantial amendments to the protocol will require health authority approval, if required per local regulations, prior to initiation except for changes necessary to eliminate an immediate hazard to study patients.
- The investigator will be responsible for the following, as applicable:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

10.1.2 Financial Disclosure

Investigators and Sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the study and for 1 year after completion of the study.

10.1.3 Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the patient and/or his/her legally authorized representative and answer all questions regarding the study.

Patients or their guardians/legally authorized representatives must be informed that study participation is voluntary. Patients or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, the Health Insurance Portability and Accountability Act of 1996, where applicable, and the IRB/IEC or study site.

As used in the protocol, the term "informed consent" includes all informed assent given by patients, informed permission by legally authorized representative, or as applicable, informed consent by the patient during study participation.

The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study (ie, before any study-specific screening evaluations are performed) and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

If determined to be necessary by the IRB/IEC, patients must be reconsented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the patient or the patient's legally authorized representative.

A patient who is rescreened is required to sign another ICF if rescreening occurs >28 days since the patient signed the initial ICF.

10.1.4 Data Protection

To comply with applicable laws governing the protection of personal data, specifically regarding the implementation of organizational and technical arrangements aiming to avoid unauthorized access to, and disclosure, dissemination, alteration, or loss of, information and processed personal data, the Sponsor has implemented and maintains the following measures across locations, personnel, and information systems:

- Restriction and monitoring of physical access to offices and information processing facilities to employees, personnel, and approved visitors;
- Ensuring appropriate and restricted user access relevant to the function and type of activity performed in relation to the clinical study;
- Implementing the pseudonymization and encryption of personal data, as appropriate. Specifically, patients will be assigned a unique identifier by the Sponsor. Any patient records or datasets that are transferred to the Sponsor and/or its designee will contain the identifier only; patient names or any other information that would make the patient identifiable will not be transferred to the Sponsor and/or its designee;
- Implementing the ability to ensure the ongoing confidentiality, integrity, availability, and resilience of information processing systems and services;
- Implementing network, application, and database security by means of firewalls and antivirus/anti-malware; ensuring detection of malware purposed for unauthorized deletion, blocking, copying of information, disabling security measures and response to such attacks;
- Implementing means to restore the availability and access to personal data in a timely manner in the event of a physical or technical incident;

- Logging of security events/incidents in information systems;
- Implementing procedures that cover reporting, analysis, monitoring, and resolution of security incidents;
- Ensuring that information systems, computers, and software involved in the study are backed up;
- Regularly testing, assessing, and evaluating the effectiveness of technical and organizational measures for ensuring the security of the processing of personal data;
- Implementing procedures to capture within a reasonable time any personal data breach occurred;
- Implementing procedures and practices for securing destruction of paper documents containing personal data; and
- Implementing business continuity procedures ensuring that the Sponsor can continue to provide services through operational interruption.

The Sponsor will ensure that the technical and organizational security measures described above are regularly reviewed and updated to take into account any evolution in technological developments. The Sponsor may apply additional specific measures, where required under national laws.

The Sponsor requires its contractors processing personal data from the study to agree contractually to implement technical and organizational measures to maintain the confidentiality of records and personal data of study patients.

The Sponsor has put in place standard operating procedures that require any data breach (ie, unauthorized access to clinical data) to be reported to the Sponsor's Quality Assurance and Legal departments to ensure appropriate handling per regulatory requirements. If the data breach is likely to affect to a significant degree the rights or safety of patients, data integrity, or the scientific value of the clinical study, the data breach also will be managed as a potential serious breach, in which case a designated team that includes representatives of Quality Assurance, Legal and other Sponsor departments will evaluate the data breach and determine whether it is required by applicable laws to be reported to the relevant authorities and/or study patients. In the event that such reporting is determined to be required, the Sponsor shall cause such reports to be made in accordance with the timelines and other requirements imposed by applicable laws.

Patients must be informed during the informed consent process that their personal data will be shared with and used by the Sponsor in accordance with local data protection law. Patients must also be informed that their medical records may be examined by auditors, the Sponsor or its representatives, IRB/IEC members and regulatory authorities, among others.

10.1.5 Committee Structure

10.1.5.1 Safety Monitoring Committee

An SMC composed of investigators, Sponsor personnel, and independent advisor(s) will review patient data as needed to assess the safety of the combination and help to determine the dose levels, regimen, potential mitigations, and ultimately the safest and most efficacious combination dose for the respective combination therapies under investigation. In the absence

of safety concerns, enrollment into the cohorts will proceed independently. The composition of the committee is dependent upon the scientific skills and knowledge required for monitoring this study. Additional details are available in the SMC charter.

10.1.5.2 Independent Data Monitoring Committee

An external IDMC has been engaged to closely monitor the safety of the interventions under investigation during this study. The IDMC will support the SMC at certain key milestones within the study, including a data review following completion of the dose escalation portion in Part 1a to support the selection of dose(s) to be further investigated in the dose validation/expansion portion in Part 1b and for the ultimate selection of the respective combination RP2Ds.

Upon completion of Part 1a, the IDMC will convene approximately every 4 months to provide ongoing oversight. The IDMC may make recommendations regarding whether adjustments to ziftomenib dose are warranted, as well as whether to continue the study as planned. The IDMC will review any DLTs that are deemed at least possibly related to ziftomenib and any suspected unexpected serious adverse reactions (SUSARs) periodically, or as needed, during the conduct of the study and may provide additional recommendations regarding ziftomenib dose and/or other modifications to study conduct. For example, dosing of current patients may be held to evaluate SUSARs that have not been described to date with respect to their nature, severity, and duration, or if there is an unexpected increase in the incidence of known AEs that exceeds expectations (with ziftomenib and/or any of the respective SOC backbone treatments). The IDMC may also formulate recommendations relating to the selection, recruitment, and retention of patients and their management. Additional details regarding the responsibility of the IDMC/its chair will be provided in the IDMC charter, as applicable.

10.1.6 Dissemination of Clinical Study Data

Study-related information and study results may be posted on the United States National Institutes of Health website www.clinicaltrials.gov, the European Union website www.clinicaltrialsregister.eu/, or other publicly accessible websites as appropriate and in accordance with local regulations. Any data disclosure (public or otherwise) will not contain personally identifiable information.

