A Multicenter, Open-Label, Single-Arm, Phase 2 Study of Zandelisib (ME-401) in Subjects with Follicular Lymphoma or Marginal Zone Lymphoma After Failure of Two or More Prior Systemic Therapies – The TIDAL Study

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SPONSOR'S PROTOCOL SIGNATURE PAGE

By signing below, the Sponsor declares that this study will be conducted in accordance with current United States (US) Food and Drug Administration Code of Federal Regulations, Good Clinical Practice (GCP) standards, the Declaration of Helsinki (Brazil 2013), and local ethical and legal requirements.

DocuSigned by:
Richard Ghalie
31-Oct-2022 | 10:50 PDT
Signer Name: Richard Ghalie
Signing Reason: I approve this document
Signing Time: 31-Oct-2022 | 10:50 PDT
F001484941F64DCEA348CE4719B5B7DA

Richard Ghalie, MD
Chief Medical Officer

Date

INVESTIGATOR'S SIGNATURE PAGE

By signing below, the Investigator agrees to adhere to the protocol as written and agrees that any changes to the protocol must be approved by MEI Pharma, Inc. before seeking approval from the Institutional Review Board (IRB)/Ethics Committee (EC).

The study will be conducted in accordance with the current International Council for Harmonisation (ICH) Guidelines, the Guidelines for Good Clinical Practice (GCP), and local ethical and regulatory requirements.

The information contained in this protocol is proprietary and provided to me in confidence, and may not be disclosed to any other party, in any form, without prior authorization from MEI Pharma, Inc., except to the extent necessary for the conduct of the study at this study site.

Principal Investigator:

Signature Date

Printed name

Institution

PROTOCOL SYNOPSIS

TITLE

A Multicenter, Open-Label, Single-Arm, Phase 2 Study of Zandelisib (ME-401) in Subjects with Follicular Lymphoma or Marginal Zone Lymphoma After Failure of Two or More Prior Systemic Therapies – The TIDAL Study

PROTOCOL NUMBER

ME-401-003

STUDY DURATION

Individual subject participation in the study will include 28 days for screening, approximately 18 months of dosing with study drug, and follow-up for survival after discontinuation of study drug. Actual subject participation in the study may be shorter or longer depending on disease response, tolerability to therapy, and duration of long-term follow-up.

For the follicular lymphoma (FL) group, the study will continue until all enrolled subjects in the Primary Efficacy Population (PEP) (except those who discontinue early) have been followed for approximately 14 months from the first dose of study drug. For the marginal zone lymphoma (MZL) group, the study will continue until all enrolled subjects (except those who discontinue early) have been followed for approximately 14 months from the first dose of study drug.

SUBJECT POPULATION

Subjects with relapsed/refractory FL or MZL after failure of at least two prior systemic therapies.

INVESTIGATIONAL PRODUCTS

Zandelisib, (code ME-401); a phosphatidylinositol-4,5-biphosphate 3-kinase delta (PI3Kδ) inhibitor

PRIMARY OBJECTIVE

- To evaluate the objective response rate (ORR) of ME-401 in relapsed or refractory FL or MZL, based on the Modified Lugano Response Criteria (Appendix 5), and determined by an Independent Response Review Committee (IRRC)

SECONDARY OBJECTIVES

- To evaluate the efficacy of ME-401 as assessed by an IRRC:
  - Duration of response (DOR)
  - Complete response (CR) rate
  - Progression-free survival (PFS)
  - Time to treatment failure (TTF)

- To evaluate the efficacy of ME-401 as assessed by the Investigator:
  - Objective response rate (ORR)
  - Duration of response (DOR)
  - Complete response (CR) rate
  - Progression-free survival (PFS)
  - Time to treatment failure (TTF)
  - Recapture of response
  - Duration of recaptured response (DORR)
- To evaluate the overall survival (OS)
- To evaluate the safety profile of ME-401
  - Overall incidence of treatment-emergent adverse events (TEAEs)
  - Incidence of adverse events of special interest (AESIs)
  - Time to occurrence of AESIs
- To evaluate the pharmacokinetics (PK) of ME-401

SUBJECT ELIGIBILITY

Inclusion Criteria

1. Signed informed consent.
2. Age ≥18 years (or age of majority).
3. Histologically confirmed diagnosis as defined in the World Health Organization (WHO) classification (Swerdlow 2016) of:

   a. FL limited to Grade 1, 2, or 3a; or
   b. MZL, including nodal, extranodal, and splenic MZL

   (histopathological report confirming diagnosis must be available during screening procedures).
4. Subjects with relapsed or refractory FL or MZL who received ≥2 prior therapy regimens. A previous regimen is defined as one of the following: at least two months of single-agent therapy or at least two consecutive cycles of polychemotherapy, autologous transplant, or radioimmunotherapy. Prior therapy must include an anti-CD20 monoclonal antibody (mAb) and an alkylating agent(s). Relapsed or refractory disease is defined as:

   a. Relapsed disease: disease progression after a response (CR or PR) lasting ≥6 months
   b. Refractory disease: no response to therapy (no CR or PR) or response lasting <6 months

5. At least one bi-dimensionally measurable nodal lesion >1.5 cm or extranodal lesions >1 cm in its longest diameter by computed tomography (CT) scan as defined by the Modified Lugano Classification (Appendix 5).
    a. Previously irradiated lesions can be selected as target lesions only in cases of unequivocal evidence of progression
    b. For subjects with splenic MZL only: diffuse spleen involvement with splenomegaly, which is defined as the splenic vertical length greater than 13 cm.
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1 (Oken 1982; Appendix 6).
7. Adequate hematologic parameters at screening unless abnormal values are due to lymphoma per Investigator assessment:
    a. Absolute neutrophil count (ANC) ≥1.0 × 109/L (≥1,000/mm3)
    b. Platelet count ≥75.0 × 109/L (≥75,000/mm3)
8. Adequate renal and hepatic function per local laboratory reference range at screening as follows:
    a. Aspartate aminotransferase (AST)/serum glutamic-oxaloacetic transaminase (SGOT), alanine aminotransferase (ALT)/serum glutamic-pyruvate transaminase (SGPT) ≤3.0 × upper limit of normal (ULN)
    b. Total bilirubin ≤2.0 × ULN or ≤3 × ULN for subjects with Gilbert's syndrome
    c. Serum creatinine ≤1.5 × ULN or estimated glomerular filtration rate (eGFR) >50 mL/min using the Cockcroft-Gault equation (Appendix 2)
9. QT-interval corrected according to Fridericia's formula (QTcF) ≤450 milliseconds (msec); subjects with QTc >450 msec but <480 msec may be enrolled provided the QTc prolongation is due to a right bundle branch block (RBBB), left bundle branch block (LBBB), or pacemaker and is confirmed stable by a cardiologist.
10. Left ventricular ejection fraction (LVEF) ≥45% as measured by echocardiogram or multigated acquisition scan (MUGA). If LVEF <45% by ECHO, a repeat measurement can be conducted within the screening period.
11. Subjects must have completed any prior systemic anti-cancer treatment within ≥4 weeks of Cycle 1 Day 1 (or ≥5 times the half-life [t½], whichever is longer); ≥8 weeks for antibody agents; ≥2 weeks for radiation therapy; and ≥3 months for high dose therapy with stem cell transplantation or CAR T-cell therapy or radioimmunotherapy.
12. All adverse events (AEs) and laboratory toxicities related to prior therapy must resolve to Grade ≤1 prior to the start of the study therapy (unless otherwise specified in eligibility criteria).
13. For females of childbearing potential, a negative serum human chorionic gonadotropin (hCG) pregnancy test within 28 days of study Day 1 and negative hCG result on study Day 1.

14. Subjects must agree to use appropriate contraception methods during the clinical study (Appendix 4).
15. Subject is willing and able to comply with all scheduled visits, treatment plans, laboratory tests, and other study procedures.

Exclusion Criteria

1. Histologically confirmed FL Grade 3b, or transformed disease (assessed by the Investigator):
    a. For patients with clinical (e.g., marked B-symptoms), laboratory (e.g., high lactate dehydrogenase [LDH]) or radiographic (e.g., high standardized uptake value by positron emission tomography [PET]) signs of rapid disease progression, a fresh tumor biopsy prior to enrollment is required to rule out transformed disease.
2. Known lymphomatous involvement of the central nervous system.
3. Major surgical procedure within 4 weeks prior to study Day 1 (minor surgical procedures, [e.g., lymph node biopsy] performed within 1 day or with an overnight stay are allowed).
4. Prior therapy with PI3K inhibitors.
5. Any uncontrolled clinically significant illness including, but not limited to, active infections requiring systemic antimicrobial therapy, hypertension, angina, arrhythmias, pulmonary disease, or autoimmune dysfunction.
6. Subjects who have tested positive for hepatitis B surface antigen and/or hepatitis B core antibody plus have a positive hepatitis B polymerase chain reaction (PCR) assay; subjects who have previously tested positive with a negative PCR assay are permitted with appropriate anti-viral prophylaxis.
7. Positive hepatitis C virus antibody (HCV Ab); subjects with positive HCV Ab are eligible if they are negative for HCV by PCR.
8. Known history of, or active human immunodeficiency virus (HIV) infection.
9. Ongoing or history of drug-induced pneumonitis.
10. Previous or concurrent cancer that is distinct in primary site or histology from indolent B cell non-Hodgkin's lymphoma (iNHL) within 3 years before start of study treatment **except** for curatively treated cervical cancer in situ, non-melanoma skin cancer, superficial bladder tumors (Ta [non invasive tumor], Tis [carcinoma in situ], and T1 [tumor invades lamina propria]), and asymptomatic localized prostate cancer with no requirement for systemic therapy (or requiring only hormonal therapy) and with normal prostate-specific antigen values within ≥12 months prior to enrollment.
11. History of clinically significant cardiovascular abnormalities such as congestive heart failure (New York Heart Association classification ≥II [NYHA 1994]), myocardial infarction within 6 months of study entry.

12. History of clinically significant gastrointestinal (GI) conditions, particularly:
    a. Known GI condition that would interfere with swallowing or the oral absorption or tolerance of study drug
    b. Pre-existing malabsorption syndrome or other clinical situation that would affect oral absorption
13. Females who are pregnant; females who plan to breastfeed during study treatment through 90 days after ending treatment.
14. Psychiatric illness/social situations that would interfere with study compliance.
15. Hypersensitivity or other clinically significant reaction to the study drug or its inactive ingredients.
16. Any other condition for which, in the opinion of the Investigator, participation would not be in the best interest of the subject.

STUDY DESIGN

This is a global, multicenter, open-label, single-arm, Phase 2 study of the PI3Kδ inhibitor ME-401 in subjects with relapsed/refractory FL or MZL. ME-401 will be administered orally at a dose of 60 mg given once a day. A cycle of treatment is 28 days in duration. Treatment with ME-401 is administered based on an intermittent schedule (IS).

The IS includes:

- continuous daily therapy for the initial 2 cycles of treatment
- the intermittent treatment begins at Cycle 3, with ME-401 administered daily for the first 7 days of every 28-day cycle (7 days on treatment and 21 days off treatment)

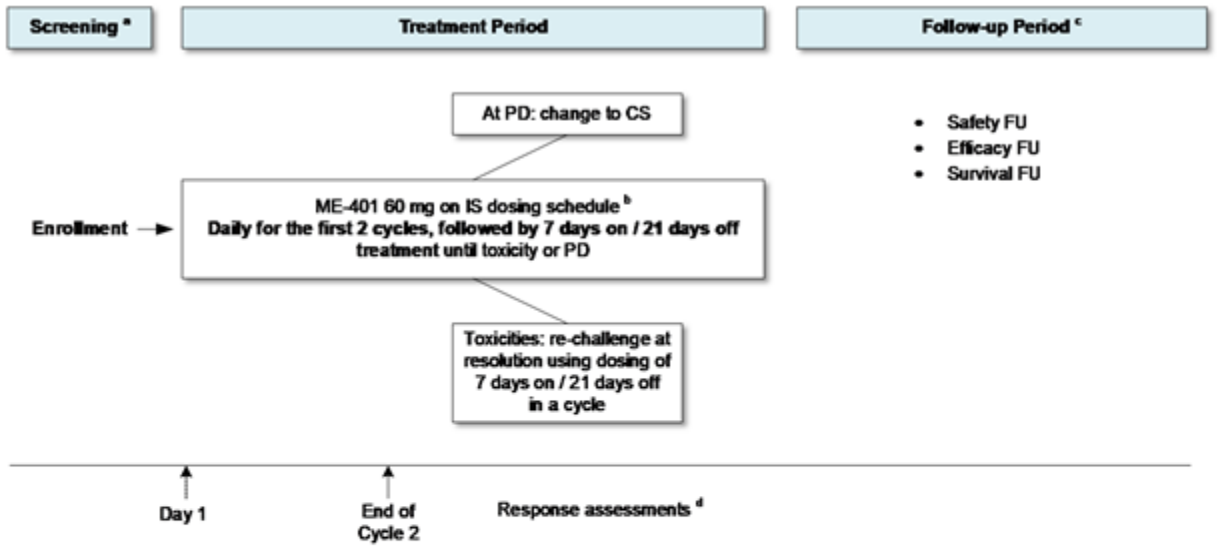
The first day of treatment is designated as Day 1. ME-401 will be administered until progressive disease (PD), development of unacceptable toxicity (despite ME-401 modified dosing schedule), or subject withdrawal.

Review of the ongoing Phase 1b study evaluating different dosing schedules for ME-401 in subjects with relapsed/refractory FL showed improved risk-benefit profile of the IS over a continuous schedule (CS), i.e., ME-401 given daily continuously). With Amendment 2, the initial CS treatment arm was terminated, and subjects were enrolled to receive therapy on the IS only. If subjects already completed 2 initial cycles of therapy, they were switched to IS dosing once they completed therapy in the ongoing cycle of treatment, and if they had not yet completed the first 2 cycles of therapy they were switched to IS dosing after completion of the first two cycles of therapy. Subjects who progress on IS dosing may be switched to CS dosing.

Upon confirmation of meeting eligibility criteria, subjects should be treated with ME-401 within a reasonable time frame (within 5 days). Once subjects are treated with ME-401, they are defined as being enrolled in the study.

The study schema is presented in Figure 1.

Figure 1: Study Schema



a. Screening from Day -28 to Day -1.
b. IS dosing schedule: 60 mg daily for the first 2 cycles (56 days) followed by 60 mg daily for 7 days of every 28-day cycle (7 days on / 21 days off treatment).
c. Follow-up Period will include: 1) EOT/30-Day Safety Follow-up visit will occur 30 (±3) days from the last day of study drug treatment. 2) Efficacy Follow-up - for subjects who discontinue study treatment due to reasons other than disease progression or death, response follow up will occur until PD or the start of a new anti-cancer therapy. 3) Survival Follow-up visits will occur every 3 months until death, and will continue for up to 3 years after the last subject is enrolled in the study.
d. Response assessments will be performed every 2 months (±7 days) for the first 6 months, every 3 months (±7 days) during the following 12 months, and every 6 months (±14 days) thereafter (starting with month 18).

Abbreviations: CS = continuous schedule; EOT = End of Treatment; FU = follow up; IS = intermittent schedule; PD = progressive disease.

For subjects who experience hematologic or non-hematologic adverse reactions, please refer to ME-401 toxicity management (Table 4) and modified dosing schedules in Section 5.3.1.

ME-401 is provided as 60 mg capsules. ME-401 is to be taken orally once a day at approximately the same time each day in accordance with the IS regimen (or CS dosing regimen if switched from IS after PD).

Subjects must receive prophylaxis treatment for *Pneumocystis jirovecii* pneumonia (PJP) as prescribed within this protocol (see Section 5.4.3).

See the Schedule of Assessments (Appendix 1) for a detailed list of study procedures.

The Modified Lugano 2014 criteria will be used for response assessment (Appendix 5). The Investigator's assessment of disease response will be used for subject management. For the primary analysis, disease/response assessment will be performed by an IRRC blinded to Investigator assessment and treatment assignment. Methods for disease/response assessment by the IRRC are described in the IRRC Charter. Disease/response assessment will occur every 2 months for the first 6 months, every 3 months during the next 12 months, and every 6 months thereafter.

Safety will be assessed by laboratory tests including hematology (complete blood count [CBC]), serum chemistry, and cytomegalovirus (CMV) serology and/or quantitative PCR; and clinical assessments including physical examination, vital signs, ECOG performance status,

and 12 lead electrocardiogram (ECG). Adverse events will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0.

Before treatment discontinuation due to any reason, including disease progression, the Investigator must review the reasons with the Sponsor's Medical Monitor or designee.

The End of Treatment (EOT)/30-Day Safety Follow-up visit will occur 30 (±3) days from the last dose of study drug. Subjects who discontinue study drug will remain in the study with follow-up conducted every 3 months from the last dose of study drug to obtain post-treatment long-term follow-up information on disease status (i.e., change in disease response, progression), start of subsequent therapy, and survival (death). Survival follow-up will continue for up to 3 years after the last subject is enrolled in the study.

Plasma samples will be obtained from all subjects to evaluate ME-401 PK and for ME-401 exposure-response and exposure-toxicity modeling. For subjects enrolled at United States (US) sites only, blood samples will be obtained for a correlative immune study. See Schedule of Assessments (Appendix 1) for blood sample collection.

The primary analysis of ORR for FL will occur after the initial 91 consecutive FL subjects administered ME-401 by IS, which defines the PEP (except those who discontinue early), have been followed for at least 6 months from the start of study drug.

The final analysis of DOR for FL will be triggered after most responders in the PEP have a minimum of 12 months of follow-up from first response.

The final analysis of ORR and DOR for MZL will be triggered after most responders in the ITT MZL population have a minimum of 12 months of follow-up from first response. This usually takes place within the first 2 cycles; therefore, 14 months from start of treatment. Analysis projected to occur approximately 14 months after the first dose of study drug in the last subject enrolled in the MZL cohort.

NUMBER OF SUBJECTS

Approximately 120 subjects with FL and 32 subjects with MZL will be enrolled and treated with ME-401 on the IS.