10.1.7 Data Quality Assurance

All patient data relating to the study will be recorded in an eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements. Study monitors will communicate with investigational sites on a regular basis regarding the study, and all protocol deviations will be appropriately documented by the investigator or designee and study monitors.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 5 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written approval of the Sponsor.

10.1.8 Data Quality and Integrity Monitoring

Data quality and integrity will be managed at multiple points throughout the data lifecycle. The specific control mechanisms implemented will be customized to the study but will include logical eCRF design and corresponding data entry guidelines to promote accurate data reporting at the time of initial entry, implement and maintain data access controls to ensure authorized and appropriate user access, data entry gates and edit checks to evaluate data format and reasonableness, cumulative data review to ensure data conformance; and holistic patient review to ensure data consistency.

10.1.9 Source Documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigational site.

The investigator or designee will prepare and maintain adequate and accurate source documents (medical records, ECGs, AE and concomitant medication reporting, and raw data collection forms) designed to record all observations and other pertinent data for each patient. All documentation shall adhere to good documentation practices (ie, Attributable, Legible, Contemporaneous, Original, and Accurate Principle Plus [ALCOA+].

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents, or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available. Local pathology reports for disease assessment of BM must be shared with the central laboratory.

10.1.10 Study and Site Start and Closure

The Sponsor or designee reserves the right to close the investigational site or terminate the study at any time for any reason at their sole discretion. An investigational site is considered closed when all required documents and study supplies have been collected and an investigational site closure visit has been performed. Portable Document Format versions of data entered in the eCRF will be distributed to the sites at time of study closure and not during an individual site close-out visit.

The investigator may initiate investigational site closure, provided there is reasonable cause and sufficient notice is given in advance of the intended termination, subject to the terms of the applicable Clinical Trial Agreement.

Reasons for the early closure of an investigational site by the Sponsor may include but are not limited to the following:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of patients by the investigator
- Discontinuation of further investigational product or combination development

If the study is prematurely terminated or suspended by the Sponsor, the Sponsor shall promptly inform the investigators, the IRBs/IECs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the patients and should ensure appropriate patient therapy and/or follow-up.

10.1.11 Publication Policy

The full terms regarding publication of the results of this study are outlined in the applicable Clinical Trial Agreement.

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.
- Since KO-MEN-008 is a global trial involving investigative sites worldwide, and it is practically impossible to predict when and where the clinical trial may end (as per the end of trial definition in Section 4.8). In order to appropriately report the summary of the results of KO-MEN-008, including the statistical analyses, the publication of the results will be within one year from the global end of the trial being reached.

10.2 Guidelines to Be Applied During Infectious Disease Outbreak

These guidelines only apply during any public health emergency related to an infectious disease outbreak declared by government authorities, in the countries where the study sites are located (eg, COVID-19).

The activities in this guideline include the following:

- Safety reporting by sites
- Adherence to protocol-specified activities
- Informed consent process

- Provision of study intervention to patients
- Site monitoring by clinical research associates
- Documentation requirements

10.2.1 Ensuring Continuity of Safety Reporting

Investigators may conduct telemedicine calls via phone/video to identify or to follow-up on AEs.

In the event that patients cannot complete a site visit, they may be directed to utilize local laboratories/primary care providers to collect laboratory tests and conduct patient assessments (eg, vitals, physical examinations), and use local imaging facilities where necessary.

If the patient cannot get to an alternative location, then the decision to continue dosing in absence of required safety laboratory assessments is made by the investigator in consultation with the medical monitor. These decisions should be made on a case-by-case basis.

The investigator should follow applicable guidelines for testing of patients and clinic personnel.

10.2.2 Maintaining Protocol Requirements, Including Schedule of Activities

Exposure to or instances of a confirmed infectious disease related to an infectious disease outbreak will not mandate early termination of a patient from the study. Continued participation in the study should be at the investigator's discretion.

However, if investigators have suspected/confirmed positive patients, then they should notify the Sponsor. The investigator and the medical monitor should make a case-by-case assessment of which procedures/samples are appropriate to continue.

10.2.3 Clinic Visits

- If patients cannot travel to the study site or the investigator cannot accommodate a visit, but can still receive care via a local provider, efforts should be made to collect data from the local provider in accordance with local privacy/data protection requirements. Data collected may include but are not limited to collection of weight and vital signs (heart rate, respiratory rate, blood pressure, and temperature). If possible, the investigator should prospectively request that data be collected according to good documentation practices (ie, ALCOA+). Alternatively, home nursing visits may be arranged to perform study assessments, as necessary. Any forms and records collected during these visits should be confidentially protected and securely kept. Any samples collected during these visits should be labeled with the patient identification number only.
- Where applicable, patient visits may be conducted virtually via telephone or video conference. Data collected during calls may include but are not limited to AE assessment, concomitant medication assessment, ECOG assessments, survival follow-up, and study intervention compliance assessment. Investigators should ensure the following:
  - Site staff or investigators are appropriately trained on how to conduct real-time video conferencing visits (ie, training on use of telemedicine for remote clinical study visits).

  - Necessary procedures and safeguards are in place to maintain a study patient's privacy.
  - Both the investigator and study patient confirm their respective identities with one another before starting a real-time video conference visit (eg, have the study patient confirm their date of birth or, if the visit is conducted via videoconference, present a form of government issued photographic identification). Consult with the Sponsor or designee to confirm the specifics of any process implemented.
  - Details about the date and time of the real-time video conference visit, the location of the study patient, the location of the investigator or staff conducting the visit should be appropriately documented.

- Radiographic imaging may be collected locally and reviewed by the investigator or applicable delegated staff member.

10.2.4 Clinical Laboratory Testing

- Clinical laboratory testing may be completed by a certified (eg, College of American Pathologists) local provider and reviewed by the investigator. Laboratory results should be reviewed prior to either administration or additional shipping of investigational medicinal product.
- Normal ranges and certifications (eg, CAP) for the laboratory need to be collected and maintained by the investigator site staff, and the source of these values (ie, coming from a local laboratory) needs to be clearly documented in the source documents and the CRFs/eCRFs.

10.2.5 Disruptions for Shipping to Central Laboratories

If the ability to ship samples to the central laboratory for analysis are impacted, then, if local facilities are available, it is permissible to store samples according to the Laboratory Manual guidelines for analysis later when disruptions are resolved. Central laboratories and/or the Laboratory Manual should be consulted to resolve any questions.