ESTIMATED NUMBER OF SITES

Approximately 125 sites will be opened globally.

STATISTICAL METHODOLOGY

This is an open-label, single-arm study. The objectives of this study are to estimate the efficacy and safety of ME-401 administered using an IS dosing regimen in patients with relapsed or refractory FL or MZL.

Sample Size for FL

The study will test the null hypothesis that the IRRC-reviewed ORR is ≤48% against the alternative hypothesis that it is ≥65.5%. The sample size for the PEP for FL is estimated to be 91 subjects, with at least 90% power and 1-sided alpha = 0.025.

With a total sample size of 120 FL subjects treated with ME-401 IS dosing regimen, if ≤15 subjects experience Grade ≥3 AESIs (i.e., subject incidence rate of ≤12.5% with 95% CI of 7.2–19.8%), the study can rule out the possibility of having a incidence rate ≥20% for Grade ≥3 AESIs with the IS dosing regimen. In addition, with a total sample size of 120 FL subjects, if ≤5 subjects experience a particular type of AE (i.e., subject incidence rate of ≤4.2% with 95% CI 1.4-9.5%), the study can rule out the possibility of having an incidence rate ≥10% for the AE.

Sample Size for MZL

Initially, the study was designed to test the null hypothesis that the IRRC-reviewed ORR is ≤46% against the alternative hypothesis that it is ≥66.5%. The sample size for the MZL population was estimated to be 64 subjects, with at least 90% power and 1-sided alpha = 0.025. Enrollment in the MZL arm was closed by the Sponsor on 31 August 2022, with 32 of the 64 planned subjects enrolled. A sample of 32 subjects will provide preliminary data on the efficacy and safety of single agent zandelisib in relapsed/refractory MZL.

Statistical Analysis

The ITT FL Population includes all FL subjects randomized per Protocol Amendment 1 (two arm design with randomization), and all enrolled FL subjects who received at least one dose of ME-401 per Protocol Amendment 2 or later amendment (single-arm, open-label design).

The ITT IS FL Population is defined as all FL subjects who are intended to receive ME-401 IS regimen, including subjects who:

- Were randomized to the ME-401 IS dosing regimen group (Group B) per Protocol Amendment 1
- Were randomized to the ME-401 CS dosing regimen group (Group A) per Protocol Amendment 1, but re-consented to Protocol Amendment 2 (for IS dosing regimen) prior to or on their Cycle 3 visit date
- Were enrolled per Protocol Amendment 2 or later amendment who received ME-401 IS dosing regimen.

The ITT CS Group is defined as all FL subjects who are randomized to the ME-401 CS regimen group (Group A) per Protocol Amendment 1 and did not switch/plan to switch to IS dosing regimen at Cycle 3 per Protocol Amendment 2.

The PEP in FL is defined as the initial 91 consecutive subjects enrolled in the ITT IS FL Population.

The primary analysis of ORR for FL will be triggered after all 91 subjects in the PEP in FL enrolled in the study (except those who discontinue early) have been followed for at least 6 months from the start of study drug.

Primary efficacy analyses for FL will be based on the PEP in FL.

The final analysis of DOR for FL will be triggered after most responders in the PEP have a minimum of 12 months of follow-up from first response.

The ITT MZL population is defined as all enrolled subjects with MZL who received at least one dose of ME-401.

The final analysis for MZL will be triggered after most responders in the MZL ITT population have been followed for at least 12 months from first response.

Efficacy analysis for MZL will be based on the ITT MZL population.

For both FL and MZL, methods for disease/response assessment by the IRRC will be described in the IRRC Charter.

Safety analyses will be performed on the Safety Population including all subjects who received at least one dose of ME-401.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AESI	adverse events of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
$AUC_{(0–last)}$	area under the concentration versus time curve from time zero to the last timepoint
B	bendamustine
BAT	basophil activation test
BCR	B-cell antigen receptor
BCRP	breast cancer resistance protein transporter
BMB	bone marrow biopsy
BP	blood pressure
BTK	Bruton tyrosine kinase
BUN	blood urea nitrogen
CAR T	chimeric antigen receptor T-cell
CBC	complete blood count
CI	confidence interval
CLL	chronic lymphocytic leukemia
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
CMR	complete metabolic response
CMV	cytomegalovirus
CR	complete response/remission
CRO	Contract Research Organization
CS	continuous schedule
CT	computed tomography
CVP	cyclophosphamide, vincristine, prednisone
CYP3A4	cytochrome P450 3A4
CYP2C8	cytochrome P450 2C8

Abbreviation	Definition
CyTOF	mass cytometry
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DOR	duration of response
DORR	duration of recaptured response
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
EC_{50}	half maximal effective concentration
EC_{90}	90% maximal effective concentration
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EE	Efficacy Evaluable
eGFR	estimated glomerular filtration rate
E_{max}	maximum possible effect
EU	European Union
FDA	Food and Drug Administration
FDG	^{18}F-fluorodeoxyglucose
FL	follicular lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
GCP	Good Clinical Practice
GELF	Groupe d'Etudes des Lymphomes Folliculaires
GI	gastrointestinal
HcT	hematocrit
HGB	hemoglobin
HR	heart rate
IC_{50}	half-maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
IND	Investigational New Drug
iNHL	indolent non-Hodgkin's lymphoma
INR	international normalized ratio
IP	investigational product
IQR	interquartile range

Abbreviation	Definition
IRB	Institutional Review Board
IRRC	Independent Response Review Committee
IS	intermittent schedule
ITT	Intent-to-Treat
IV	intravenous
kg	kilogram
KM	Kaplan-Meier
L	liter
LDH	lactate dehydrogenase
mAb	monoclonal Antibody
MCH	mean corpuscular hemoglobin
mm^3	cubic millimeter
mg	milligram
mL	milliliter
MTD	maximum tolerated dose
MUGA	multigated acquisition scan
MZL	marginal zone lymphoma
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NDA	New Drug Application
NE	not evaluated
NHL	non-Hodgkin's lymphoma
NIP	non-infectious pneumonitis
NMR	no metabolic response
NOS	not otherwise specified
OI	opportunistic infection
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
PCP	*Pneumocystis* pneumonia
PD	pharmacodynamic (in the context of the effect of a drug on biomarkers)
PD	progressive disease (in the context of tumor response)
PEP	primary efficacy population
PET/CT	positron emission tomography/computed tomography
PFS	progression-free survival

Abbreviation	Definition
P-gp	P-glycoprotein
PI	prescribing information
PI3K	phosphatidylinositol 3-kinase
PI3Kδ	phosphatidylinositol 3-kinase delta
PJP	*Pneumocystis jirovecii* pneumonia
PK	pharmacokinetic(s)
PMD	progressive metabolic disease
PMR	partial metabolic response
PR	partial response
PT	prothrombin time
QTc	QT corrected (corrected QT-interval)
QTcF	QT-interval corrected according to Fridericia's formula
R	rituximab
R-B	rituximab, bendamustine
RBC	red blood cell
R-CVP	rituximab, cyclophosphamide, vincristine, prednisone
R-CHOP	rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone
R-L	rituximab-lenalidomide
RP2D	Recommended Phase 2 Dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvate transaminase
SLL	small lymphocytic lymphoma
SOC	standard of care
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TMP-SMX	trimethoprim-sulfamethoxazole
TREG	T regulatory cell
TTF	time to treatment failure
$t_{½}$	half-life
ULN	upper limit of normal
US(A)	United States (of America)
WBC	white blood cell
WHO	World Health Organization

1. BACKGROUND

Non-Hodgkin's lymphoma (NHL) is one of the most common cancers in the world ranking as the 5th to 9th among cancer in most countries. In 2020, the reported incidence of new cases of NHL was approximately 545,000 globally and resulted in approximately 260,000 deaths (Sung 2021). It is estimated that in 2022 approximately 80,500 people will be diagnosed with NHL and approximately 20,250 will die from this cancer in the United States (US) (NCI 2022).

NHL comprises more than 30 types; classification is based on the type of lymphocyte involved, B-cells or T-cells. NHL is further classified by other factors, including whether it is aggressive (fast-growing) or indolent (slow-growing) (Swerdlow 2016).

1.1. Follicular Lymphoma

Follicular lymphoma (FL) is typically a slow-growing or indolent form of B-cell NHL (i.e., iNHL). This lymphoma subtype accounts for 20–30% of all NHL cases (Provencio 2017). Of the approximately 80,500 cases of NHL diagnosed in 2022 in the US, approximately 20% were likely to be FL (NCI 2022). About 18,000 and 25,000 new cases of FL were expected in the US and the European Union (EU), respectively, in 2015 (Dreyling 2014, Howlader 2020). No sex preponderance is seen for FL, but the incidence increases with age, and varies across racial groups and geographic regions. The incidence of FL is low in China and Japan, but people of Ashkenazi Jewish ancestry have a higher incidence of lymphoma. In the US, the incidence is 2-3 times higher in White individuals than in those of African descent (Nabhan 2012).

Transformation to diffuse large-cell lymphoma is associated with rapid progression of the disease including increasing adenopathy, development of systemic symptoms, and infiltration of extranodal sites. Recent estimates suggest that the ratio of histologic transformation may be 2-3% per year (Tan 2013, Al-Tourah 2008).

The overall survival (OS) rate of patients with FL is 77–86% at 5 years with a median survival of approximately 20 years for all patients, and is better for younger patients and those with better performance status, and significantly lower for patients with transformed disease (Provencio 2017, Mozas 2020). The majority of patients are diagnosed with advanced (i.e., Stage III and IV) disease. Both the Groupe d'Etudes des Lymphomes Folliculaires (GELF) and the Follicular Lymphoma International Prognostic Index (FLIPI) can provide prognostic information for specific patients (Solal-Céligny 1998, Swenson 2005).

Several systemic therapeutic options are available for patients with FL, ranging from single agent anti-CD20 immunotherapy (most commonly with rituximab (Rituxan®; [R]) (McLaughlin 1998, Hainsworth 2005); to anti-CD20-based immunochemotherapy (most commonly the combination of R with cyclophosphamide, hydroxydoxorubicin, vincristine, and prednisone [CHOP] designated as R-CHOP [Czuczman 1999] or the alkylating agent bendamustine [B] designated as R-B [Rummel 2005, Robinson 2008]). Other chemotherapy regimens are also acceptable in combination with an anti-CD20 antibody. Immunochemotherapy is typically preferred in younger and fit patients, and achieves an objective response rate (ORR) >90%, with a substantial proportion of complete responses (CRs), and a progression-free survival (PFS) of 65.5% at 5 years of follow-up (Flinn 2019).

Rituximab-lenalidomide (R-L) combination has been evaluated in randomized studies in patients with relapsed/refractory iNHL (Leonard 2019) and for treatment of previously untreated patients

with FL (Morschhauser 2018). It has been reported that efficacy in patients treated with R-L as front-line therapy are comparable with results in patients treated with chemoimmunotherapy, where the overall response rate was 61% in the R-L arm and 65% in the R-chemotherapy arm, with PFS at three years of follow-up being 77% and 78% for R-L and R-chemotherapy, respectively (Leonard 2019).

For subjects with relapsed disease, a similar immunochemotherapy approach, utilizing a chemotherapy regimen not previously administered, can be used. The combinations of R-CHOP or R-B showed satisfactory rates of objective response, ranging from 50–90%, and PFS, with median PFS ranging from 18–36 months (Czuczman 1999, Rummel 2005, Robinson 2008). Although the current treatments for iNHL are initially effective in inducing responses in most patients, they are not curative and show decreasing efficacy and development of resistance to therapy with repeated administrations.

However, the disease will inevitably relapse; therefore, active agents with different mechanisms of action than cytotoxic chemotherapy are needed for this patient population, with the goal of extending the duration of disease control at relapse from initial therapy. Furthermore, since the median age of patients with FL and marginal zone lymphoma (MZL) at relapse is >60 years, new treatment options must be well tolerated and avoid the toxicities typically reported with chemotherapy.

1.2. Marginal Zone Lymphoma

Marginal zone lymphoma represents approximately 5–15% of all NHLs (Zucca 2020) and is the third most common type among iNHLs (Al-Hamadani 2015); however, it remains largely understudied. Frontline therapy for MZL differs greatly based upon the subtype (extranodal, nodal, mucosal) (Swerdlow 2016), and the underlying etiology; hence, defining a standard treatment regimen for MZL has been difficult (Noy 2017). Treatments include anti-CD20 antibody (rituximab) based regimens either as monotherapy or in combination with systemic chemotherapy. Targeted therapy with ibrutinib (a Bruton tyrosine kinase [BTK] inhibitor) is also now used in relapsed/refractory cases across MZL subtypes (Denlinger 2018) for patients who have received at least one prior anti-CD20 based therapy (Imbruvica® US Prescribing Information); ORR with ibrutinib was 48% and median PFS was 14.2 months (95% confidence interval [CI]: 8.3 to not estimable). Outcomes were also analyzed by MZL subtypes, the median PFS was 13.8 months (95% CI: 8.3 to not estimable) for extranodal MZL, 19.4 months (95% CI: 8.2 to not estimable) for splenic MZL, and 8.3 months (95% CI: 2.8 to not estimable) for nodal MZL. The estimated 18-month OS rate was 81% (95% CI: 68 to 89; Noy 2017).

No standard of care is available for patients who relapse after initial treatment and depending on disease characteristics and previously used therapies various regimens combining rituximab and chemotherapy-containing regimens have classically been the treatment of choice in the second line of treatment, resulting in ORR of 85–93% and CR rate of 54–78% (Brown 2009, Cervetti 2010, Orciuolo 2010, Laribi 2016, Zucca 2017). Treatment-related toxicities with these therapies such as Grade 3 and 4 myelosuppression frequently limit treatment participation in many patients (Noy 2017). Autologous and allogeneic hematopoietic progenitor cell transplantation has been performed in selected patients with relapsed/refractory MZL, achieving durable remissions and frequently cures, albeit at cost of significant morbidity (Shimoni 2017).

In the current landscape of MZL, standardized treatment algorithms still lack sufficient evidence-based guidelines required to guide optimal therapy. Combination therapies that include BTK inhibition as well as other agents are ongoing. PI3K inhibitors have shown strong activity in iNHL.

1.3. Therapeutic Options for Third-Line Treatment

For patients with advanced-stage FL and MZL requiring systemic lymphoma-directed treatment, there are currently no approved drugs for third-line therapy, justifying the use of an investigational agent such as ME-401.

1.4. Phosphatidylinositol-4,5-bisphosphate 3-kinase δ (PI3Kδ)

Signaling through the BCR provides a strong proliferative and survival stimulus to the cell; interfering with such signaling is therefore a rational approach to the treatment of B-cell malignancies. In leukocytes, BCR signaling is mediated partly by the activation of PI3Kδ. The activation of PI3Kδ ultimately leads to cell survival, proliferation, and immune regulation (Herman 2012).

PI3Kδ is frequently active in B-cell malignancies and is central to multiple signaling pathways that drive proliferation, survival, homing, and retention of malignant B-cells in lymphoid tissue and bone marrow. Because PI3Kδ is the main PI3K isoform expressed in lymphoid cells, but is expressed at low or undetectable levels in most other tissues, inhibitors against PI3Kδ should be selective for the immune system and relatively non-toxic in other organs (Brown 2014).

Four drugs with PI3Kδ inhibitory activity, Zydelig® (idelalisib), Aliqopa™ (copanlisib), Copiktra® (duvelisib), and Ukoniq™ (umbralisib) have been approved in the US for clinical use in patients with FL, and MZL (for Ukoniq), based on single arm studies. Approvals in FL and MZL were withdrawn in the US for Zydelig, Copiktra, and Ukoniq due to inability to initiate or complete the required confirmatory Phase 3 study.

With the withdrawal in the US of all 3 oral PI3Kδ inhibitors, the treatment choices for relapsed FL and MZL patients is more limited. Therefore, there is a need for new treatment options for patients with relapsed indolent B-cell NHL, including efficacious and safer PI3Kδ inhibitors.

1.5. ME-401

Zandelisib (ME-401) is an orally bioavailable PI3Kδ inhibitor with optimal pharmacologic properties, including high potency with half-maximal inhibitory concentration (IC_{50}) for PI3Kδ of 0.6 nM in a cellular assay, plasma half-life ($t_{½}$) of approximately 28 hours supporting once-daily dosing, high volume of distribution indicating wide access to tissues, high specificity to the δ isoform at clinically relevant concentrations, and prolonged residence time on the target.

ME-401 has demonstrated substantial single-agent anti-tumor activity in a Phase 1b dose-escalation study in patients with relapsed FL, small lymphocytic lymphoma (SLL), and chronic lymphocytic leukemia (CLL), with an ORR of 90% (Soumerai 2018) and manageable toxicity; 4 subjects with relapsed/refractory MZL treated on the intermittent schedule (IS) showed a 100% ORR (25% CR). These encouraging preliminary results justify the evaluation of ME-401 in a larger cohort of patients with FL and MZL.

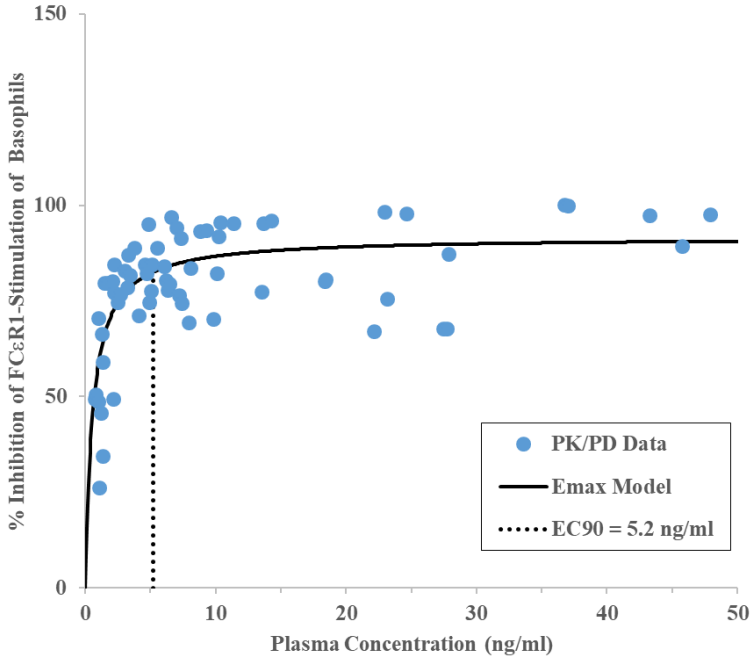
1.6. Experience with ME-401

1.6.1. Single Ascending Dose Healthy Volunteer Study

A single ascending dose study of zandelisib across a range of dose levels from 10 to 150 mg was conducted in normal healthy volunteers. Both maximum plasma concentration (C_{max}) and area under the concentration versus time curve from time zero to the last timepoint ($AUC_{[0\ last]}$) demonstrated linear increases over the dose range of 10 to 150 mg, with a time to maximum plasma concentration (t_{max}) of 5–6 hours.

To assess the on-target pharmacodynamic (PD) effect of ME-401, inhibition of PI3K signaling in peripheral blood basophils was measured using a PD assay (basophil activation test [BAT]), which measured basophil activation by CD63 upregulation following ex-vivo stimulation with an anti-FCεεR1 monoclonal antibody. From the fitted maximum possible effect (E_{max}) model, the concentrations of ME-401 estimated to give 50% and 90% BAT inhibition (i.e., EC_{50} and EC_{90}, respectively) of the maximum effect (E_{max} 91.6%) were 0.6 ng/ml and 5.2 ng/mL, respectively (Figure 2). Further pharmacokinetic (PK) modeling projected that a daily ME-401 dose of 60 mg will result in steady-state minimum plasma concentration (C_{min}) in excess of 5 ng/mL, the EC_{90} in the BAT assay. This led to the selection of 60 mg as the initial dose level in the Phase 1b dose escalation study in subjects with indolent B-cell malignancies, a dose lower than the starting dose for oncology trials calculated based on animal toxicokinetic studies.

Figure 2: BAT Response Curve for ME-401 in Normal Volunteers



1.6.2. Phase 1b Study in Relapsed FL and CLL/SLL (ME-401-002)

A Phase 1b study is currently ongoing evaluating zandelisib as a single agent and in combination with rituximab or zanubrutinib. As of 30 November 2019, a total of 103 subjects were enrolled: 31 in the single-agent dose-escalation group, 41 in the rituximab combination safety group, 24 in a single-agent expansion cohort, and 7 in the zanubrutinib combination safety group. Enrollment in the single agent dose-escalation group was completed, and the Sponsor concluded that 60 mg is the Recommended Phase 2 Dose (RP2D) for future development. Enrollment is ongoing in an expansion cohort of ME-401 monotherapy at 60 mg in subjects with relapsed FL and CLL/SLL. Enrollment in the rituximab combination safety group is now completed. The Sponsor has concluded that ME-401 at 60 mg plus rituximab at 375 mg/m^2 is well tolerated and is currently being evaluated in subjects with relapsed FL, CLL/SLL, MZL, diffuse large B-cell lymphoma not otherwise specified (DLBCL NOS) (germinal center B-cell type or activate B-cell type), and high-grade B--cell lymphoma (NOS or with MYC and BCL2 and/or BCL6 rearrangements). Enrollment in the arm assessing safety and efficacy of combination with BTK inhibitor zanubrutinib is ongoing.

As of 09 June 2022, 164 subjects have been treated in the study, 38 dosed on continuous daily dosing (CS) and 126 dosed on the IS (see Section 1.6.2.3). Sixty subjects have received zandelisib monotherapy, 41 subjects have received zandelisib at 60 mg in combination with rituximab, and 63 subjects have received zandelisib 60 mg in combination with zanubrutinib.

For a more detailed description of safety and efficacy findings in ME-401-002 study please refer to the most recent edition of the IB, currently Edition 9 as of the date of this amendment, and the published manuscript (Pagel 2022).

1.6.2.1. Dose-Escalation and Expansion (Monotherapy)

A dose-escalation with adaptive design using a modified continuous reassessment model was utilized in the single-agent dose-escalation part of the study. Six subjects per dose level (60, 120, and 180 mg) were enrolled to assess dose-limiting toxicity (DLT) with an option to enroll 6 additional subjects at any dose level with a response rate ≥30% in the first 6 subjects. A total of 31 subjects were enrolled at 3 dose levels and no DLT was observed in the 56-day DLT window period. Dose-escalation was stopped at 180 mg because there was a comparable and high ORR at the initial 3 dose levels with similar safety. The maximum tolerated dose (MTD) was not identified and the RP2D was declared as 60 mg because of the high response rate observed at this dose, manageable toxicities, and trough plasma concentrations exceeding the EC_{90} from the BAT assay in all subjects administered ME-401 at 60 mg. In addition, 21 subjects were enrolled in the expansion cohort evaluating ME-401 at 60 mg in relapsed FL and CLL/SLL.

In subjects treated in the ME-401 dose-escalation cohorts (N = 31) and monotherapy expansion cohort (N = 21), there were no treatment-emergent adverse events (TEAEs) leading to death and 5 TEAEs leading to treatment withdrawal. Overall, 51 of 52 subjects (98.1%) had at least one TEAE; 25 (48.1%) experienced a Grade 3 TEAE, and 4 (7.7%) experienced a Grade 4 TEAE. The most common TEAEs in ≥25% of subjects were diarrhea (28 [53.8%] subjects), cough (17 [32.7%] subjects), fatigue and nausea (16 [30.8%] subjects each), and rash maculo-papular (13 [25.0%] subjects). All other TEAEs in the ME-401 monotherapy arm occurred in <25% of subjects.

As of 09 June 2019, 22 of 52 subjects (42.3%) in the monotherapy cohorts have discontinued therapy, with a median follow up of 236.5 days (range: 28–869, interquartile range [IQR]: 131.5–605.5): 5 due to an adverse event (AE), 9 due to disease progression, 4 due to the subject withdrawing consent, and 4 for stem cell transplant.

1.6.2.2. ME-401 + Rituximab (Combination Therapy)

Overall, 34 of 38 subjects (89.5%) in the ME-401 + rituximab combination arm had at least one TEAE; 8 (21.1%) experienced a Grade 3 TEAE; and 1 (2.6%) experienced a Grade 4 TEAE. The most common TEAEs were aspartate aminotransferase (AST) increased, diarrhea, fatigue (9 [23.7%] subjects each); alanine aminotransferase (ALT) increased and nausea (7 [18.4%] subjects each).

In the combination arm (ME-401 + rituximab), median follow up was 89 days (range: 16–571, IQR: 56–268). Of the 38 subjects enrolled, 12 have discontinued therapy: 1 due to an AE, 9 due to disease progression, 1 due to the Investigator's decision, and 1 due to the subject withdrawing consent.

1.6.2.3. Continuous and Intermittent Dosing Schedules

Initially, the Phase 1b study explored the CS of ME-401 dosing when the product was given daily continuously. To address the potential for delayed AEs, the protocol was amended to include a modified dosing schedule strategy with an intermittent schedule (IS) of ME-401 administered once daily for 7 days followed by 21 days without therapy in each 28-day cycle. Intermittent therapy was introduced after an initial 2 cycles of daily dosing. The rationale for these treatment-free intervals was to potentially enable reconstitution of T regulatory cells (TREGs). The kinetics of TREGs repopulation following the administration of TREG-specific cytotoxic therapy has been studied by others and, in general, numeric recovery of the CD4+/CD25+/FoxP3+ cell population requires approximately 2 weeks (Mahnke 2007). This suggested that a 3-week treatment break might be reasonable, allowing approximately 1 week for ME-401 wash-out (approximately 5 half-lives) and 2 weeks for functional TREGs recovery.

Overall, 46 of 47 subjects (97.9%) on CS dosing (including subjects with no switch to IS dosing or switched later than Cycle 3) had at least one TEAE; 22 (46.8%) experienced a Grade 3 TEAE and 3 (6.4%) experienced a Grade 4 TEAE. The most common TEAEs in ≥25% of subjects were diarrhea (19 [40.4%] subjects), cough (15 [31.9%] subjects), and fatigue (13 [27.7%] subjects). All other TEAEs on CS dosing occurred in <25% of subjects.

On CS dosing, median follow up was 210 days (range: 28–869, IQR: 99–627). Of the 47 subjects, 21 (44.7%) have discontinued therapy: 4 due to an AE, 9 due to disease progression, 1 due to the Investigator's decision, 4 due to the subject withdrawing consent, and 3 for stem cell transplantation.

All subjects who had completed at least 2 cycles of treatment at the time Amendment 6 was implemented were planned to switch to IS dosing. Overall, 39 of 43 subjects (90.7%) in the IS dosing group had at least one TEAE; 11 (25.6%) experienced a Grade 3 TEAE and 2 (4.7%) experienced a Grade 4 TEAE. The most common TEAEs were diarrhea (18 [41.9%] subjects), fatigue and nausea (12 [27.9%] subjects, each), and AST increased (9 [20.9%] subjects).

On the IS, median follow up was 155 days (range: 16–552, IQR: 57–308). Of the 43 subjects, 13 (30.2%) have discontinued therapy: 2 due to AE, 9 due to disease progression, 1 due to the subject withdrawing consent, and 1 for stem cell transplantation.

For more details, please refer to most current Investigator's Brochure.

1.6.2.4. Efficacy

The efficacy analysis is based on 28 April 2019 data-cut off and is focused on subjects with relapsed or refractory FL and CLL/SLL. The Efficacy analysis set included 64 subjects who had at least one response assessment after baseline and included 50 subjects with FL and 14 subjects with CLL/SLL. The ORR was 80% for subjects with FL and 100% for subjects with CLL/SLL. There was no significant difference in response between subjects who received ME-401 as a single agent or in combination with rituximab, and no significant difference between treatment schedules (CS vs IS). Among all the subjects achieving a partial response (PR) or CR, the responses occurred rapidly for the majority of subjects (48/54, 89%), with response being assessed after the first 2 cycles of therapy. Median duration of response (DOR) for the IS group is 11.2 months, with a median (IQR) -follow up time on study of 8.8 (4.9–12.0) months. The median DOR for the CS group has not been reached, with a median (IQR) follow-up time on study of 8.3 (4.6–17.5) months. Updated data on efficacy and safety of ME-401 from the ongoing Phase 1b study is presented in Section 2.3.

2. RATIONALE FOR CURRENT STUDY

While first line CD20-based immunotherapy, chemotherapy, or immunochemotherapy achieves responses in most patients with FL or MZL, relapses are inevitable and subsequent remissions after a relapse are of progressively shorter duration. In addition, patients develop primary and secondary resistance to treatment with anti-CD20 mAb (Davis 2000, Czuczman 2012). The choice of therapy at relapse requires consideration of many factors including age, comorbidities, duration of prior response, and future treatment possibilities; hence, it is highly individualized. This study will evaluate ME-401 as a treatment option in patients with FL or MZL after failure of at least two prior therapies.

2.1. Patient Population

Treatment with an anti-CD20 antibody is considered standard of care (SOC) as front-line therapy in FL and MZL as it was shown to improve disease outcome in several randomized trials. Chemotherapy for FL and MZL consists of an alkylating agent either given as a single agent (i.e., bendamustine) or in combination regimens (e.g., CHOP; cyclophosphamide, vincristine, prednisone [CVP]; or similar). Purine analogues such as fludarabine, typically administered in combination with other chemotherapy agents, are also accepted treatment options for FL and MZL. Anti-CD20-based radioimmunotherapy is also an accepted treatment option for FL and MZL. For eligible patients, high dose chemotherapy followed by allo- or autologous stem cell transplantation is considered an acceptable option as a salvage therapy. However, all patients will eventually relapse and duration of remission with every line of treatment will get shorter. Unlike DLBCL, FL and MZL are still generally considered incurable diseases.

The high frequency of PI3Kδ pathway alterations in NHL led to the development of PI3Kδ inhibitors in this disease. The approval and later withdrawal (see Section 1.4) of several of the PI3K inhibitors for relapsed or refractory FL such as idelalisib, umbralisib, and duvelisib in the US, has created a treatment gap and limited the treatment options targeted to this pathway for subjects with FL after failure of at least 2 prior lines of therapy. Despite ongoing efforts in recent years to provide new therapies for patients with relapsed FL and MZL, the high unmet clinical need remains, as patients need active and well-tolerated therapy to delay time to the next disease progression. As the majority of patients are >65 years old, finding effective and well tolerated therapeutic options for patients who failed initial treatment remains a high clinical unmet need in this patient population.

2.2. Rationale for a 60 mg Dose

- A dose of 60 mg has been identified for evaluation in this study on the basis of a high response rate, acceptable toxicity, and plasma concentrations at or above the EC_{90} of the BAT assay.
- No MTD had been reached in the dose escalation part of the ongoing Phase 1b study.
- The ORR that was observed in 31 evaluable subjects with FL (n = 22) and CLL/SLL (n = 9) was 90%, and 86% in subjects with FL was comparable at all 3 doses evaluated (i.e., 60, 120, 180 mg).
- PK/PD analysis confirmed target saturation at 60 mg. The steady state mean C_{min} concentrations at all 3 dose levels studied were at or above the BAT EC_{90}. This supports the Sponsor's hypothesis that maximal anti-tumor activity is dependent on complete inhibition of PI3Kδ signaling and that higher doses do not result in greater inhibition nor greater anti-tumor activity. Therefore, 60 mg daily was selected as a recommended dose for expansion cohorts in the ME-401-002 study and for this Phase 2 study.

2.3. Rationale for ME-401 Intermittent Schedule Dosing Regimen

Recently presented data about treatment patterns of patients with relapsed or refractory FL treated in community practice with the first-approved PI3Kδ inhibitor idelalisib indicates that many patients cannot tolerate long term therapy, with 46.9–91.7% discontinuing therapy due to toxicities, and median duration of therapy of 5.5 months (Andorsky 2019). Establishing an effective, but at the same time well-tolerated inhibitors of the BCR-signaling pathway is very important to find optimal treatment for patients with B-cell malignancies.

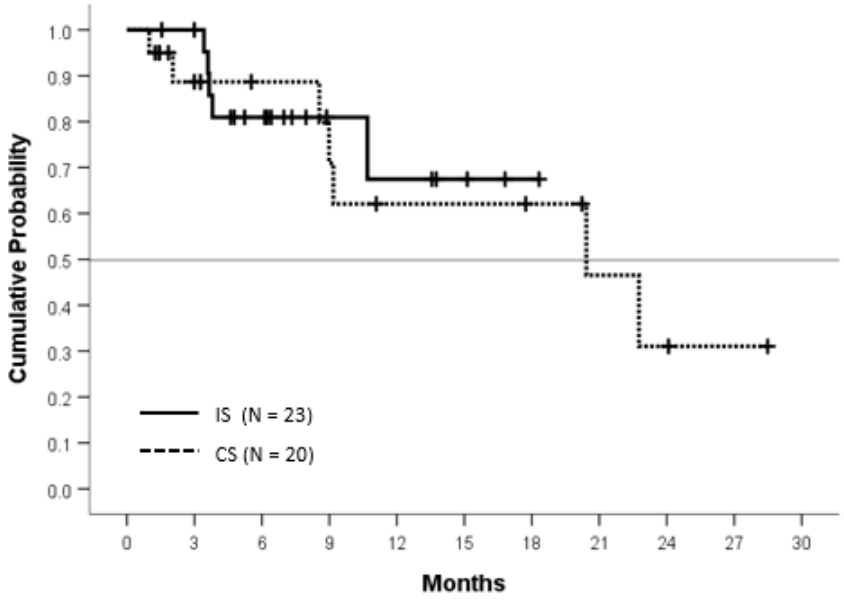
Additional data from the ongoing Phase 1b study (ME-401-002) allowed the Sponsor to evaluate the efficacy and safety of two different treatment schedules – CS and IS. As of 16 September 2019, 96 subjects received ME-401 as a single agent or in combination with rituximab. Subjects were treated with ME-401 either on CS or IS. Evaluation of preliminary efficacy in subjects with FL indicated there was comparable efficacy between treatment arms (CS or IS), with an ORR of 78% in all subjects, and slightly better ORR in the IS group versus the CS group (79% and 77%, respectively) (Table 1). With a median follow-up time of 9.2 months in the IS group and 11.5 months in the CS group, the median DOR has not been reached yet for subjects in the IS group, indicating sustained efficacy of ME-401 with the intermittent dosing schedule (Figure 3).

Table 1: Objective Response Rate in CS and IS Groups in FL – Study ME-401-002

	Evaluable Subjects N	Objective Response Rate n (%)
All subjects	55	43 (78)
IS group	29	23 (79)
CS group	26	20 (77)

Abbreviations: CS = continuous schedule; IS = intermittent schedule; N = number of subjects; n = number of subjects in the category.

Figure 3: Duration of Response in CS and IS Arms in FL – Study ME-401-002



Follow-up median (range).
IS (N = 23): 9.2 months (3.4–20.7); CS (N = 20): 11.5 months (3.0–30.4).
Abbreviations: CS = continuous schedule; IS = intermittent schedule; N = number of subjects.
Source: Zelenetz 2019.

Review of safety data indicated that subjects in the IS group tolerated ME-401 better than those in the CS group, with differences observed in all categories of reported AEs (Table 2). There is a lower incidence of Grade 3 AEs in subjects in the IS group: diarrhea/colitis were reported in only 7% of subjects in IS groups (5% were related) compared to 25.6% (23% related) in the CS group; there was only one case of Grade 3 rash (0% related) observed in the IS group while 10.3% (8% related) observed in the CS group; no Grade 3 increase in transaminases were observed in subjects treated in the IS group, and overall incidence of Grade 3 AESIs was very low (Table 2, Table 3). No Grade 4 toxicities have occurred in subjects treated with either the IS or CS regimen in this study to date.