For delays in shipping of samples required for centralized analysis to determine patient eligibility and/or samples that require same-day shipment at controlled ambient temperature, the Sponsor should be consulted to ensure best shipping and/or processing of the samples, as the sample integrity may be at risk.

10.2.6 Informed Consent Process

When it is not possible to obtain informed consent in a face-to-face consent interview, it is permissible to obtain informed consent virtually. Such virtual consent interviews need to ensure that an adequate exchange of information and documentation occurs. In addition, there needs to be a method to ensure that the person who plans to enroll as a patient (or who is already enrolled as a patient in the case of a revised ICF) is actually the person who signs the ICF. This virtual process can involve, for example, telephone or other videoconference mechanisms, along with the patient providing photographic or facsimile evidence of completing the ICF.

Consult with the Sponsor or designee to confirm the specifics of any process implemented.

10.2.7 Ensuring Continuity of Drug Supply to Patients - Study Intervention Shipping

- If site visit restrictions are anticipated but are not yet in effect, additional study intervention (beyond 1 cycle) may be administered via home nursing or at an alternative site at the investigator's discretion.
- If site visit restrictions are implemented between patient visits, study intervention may be administered via home nursing or at an alternative site. Study intervention will be shipped directly from sites to patients under the investigator's supervision via overnight courier along with instructions for dosing and documentation of dosing. Delivery signature confirmation should be requested whenever possible. Study intervention should be shipped at ambient temperature using an insulated package/container. Appropriate safeguards should be used to ensure appropriate shipping and receipt, including documentation of receipt (signature of receiver) and condition of package (eg, ensuring no tamper proof seal had been broken).
- The study intervention may be shipped at ambient temperature in credo with no temperature monitoring device.
- Consult with the Sponsor, or designee, as needed to assign study intervention.

10.2.8 Managing Restrictions to Site Monitoring by Clinical Research Associates

Where there are physical access restrictions to clinical sites or country-specific travel limitations, implementation of remote or off-site monitoring visits may be conducted in lieu of on-site visits whenever possible.

Off-site monitoring visits should not place an extra burden on study sites, and patients must consent to any sharing of their personal information outside the study site.

10.2.9 Documentation of Infectious Disease Outbreak Related Guidelines or Other Measures

It is important to document the reason for implementing any of these contingency measures. Such documentation should include details on how restrictions related to the infectious disease outbreak led to the use of these contingency measures during study conduct, the duration of those changes, which study patients were impacted, and how those study patients were impacted. When any nonstudy site laboratory tests are needed, these should be clearly documented so that the Sponsor can align on usability of the data on a case-by-case basis. When adopting or implementing these guidelines, Investigators should make every effort to minimize any impacts on study integrity. If any additional changes are required that are not covered in these guidelines, investigators should act according to local guidelines and regulations, but above all to assure the safety of study patients, maintaining compliance with GCP, and minimizing risks to study integrity. Any changes made should be appropriately documented as protocol deviations.

In advance of any interim analyses/planned database locks, the Sponsor will ensure that the impact from study visit changes are assessed and will revise the SAP accordingly.

11 APPENDICES

Appendix 1 Clinical Laboratory Tests

- The tests detailed in Table 23 may be performed by a central or local laboratory. The tests detailed in Table 23 can be performed locally in order to assess patient eligibility and inform treatment decisions, except where indicated.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Any laboratory result(s) that is abnormal and considered clinically significant (eg, requires intervention) must be reported as an adverse event/serious adverse event when applicable.

Table 23 Protocol-Required Safety Laboratory Tests

Laboratory Tests	Parameters
• Chemistry	• Blood glucose, amylase, and lipase • Blood urea nitrogen/urea, creatinine, sodium, potassium, calcium, inorganic phosphorus, total protein, albumin, total bilirubin, ALP[a], ALT, AST, lactate dehydrogenase, uric acid, and Cystatin C. Bicarbonate (or total CO_2) is optional.
• Hematology	• CBC including manual differential
• Differentiation syndrome monitoring	• Cardiac markers • Coagulation profile o APTT, PT/INR o Fibrinogen, D-dimer, and peripheral blood smear for microangiopathic hemolytic anemia (performed locally as per investigator discretion based upon clinical picture) • Inflammatory markers o Ferritin levels, CRP, and ESR (performed locally, if available)
• Tumor lysis syndrome monitoring	• Complete blood cell count, serum electrolytes (calcium, sodium, potassium, and inorganic phosphorous), creatinine, uric acid, lactate dehydrogenase, and blood urea nitrogen • **NOTE:** At timepoints where chemistry and hematology draws are also performed, a repeat laboratory draw for TLS laboratories is not required.
• Dipstick urinalysis[b]	• pH, glucose, erythrocytes, leukocytes, protein, nitrite, color, and clarity/appearance
Other	Hemoglobin A1c[c] Creatine Phosphokinase[d] [Cohort A-3 only]
• Pregnancy testing	• Highly sensitive serum (screening or postscreening) or urine (postscreening only) hCG pregnancy test as needed for women of childbearing potential)[e, f]

Abbreviations: ALP=alkaline phosphatase; ALT=alanine aminotransferase; APTT=activated partial thromboplastin time; AST=aspartate aminotransferase; CBC=complete blood count; CRP=C-reactive protein; ESR=erythrocyte sedimentation rate; hCG=human chorionic gonadotropin; IDMC=Independent Data Monitoring Committee; IEC=Independent Ethics Committee; IRB=Institutional Review Board; PT/INR=prothrombin time/international normalized ratio; SMC=Safety Monitoring Committee; SoA=schedule of activities.

a. If ALP is elevated, consider fractionating.
b. If abnormalities are noted, these should be recorded, and a microscopic analysis should be conducted and recorded.
c. Hemoglobin A1c should only be done at screening and as clinically indicated.
d. For Cohort A-3 patients only. To be performed locally on Cycle 1 Day 1, Cycle 1 Day 15, and Day 1 of every subsequent cycle.
e. Local urine testing should be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.
f. If a positive urine pregnancy test is obtained, a confirmatory serum pregnancy test should be conducted.

Investigators must document their review of each laboratory safety report.

Appendix 2 Contraceptive Barrier Guidance

Ziftomenib

Embryo-fetal development studies were conducted with ziftomenib in time-mated CD-1 mice. As evidence of teratogenicity was noted in ziftomenib-treated mice, confirmatory studies in a second species (eg, rabbits) were not warranted.

Additional details can be found in the ziftomenib Investigator's Brochure. As the potential effects of ziftomenib on embryofetal development in humans are unknown, precautions to prevent pregnancy with appropriate double-barrier contraceptive methods in female patients and female partners of male patients should be taken.

In light of the observations in nonclinical testing, both female patients and male patients with female partners of childbearing potential must agree to use a highly effective method of contraception as well as use a barrier method (eg, a condom), as defined below and as applicable to local guidelines and regulations, as well as a double-barrier method from the first dose of study intervention, during treatment, and at least 180 days after last dose of study intervention for females and 120 days for males. Female patients of childbearing potential must have a negative serum pregnancy test within 72 hours prior to start of study intervention. Female patients must agree not to donate eggs throughout the study and for 180 days after the last dose of study treatment.

Fludarabine

Based on its mechanism of action, fludarabine (Cohorts A-1 and B-1) can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of fludarabine phosphate injection in pregnant women. In rats, repeated intravenous (IV) doses of fludarabine phosphate at 2.4 times and 7.2 times the recommended human IV dose (25 mg/m^2) administered during organogenesis caused an increase in resorptions, skeletal and visceral malformations (cleft palate, exencephaly, and fetal vertebrae deformities) and decreased fetal body weights. Maternal toxicity was not apparent at 2.4 times the human IV dose, and it was limited to slight body weight decreases at 7.2 times the human IV dose. In rabbits, repeated IV doses of fludarabine phosphate at 3.8 times the human IV dose administered during organogenesis increased embryo and fetal lethality as indicated by increased resorptions and a decrease in live fetuses. A significant increase in malformations including cleft palate, hydrocephaly, adactyly, brachydactyly fusions of the digits, diaphragmatic hernia, heart/great vessel defects, and vertebrae/rib anomalies were seen in all dose levels (2: 0.5 times the human IV dose). If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

Cytarabine

Cytarabine injection (Cohorts A-1, A-2, B-1, and B-2) can cause fetal harm when administered to a pregnant woman. Cytarabine causes abnormal cerebellar development in the neonatal hamster and is teratogenic to the rat fetus. There are no adequate and well-controlled studies in pregnant women. Advise pregnant women and women of reproductive potential of the potential risk to a fetus.

Gilteritinib (Cohort A-3)

The following items should be discussed with the patient:

- Advise female patients with reproductive potential to use effective contraceptive methods while receiving gilteritinib and to avoid pregnancy while on treatment and for 6 months after completion of treatment.
- Advise patients to notify their healthcare provider immediately in the event of a pregnancy or if pregnancy is suspected during gilteritinib treatment.
- Advise males with female partners of reproductive potential to use effective contraception during treatment with gilteritinib and for at least 4 months after the last dose.
- Consult the manufacturers prescribing information for more details.

Definition of Females of Nonchildbearing Potential:

A female is considered to be of nonchildbearing potential if she meets 1 of the following criteria:

- Postmenopausal with at least 12 months of spontaneous amenorrhea
- Has had a bilateral oophorectomy
- Has had a bilateral salpingectomy
- Has had a hysterectomy

Birth Control Methods Considered as Highly Effective:

According to the Clinical Trials Facilitation Group, "Recommendations related to contraception and pregnancy testing in clinical trials" methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. These include the following:

- Combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation[a] (oral, intravaginal, transdermal)
- Progesterone-only hormonal contraception associated with inhibition of ovulation[a] (oral, injectable, implantable[b])
- Intrauterine device[b]
- Intrauterine hormone-releasing system[b]
- Bilateral tubal occlusion[b]
- Vasectomized partner[b,c]
- Sexual abstinence[d]

a. Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraception method.
b. Contraception methods in the context of this guidance are considered to have low user dependency.
c. Vasectomized partner is highly effective birth control method provided that the partner is the sole sexual partner of the woman of childbearing potential study patient and that the vasectomized partner has received medical assessment of the surgical success.
d. In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient.

Appendix 3 Eastern Cooperative Oncology Group Performance Status

Source: Oken et al, 1982

Table 24 Eastern Cooperative Oncology Group Performance Status Definitions

Grade	Description
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Appendix 4 Tumor Lysis Syndrome Classification

Source: Howard et al, 2011

Table 25 TLS Classifications

Metabolic Abnormality	Criteria for Classification of Laboratory TLS[a]	Criteria for Classification of Clinical TLS[b]
Hyperuricemia	Uric acid >8 mg/dL (475.8 µmol/liter)	N/A
Hyperphosphatemia	Phosphorus >4.5 mg/dL (1.5 mmol/liter)	N/A
Hyperkalemia	Potassium >6 mmol/liter	Cardiac dysrhythmia or sudden death probably or definitely caused by hyperkalemia
Hypocalcemia	Corrected calcium <7.0 mg/dL (1.75 mmol/liter) or ionized calcium <1.12 mg/dL (0.3 mmol/liter)[c]	Cardiac dysrhythmia, sudden death, seizure, neuromuscular irritability (tetany, paresthesias, muscle twitching, carpopedal spasm, Trousseau's sign, Chvostek's sign, laryngospasm, or bronchospasm), hypotension, or heart failure probably or definitely caused by hypocalcemia
Acute kidney injury[d]	N/A	Increase in the serum creatinine level of 0.3 mg/dL (26.5 µmol/liter) or the presence of oliguria (average urine output of <0.5 mL/kg/hr over a 6-hour period)

Abbreviations: N/A=not applicable; TLS=tumor lysis syndrome.

a. Laboratory TLS requires 2 or more metabolic abnormalities must be present during the same 24-hour period within 3 days before the start of therapy or up to 7 days afterward.
b. Clinical TLS requires the presence of laboratory TLS plus 1 or more findings from the clinical TLS column.
c. Corrected calcium=measured calcium level in mg/dL +0.8× (4 – albumin in gm/dL).
d. Acute kidney injury, unless attributable to another cause, represents clinical TLS even if criteria for laboratory TLS are not satisfied.