Table 2: Most Common (≥20%) Adverse Events in the CS and IS Groups – Study ME-401-002 (N = 96)

Preferred Term, n (%)	All Grades		Grade 3*	
	CS (N = 39)	IS (N = 57)	CS (N = 39)	IS (N = 57)
Diarrhea/colitis	19 (48.7)	21 (36.8)	10 (25.6)	4 (7.0)
Rash (all types)	15 (38.5)	8 (14.0)	4 (10.3)	1 (1.8)
Cough	14 (35.9)	9 (15.8)	0	0
Fatigue	12 (30.8)	14 (24.6)	1 (2.6)	0
Nausea	11 (28.2)	14 (24.6)	1 (2.6)	0
Decreased appetite	10 (25.6)	3 (5.3)	0	0
Pyrexia	9 (23.1)	5 (8.8)	1 (2.6)	0
Nasal congestion	9 (23.1)	5 (8.8)	0	0
Aspartate aminotransferase increased	8 (20.5)	11 (19.3)	2 (5.1)	0
Abdominal pain	8 (20.5)	8 (14.0)	0	0
Gastroesophageal reflux	8 (20.5)	4 (7.0)	0	0

Abbreviations: Aes = adverse events; CS = continuous schedule; IS = intermittent schedule; N = number of subjects; n = number of subjects in the category.
* There were no Grade 4 or 5 AEs reported.

Table 3: Grade 3* Drug-Related Adverse Events of Special Interest (AESI) in the CS and IS Groups – Study ME-401-002 (N = 96)

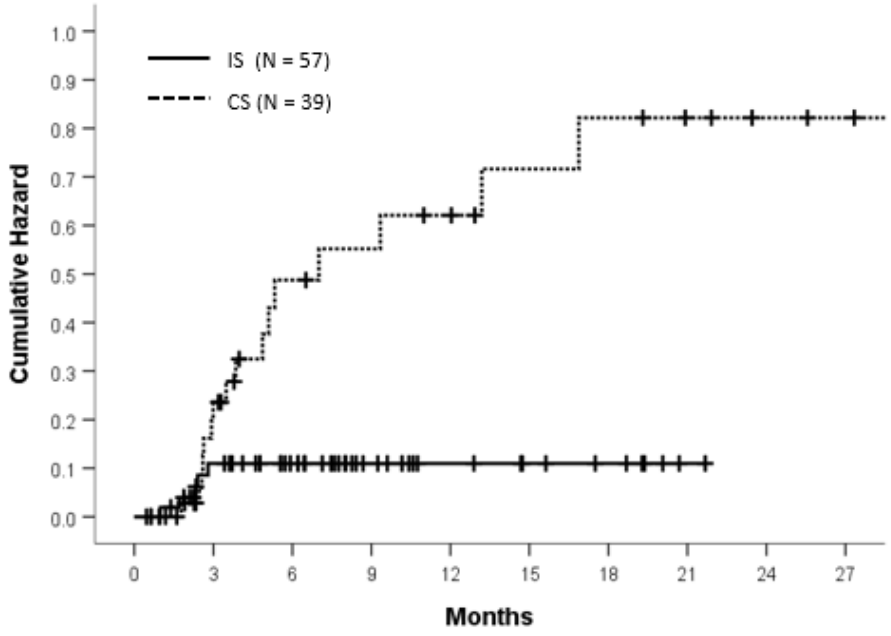
AESI, n (%)	CS Group (N = 39)	IS Group (N = 57)
Diarrhea/colitis	9 (23)	3 (5)
Rash, all types	3 (8)	0
AST/ALT increased	3 (8)	1 (2)
Mucositis	1 (3)	0
Pneumonia/pneumonitis	4 (10)	1 (2)

Abbreviations: AESI = adverse events of special interest; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CS = continuous schedule; IS = intermittent schedule; N = number of subjects; n = number of subjects in the category.
* There were no Grade 4 or 5 AEs reported.

It is hypothesized that delayed toxicities, such as diarrhea/colitis, rash, increases in transaminases, and pulmonary toxicities associated with PI3Kδ inhibitors therapy might be due to an effect on regulatory T cells. To avoid such on-target side effects that are associated with continuous dosing schedules with other products in this class, the alternative option is to mitigate those toxicities by utilizing an intermittent dosing schedule. Preliminary data with ME-401 indicates that overall incidence of such events, especially clinically significant Grade 3 events, is lower in subjects treated with the IS. Figure 4 represents time to adverse events of special interest (AESIs) in subjects treated in the CS and IS groups, with only 5 (9%) subjects who

experienced a related Grade 3 AESI compared to those in the CS group (16 [41%] subjects). This data indicates that the IS may significantly reduce a potential risk of developing immune-mediated adverse reactions.

Figure 4: Number of Subjects and Time to Grade 3 Drug-Related AESIs in CS and IS Groups – Study ME-401-002 (N = 96)



Dosing Group	Subjects with Grade 3 AESI, n (%)
CS (N = 39)	16 (41)
IS (N = 57)	5 (9)

Abbreviations: AESI = adverse event of special interest; CS = continuous schedule; IS = intermittent schedule; N = number of subjects; n = number of subjects in the category.
Source: Zelenetz 2019.

Observations in the ongoing clinical Phase 1b study indicated that treatment with the IS dosing regimen is as active as daily dosing, and at the same time associated with improved tolerability. These findings warranted a protocol amendment for the Phase 2 study (i.e., Amendment 2) to discontinue enrollment of subjects in the CS arm, and continuation of the study with the IS arm only. While subjects in the CS arm in the Phase 1b study did not experience significant or life-threatening toxicities, overall assessment of the risk-benefit profile indicates that IS dosing is favorable and may potentially provide subjects with potentially highly effective and well-tolerated therapy over the long term. Once Amendment 2 of the study protocol had been approved by local regulatory authorities and Institutional Review Boards (IRBs)/Ethics Committees (ECs), subjects who were randomized to the CS arm under Amendment 1 continued therapy with a switch to the IS. If subjects already completed 2 initial cycles of therapy, they were switched to IS dosing once they completed therapy in the ongoing cycle of treatment, and if they had not yet completed the first 2 cycles of therapy they switched to IS dosing after completion of the first two cycles of therapy. Subjects who experienced disease progression

during treatment on the IS could continue therapy with ME-401 on the CS after discussion of available options with the Investigator. Continuation of treatment was allowed after consultation with the study Medical Monitor or designee after radiographic confirmation of disease progression.

While it was established that PI3K inhibitors provide strong efficacy in patients with relapsed or refractory iNHL, duration of therapies might be limited by intolerable side effects leading to treatment discontinuation. Finding effective and well-tolerated therapies remains a high clinical unmet need for patients with relapsed or refractory FL or MZL. An intermittent dosing schedule of ME-401 may provide substantial benefit for this population of patients.

2.4. Risk-Benefit of Study Participation

As of the date of zandelisib IB Edition 9, more than 422 subjects with B-cell malignancies have been dosed with ME-401 from the ongoing Phase 1b, and Phase 2 (ME-401-003) and Phase 3 (ME-401-004) studies. Treatment with ME-401 as single agent or in combination with rituximab, given on IS dosing, has been associated with high ORR and is well tolerated with few discontinuations due to toxicity. For details of the risk-benefit of zandelisib refer to the current edition of the IB, Edition 9 as of the date of this amendment.

One Phase 1 study (PWT-001) has been completed in healthy subjects to evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of ME-401. In addition to this Phase 2 study, there is an ongoing Phase 1b study (ME-401-002) evaluating the safety, efficacy, and PK of ME-401 in subjects with relapsed B-cell malignancies an ongoing randomized Phase 3 study (ME-401-004) evaluating zandelisib + rituximab versus standard immunochemotherapy in subjects with relapsed or refractory FL or MZL who received ≥1 line of prior systemic therapy, and an ongoing Phase 1 study (ME-401-K01) sponsored by Kyowa Kirin Co., Ltd, evaluating the safety and tolerability of ME-401 monotherapy in Japanese subjects with relapsed or refractory B-cell malignancies. With more than 422 subjects treated with zandelisib (monotherapy or in combination with another drug) the available safety/efficacy data indicate a favorable risk-benefit profile.. Additional information is available in the Investigator's Brochure.

Diarrhea/colitis, rash, transaminitis, and stomatitis are AEs of interest that may be attributed to immune-related dysfunction due to TREGs suppression, which is indirectly affected by PI3Kδ inhibition. Other possible events such as pneumonitis, pneumonia, and opportunistic infections (OIs) have been observed in similar-class drugs and have been observed in the Phase 1b study evaluating ME-401. All subjects should be closely monitored for signs of acute toxicities, such as anaphylactic and other hypersensitivity reactions after receiving ME-401.

To be eligible for the study, potential subjects must have experienced disease progression after receiving at least 2 prior lines of standard systemic anti-lymphoma therapy. This is a patient population with a poor prognosis and participation in a clinical trial is generally considered a reasonable option for such patients according to clinical practice guidelines (NCCN Guidelines V4.2019). Preliminary data suggests strong efficacy and manageable toxicities in subjects with B-cell malignancies treated with ME-401 as a single agent or in combination with rituximab. As of Protocol Amendment 2, the study is enrolling subjects into an open-label, single-arm study to evaluate the efficacy and safety of IS dosing for ME-401. As indicated above (Section 2.3), preliminary results from the ongoing clinical Phase 1b study indicate that the IS dosing regimen provides high ORR in patients with multiple relapsed disease

and is well-tolerated. An independent Data Safety Monitoring Board (DSMB) will be evaluating safety and efficacy in this clinical study on an ongoing basis to assure that subjects are not exposed to an undue risk (Section 6.9). There are no standards of care available for patients with relapsed or refractory FL or MZL who have received ≥2 lines of prior therapy. Therefore, the potential benefit for subjects in the ME-401-003 clinical study may outweigh the potential risks. The Investigator should discuss the risks and benefits of participating in the study with potential subjects to ensure that they are aware of any alternative treatment options.

3. STUDY OBJECTIVES

This is a single-arm study. The objectives of this study are to evaluate the efficacy and safety of the IS dosing regimen of ME-401.

3.1. Primary Objective

- To evaluate the objective response rate (ORR) of ME-401 in relapsed or refractory FL or MZL, based on the Modified Lugano Response Criteria (Appendix 5), and determined by an Independent Response Review Committee (IRRC)

3.2. Secondary Objectives

- To evaluate the efficacy of ME-401 as assessed by an IRRC:
  - Duration of response (DOR)
  - Complete response (CR) rate
  - Progression-free survival (PFS)
- To evaluate the efficacy of ME-401 as assessed by the Investigator:
  - Objective response rate (ORR)
  - Duration of response (DOR)
  - Complete response (CR) rate
  - Progression-free survival (PFS)
  - Time to treatment failure (TTF)
  - Recapture of response
  - Duration of recaptured response (DORR)
- To evaluate overall survival (OS)
- To evaluate the safety profile of ME-401
  - Overall incidence of TEAEs
  - Incidence of AESIs
  - Time to occurrence of AESIs
- To evaluate the pharmacokinetics (PK) of ME-401

4. SUBJECT ELIGIBILITY

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom participation in the study is considered appropriate. All relevant medical conditions and alternative treatment options should be taken into consideration when deciding whether a particular subject is suitable for this protocol.

4.1. Inclusion Criteria

1. Signed informed consent.
2. Age ≥18 years (or age of majority).
3. Histologically confirmed diagnosis as defined in the World Health Organization (WHO) classification (Swerdlow 2016) of:
   a. FL limited to Grade 1, 2, or 3a; or
   b. MZL, including nodal, extranodal, and splenic MZL (histopathological report confirming diagnosis must be available during screening procedures).
4. Subjects with relapsed or refractory FL or MZL who received ≥2 prior therapy regimens. A previous regimen is defined as one of the following: at least two months of single-agent therapy or at least two consecutive cycles of polychemotherapy, autologous transplant, or radioimmunotherapy. Prior therapy must include an anti-CD20 monoclonal antibody (mAb) and an alkylating agent(s). Relapsed or refractory disease is defined as:
   a. Relapsed disease: disease progression after a response (CR or PR) lasting ≥6 months
   b. Refractory disease: no response to therapy (no CR or PR), or response lasting <6 months
5. At least one bi-dimensionally measurable nodal lesion >1.5 cm or extranodal lesions >1 cm in its longest diameter by computed tomography (CT) scan as defined by the Modified Lugano Classification (Appendix 5).
   a. Previously irradiated lesions can be selected as target lesions only in cases of unequivocal evidence of progression.
   b. For subjects with splenic MZL only: diffuse spleen involvement with splenomegaly, which is defined as the splenic vertical length greater than 13 cm.
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1 (Oken 1982; Appendix 6).
7. Adequate hematologic parameters at screening unless abnormal values are due to lymphoma per Investigator assessment:
   a. Absolute neutrophil count (ANC) ≥1.0 × 10^9/L (≥1,000/mm^3)
   b. Platelet count ≥75.0 × 10^9/L (≥75,000/mm^3)
8. Adequate renal and hepatic function per local laboratory reference range at screening as follows:

a. Aspartate aminotransferase (AST)/serum glutamic-oxaloacetic transaminase (SGOT), alanine aminotransferase (ALT)/serum glutamic-pyruvate transaminase (SGPT) ≤3.0 × upper limit of normal (ULN)
b. Total bilirubin ≤2.0 × ULN or ≤3 × ULN for subjects with Gilbert's syndrome
c. Serum creatinine ≤1.5 × ULN or estimated glomerular filtration rate (eGFR) >50 mL/min using the Cockcroft-Gault equation (Appendix 2)

9. QT-interval corrected according to Fridericia's formula (QTcF) ≤450 milliseconds (msec); subjects with QTc >450 msec but <480 msec may be enrolled provided the QTc prolongation is due to a right bundle branch block (RBBB), left bundle branch block (LBBB), or pacemaker and is confirmed stable by a cardiologist.
10. Left ventricular ejection fraction (LVEF) ≥45% as measured by echocardiogram or multigated acquisition scan (MUGA). If LVEF <45% by ECHO, a repeat measurement can be conducted within the screening period.
11. Subjects must have completed any prior systemic anti-cancer treatment within ≥4 weeks of Cycle 1 Day 1 (or ≥5 times the half-life [$t_{½}$], whichever is longer); ≥8 weeks for antibody agents; ≥2 weeks for radiation therapy; and ≥3 months for high dose therapy with stem cell transplantation or CAR T-cell therapy or radioimmunotherapy.
12. All AEs and laboratory toxicities related to prior therapy must resolve to Grade ≤1 prior to the start of the study therapy (unless otherwise specified in eligibility criteria).
13. For females of childbearing potential, a negative serum human chorionic gonadotropin (hCG) pregnancy test within 28 days of study Day 1 and negative hCG result on study Day 1.
14. Subjects must agree to use appropriate contraception methods during the clinical study (Appendix 4).
15. Subject is willing and able to comply with all scheduled visits, treatment plans, laboratory tests, and other study procedures.

4.2. Exclusion Criteria

1. Histologically confirmed FL Grade 3b, or transformed disease (assessed by the Investigator):
   a. For patients with clinical (e.g., marked B-symptoms), laboratory (e.g., high lactate dehydrogenase [LDH]), or radiographic (e.g., high standardized uptake value by positron emission tomography [PET]) signs of rapid disease progression, a fresh tumor biopsy prior to enrollment is required to rule out transformed disease.
2. Known lymphomatous involvement of the central nervous system.
3. Major surgical procedure within 4 weeks prior to study Day 1 (minor surgical procedures, [e.g., lymph node biopsy] performed within 1 day or with an overnight stay are allowed).
4. Prior therapy with PI3K inhibitors.

5. Any uncontrolled clinically significant illness including, but not limited to, active infections requiring systemic antimicrobial therapy, hypertension, angina, arrhythmias, pulmonary disease, or autoimmune dysfunction.
6. Subjects who have tested positive for hepatitis B surface antigen and/or hepatitis B core antibody plus have a positive hepatitis B polymerase chain reaction (PCR) assay; subjects who have previously tested positive with a negative PCR assay are permitted with appropriate anti-viral prophylaxis.
7. Positive hepatitis C virus antibody (HCV Ab); subjects with positive HCV Ab are eligible if they are negative for HCV by PCR.
8. Known history of, or active human immunodeficiency virus (HIV) infection.
9. Ongoing or history of drug-induced pneumonitis.
10. Previous or concurrent cancer that is distinct in the primary site or histology from indolent B-cell NHL within 3 years before start of study treatment **except** for curatively treated cervical cancer in situ, non-melanoma skin cancer, superficial bladder tumors (Ta [non-invasive tumor], Tis [carcinoma in situ], and T1 [tumor invades lamina propria]), and asymptomatic localized prostate cancer with no requirement for systemic therapy (or requiring only hormonal therapy) and with normal prostate-specific antigen values within ≥12 months prior to enrollment.
11. History of clinically significant cardiovascular abnormalities such as congestive heart failure (New York Heart Association classification ≥II [NYHA 1994]), myocardial infarction within 6 months of study entry.
12. History of clinically significant gastrointestinal (GI) conditions, particularly:
    a. Known GI condition that would interfere with swallowing or the oral absorption or tolerance of study drug
    b. Pre-existing malabsorption syndrome or other clinical situation that would affect oral absorption
13. Females who are pregnant; females who plan to breastfeed during study treatment through 90 days after ending treatment.
14. Psychiatric illness/social situations that would interfere with study compliance.
15. Hypersensitivity or other clinically significant reaction to the study drug or its inactive ingredients.
16. Any other condition for which, in the opinion of the Investigator, participation would not be in the best interest of the subject.

5. STUDY DESIGN

5.1. Overall Study Design

This is a global, multicenter, open-label, single-arm, Phase 2 study of the PI3Kδ inhibitor ME-401 in subjects with relapsed/refractory FL or MZL. ME-401 will be administered orally

at a dose of 60 mg given once a day. A cycle of treatment is 28 days in duration. Treatment with ME-401 is administered based on an intermittent schedule (IS).

The IS includes:

- continuous daily therapy for the initial 2 cycles of treatment
- the intermittent treatment begins at Cycle 3, with ME-401 administered daily for the first 7 days of every 28-day cycle (7 days on treatment and 21 days off treatment)

The first day of treatment is designated as Day 1. ME-401 will be administered until progressive disease (PD), development of unacceptable toxicity (despite ME-401 modified dosing schedule), or subject withdrawal.

Review of the ongoing Phase 1b study evaluating different dosing schedules for ME-401 in subjects with relapsed/refractory FL showed improved risk-benefit profile of the IS over a continuous schedule (CS, i.e., ME-401 given daily continuously). With Amendment 2, the initial CS treatment arm was terminated, and subjects were enrolled to receive therapy on the IS only. If subjects already completed 2 initial cycles of therapy, they were switched to IS dosing once they completed therapy in the ongoing cycle of treatment, and if they had not yet completed the first 2 cycles of therapy they were switched to IS dosing after completion of the first two cycles of therapy. Subjects who progress on IS dosing may be switched to CS dosing.

Upon confirmation of meeting eligibility criteria, subjects are enrolled and should be treated with ME-401 within a reasonable time frame (within 5 days). It is important to ensure that subjects continue meeting protocol specified eligibility criteria to enroll in the study, and if there are >7 days between screening laboratory assessments and expected Cycle 1 Day 1 dosing, then the laboratory assessments should be repeated and reviewed prior to the first dose of ME-401.

The study schema is presented in Figure 1.

For subjects who experience hematologic toxicity; diarrhea/colitis, cutaneous reactions (including rash and mucositis), AST/ALT elevation, or non-infectious pneumonitis (NIP); or other toxicities, refer to ME-401 toxicity management (Table 4) and modified dosing schedules in Section 5.3.1. Study treatment interruption is acceptable due to observed adverse reactions, and is allowed for up to 6 continuous weeks from drug interruption. Once a subject has recovered from a toxicity, treatment may be resumed beginning at Day 1 of the subsequent cycle of therapy according to the toxicity management indicated in Table 4.

Study drug administration, study visits, and protocol-mandated assessments are conducted in 28-day cycles. Subject participation in the study is expected to be approximately 3-4 years, including 28 days for screening, 18 months of dosing with study drug, and up to 3 years of follow-up for survival after discontinuation of study drug. This is an estimated average duration of subject participation; actual duration may be shorter or longer based on disease response, tolerability to therapy, and duration of the long-term follow-up period.

Disease/response assessments utilizing diagnosis quality scans (CT scan with contrast, diagnostic quality PET/CT scan) will be initially performed at screening, after 4 months and 12 months on therapy, and at any time to confirm CR. Once a CR has been documented, ^{18}F-fluorodeoxyglucose (FDG)-PET scan is no longer required to monitor disease response and a CT scan is an appropriate imaging test. CT scans will be performed at all other protocol

prespecified timepoints for disease/response assessment. The disease/response assessment will be performed every 2 months (±7 days) for the first 6 months on study, every 3 months (±7 days) during the following 12 months, and every 6 months (±14 days) thereafter.

Disease/response assessment will be based on radiological tumor evaluation of neck, chest, abdomen, and pelvis by using IV (and oral, if indicated, per Imaging Manual) contrast enhanced CT/magnetic resonance imaging (MRI) and/or PET-CT imaging modalities at screening and at follow-up visits at the frequency described in the Schedule of Assessments (Appendix 1), and disease response will be based on the Modified Lugano Classification response criteria (Appendix 5). Please see Table 7 for overall guidance on response assessment criteria based on Lugano Classification response criteria. In this clinical study, additional modifications to the Lugano Classification response criteria are incorporated per regulatory request to clarify rules for partial response (PR) assessment. These modifications highlight that morphologic (CT scan based) response will be the basis for PR assessment and not metabolic (FDG-PET scan) based assessment of response. Please see Table 8 for details regarding combined response assessment criteria based on beforementioned modified Lugano Classification. For subjects followed by CT scans only, a bone marrow biopsy will be required to confirm a CR in a subject who achieve a morphologic CR by CT scan. To rule out a potential of false positive diagnosis of disease progression in ambiguous cases, it is highly recommended to repeat imaging assessments within 4-8 weeks after initial suspicion of PD. The Investigator's assessment of disease response will be used for subject management. For the final analysis of study efficacy endpoints, disease/response assessment will be performed by an IRRC blinded to Investigator assessment. For subjects with gastric MZL, endoscopy with biopsy must be performed to confirm CR.

Safety will be assessed by laboratory safety tests including hematology (complete blood count [CBC]), serum chemistry, and cytomegalovirus (CMV) using quantitative PCR; and clinical assessments including physical examination, vital signs, ECOG performance status, and 12-lead electrocardiogram (ECG). Adverse events will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0.

Subjects will continue to receive study drug in accordance with the IS dosing regimen (or CS dosing regimen if switched from IS after PD) until Investigator-assessed disease progression or unmanageable toxicity requiring treatment discontinuation, subject's decision to withdraw their consent to participate on study, or study closure by the Sponsor. A notification to the Medical Monitor will be sent prior to subject discontinuation. The End of Treatment (EOT)/30-Day Safety Follow-up visit will occur 30 (±3) days from the last dose of study drug.

Subjects who discontinue study drug will remain in the study with follow-up conducted every 3 months from the last dose of study drug to obtain post-treatment long-term follow-up information on disease status (i.e., change in disease response, progression), start of subsequent therapy, and survival (death). During this post-treatment follow-up phase, all subjects discontinued for reasons other than PD must continue imaging tests to assess disease status, performed per the original protocol-defined schedule for disease/response assessment, or earlier if clinically indicated. Imaging test results will no longer be collected when a subject starts a new therapy or disease progression occurs. The progression will be documented in the post-treatment long-term follow-up phase. Survival follow-up will continue for up to 3 years after the last subject is enrolled in the study.

Plasma samples will be obtained from all subjects to evaluate ME-401 PK and to serve for ME-401 exposure-response and exposure-toxicity modeling. For subjects enrolled at US sites only, blood samples will be obtained for a correlative immune study. See Schedule of Assessments (Appendix 1) for blood sample collection.

The primary analysis of ORR for FL will occur after the initial 91 consecutive subjects randomized to or assigned to the IS arm, which represent the Primary Efficacy Population (PEP) (except those who discontinue early), have been followed for at least 6 months from the start of study drug. The final analysis of DOR for FL will occur after most responders in the PEP have at least 12 months of follow-up from first response.

Enrollment in the MZL arm was closed by the Sponsor on 31 August 2022, with 32 of the 64 planned subjects enrolled. The reason for early closure of enrollment was to focus the enrollment of subjects with MZL in the global Phase 3 study ME-401-004. Early enrollment closure was communicated to all investigators in August 2022 and is being formalized in Amendment 5.

The final analysis of ORR and DOR for MZL will be triggered after most responders in the ITT MZL population (except those who discontinue early) have been followed for at least 12 months from first response. This is projected to occur approximately 14 months after first dose of the last subject with MZL enrolled in the study.

5.2. Study Product: ME-401

5.2.1. Preparation and Administration of ME-401

Zandelisib (code ME-401) is provided as 60 mg capsules, which require no preparation prior to administration. Subjects should be instructed to swallow the capsules whole and to not chew or crush them.

ME-401 is dosed on a milligram (mg) basis with no adjustment in dosing based on subject weight. ME-401 is to be taken orally once a day at approximately the same time each day in accordance with the IS dosing regimen (or CS dosing regimen if switched from IS after PD).

ME-401 should be taken with a glass of water on an empty stomach (i.e., at least 1 hour prior to food intake or 2 hours after food intake). If a subject routinely experiences discomfort with dosing, he or she is permitted to take ME-401 with a light, non-fatty snack. If a dose is missed it may be taken up to 12 hours after the specified time. After 12 hours the missed dose should be omitted. If possible, the subject should be advised to separate administration of ME-401 capsules from that of concomitant medications that have a known effect on P-glycoprotein (P-gp) and breast cancer resistance protein transporter (BCRP) (see Section 5.5 for prohibited concomitant medications).

5.2.2. Storage of ME-401

ME-401 should be protected from direct sunlight and stored in a cool place (at the subject's home) or at room temperature, 15–25°C (59–77°F).

5.2.3. ME-401 Accountability and Compliance

The Principal Investigator or their representative will account for all ME-401 provided by the Sponsor. All ME-401 will be stored at the site in a secure and locked location. The Principal Investigator shall maintain adequate records of the disposition of ME-401, including dates, quantity, and use by subjects. Upon completion of the study, all remaining ME-401 will be accounted for and unused material will either be returned to the Sponsor (or designee) by a traceable method (UPS, FedEx, etc.) or destroyed (with documentation of drug destruction provided to the Sponsor), as instructed by the Sponsor.

5.3. ANTICIPATED TOXICITIES

As of the 09 June 2019 data cut-off date, the most common Grade ≥3 AEs noted in the Phase 1b study for the 52 subjects administered ME-401 alone consisted of diarrhea/colitis in 14 (26.9%) subjects; neutrophil count decreased in 4 (7.7%) subjects; and ALT increased, AST increased, and rash in 2 (3.8%) subjects each. There were no DLTs reported across all dose levels in the 56-day DLT window period.

Refer to Section 5.3.1 for study drug dose interruption or treatment discontinuation in a subject if such toxicity occurs and is not considered related to the underlying disease. Subject management will be determined by the treating physician and may include administration of a hematopoietic growth factor for neutropenia, administration of corticosteroids for the treatment of colitis, pneumonitis, and other AEs considered immune mediated (Table 4), and antimicrobial or anti-viral treatment for the prevention and/or management of OIs (Section 5.4).

Refer to the current Investigator's Brochure for more details.

5.3.1. Modified Dosing Schedules

Modification of the dosing schedule and dosing interruptions are utilized for toxicity management in this study. For subjects who experience toxicity during the first 2 cycles while receiving daily therapy with ME-401, dose interruption followed by a switch to intermittent schedule daily dosing for the first 7 days of every 28-day cycle is allowed. Subjects who experience toxicities on the IS will be managed by the instructions for management of potential drug-related toxicity in Table 4, which may include dose interruption or permanent discontinuation of ME-401. All treatment interruptions (including any missed doses, treatment delays) and discontinuations and their reasons are to be recorded in the electronic case report form (eCRF). Interrupted treatment is resumed on the IS after subjects recover to the grade specified in the table (subjects who permanently discontinue ME-401 dosing will proceed to the EOT/30-Day Safety Follow-up visit). Subjects on the IS who recover within the same treatment cycle, will complete the planned days off, and resume treatment on Day 1 of the next planned cycle.

Subjects who interrupt study drug dosing for >6 continuous weeks will have ME-401 permanently discontinued unless restarting ME-401 is authorized by the study Medical Monitor. Consultation with the Sponsor's Medical Monitor or designee is recommended before treatment interruption or discontinuation due to any reason.

Table 4: ME-401 Toxicity Management

Toxicity	Grade*	Management of ME-401	Management of Toxicity
Diarrhea/colitis	**2**	• Hold ME-401 unless diarrhea is confirmed to be due to an infectious agent. • If ME-401 is held, once diarrhea resolves to Grade ≤1, resume ME-401 at 60 mg administered on IS (the first 7 days of each 28-day cycle).	• If infectious cause of the diarrhea, including clostridium difficile, was ruled out then proceed with following management steps: • Hold ME-401 and start loperamide or similar anti-diarrheal agent. • If no improvement occurs within 48 hours, start prednisolone 0.5–1 mg/kg IV or oral budesonide 9 mg daily. • Based on data from the Phase 1b study, subjects with diarrhea that was preceded by rash in the prior 1–2 weeks often experienced more prolonged and severe diarrhea. Thus, if diarrhea is preceded by rash in the prior weeks, start prednisolone 0.5–1 mg/kg IV or oral budesonide 9 mg daily at the time when a subject experiences rash.
	3	• Hold ME-401 until AE resolves to Grade ≤1, then, if clinically indicated, resume ME-401 at 60 mg administered on IS. • For recurrence of Grade 3 diarrhea/colitis, discontinue study drug permanently.	• Subjects should be hydrated as clinically indicated and administered (methyl) prednisolone 1–2 mg/kg/day IV or equivalent oral systemic steroids. ○ If no improvement occurs within 2–3 days, the corticosteroid dose should be increased to 2 mg/kg/day IV or equivalent oral systemic steroids. • Once improved to Grade ≤1, start tapering the corticosteroid as clinically indicated.
	4	• Permanently discontinue ME-401.	• Treat per institutional standard of care.

Table 4: ME-401 Toxicity Management (Continued)

Toxicity	Grade*	Management of ME-401	Management of Toxicity
Cutaneous Reactions and Mucositis	**2**	• Hold ME-401 unless rash ascertained to be unrelated to study drug. • If ME-401 is held, once AE resolves to Grade ≤1, resume ME-401 at 60 mg administered on the IS.	• Monitor subjects and determine cause of rash. • Per Investigator's discretion, antihistamines, topical steroids, and systemic steroids may be given.
	≥3	• Hold ME-401 until AE resolves to Grade ≤1, then, if clinically indicated, resume ME-401 at 60 mg administered on the IS. • For recurrence of Grade 3, permanently discontinue ME-401.	• Monitor subjects as clinically indicated until resolution. • Oral antihistamines and systemic corticosteroids such as prednisone 0.5–1 mg/kg/day (or equivalent dose of methylprednisolone) should be given until rash resolves to Grade ≤1.
	Any	• Permanently discontinue ME-401 for life-threatening toxicity, Stevens-Johnson syndrome of any grade, and TENS of any grade.	• Treat per institutional standard of care.
Hepatotoxicity	**2**	• For ALT/AST >3–5 × ULN but <5 × ULN, maintain ME-401 treatment dose and schedule.	• Monitor ALT/AST weekly until resolved to Grade ≤1 or baseline level.
	3	• For ALT/AST >5–20 × ULN, hold ME-401. • Resume ME-401 at 60 mg administered on the IS. • For recurrence of Grade 3, permanently discontinue ME-401.	• Monitor ALT/AST once a week until resolved to Grade ≤1 or baseline level. • Treat per institutional standard of care, which may include a course of corticosteroids if clinically indicated. • Assess if Hy's law applies.
	4	• For ALT/AST >20 × ULN, permanently discontinue ME-401.	• Assess if Hy's law applies. • Treat per institutional standard of care, which may include a course of corticosteroids if clinically indicated.
Non-infectious pneumonitis (NIP)	**2**	• Hold ME-401 until AE resolves to Grade ≤1. • Resume ME-401 at 60 mg administered on the IS.	• Rule out infectious etiology of pneumonitis based on institutional guidance, utilizing following methods: chest X-ray, CT scan, pulsometry, nasal swab, sputum culture and sensitivity, blood culture and sensitivity, urine culture and sensitivity. • Treat with corticosteroids and per institutional standard of care.

Table 4: ME-401 Toxicity Management (Continued)

Toxicity	Grade*	Management of ME-401	Management of Toxicity
	≥3	• Permanently discontinue ME-401.	• Treat per institutional standard of care, including systemic corticosteroids.
Lung Infection/ Pneumonia	**2**	• Holding ME-401 is not required. Continue ME-401. • Dosing may continue at 60 mg administered on the IS.	• Treat per institutional standard of care.
	3	• Hold ME-401 until AE resolved to Grade ≤1 or baseline. • Resume ME-401 at 60 mg administered on the IS. • Discontinue if same event occurs a third time.	• Treat per institutional standard of care.
	4	• Permanently discontinue ME-401.	• Treat per institutional standard of care.
Cytomegalovirus (CMV)	**Any**	• If test is positive (PCR or antigen assessment) based on local laboratory assessments and requires treatment, then hold ME-401 until recovery. • Resume ME-401 on the IS after resolution of asymptomatic CMV reactivation if all the following conditions are met: o CMV reactivation is resolved per the Investigator assessment • CMV reactivation was not associated with end organ disease (e.g., pneumonia, hepatitis, gastroenteritis, retinitis, encephalitis).	• Treat per institutional standard of care. • If all conditions for restarting study drug are met, then secondary CMV prophylaxis must be maintained as per institutional guidelines.
Hematological Toxicity	**3**	• Grade 3 neutropenia, febrile neutropenia or thrombocytopenia: ME-401 dosing may continue.	• Perform CBC weekly until resolves to Grade ≤2 (unless myelosuppression is due to follicular lymphoma).
	4	• Grade 4 thrombocytopenia or Grade 4 neutropenia or febrile neutropenia: Hold ME-401 until AE resolves to Grade ≤3. Resume ME-401 at 60 mg administered on the IS.	• Perform CBC weekly until resolves to Grade <3.

Table 4: ME-401 Toxicity Management (Continued)

Toxicity	Grade*	Management of ME-401	Management of Toxicity
		• Grade 4 neutropenia without associated symptoms: ME-401 therapy may continue. If symptoms persist despite adequate supportive care, ME-401 should be held until toxicity resolves to Grade ≤1 or baseline values and then ME-401 may be resumed at 60 mg administered on the IS.	• Initiate growth factor support if clinically indicated. If subject is receiving filgrastim support or equivalent, CBC should be repeated after 3 days. Weekly CBCs should continue until resolves to Grade <3.
		• Grade 4 thrombocytopenia without associated symptoms, ME-401 therapy may continue if Investigator deems safe.	• Check platelets every 3 days until resolves to Grade <3.
Other, not listed above, that are considered related to ME-401	**2**	• Holding ME-401 is not required. Continue ME-401. • Dosing may continue at the current dose or at 60 mg administered on the IS.	• Treat per institutional standard of care.
	3 [a]	• Hold ME-401 until AE resolves to Grade ≤1 or baseline. • Resume ME-401 at 60 mg administered on the IS. • For recurrence of the same Grade 3, permanently discontinue ME-401.	• Treat per institutional standard of care.
	4	• Permanently discontinue ME-401.	• Treat per institutional standard of care.