Appendix 5 Suggested Recommendation for Initial Management of Electrolyte Abnormalities and Prevention of Tumor Lysis Syndrome

Table 26 Suggested Recommendations for Managing Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome

Abnormality	Management Recommendations
Hyperkalemia (including rapidly rising potassium)	
Potassium ≥0.5 mmol/L increase from prior value (even if potassium WNL)	• Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour STAT. If further ≥0.2 mmol/L increase in potassium, but still <ULN, manage per potassium ≥ULN. Otherwise, recheck in 1 hour. • Resume per protocol testing if change in potassium is <0.2 mmol/L, and potassium <ULN, and no other evidence of tumor lysis. • At discretion of investigator, may recheck prior to hospitalization. If stable or decreased, and still WNL, hospitalization is at the discretion of the investigator. Potassium, phosphorus, uric acid, calcium, and creatinine must be rechecked within 24 hours.
Potassium >upper limit of normal	• Perform STAT ECG and commence telemetry. • Nephrology (or other acute dialysis service) notification with consideration of initiating dialysis. • Administer Kayexalate 60 g (or Resonium A 60 g). • Administer furosemide 20 mg IV ×1. • Administer calcium gluconate 100 – 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour STAT. • If potassium <ULN 1 hour later, repeat potassium, phosphorus, uric acid, and calcium.
Potassium ≥6.0 mmol/L (6.0 mEq/L) and/or symptomatic (eg, muscle cramps, weakness, paresthesias, nausea, vomiting, diarrhea)	• Perform STAT ECG and commence telemetry. • Nephrology (or other acute dialysis service) assessment with consideration of initiating dialysis. • Administer Kayexalate 60 g (or Resonium A 60 g). • Administer furosemide 20 mg IV ×1. • Administer insulin 0.1 U/kg IV + D25 2 mL/kg IV. • Administer sodium bicarbonate 1 – 2 mEq/kg IV push. • If sodium bicarbonate is used, rasburicase should not be used as this may exacerbate calcium phosphate precipitation. • Administer calcium gluconate 100 – 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. Do not administer in same IV line as sodium bicarbonate. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine every hour STAT.
Hyperuricemia	
Uric acid ≥8.0 mg/dL (476 µmol/L)	• Consider rasburicase (prior to rasburicase administration, please refer to local label for tests to be performed, contraindications, and precautions. Dosing is per institutional guidelines). • If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour STAT.

Abnormality	Management Recommendations
Uric acid ≥10 mg/dL (595 µmol/L) OR Uric acid ≥8.0 mg/dL (476 µmol/L) with 25% increase and creatinine increase ≥0.3 mg/dL (≥0.027 mmol/L) from predose level	• Administer rasburicase (prior to rasburicase administration please refer to local label for tests to be performed, contraindications, and precautions. Dosing is per institutional guidelines). • If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Notify nephrology (or other acute dialysis service). • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour STAT. • If uric acid <8.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 2 and 4 hours later if no other evidence of tumor lysis.
Hypocalcemia	
Calcium ≤7.0 mg/dL (1.75 mmol/L) AND Patient symptomatic (eg, muscle cramps, hypotension, tetany, cardiac arrhythmias)	• Administer calcium gluconate 50 to 100 mg/kg IV slowly with ECG monitoring. • Telemetry. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour STAT. • If calcium normalized 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 2 and 4 hours later if no other evidence of tumor lysis. • Calculate corrected calcium and check ionized calcium if albumin is low.
Hyperphosphatemia	
Phosphorus ≥5.0 mg/dL (1.615 mmol/L) with ≥0.5 mg/dL (0.16 mmol/L) increase	• Administer a phosphate binder (eg, aluminum hydroxide, calcium carbonate, sevelamer hydroxide, or lanthanum carbonate). • Nephrology (or other acute dialysis service) notification (dialysis required for phosphorus ≥10 mg/dL). • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour STAT. • If phosphorus <5.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 2 and 4 hours later if no other evidence of tumor lysis.
Creatinine	
Increase ≥25% from baseline	• Start or increase rate of IV fluids. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 to 2 hours STAT.

Abbreviations: ECG=electrocardiogram; IV=intravenous; ULN=upper limit of normal; WNL=within normal limits.

Appendix 6 AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

Definition of AE

AE Definition

- An adverse event (AE) is defined as any untoward medical occurrence in a patient who is administered an investigational medicinal product (IMP).
- An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not related to the IMP.

For all AEs, the investigator and/or designee(s) is responsible for obtaining accurate and complete information to determine the following:

- Appropriate descriptive/verbatim term: AEs should be reported using concise medical terminology, preferably referring to the syndrome/diagnosis rather than symptoms, when possible.
- Event severity: AE severity should be primarily assessed using the most current version of National Cancer Institute Common Terminology for Adverse Events v5.0.
- Onset and resolution dates.
- Outcome.
- Causality: The relationship of each AE to study intervention should be defined as "not related" or "related" as follows:
    - Not related: There is little or no possibility that the study intervention caused the reported AE and other factor(s) including concurrent illnesses, progression and expression of the disease state, concurrent medications, or a reaction to concurrent medications, or appear to explain the AE.
    - Related: There exists at least a reasonable possibility that the study intervention caused or contributed to the AE. An inability to identify an alternate etiology for an AE should not, by itself, justify a "related" attribution.
- Whether it meets the criteria for classification as a serious adverse event (SAE).

Events NOT Meeting the AE Definition

Events NOT Meeting the AE Definition

- Progression of underlying disease/disease progression/progressive disease should not be reported as a stand-alone AE or SAE.
- Findings/symptoms that are clearly consistent with the expected progression of the underlying cancer should also not be reported as an AE or SAE, and hospitalizations due to the progression of cancer do not qualify as an SAE.
- If there is any uncertainty about a finding or event being due solely to progression of neoplasia, the finding or event should be reported as an AE or SAE as appropriate.

Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets 1 or more of the criteria listed:

a. Results in death

b. Requires initial or prolonged inpatient hospitalization

- Any initial admission (24 hours or longer) to a healthcare facility meets these criteria.
- Any event occurring while the patient is hospitalized, which would otherwise prolong hospitalization or increases in severity thus requiring transfer within the hospital to an acute/intensive care unit should also be reported under this criterion.

- This criterion would exclude hospitalization in the absence of a precipitating AE, such as admission for treatment of a pre-existing condition not associated with a new/worsening AE, or admission for elective surgery.
- This criterion would exclude admission to rehabilitation/hospice/nursing facilities and outpatient admission for same-day surgeries, as these are not considered "hospitalizations" for the purpose of this criterion.

c. Is life-threatening (immediate risk of dying)

d. Results in persistent or significant disability/incapacity

e. Results in congenital anomaly/birth defect

f. Other important medical event (IME)

– Medical and scientific judgment should be exercised in determining whether an event is an IME. An IME may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient and/or may require intervention to prevent one of the other outcomes, the IME should be reported as serious.

– Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

"Progression of underlying disease/disease progression" should not be reported as a stand-alone AE or SAE. Findings/symptoms that are clearly consistent with the expected progression of the underlying cancer should also not be reported as an AE or SAE.

Recording, Reporting, and Follow-up of AE and/or SAE

AE and SAE Recording and Reporting

The investigator is to record all AEs (directly observed and/or spontaneously reported) by the patient in the electronic case report form (eCRF). In addition, each study patient should be questioned about AEs throughout the study.

All AEs should be reported on the AE page(s) of the eCRF.

AEs that are further assessed as SAEs should also be reported on the Safety Event Form of the eCRF.

AEs should be recorded and monitored starting at the time of first dose of study intervention.

SAEs should be recorded and monitored starting at the time of signing the informed consent.

AE/SAE recording and monitoring will continue:

- through the treatment period, and up to and including 28 days after last dose of study treatment, or
- until the patient is lost to follow-up, whichever comes first.

All SAEs should be followed until considered resolved or stable (unchanging) or confirmed to be 'lost to follow-up' by the treating investigator.

Any SAE that is assessed as related to study intervention that occurs any time after any of the above must be promptly reported.

All SAEs must be reported via the study eCRF system, within 24 hours of the site's awareness of the event, irrespective of the extent of available information. When reporting an SAE, the AE, and Safety Event pages of the eCRF must be completed. If timely reporting of SAE is not possible via the eCRF, an SAE Form (paper or electronic) should be completed and submitted. At a minimum, the following should be provided:

- Complete site information
- Complete patient information
- SAE verbatim term
- Serious criteria (with onset date, if available)
- Causal assessment (Not Related or Related; leaving a blank will result in a default of related)
- Study intervention information

All completed forms for SAEs and pregnancy should be submitted to: AEReporting@kuraoncology.com.

This timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports. The investigator is obligated to pursue additional information required for thorough evaluation of each SAE as may be requested by the Sponsor (or designee).

SAE reporting to regulatory authorities and all participating investigators will be conducted by the Sponsor (or designee) in accordance with 21 Code of Federal Regulations 312.32 and international regulations, as appropriate.

For patients who undergo HSCT, AEs and SAEs should continue to be collected for 28 days following the last dose of ziftomenib at the start of conditioning, excluding any common transplant-related events. Any ziftomenib-related SAEs should continue to be reported regardless of timing.

Rapid Notification of Adverse Events of Importance

In addition to SAEs, the following AEs should be reported to the Sponsor and relevant regulatory authorities and IRBs using the same rapid notification procedures that are used for SAEs, even if the nature of the AE is not deemed serious:

- Differentiation syndrome (refer to Section 6.5.4.1)
- Tumor lysis syndrome (TLS) in association with DS after the start of ziftomenib
- Drug-induced liver injury (DILI) (refer to Section 6.5.4.2).
    - Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event.
    - Potential DILI is defined as follows:
        - Transaminases (alanine aminotransferase or aspartate aminotransferase) elevation >3.0× upper limit of normal (ULN)

          AND
        - Total bilirubin >2.0× ULN, without initial findings of cholestasis (ie, elevated serum alkaline phosphatase)

          AND
        - No other immediately apparent possible causes of transaminase elevation and hyperbilirubinemia, including but not limited to viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.
    - For patients undergoing HSCT, the following AESIs should be collected until ziftomenib is restarted following HSCT: VOD/SOS, aGvHD Grade II-IV (MAGIC criteria Appendix 7), cGvHD (NIH Consensus Criteria, Jagasia et al, 2015).

Pregnancy and in Utero Exposure

Pregnancy and in Utero Exposure

Details of all pregnancies in female patients and female partners of male patients should be collected after the start of study intervention and until the end of the follow-up period (28 days post-last dose).

If a female study patient becomes pregnant, the study treatment should be stopped. If a female partner of a male patient becomes pregnant, the outcome should be collected.

To ensure patient safety, each pregnancy occurring after signing the informed consent must be reported per the Pregnancy Form Completion Guidelines within 24 hours of learning of its occurrence. Site staff should use the Pregnancy Notification Form followed by the Pregnancy Outcome Form as outlined below.

The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication (mother or baby) or elective or spontaneous termination of a pregnancy should be reported as an AE or SAE as appropriate. If any of these events meet any of the SAE criteria, an SAE Form must be completed and signed and sent to the Sponsor.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and should be reported as such.

The patient/pregnant female partner should be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the patient/pregnant female partner and the neonate. The site will complete the Pregnancy Outcome Form and submit per the Pregnancy Form Completion Guidelines. Newborns should be followed for the first 12 months.

Any poststudy pregnancy-related SAE(s) considered reasonably related to the study intervention by the investigator should be reported. While the investigator is not obligated to actively seek this information in former study patients/pregnant female partner, he or she may learn of an event through spontaneous reporting.

Appendix 7 Diagnosis, Staging, and Grading of Graft-Versus-Host Disease

Acute and chronic graft-versus-host disease (GvHD) is defined according to the proposal of the National Institutes of Health Consensus Criteria (Jagasia et al, 2015), which recognizes 2 categories of GvHD:

1. **acute GvHD** (absence of features consistent with chronic GvHD), comprising:
   a. classic acute GvHD (before day 100), and, persistent, recurrent, or late acute GvHD (after day 100, often upon withdrawal of immunosuppression);
2. **chronic GvHD**, comprising:
   a. classic chronic GvHD (no signs of acute GvHD), and, an overlap syndrome, in which features of both acute and chronic GvHD are present.

Staging and grading of acute GvHD

For staging and grading (Harris et al, 2016).