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CBC = complete blood count; CMV = cytomegalovirus; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; IS = intermittent schedule; IV = intravenous; NIP = non-infectious pneumonitis; PCR = polymerase chain reaction; TENS = toxic epidermal necrolysis syndrome; ULN = upper limit of normal.

* Toxicity graded per CTCAE v5.0.

Hy's law is defined as: cases of drug-related hepatocellular injury are defined as elevated ALT or AST ≥3 × ULN, plus elevated total bilirubin >2 × ULN without findings of cholestasis (defined as serum alkaline phosphatase [ALP] activity <2 × ULN), and no other reason can be found to explain.

[a.] For Grade 3 AEs not related to study drug, it is upon the discretion of the Investigator if holding ME-401 is warranted. Treatment interruption must be discussed with the Sponsor's Medical Monitor or designee in such cases.

5.3.2. Adverse Events of Special Interest (AESIs)

In this study, the following are considered AESIs:

- Cutaneous reactions, including skin rash Grade ≥2 (see Appendix 3 for guidance for toxicity assessment)
- Oral mucositis or stomatitis Grade ≥2
- Diarrhea/colitis Grade ≥2

- It is important to differentiate infectious diarrhea from non-infectious diarrhea, as treatment and management of subjects will depend on the identified cause (see Table 4 for management of non-infectious diarrhea). To confirm suspected colitis, utilize colonoscopy or diagnostic methods as per institutional standards.
- AST/ALT Grade ≥2
- Non-infectious pneumonitis (NIP) of any grade
- Lung infection/pneumonia Grade ≥2
- Cardiomyopathy of any grade

Refer to Table 4 for ME-401 Toxicity Management.

5.3.3. Other Potential Toxicities

5.3.3.1. Phototoxicity

Based on neutral red uptake phototoxicity assay of ME-401 in BALB/c 3T3 mouse fibroblasts, ME-401 did not demonstrate phototoxic potential.

5.4. Monitoring and Prophylaxis of Opportunistic Infection

5.4.1. Monitoring for Opportunistic Infection

In addition to the clinical review and laboratory tests outlined in the Schedule of Assessments (Appendix 1), the following should be performed in all subjects prior to start of every cycle of treatment with ME-401:

- Evaluation of any new onset or worsening of pulmonary symptoms (i.e., cough, dyspnea, or fever) that includes a lung examination at each visit prior to treatment to rule out opportunistic infection (OI), including PJP *Pneumocystis jirovecii* pneumonia/PCP (*pneumocystis* pneumonia).
- Laboratory tests:
  - CD4 (for subjects with signs of infection)
  - Blood cultures if febrile neutropenia occurs, or when ANC by NCI CTCAE is Grade 4
  - PCR for CMV (every cycle for first 6 months of treatment and every 3 months thereafter). If PCR test is positive for CMV and treatment is initiated, then treatment with ME-401 should be delayed until recovery. Treatment of CMV should be initiated based on local SOC. Retreatment with ME-401 will be allowed on the IS once PCR test for CMV is negative. Please note: quantitative results from PCR measurements must be reported for all CMV assessments.

Implement enhanced monitoring prior to start of every cycle of treatment with ME-401 when prior medical history or laboratory parameters could be associated with one of the following risk factors:

- Intensive chemotherapy (≥2 lines of myelosuppressive cytotoxic therapy)

- History of symptomatic CMV infection, systemic herpes
- History of lower respiratory tract infection
- History of immunodeficiency in the last 12 months (excluding lymphoma)
- Lymphocyte count <500/mm^3 while on treatment in clinical study

For subjects with identified risk factors and those who developed an OI while on study treatment, additional assessments may include:

- CD4 and CD8 count and ratio, c-reactive protein, blood cultures
- Any additional laboratory and diagnostic methods according to local SOC reported as unscheduled laboratory and diagnostic methods of assessment
- Radiological imaging (i.e., chest X-ray or CT scans)
    - Note: Treatment of the OI that started while on study should be based on local SOC.

5.4.2. Prophylaxis of OI Other Than PJP/PCP

Mandatory prophylactic therapy is not mandated in all subjects for the following reasons:

- Mandatory prophylaxis may cause a higher risk of side effects associated with supportive treatment where no risk factors are present
- The current schedule of assessments and additional steps noted above provide frequent monitoring and flexibility for prophylaxis based on local SOC

Although not mandated in all subjects, OI prophylaxis may be initiated at the discretion of the treating Investigator's judgment of the risk-benefit ratio in any subject, irrespective of whether a high-risk feature is present. Treatment, dosage, and route of administration must be reported on the concomitant medication page of the eCRF.

Prophylactic treatment of OI should be initiated based on SOC in subjects when high risk factors are identified (Section 5.4.1).

5.4.3. Prophylaxis of PJP/PCP

Prophylaxis against PJP/PCP is mandatory; the preferred treatment is trimethoprim-sulfamethoxazole (TMP-SMX) option because of ease of administration and is typically achieved with one tablet (TMP 80 mg/SMX 400 mg) administered once or twice daily, 3 times/week on consecutive or alternate days. However, TMP/SMX is (1) a selective inhibitor of CYP2C8, a cytochrome P450 isoform that affects zandelisib metabolism, and (2) can be associated with myelosuppression, requiring a switch to an alternate option. If TMP-SMX is not tolerated, PJP prophylaxis with either atovaquone or aerosolized pentamidine is recommended. Because dapsone has been associated with methemoglobinemia in the zandelisib Phase 1b study, it should not be used for PJP prophylaxis.

The mandatory PJP prophylaxis should start within one week of starting zandelisib until the completion of 30-day safety follow up from the last dose of zandelisib treatment.

When Prophylaxis is used for OI and PJP, treatment, dosage, and route of administration must be reported on the concomitant medication page of the eCRF.

5.5. Prohibited Treatments and Cautions for Concomitant Medications

The following medications/therapies are **prohibited** during the study:

- Other investigational agents
- Cancer therapies not mentioned in this protocol
- Dapsone (for PJP prophylaxis)
- Drugs that are strong inhibitors/inducers of CYP3A4 (Appendix 8)
- Systemic corticosteroids in doses >10 mg in prednisone equivalency are prohibited for one week prior to Cycle 1 Day 1 and during the study, except when used:
  1) for the treatment of an adverse reaction or other acute clinical situations
  2) for the treatment of an exacerbation of known chronic conditions

The following medications/therapies should be used **with caution**

- Drugs that are strong inhibitors/inducers of CYP2C8 (Appendix 7).
- Drugs that are known to prolong the QT/QTc interval should be used with caution (Appendix 9)
- Orally administered drugs known to interact with drugs that inhibit the intestinal transporters BCRP and P-gp should be used with caution

Note: Palliative radiation therapy of non-curative intent is permitted on study **except** to target and non-target lesions.

5.6. Advisory on COVID-19 Vaccination, Management, and Risk Assessment

COVID-19 vaccination, where authorized or approved by national regulatory authorities, is recommended for patients who are currently enrolled in this study, in accordance with COVID-19 vaccination guidance from scientific and medical associations (e.g., American Society of Hematology, American Society of Clinical Oncology, NCCN, and European Hematology Association).

The Sponsor completed a risk assessment for COVID-19 vaccination of patients while on study drug and concluded the benefit of receiving anti-lymphoma therapy for patients with R/R FL and MZL outweigh the potential risk of delaying treatment due to scheduled COVID-19 vaccination. Potential risks associated with COVID-19 vaccination while on study drug have not been fully established.

Vaccination is recommended, whether administered prior to enrollment or during study participation. Investigators are advised to adhere to local regulatory and institutional guidance for vaccination.

Information about vaccination should be recorded as a concomitant medication with the dates of each dose of vaccination.

If COVID-19 infection is confirmed, COVID-19 infection should be managed per local guidance until the subject recovers. In the event of a positive COVID-19 case, the investigator must determine the risk and benefit of interruption versus continuation of zandelisib. Zandelisib should be temporally interrupted. After the subject recovers from the COVID-19 event, zandelisib treatment should be resumed. Permanent discontinuation of study drug (if COVID-19 test is positive or if symptomatic COVID is diagnosed) must be discussed with the study medical monitor. If a subject is found to have a positive COVID-19 test, enter the COVID-19 results in the AE CRF page. Also, enter any AEs associated with COVID-19 infection in the AE CRF page.

5.7. Discontinuation of ME-401 Treatment

Administration of ME-401 will continue unless one of the following occurs:

- Progressive disease, unless the Investigator deems a switch to continuous dosing is in the best interest of the subject and the subject agrees to continue treatment with CS dosing
- Unacceptable AE(s) considered related/possibly related to ME-401 despite appropriate therapy and modified dosing schedule
- Withdrawal of consent by the subject
- Changes in the subject's medical condition that render further administration of ME-401 unacceptable in the judgement of the Principal Investigator or Sponsor
- Non-compliance
- Termination of study by Sponsor

Subjects who discontinue from therapy should be followed for efficacy and survival unless they withdraw consent to participate.

5.8. Discontinuation of Subjects from Study

Subjects may be discontinued from the study for any of the following reasons:

- Withdrawal of consent for further participation or follow-up
- Subject is lost to follow-up
- Termination of study by Sponsor

5.9. Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Non-compliance with International Council for Harmonisation Good Clinical Practice (ICH-GCP) guidelines
- Inadequate rate of subject recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording

- No study activity (i.e., all subjects have completed, and all obligations have been fulfilled)

5.10. Study Termination

Study termination is defined as the time when all study treatments, study-specific assessments, and study data collection are completed. Upon termination of the study, the Sponsor or designee will conduct site closure activities with the Investigator or site staff (as appropriate), in accordance with applicable regulations.

The Sponsor reserves the right to temporarily suspend or terminate the study at any time for reasons including, but not limited to, safety issues or ethical reasons. The Sponsor or designee will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action, when applicable. Where required by applicable regulations, the Investigator or head of the medical institution must inform the IRB/EC.

6. SAFETY PARAMETERS, DEFINITIONS, AND REPORTING

Safety assessments will consist of monitoring and recording AEs, serious AEs (SAEs), non-serious AESIs listed in Section 5.3.2; performing protocol-specified laboratory assessments; measuring -protocol-specified vital signs; and conducting other protocol-specified tests that are deemed critical to the evaluation of ME-401.

The Investigator will assess AEs for severity and relationship to study drug and determine if an AE meets the criteria for an SAE. Each AE will be graded in the source documents using NCI CTCAE v5.0.

All AEs observed within 30 days after study drug last dose should be reported recorded. All SAEs will be reported for up to 90 days after the last dose of study drug. All SAEs that are deemed related to the study drug must be reported even if beyond 90 days after last dose of study drug, if they become known to the investigator. All deaths should be reported and communicated to the sponsor or designee. Death not due to disease progression should be reported as an SAE. Death associated with disease progression is not an SAE.

6.1. Adverse Event (AE)

An AE is any untoward medical event that occurs in a subject following the start of study drug administration, whether or not the event is considered drug-related (ICH Guideline E6 §1.2). An AE can therefore be any of the following:

- A pre-existing medical condition can be recorded as an AE if the condition worsens by at least one grade following the start of study drug administration and if the frequency, severity, or character of the condition worsens during the study. When recording on the eCRF it is important to capture applicable descriptors (e.g., more frequent arthritic pain).
- Disease-related out-of-range laboratory values will not be considered AEs/SAEs if there is no change from the screening laboratory values. Any deterioration in a laboratory value or other clinical test that is associated with symptoms, or leads to a change in study

treatment or concomitant treatment, or discontinuation from study product, or deemed clinically significant by the Investigator will be considered an AE.

Adverse events will be recorded using the terminology defined in the NCI CTCAE v5.0.

Adverse events will be captured from the time of the first dose of study drug on Cycle 1 Day 1 and continue until 30 days after the last dose of study drug.

Any TEAE of Grade 2 or higher should be followed for resolution until either:

- The start of subsequent anti-cancer therapy
- Death

A TEAE is defined as an AE starting after the first dose until 30 days after the last dose of study drug.

Death related to disease progression is not considered an AE. Signs and symptoms related to disease progression are not considered AEs. Anticipated fluctuations of pre-existing conditions, including the disease under study that do not represent a clinically significant exacerbation or worsening, are not considered AEs.

Only one AE term should be recorded in the event field on the AE eCRF if a specific AE is attributable to a primary diagnosis. Adverse events that are secondary to other events should be identified by their primary cause, with the exception of severe or serious secondary events. For example:

- If a subject initially had diarrhea and is subsequently diagnosed with colitis, this event should be consolidated to one event, colitis
- If a subject had diarrhea that resulted in mild dehydration, only diarrhea should be reported in the eCRF
- If a subject who had diarrhea developed acute renal failure, both acute renal failure and diarrhea should be reported in the eCRF

For AEs, a diagnosis should be recorded on the AE eCRF rather than individual signs and symptoms (e.g., record only colitis rather than diarrhea, abdominal pain, decreased appetite). However, if a constellation of signs and symptoms cannot be medically characterized as a single diagnosis or syndrome, each individual event should be reported on the AE eCRF. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced on the AE eCRF based on a single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

6.2. Assessment of Severity

The term “severity” is used to describe the intensity of an AE. Severity will be graded according to NCI CTCAE v5.0. For AEs not covered by CTCAE, each AE will be assigned a category by the Investigator as described in Table 5.

Table 5: NCI CTCAE v5.0 Adverse Event Grading System

Grade	Comments
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL [a]
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL [b]
4	Life-threatening; urgent intervention indicated
5	Death related to AE

Abbreviations: ADL = activities of daily living; AE = adverse event

[a.] Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b.] Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

6.3. Action Taken with Study Drug in Response to the AE

The Investigator will record the action taken regarding the study treatment in response to an AE:

- Dose not changed
- Dosing schedule changed from CS to IS
- Drug interrupted
- Drug withdrawn
- Not Applicable
- Unknown

6.4. Outcome of AE

The Investigator will record the outcome of the AE as follows:

- Recovered/resolved
- Recovered/resolved with sequelae
- Not recovered/not resolved
- Death
- Unknown

All AEs should be followed until the event has resolved or the condition is stabilized as assessed by the Investigator.

6.5. Serious Adverse Event (SAE) Definition

Per ICH Guideline E2A §II.B, an SAE is any untoward medical occurrence (i.e., AE) that at any dose results in any of the following outcomes:

- Death
- A life-threatening condition
- An inpatient hospitalization or prolongation of an existing hospitalization
- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Any other medically important event: defined as an event that may jeopardize the subject or may require intervention to prevent one of the outcomes listed above. Medical and scientific judgement must be exercised in deciding whether an event is serious. Any new primary cancer must be reported as an SAE.

The term "life-threatening" in the definition refers to an event in which the subject was at risk of death at the time of the event; it does not include any AE that had it occurred in a more severe form or was allowed to continue might have caused death.

Elective hospitalizations not in response to an AE are not considered SAEs. Hospitalizations related to disease progression are not considered SAEs. A procedure (e.g., surgery) is not an AE in itself, but the reason for the procedure may be an AE. Admission for social reasons, without an underlying medical condition, including hospice, will not be reported as an SAE.

- After informed consent has been obtained and prior to start of study drug, only SAEs caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies) should be reported (see Section 6.6 for SAE reporting instructions).
- All SAEs will be reported for up to 90 days after last dose of study drug. After 90 days following last dose of study drug, SAEs deemed related to study treatment must be reported to the Sponsor or Sponsor's designee if they become known to the Investigator.

Severity and seriousness are independent of each other and need to be independently assessed for each AE recorded on the eCRF.

6.6. Serious Adverse Event Reporting

All SAEs must be reported to the Sponsor or Sponsor's designee (the Contract Research Organization [CRO]), namely Parexel, within 24 hours of the Investigator becoming aware of the SAE.

To report an SAE, please refer to the applicable study manual or SAE Form instructions.
An SAE shall be reported to MEI254808@Parexel.com.

Sites must follow-up with Parexel to confirm receipt of the SAE Report.

The 4 minimum criteria for a valid SAE report include:

- Study identifier

- Subject identifier
- Event term
- Study drug

The Investigator must report new significant follow-up information for these events to the CRO immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

All SAEs also must be reported by each site to the appropriate IRB/EC in accordance with local requirements for reporting SAEs to their IRB/EC.

Reporting requirements will also be based on the Investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor.

All deaths should be recorded and reported to the Sponsor or Sponsor's designee. Disease progression, hospitalization to assess disease progression, and death due to disease progression as determined by the Investigator, are not considered SAEs. All other causes of death must be reported as SAEs. The Investigator should make every effort to obtain and send death certificates and autopsy reports for all deaths to the Sponsor.

In the event of a medical emergency (requiring immediate attention regarding operation of the clinical study and/or the use of study product), study site staff will apply appropriate medical intervention according to current standards of care and will contact the Medical Monitor or designee (e.g., CRO representative) for further consultation and guidance. The Sponsor will be reporting all AEs, SAEs, and expedited safety reports (suspected unexpected serious adverse reactions [SUSARs]) according to local regulatory requirements.

6.7. Relationship of Adverse Events to Study Drug

The Investigator is obligated to assess the relationship between study drug and the occurrence of each AE. The Investigator is to use his/her best medical judgement in determining the likely relationship of the AE to study drug. The relationship of an AE or SAE to study drug is to be classified as:

- Related
- Possibly Related
- Not Related

6.8. Pregnancies

To ensure subject safety, each pregnancy in a subject on study treatment must be reported within 24 hours of learning of its occurrence on a Pregnancy Report Form using email and fax number listed in Section 6.6. Pregnancy occurring up to 3 months after receiving the last dose of study drug must be reported.

Study drug must be discontinued in a subject who becomes pregnant. The pregnancy must be followed 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. Subjects must be followed at least 8 weeks after giving birth to a child.

Pregnancy is not an AE but should be recorded on a Pregnancy Form and reported by the Investigator to the Sponsor or Designee. Pregnancy follow-up should be recorded and should include an assessment of the possible relationship to the study product of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form as described in in Section 6.6. Examples of pregnancy outcomes that are SAEs include reports of:

- Congenital anomalies or developmental delay in the fetus or the child
- Fetal death or spontaneous abortion
- Suspected adverse reactions in the neonate that are classified as serious

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

6.9. Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) will be established to review safety and efficacy data collected in the study on a regular basis with the primary purpose of protecting the safety of trial participants, the credibility of the trial, and the validity of trial results. It is expected the DSMB will meet at least once every 6 months but may meet more frequently if deemed necessary. Details regarding the DSMB are contained in a separate DSMB Charter document.