Stage	Skin (active erythema only)	Liver (bilirubin)	Upper GI	Lower GI (stool output/day)
0	No active (erythematous) GvHD rash	<2mg/dl	No or intermittent nausea, vomiting or anorexia	Adult: <500 ml/day or <3 episodes/day
1	Maculopapular rash <25% BSA	2-3 mg/dl	Persistent nausea, vomiting or anorexia	Adult: 500-999 ml/day or 3-4 episodes/day
2	Maculopapular rash 25-50% BSA	3.1-6 mg/dl	-	Adult: 1000-1500 ml/day or 5-7 episodes/day
3	Maculopapular rash >50% BSA	6.1-15 mg/dl	-	Adult: >1500 ml/day or >7 episodes/day
4	Generalized erythrodema (>50% BSA) plus bullous formation and desquamation >5% BSA	> 15 mg/dl	-	Severe abdominal pain with our without ileus, or grossly bloody stool (regardless of stool volume)
Grade	Overall clinical grade (based upon most severe target organ involvement):			
0	No stage 1-4 of any organ			
I	Stage 1-2 skin without liver, upper GI, or lower GI involvement			
II	Stage 3 rash and/or stage 1 upper GI and/or stage 1 lower GI			
III	Stage 2-3 liver and/or stage 2-3 lower GI, with stage 0-3 skin and/or stage 0-1 upper GI			
IV	Stage 4 skin, liver, or lower GI involvement, with stage 0-1 upper GI			

Abbreviations: BSA = body surface area; GI=gastrointestinal; GvHD=graft-versus-host disease;.

Staging of Chronic Graft-versus-Host Disease

Signs and symptoms of chronic GvHD according to the NIH Consensus Criteria (Jagasia et al, 2015):

Organ or Site	Diagnostic (Sufficient to Establish Diagnosis of Chronic GvHD)	Distinctive1 (Seen in Chronic GvHD, but Insufficient Alone to Establish a Diagnosis of Chronic GvHD)	Other Features2	Common3 (Seen with Both Acute and Chronic GvHD)
Skin	Poikiloderma Lichen planus-like features Sclerotic features Morphea-like features Lichen sclerosus-like features	Depigmentation Papulosquamous lesions	Sweat impairment Ichthyosis Keratosis pilaris Hypopigmentation Hyperpigmentation	Erythema Maculopapular rash Pruritus
Nails		Dystrophy Longitudinal ridging, splitting, or brittle features Onycholysis Pterygium unguis Nail loss (usually symmetric; affects most nails)		
Scalp and body hair		New onset of scarring or nonscarring scalp alopecia (after recovery from chemoradiotherapy) Loss of body hair Scaling	Thinning scalp hair, typically patchy, coarse, or dull (not explained by endocrine or other causes) Premature gray hair	
Mouth	Lichen planus-like changes	Xerostomia Mucoceles Mucosal atrophy Pseudomembranes Ulcers		Gingivitis Mucositis Erythema Pain
Eyes		New onset dry, gritty, or painful eyes Cicatricial conjunctivitis Keratoconjunctivitissicca Confluent areas of punctate keratopathy	Photophobia Periorbital hyperpigmentation Blepharitis (erythema of the eyelids with edema)	

Organ or Site	Diagnostic (Sufficient to Establish Diagnosis of Chronic GvHD)	Distinctive1 (Seen in Chronic GvHD, but Insufficient Alone to Establish a Diagnosis of Chronic GvHD)	Other Features2	Common3 (Seen with Both Acute and Chronic GvHD)
Genitalia	Lichen planus-like features Lichen sclerosus-like features Females: vaginal scarring or clitoral labial agglutination Males: phimosis or urethral/meatus scarring or stenosis	Erosions Fissures Ulcers		
GI tract	Esophageal web Strictures or stenosis in the upper- to mid-third of the esophagus		Exocrine pancreatic insufficiency	Anorexia Nausea Vomiting Diarrhea Weight loss Failure to thrive (infants and children)
Liver				Total bilirubin, ALP >2×ULN ALT or AST >2×ULN
Lung	Bronchiolitis obliterans diagnosed with lung biopsy Bronchiolitis obliterans[4]	Air trapping and bronchiectasis on chest CT	Cryptogenic organizing pneumonia Restrictive lung disease[5]	
Muscles, fascia, joints	Fasciitis Joint stiffness or contractures secondary to fasciitis or sclerosis	Myositis or polymyositis[6]	Edema Muscle cramps Arthralgia or arthritis	
Hematopoietic and immune			Thrombocytopenia Eosinophilia Lymphopenia Hypo- or hyper-gammaglobulinemia Autoantibodies (AIHA and ITP) Raynaud's phenomenon	

Organ or Site	Diagnostic (Sufficient to Establish Diagnosis of Chronic GvHD)	Distinctive1 (Seen in Chronic GvHD, but Insufficient Alone to Establish a Diagnosis of Chronic GvHD)	Other Features2	Common3 (Seen with Both Acute and Chronic GvHD)
Other			Pericardial or pleural effusions Ascites Peripheral neuropathy Nephrotic syndrome Myasthenia gravis Cardiac conduction abnormality or cardiomyopathy	

Abbreviations: AIHA = autoimmune hemolytic anemia; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GI = gastrointestinal; GvHD = graft-versus-host disease; ITP = immune thrombocytopenic purpura; PFT = pulmonary function testing.

1. In all cases, infection, drug effect, malignancy, or other causes must be excluded.
2. Can be acknowledged as part of the chronic GvHD manifestations if diagnosis is confirmed.
3. Common refers to shared features by both acute and chronic GvHD.
4. Bronchiolitis obliterans can be diagnostic for lung chronic GvHD only if distinctive sign or symptom present in another organ.
5. Pulmonary entities under investigation or unclassified.
6. Diagnosis of chronic GvHD requires biopsy.