7. RESPONSE ASSESSMENT AND STUDY ENDPOINTS

7.1. Overview

Efficacy assessments will be based on the Modified Lugano Classification response criteria (Appendix 5).

Response to treatment based on the Investigator evaluation of imaging tests will be the basis for subject management.

An IRRC composed of radiologists and oncologists will review all imaging tests, and clinical data if necessary, to determine disease response and progression. All radiographic images/scans will be sent by the study sites to the central imaging vendor and archived for potential future

evaluation (e.g., evaluation using Cheson criteria). The process for image collection and transmission to the central imaging vendor can be found in the Study Manual.

Tumor imaging (neck, chest, abdomen, and pelvis) should be performed by contrast-enhanced CT and/or FDG-PET scan. Because FL and MZL is typically (FDG)-avid, as per Modified Lugano Classification (Appendix 5) FDG-PET scan is the preferred method for disease/response assessment to confirm CR. If a combined/dual PET/CT scanner is the available modality, then the CT portion of a PET/CT may be used instead of a dedicated CT provided that the CT scan is performed with a high-resolution imaging quality to ensure optimal measurement for disease/response assessment. CT scans must be performed using intravenous (IV) contrast. For subjects who are intolerant to contrast agents, the CT scan will be performed with oral contrast or MRI scans will be used. If a PET/CT is not available or is not evaluable, bone marrow biopsy will be utilized to confirm a morphologic CR documented by CT scan. The imaging schedule is described in Appendix 1- Response Assessment. In summary, imaging scans (CT scan or PET/CT scan) will be obtained with the following frequency:

- Every 2 months (±7 days) for the first 6 months on study
- Every 3 months (±7 days) for the next 12 months on study
- Every 6 months (±14 days) thereafter, starting with month 18

For subjects with gastric MZL, endoscopy with biopsy must be performed to confirm CR.

For those subjects who switch to CS after disease progression on the IS, the date of PD will be designated as a new baseline, and subsequent response assessments will be scheduled per the protocol-specified frequency (Appendix 1- Response Assessment): every 2 months for the first 6 months, then every 3 months during the next 12 months up to month 18, and every 6 months thereafter. The date of PD and CT scan at PD will be the new baseline date and CT scan for reference for assessment of recapture of response. The determination that a subject has experienced disease progression should be based on the results of a diagnostic quality CT or FDG-PET scan performed with contrast. Please refer to the Schedule of Assessments for details (Appendix 1).

To rule out a potential of false positive diagnosis of disease progression in ambiguous cases, it is highly recommended to repeat imaging assessments within 4–8 weeks after initial suspicion of PD. In case of unequivocal disease progression, repeat of scans is not necessary.

7.2. Efficacy Endpoints

The primary analysis of ORR for FL will be triggered after all 91 subjects in the FL PEP enrolled in the study (except those who discontinue early) have been followed for at least 6 months from the start of study drug.

The final analysis of ORR and DOR for MZL will be triggered after all 32 MZL subjects enrolled in the study (except those who discontinue early) have been followed for at least 14 months from the start of study drug.

7.2.1. Objective Response Rate (ORR)

The primary efficacy endpoint is ORR as determined by the IRRC, defined as the proportion of subjects achieving the best response rating of CR or PR based on the Modified Lugano Classification. ORR will also be assessed by the Investigator as a secondary endpoint.

7.2.2. Duration of Response (DOR) and Duration of Recaptured Response (DORR)

Duration of response (DOR) will be evaluated as a secondary endpoint and is defined as the time from documentation of the first CR or PR to the time of first disease progression based on the Modified Lugano Response Criteria. The endpoint DOR will be assessed by the IRRC and Investigator independently. To evaluate the duration of response for subjects who had recapture of response (Section 7.2.5) on the CS dosing, duration of recaptured response (DORR) is defined as the time from recapture of response to the time of second disease progression. The endpoint DORR will be assessed by the Investigator only.

7.2.3. Progression-Free Survival (PFS)

Progression-free survival (PFS) will be assessed as a secondary endpoint and is defined as the time from initiation of treatment (Day 1) until first disease progression or death from any cause. Disease progression criteria are defined per Modified Lugano Response Criteria and will be assessed by the IRRC and Investigator independently.

7.2.4. Time to Treatment Failure (TTF)

Time to treatment failure will be assessed as a secondary endpoint and is defined as the time from first dose of study drug to treatment failure.

Treatment failure is defined as any treatment discontinuation due to disease progression, toxicity, or death.

7.2.5. Recapture of Response

Recapture of response is defined as achieving a second documented CR or PR after experiencing the first PD.

Recapture of response rate will be assessed by the Investigator as a secondary endpoint, and is defined as the proportion of subjects who achieved a CR or PR followed by a PD during IS dosing and subsequently switched to CS dosing and achieved a second documented CR or PR.

Time to recapture of response will be assessed as a secondary endpoint, and is defined as the time from the first PD until the second documented CR or PR.

7.2.6. Overall Survival (OS)

Overall survival (OS) will be assessed as a secondary endpoint and is defined as the time from initiation of treatment (Day 1) until death from any cause independently from the study period or dosing schedule. Overall survival time will be censored at the last date the subject is known to be alive when the confirmation of death is absent or unknown.

7.3. Safety Endpoints

7.3.1. Overall Incidence Rate of Treatment-Emergent Adverse Events (TEAEs)

A TEAE is defined as any new or worsening AE occurred after first dose of study drug until 30 days after last dose of ME-401.

The overall incidence rate of TEAEs is a secondary safety endpoint. It is calculated as the proportion of subjects with at least one TEAE.

The overall incidence rate of SAEs will also be calculated.

7.3.2. Incidence Rate of AESIs

The rate of AESIs is a secondary safety endpoint. It is calculated as the proportion of subjects with at least one AESI.

7.3.3. Time to Occurrence of AESIs

Time to occurrence of AESIs will be assessed as a secondary endpoint and is defined as the time from first dose of study drug to first occurrence of an AESI.

7.3.4. Other Safety Endpoints

Other safety endpoints are the additional safety measures described in Section 11.2.2.

7.4. Pharmacokinetics

To enable PK/PD modeling, sparse PK sampling will be obtained on all subjects as shown in Table 6.

Table 6: Pharmacokinetics Sampling Schedule

Cycle	Sampling Time Within a Cycle [a]

Cycle 1	• Day 1: pre-dose
	• Day 15:
	  ○ pre-dose
	  ○ 3 hours post intake of study drug

Cycle 2	• Day 1: pre-dose
Cycle 4 and Cycle 6	• Day 7: pre-dose

[a] Pre-dose PK samples are to be obtained within 1 hour before study drug administration on Cycle 1 Day 1, Cycle 2 Day 1, Cycle 4 Day 7, and Cycle 6 Day 7. Pre-dose PK samples collected after Cycle 1 Day 1 are to be obtained within ±60 minutes of the scheduled time, which is based on the Cycle 1 Day 1 dosing time. For the 3 hours post-dose sample on Cycle 1 Day 15, the allowable window is ±30 minutes from the indicated time.

For better modeling of efficacy/exposure and safety/exposure, an accurate estimate of the time from drug intake to PK sample collection is needed. Collect accurate study drug dosing history (i.e., time of intake) on days when PK samples are collected. The subject will be asked to record information on food intake on the day preceding and on the day of the visit on which blood samples are obtained for plasma concentrations measurement.

Detailed instructions on collection of plasma for determination of ME-401 PK will be provided in a study manual.

8. STUDY PROCEDURES

See the Schedule of Assessments (Appendix 1) for a detailed list of study procedures and assessments. Instructional details (where applicable) for procedures are contained in Section 9.

8.1. Informed Consent

Each subject's signature must be obtained on a written Inform Consent Form (ICF) that has been approved by an IRB, EC, or Ethical Review Board (ERB) prior to any study-specific procedures being performed. The ICF must incorporate a Release of Medical Information that authorizes release of medical records to the trial Investigators, monitors, Sponsor and its designees, the Food and Drug Administration (FDA), or other regulatory authority. The ICF must be in a language fully comprehensible to the prospective subject. The consenting process must be documented in the medical chart and a signed copy of the ICF provided to the subject.

8.2. Screening Period

Subjects will be screened during the 28-day period prior to Cycle 1 Day 1 to ensure they meet the entry criteria for the study. During the screening period, the Investigator should carefully review each subject's medical history to ensure eligibility. All inclusion and exclusion criteria should be supported by corresponding documentation in the medical records, including a pathology report confirming the diagnosis of FL or MZL.

The Investigator or an appropriate designee will obtain informed consent from each subject prior to conducting any study-specific procedures. Bone marrow biopsies performed as part of the subject's medical care within 12 weeks of Cycle 1 Day 1 may be used for screening and eligibility determination. PET/CT or CT scans performed within 6 weeks of Cycle 1 Day 1 may be used for screening and eligibility determination as long as they meet the minimum requirements per Lugano criteria (i.e., includes all appropriate anatomical areas of the body, a slice thickness ≤5 mm). This avoids unnecessary repeat tests and undue burden on subjects.

8.3. Subject Enrollment

As of this amendment, 121 subjects with FL and 32 subjects with MZL have been enrolled and treated with ME-401 on the IS. Enrollment in this study is now closed.

Subjects will be enrolled using an Interactive Web Response System (IWRS) process.

8.4. Cycle 1 Day 1 Tests and Administration of ME-401

All Cycle 1 Day 1 tests and procedures outlined in the Schedule of Assessments (Appendix 1) must be performed prior to study drug administration. Laboratory assessments need not be repeated on Cycle 1 Day 1 if they were performed during screening period within 7 days prior to the start of treatment. Physical examination need not be performed on Cycle 1 Day 1 if it was

performed during screening within 7 days prior to the start of treatment. The Investigator should assess any changes in the subject's medical condition or history since the Screening visit.

A record of the administration of the first dose of study drug will be documented in the source documents.

8.5. Treatment Phase

The treatment phase begins from the time study drug is first administered (Day 1 of Cycle 1), and continues until the subject discontinues study treatment. Each cycle during the treatment period will consist of 28 days and will be denoted numerically (Cycle 1, Cycle 2, etc.).

After the initial 2 cycles of therapy, study visits will occur on Day 1 of each cycle for Cycles 3 to 7, then every 3 cycles thereafter (i.e., Day 1 of Cycle 10, 13, etc.) as long as the subject continues to receive study drug. The modified dosing schedule for AEs is described in Table 4.

Response assessments, as defined in Section 7, will be performed according to the Schedule of Assessments (Appendix 1) and detailed in Appendix 5. The disease/response assessment will be performed every 2 months (±7 days) for the first 6 months on study, every 3 months (±7 days) during the following 12 months, and every 6 months (±14 days) thereafter.

For those subjects who switch to CS after disease progression on IS, the date of PD will be designated as a new baseline, and subsequent response assessments will be scheduled per the protocol-specified frequency using the new baseline date and CT scan for reference.

8.6. End of Treatment (EOT) Visit (30-Day Safety Follow-up Visit)

Upon discontinuation of ME-401, an End of Treatment (EOT)/30-Day Safety Follow-up visit will occur 30 (±3) days from the last dose of study drug.

All ongoing and new AEs should be reviewed and entered on the eCRF. All assessments as indicated per the Schedule of Assessments should be completed (Appendix 1).

8.7. Post-Treatment Long-Term Follow-up

All subjects who stop study drug treatment will be followed long-term by the site every 3 months from the last dose of study drug to obtain data regarding changes in efficacy assessments, death, or subsequent therapy based on SOC assessments, which includes tumor imaging tests based on the original protocol-defined schedule for response assessment. This will be captured on the post-treatment eCRF. All subjects will be followed for survival. Survival follow-up will continue for up to 3 years after the last subject is enrolled in the study. Follow-up will be discontinued if the subject withdraws consent to participate in the study.

9. STUDY ASSESSMENTS

The following sections describe the methods for assessments of clinical and functional outcomes included in the trial. Refer to the Schedule of Assessments (Appendix 1) for frequency of assessments.

9.1. Medical History

A complete medical history will be collected during screening. Data associated with any interventional procedure, surgical operation (for any reason), and all prior cancer therapies will be collected. If known, record in the medical history information on COVID-19 vaccination administered at any time prior to subject consent to participate in the study.

9.2. Demographics

Subject demographic data including date of birth (year of birth required at a minimum), sex, and ethnicity and/or race will be recorded in the eCRFs.

9.3. Concomitant Medication

Data on concomitant prescription and over-the-counter medications will be collected. This data will be recorded from 28 days prior to Cycle 1 Day 1 and continues until 30 days after the last dose of study drug or start of new anti-cancer therapy. Information on COVID-19 vaccination administered while in the study, i.e., from when the subject signs the ICF until the subject discontinues from the study should be recorded as concomitant medication.

9.4. Physical Examination and Vital Signs

The physical examination will include the measurements of height (Screening visit only) and weight, and examination of all organ systems (at the Investigator's discretion, genitourinary system may be excluded). Vital sign measurements will include systolic and diastolic blood pressure, heart rate, and body temperature.

A symptom-directed exam will be performed on Cycle 1 Day 8, Cycle 1 Day 15, and Cycle 2 Day 15, only if needed/indicated, based on interim history.

Cutaneous assessments: For subjects who develop a rash, a detailed skin assessment is required (see Appendix 3). If a dermatology referral is warranted, biopsy results (if any) will be collected, including assessments from dermatology and pictures of rashes.

Gastrointestinal assessments: For subjects who develop diarrhea and/or colitis and undergo colonoscopy and biopsy, the results will be collected in the eCRF including pathology results.

9.5. Adverse Events

Adverse events will be collected at each visit as described in Section 6, and will be recorded from the time of dosing on Cycle 1 Day 1 until 30 days after last dose of study drug or start of new anti-cancer treatment.

Any SAE due to protocol-mandated procedures will be collected from the time of informed consent. Other SAEs will be collected from the start of study drug.

9.6. Cardiac Evaluation

12-lead ECGs will be performed at the following visits:

- Screening

- Pre-dose on Cycle 1 Day 1 (unless the Screening visit is within 3 days prior to Day 1)
- Pre-dose on Day 1 of Cycles 3, 6, 13, 19, and 25
- On Day 1 of Cycles 1 and 3 at the expected time of C_{max} (3–5 hours after dosing)
- After Cycle 25, every 6 months, pre-dose
- EOT/30-Day Safety Follow-up visit
- As clinically indicated

Left ventricular ejection fraction measurement by echocardiogram or MUGA will be performed at screening, EOT/30-Day Safety Follow-up visit, and as clinically indicated.

9.7. Laboratory Tests

Laboratory tests listed on the Schedule of Assessments (Appendix 1) will be analyzed at the investigative site's local laboratory and used in all safety analyses and response assessments (see Appendix 5); PK samples discussed in Section 7.4 will be shipped to a central laboratory for analysis.

The following tests are to be performed:

- CBC with differential: white blood cell (WBC), ANC, red blood cell (RBC), hemoglobin (HGB), hematocrit (HcT), lymphocytes, eosinophils, monocytes, basophils, platelets, mean corpuscular hemoglobin (MCH)
- Serum chemistry: glucose, blood urea nitrogen (BUN) or urea, creatinine, sodium, potassium, chloride, calcium, alkaline phosphatase (ALP), AST, ALT, total bilirubin, total protein, albumin, LDH, phosphorus
- Coagulation: activated partial thromboplastin time (aPTT), prothrombin time (PT)/ international normalized ratio (INR)
- Urinalysis: Dipstick or urine test (pH, specific gravity, glucose, ketones, blood, protein)
- Pharmacokinetic sampling (see Section 7.4)
- Pregnancy test
- HIV testing
- Hepatitis B and Hepatitis C testing
- PCR test for CMV
- OI monitoring:
    - CD4 (for subjects with signs of infection)
    - Blood cultures if febrile neutropenia occurs, or when ANC is NCI CTCAE Grade 4
    - PCR for CMV (every cycle for first 6 months of treatment and every 3 months thereafter). If PCR test is positive for CMV, treatment should be delayed until recovery. Treatment of CMV should be initiated based on local SOC. Retreatment

with ME-401 will be allowed without dose reduction once PCR test for CMV is negative.

Subjects with identified risk factors will have the following tests performed:

- CD4 and CD8 count and ratio, c-reactive protein, blood cultures
- Any additional laboratory and diagnostic methods according to local SOC reported as unscheduled laboratory and diagnostic methods of assessment
- Radiological imaging (i.e., chest X-ray or CT scans)

Note: Treatment of the OI that started while on study should be based on local SOC.

- Bone marrow aspiration/biopsy: performed at screening at the discretion of the Investigator and repeated as indicated for subjects with known or suspected marrow involvement. Bone marrow aspiration/biopsy is to include surgical pathology, immunohistochemistry, and flow cytometry as per SOC. Bone marrow aspiration/biopsy is required to confirm a CR when a nodal CR is documented by a CT scan.
- There is no requirement for routine COVID-19 testing. However, if a patient is found to have a positive COVID-19 test, enter the COVID-19 results in the AE CRF page. Also, enter any AEs associated with COVID-19 infection in the AE CRF page.

9.8. Disease/Response Assessment

All CT scans, PET/CT scans, bone marrow biopsy, and laboratory evaluation will be completed as appropriate for individual subjects (scan should be conducted using IV, or oral if indicated, contrast enhanced CT/MRI and/or PET-CT imaging modalities). Efficacy assessments will be based on the Modified Lugano Classification response criteria in Appendix 5.

All radiographic images/scans will be sent by the study sites to the central imaging vendor and archived for potential future evaluation. The process for image collection and transmission to the central imaging vendor can be found in the Study Manual.