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
PERFORMANCE SCORE: ☐ **KPS ECOG LPS**	Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	Symptomatic, ambulatory, capabl of self-care, >50% of waking hours ou of bed (ECOG 2, KPS or LPS 60-70%)	Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
SKIN† ☐ **SCORE % BSA**				
GVHD features to be scored by BSA:	No BSA involved	1-18% BSA	19-50% BSA	>50% BSA
Check all that apply: Maculopapular rash/erythema; Lichen planus-like features; Sclerotic features; Papulosquamous lesions or ichthyosis; Keratosis pilaris-like GVHD				
SKIN FEATURES SCORE:	No sclerotic features		**S**uperficial sclerotic features "not hidebound" (able to pinch)	**Check all that apply:** Deep sclerotic features; "Hidebound" (unable to pinch); Impaired mobility; Ulceration
Other skin GVHD features (NOT scored by BSA) **Check all that apply:** Hyperpigmentation; Hypopigmentation; Poikiloderma; Severe or generalized pruritus; Hair involvement; Nail involvement; *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				
MOUTH *Lichen planus-like features present:* **Yes** **No**	No symptoms	Mild symptoms **with** disease signs but not limiting oral intake significantly	Moderate symptoms with disease signs **with** partial limitation of oral intake	Severe symptoms with disease signs on examination **with** major limitation of oral intake
*Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
EYES *Keratoconjunctivitis sicca (KCS) confirmed by ophthalmologist:* **Yes** **No** **Not examined**	No symptoms	Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day)	Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs), **WITHOUT** new vision impairment due to KCS	Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision due to KCS
*Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				
GI Tract ***Check all that apply:*** Esophageal web/ proximal stricture or ring Dysphagia Anorexia Nausea Vomiting Diarrhea Weight loss ≥5%* Failure to thrive	No symptoms	Symptoms without significant weight loss* (<5%)	Symptoms associated with mild to moderate weight loss* (5-15%) **OR** moderate diarrhea without significant interference with daily living	Symptoms associated with significant weight loss* >15%, requires nutritional supplement for most calorie needs **OR** esophageal dilation **OR** severe diarrhea with significant interference with daily living
*Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				
LIVER	Normal total bilirubin and ALT or AP < 3 x ULN	Normal total bilirubin with ALT ≥3 to 5 x ULN or AP ≥ 3 x ULN	Elevated total bilirubin but ≤3 mg/dL or ALT > 5 ULN	Elevated total bilirubin > 3 mg/dL
Abnormality present but explained entirely by non-GVHD documented cause (specify):				
LUNGS**				
Symptom score:	No symptoms	Mild symptoms (shortness of breath after climbing one flight of steps)	Moderate symptoms (shortness of breath after walking on flat ground)	Severe symptoms (shortness of breath at rest; requiring 0_2)
Lung score: **%** FEV1 ☐	FEV1≥80%	FEV1 60-79%	FEV1 40-59%	FEV1 ≤39%
Pulmonary function tests Not performed				
*Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				

¶

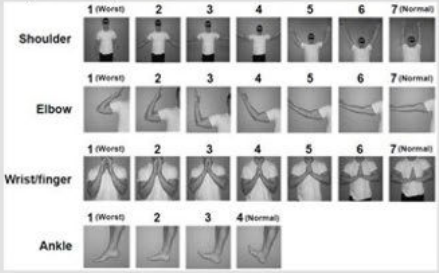
	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA P-ROM score *(see below)* Shoulder (1-7):___ Elbow (1-7): ____ Wrist/finger (1-7):___ Ankle (1-4):___	No symptoms	Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	Tightness of arms or legs **OR** joint contractures, erythema thought due to fasciitis, moderate decrease ROM **AND** mild to moderate limitation of ADL	Contractures **WITH** significant decrease of ROM ***AND*** significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
*Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				
GENITAL TRACT (*See Supplemental figure*‡) Not examined *Currently sexually active* Yes No	No signs	Mild signs‡ and females with or without discomfort on exam	Moderate signs‡ and may have symptoms with discomfort on exam	Severe signs‡ with or without symptoms
*Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				

Other indicators, clinical features or complications related to chronic GVHD (check all that apply and assign a score to severity (0-3) based on functional impact where applicable none – 0,mild -1, moderate -2, severe – 3)

Ascites (serositis)___	Myasthenia Gravis___	
Pericardial Effusion___	Peripheral Neuropathy___	Eosinophilia > 500/µl___
Pleural Effusion(s)___	Polymyositis___	Platelets <100,000/µl ___
Nephrotic syndrome___	Weight loss>5%* without GI symptoms ___	Others (specify):_____

Overall GVHD Severity *(Opinion of the evaluator)* ❑ **No GVHD** ❑ **Mild** ❑ **Moderate** ❑ **Severe**

Photographic Range of Motion (P-ROM)



† Skin scoring should use both percentage of BSA involved by disease signs and the cutaneous features scales. When a discrepancy exists between the percentage of total body surface (BSA) score and the skin feature score, OR if superficial sclerotic features are present (Score 2), but there is impaired mobility or ulceration (Score 3), the higher level should be used for the final skin scoring.

* Weight loss within 3 months.

**Lung scoring should be performed using both the symptoms and FEV1 scores whenever possible. FEV1 should be used in the final lung scoring where there is discrepancy between symptoms and FEV1 scores.

Abbreviations: ECOG (Eastern Cooperative Oncology Group), KPS (Karnofsky Performance Status), LPS (Lansky Performance Status); BSA (body surface area); ADL (activities of daily living); LFTs (liver function tests); AP (alkaline phosphatase); ALT (alanine aminotransferase); ULN (normal upper limit).

‡ To be completed by specialist or trained medical providers (see Supplemental Figure).

Diagnosis and Classification for chronic GVHD

Signs and symptoms of chronic GVHD according to the NIH Consensus Criteria (Jagasia et al, 2015):

Diagnosis of cGvHD according to NIH	
1) Presence of 1 diagnostic finding	
2) Presence of 1 distinctive finding confirmed by histological, radiological, or any other investigation (eg, Schirmer test), excluding any other potential cause	
Classification of cGvHD according to NIH	
1) Mild:	≤2 organs locations involved with no more than score 1 *plus* lung score 0
2) Moderate:	3 or more organs involved with no more than score 1 OR At least 1 organ (not lung) with a score of 2 OR Lung score 1
3) Severe:	At least 1 organ with a score of 3 OR Lung score of 2 or 3
Organ Scoring according to NIH	
0	No symptoms or manifestations
1	No significant impairment of function or activities of daily living
2	Significant impairment of activities of daily living but no major disability
3	Significant impairment of activities of daily living with major disability

Abbreviations: ADL = activities of daily living; ALT = alanine aminotransferase; AP = alkaline phosphatase; AST = aspartate aminotransferase; BSA = body surface area; cGVHD = chronic graft-versus-host disease; DLCO = diffusing capacity of the lungs for carbon monoxide; ECOG = Eastern Cooperative Oncology Group; FEV1 = forced expiratory volume in 1 second; GVHD = graft-versus-host disease; KPS = Karnofsky Performance Status; LFS = lung function score; LFT = liver function test; LPS = Lansky Performance Status; NIH = National Institutes of Health; PFT = pulmonary function testing; ROM = range of motion; ULN = upper limit of normal.

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