For subjects with gastric MZL, endoscopy with biopsy will be performed to confirm CR.

9.9. Compliance Diary

A compliance diary will be provided to the subject at Cycle 1 Day 1 to record daily study drug administration. A new compliance diary will be provided at each study drug dispensing, according to the Schedule of Assessments (Appendix 1).

9.10. Dispensing of ME-401

Zandelisib (ME-401) is to be taken orally once a day at approximately the same time each day in accordance with the IS regimen (or CS dosing regimen if switched from IS after PD). ME-401 should be taken with a glass of water on an empty stomach (i.e., at least 1 hour prior to food intake or 2 hours after food intake). If a subject routinely experiences discomfort with dosing, he or she is permitted to take ME-401 with a light, non-fatty snack. On days with PK sampling, subjects should be instructed not to take study drug until after the PK sample is collected.
A compliance diary assessment and returned study drug accountability will be performed at each visit which includes study drug dispensing.

9.11. Managing the Impact of COVID-19 on Study Assessments

In light of the emerging COVID-19 pandemic, MEI acknowledges that at times it might not be feasible for ongoing study patients to visit a site due to local requirements to remain at home or existing health problems that increase their risk of infection with the novel coronavirus. To allow subjects who are enrolled in the study to continue on treatment if it is deemed in their best interest, the following mitigation activities are allowed:

- If a subject cannot visit a site for investigational product (IP) dispensing, IP may be shipped directly to the subject or be dispensed to a family member if this is acceptable per institutional procedures and local regulations. If IP is shipped to a subject's home, this should be recorded in the source documents. If the subject will require additional compliance diaries, these should be included in the IP shipment. The site should follow up with the subject to ensure receipt of IP, enter the date of receipt in the source documents, and remind the subject to complete the compliance diary. Subjects should be instructed to return all used IP containers and compliance diaries to the site at their next study visit.
- Safety laboratory assessments may be conducted at any accredited laboratory. The Investigator should review laboratory results from tests conducted at another lab to determine if the subject should continue to receive ME-401. If safety laboratory assessments are conducted at a facility that is not listed on the site's form FDA-1572 or equivalent document, this should be recorded in the source documents. All laboratory results should be entered into the eCRF as soon as possible. Laboratory accreditation certificates and normal ranges should be collected whenever feasible for any alternative laboratories that are used.
- If an onsite study visit cannot be conducted as scheduled, site personnel should contact the subject by telephone or e-mail to assess his or her current status. Telemedicine visits are allowed if acceptable per institutional procedures or local regulations. Any new AEs or changes in AEs should be recorded in the source documents and entered into the eCRF as soon as possible. Any new concomitant medications or changes to existing concomitant medications should be recorded in the source documents and entered into the eCRF as soon as feasible. Any procedures that cannot be conducted remotely or at another facility, such as vital signs or physical examinations, should be documented in the source and will be recorded as protocol deviations.
- If the subject cannot have imaging for disease assessment conducted at the facility that is approved for the study, the imaging may be delayed or conducted at an alternate facility. If imaging is conducted at another facility, please obtain the imaging report and inform your CRA. If possible, images acquired at an alternate facility should be submitted to the central imaging vendor to determine whether the imaging results are of acceptable quality and may be used for disease assessment.
- If it is not feasible to obtain PK samples, please record this in the source documents. Any missing PK samples will be considered as minor protocol deviations as PK data are not critical for assessing safety or efficacy for this study.

If a study visit or procedure is delayed due to COVID-19, this should be recorded in the source documents. If an entire study visit is missed due to COVID-19, this should be recorded in the source documents. All missed or delayed study visits or procedures will be reported as protocol deviations.

10. CORRELATIVE IMMUNE STUDY (US SITES ONLY)

A correlative immune study will be performed to characterize the effects of ME-401 over time on T-cell numbers and function, the pattern of T-cell recovery during the 3-week treatment holiday in the IS, and potential correlation between T-cells number and function and the development of delayed AEs. Because the assays for these immune studies require fresh blood samples, only US sites will be participating in this sub-study. This study is optional for subjects enrolled at US sites. Fresh blood samples will be collected and shipped overnight to a central laboratory for analysis. Samples may be shipped only Monday to Thursday. Samples may not be shipped for delivery on weekends or holidays.

Samples will be obtained pre-dose on Day 1 of Cycle 1, and then pre-dose on the following visits: Day 15 of Cycle 1; Day 1 of Cycles 2, 3, 5, 7, 10; then every 3 cycles thereafter; and at the EOT/30-Day Safety Follow-up visit. If possible, a sample will also be obtained when a subject develops a late onset Grade 2 AE of diarrhea/colitis, rash/mucositis, transaminase elevation, or NIP, or when a subject discontinues study drug permanently for another reason. Samples will be collected at the first visit of the AE, at the time when treatment is held, and at the time when treatment is resumed.

Two sets of assays will be performed on these samples:

- Mass cytometry (CyTOF) assay evaluating approximately 37 separate cell markers to measure T-cell count and function
- Luminex assay to assess changes in the chemokines CCL3, CCL4, IL-6, and TNF

Blood sample collection and processing will be described in the Study Manual.

11. STATISTICS

11.1. Sample Size

This is an open-label, single-arm study. The objectives of this study are to evaluate the efficacy and safety of ME-401 administered using an IS dosing regimen in patients with relapsed or refractory FL or MZL.

Sample Size for FL

The study will test the null hypothesis that the IRRC-reviewed ORR is ≤48% against the alternative hypothesis that it is ≥65.5%. The sample size for the PEP for FL is estimated to be 91 subjects, with at least 90% power and 1-sided alpha = 0.025.The selection of a null hypothesis of 48% was based on a review of the ORR reported with therapies that have full approval in the US for the treatment of relapsed FL (single agent rituximab, single agent bendamustine, lenalidomide plus rituximab, and obinutuzumab plus bendamustine) and therapies that have

accelerated approval in the US for the treatment of relapsed FL (tazemetostat [Tazverik® US PI], duvelisib, umbralisib (Ukoniq™ US PI), idelalisib, copanlisib), focusing on ORR reported in patients who have received ≥2 lines of therapy prior to enrollment. The selection of the alternative hypothesis of 65.5% was based on the results achieved with single agent zandelisib in Study ME-401-002, with an ORR of 70% observed in patients enrolled in the study after failure of ≥2 prior therapies (data on record).

Safety analysis will be performed based on the Safety Population, with analysis focused on the IS FL subjects at the primary analysis database lock for FL. With a total sample size of 120 FL subjects treated with ME-401 IS dosing regimen, if ≤15 subjects experience Grade ≥3 AESIs (i.e., subject incidence rate of ≤12.5% with 95% CI of 7.2–19.8%), the study can rule out the possibility of having a incidence rate ≥20% for Grade ≥3 AESIs with the IS dosing regimen. In addition, with a total sample size of 120 FL subjects, if ≤5 subjects experience a particular type of AE (i.e., subject incidence rate of ≤4.2% with 95% CI 1.4-9.5%), the study can rule out the possibility of having an incidence rate ≥10% for the AE.

Sample Size for MZL

Initially, the study was designed to test the null hypothesis that the IRRC-reviewed ORR is ≤46% against the alternative hypothesis that it is ≥66.5%. The sample size for the MZL population was estimated to be 64 subjects, with at least 90% power and 1-sided alpha = 0.025.

The selection of a null hypothesis of 46% was based on a review of the ORR reported with therapies that have full or accelerated approval in the US for the treatment of relapsed MZL (single agent lenalidomide plus rituximab, ibrutinib, umbralisib), adjusting for the requirement that subjects with MZL enrolled in the TIDAL study must have received ≥2 prior lines of therapy including an anti-CD20 antibody and chemotherapy. The selection of the alternative hypothesis was based on a clinically meaningful increase in the ORR by 20.5%.

Enrollment in the MZL arm was closed by the Sponsor on 31 August 2022, with 32 of the 64 planned subjects enrolled. The reason for early closure of enrollment is to focus enrollment of subjects with MZL in the global Phase 3 study ME-401-004. Early enrollment closure was communicated to all investigators in August 2022 and is being formalized in Amendment 5. A sample of 32 subjects will provide preliminary data on the efficacy and safety of single agent zandelisib in relapsed/refractory MZL.

11.2. Statistical Analysis

11.2.1. Analysis Populations and Analysis Sets Definitions

Detail on populations definition will be provided in the Statistical Analysis Plan (SAP). In brief:

- Safety Population includes all subjects who receive at least one dose of study drug
- Intent-to-Treat (ITT) FL Population includes all FL subjects randomized per Protocol Amendment 1 (two-arm design with randomization), and all enrolled FL subjects who received at least one dose of ME-401 per Protocol Amendment 2 or later amendment (single-arm, open-label design).

- The ITT IS FL Population is defined as all FL subjects who are intended to receive ME-401 IS regimen, including subjects who:
  - Were randomized to the ME-401 IS dosing regimen group (Group B) per Protocol Amendment 1
  - Were randomized to the ME-401 CS dosing regimen group (Group A) per Protocol Amendment 1, but re-consented under Protocol Amendment 2 (for IS dosing regimen) prior to or on their Cycle 3 visit date
  - Were enrolled per Protocol Amendment 2 or later amendment who received ME-401 IS dosing regimen.
- The ITT CS Group is defined as all FL subjects who are randomized to the ME-401 CS regimen group (Group A) per Protocol Amendment 1 and did not switch/plan to switch to the IS dosing regimen at Cycle 3 visit per Protocol Amendment 2. More specifically, this population includes subjects who were originally randomized to the ME-401 CS dosing regimen group (Group A) per Protocol Amendment 1, had their Cycle 3 visits prior to when the subjects re-consented to Protocol Amendment 2, or discontinued treatment without being re-consented under Protocol Amendment 2.
- The ITT MZL population is defined as all enrolled subjects with MZL who received at least one dose of ME-401 per Protocol Amendment 3.
- The PEP in FL is defined as the initial 91 consecutive subjects enrolled in the ITT IS FL Population.
- The DOR Primary Analysis Set for FL will include subjects in the FL PEP who achieved PR or CR prior to first PD, that is reported before the data cutoff date for the FL primary analysis.
- The DOR Supportive Analysis Set for FL will include subjects in the ITT IS FL who achieved PR or CR prior to first PD, that is reported before the data cutoff date for the primary analysis of DOR for FL.
- The DOR Analysis Set for MZL will include subjects in the ITT MZL who achieved PR or CR prior to first PD, that is reported before the data cutoff date for the MZL primary analysis.
- Efficacy Evaluable (EE) Population includes all subjects who receive at least one dose of study drug and have at least one response assessment post baseline.
- PK Population includes all subjects who receive at least one dose of study drug and who have evaluable PK data.

11.2.2. Statistical Analyses

The primary analysis of ORR for FL will be triggered after all 91 subjects in the PEP enrolled in the study (except those who discontinue early) have been followed for at least 6 months from the start of study drug.

The final analysis of DOR for FL will be triggered after most responders in the Primary Efficacy Population have a minimum of 12 months of follow-up from first response.

The final analysis of ORR and DOR for MZL will be triggered after most of the responders in the MZL ITT population (except those who discontinue early) have been followed for at least 12 months from first response.

Summary statistics for continuous variables will include the mean, standard deviation, median, and range (minimum/maximum). Categorical variables will be presented as frequency counts and percentages. Time-to-event variables will be summarized using Kaplan-Meier (KM) methods (median, 95% CI, number of events, number censored, KM figures). Data listings will be created to support each table and to present all data.

The efficacy analysis of ORR for MZL as determined by the IRRC will be based on the ITT MZL Population, utilizing the best overall ORR prior to first PD. The CR rate as determined by the IRRC will be reported similarly. The ORR as determined by the IRRC in the EE Population will be reported as a sensitivity analysis.

Secondary efficacy endpoints including DOR, DORR, PFS, TTF, time to recapture of response (as assessed by the IRRC and/or Investigator); and overall survival (OS) will be summarized using KM summary statistics for the ITT IS FL Population and ITT MZL Population respectively.

Similarly, the efficacy endpoints based on Investigator assessments will be summarized as supportive analyses.

Safety analyses will be performed on the Safety Population, as defined in Section 11.2.1.

Overall summary of safety will include but not limited to the following analyses:

- TEAEs, including severity and possible relationship to study drug and/or study treatment
- AESIs
- treatment-emergent SAEs
- discontinuations from study treatment due to AEs
- treatment-emergent abnormal changes in laboratory values
- treatment-emergent abnormal changes in vital signs.

The rate of AESIs and the respective 95% CI will be calculated by dosing group (CS and IS) and overall.

Time to AESIs will be calculated from the first day of study treatment to first occurrence of AESI, utilizing KM methodology.

Safety variables including TEAEs, AESIs, laboratory tests, vital signs, and ECGs will be summarized descriptively.

Further safety and efficacy analyses, handling of missing information, and subset analyses will be detailed in the study SAP.

Population PK analyses will be described in the Population PK Analysis Plan.

12. REGULATORY AND REPORTING REQUIREMENTS

12.1. Compliance with Laws and Regulations

The study will be conducted according to the principles of the Declaration of Helsinki (World Medical Association 2013), the International Council for Harmonisation Guideline E6 (R2) Good Clinical Practice (ICH 2016), the applicable laws and regulations of the country in which the research is conducted, and the requirements of all local regulatory authorities regarding the conduct of clinical trials and the protection of human subjects. The study will be conducted by scientifically and medically qualified persons and the rights and welfare of the subjects will be respected.

12.2. Informed Consent

The Investigator or an appropriate designee is responsible for obtaining written informed consent(s) from each study subject prior to conducting any study-specific procedures. The Investigator must use the most current IRB/EC-approved consent form when obtaining consent.

At any time, all signed and dated consent forms must be available for Sponsor/designee verification.

12.3. Institutional Review Board/Ethics Committee

Approval of this study will be obtained from an IRB/EC prior to enrolling subjects and will be reviewed and approved on an annual basis by the IRBs/ECs representing the participating institutions. Such IRBs/ECs must be appropriately constituted and meet all requirements as described in Title 21, Part 56 of the Code of Federal Regulations. The review must include the protocol, subject recruitment materials, the Investigator's Brochure, the ICF, and any other study-specific material that will be provided to subjects (including study product compliance diaries). A copy of the letter or notice of approval from the IRB/EC must be received by the Sponsor prior to shipment of drug supplies to the Investigator. The IRB/EC membership list or Federal Wide Assurance (FWA) number must be submitted to the Sponsor with the written IRB approval, and lists must be updated, if applicable.

12.4. Public Clinical Trial Registry

This study will be listed on a public clinical trial registry such as www.clinicaltrials.gov as per applicable regulations.

12.5. Confidentiality and Data Protection

The Principal Investigator and designees, employees, and agents involved with this study will comply with relevant local, state, federal and regional laws, as applicable, relating to the confidentiality, privacy, and security of subjects' health information. Data generated during this study or disclosed by the Sponsor to the Investigator will only be used as appropriate for the execution, analysis, review, and reporting of this study. Such information shall not be used for any other purposes and will remain confidential.

In order to verify subject eligibility criteria and ensure ongoing subject safety during the study and preserve the integrity of study data, notwithstanding source data verification at the study site, the Sponsor/CRO may request to review subject source medical data. Should the Sponsor request copies of subject medical data, the rationale for such request will be ethically and scientifically justified. Such records will promptly be destroyed by the Sponsor/CRO when the purpose of the review has been met.

Though the results of the study may be presented in reports, published in scientific journals, or presented at medical meetings, subject names will never be used.

12.6. Financial Disclosure

Investigators must maintain compliance with the current country-specific guidelines and regulations concerning financial disclosure.

12.7. Data Quality Assurance

Good Clinical Practice (GCP) guidelines regarding clinical data management practices and procedures are to be utilized to ensure accurate, consistent, and reliable data. The Sponsor or designee will establish a Data Management Plan for this study.

12.8. Insurance

The Sponsor will obtain liability insurance, which covers health impairments resulting from drugs and/or substances/IPs administered in the course of this study for which the subject has given his/her written Informed Consent.

13. DATA MANAGEMENT

13.1. Use of Electronic Case Report Forms

Study data will be stored and transmitted using eCRFs, using a system determined by the Sponsor. The Sponsor will provide secure access and eCRF completion guidelines, as well as study-specific training, as needed, to each site.

Data recorded in the eCRFs must be supported by information captured in source documents, which must be available at all times for inspection by authorized representatives of the Sponsor, the FDA, or other regulatory agencies. The eCRFs must be completed as soon as possible after each study visit or contact.

13.2. Study Site Monitoring

A Sponsor-designated study monitor will conduct a site initiation visit prior to the first subject signing the ICF. The study monitor will conduct routine monitoring visits at periodic intervals during the course of the study, including a visit shortly after enrollment of the first subject, as per the study-specific monitoring plan. Monitoring visits may be conducted onsite or remotely. Source data verification may be conducted remotely if allowable per institutional guidelines and local regulations.

The primary purposes of monitoring visits are to:

- Ensure the safety and welfare of study subjects
- Ensure the accuracy and completeness of eCRF entries, as verified against the source documentation
- Verify that the conduct of the study adheres to the written protocol approved by the IRB/EC, as well as regulatory requirements
- Verify that regulatory and other study-specific documentation is maintained and current
- Perform study drug product accountability (reconcile study product receipt, storage, dispensing, and return records)

13.3. Record Retention

The Investigator will retain the records of the study for two (2) years following the last date that a marketing application for ME-401 is approved in any ICH region, or if marketing approval is not obtained, for two (2) years after the IND for ME-401 has been closed in the US or until there are no pending contemplated marketing applications in an ICH region. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. The Sponsor will notify Investigators when study records retention is no longer required.

For studies conducted outside the US, the Principal Investigator must comply with the record -retention requirements set forth in the US FDA IND regulations and the relevant national or local health authorities, whichever is longer.

The site will retain copies of all versions of the protocol, Investigator's Brochure, correspondence with the IRB/EC (including submission and approval letters, approved ICFs), curricula vitae and medical licenses of the Investigator and sub-Investigator(s), forms FDA-1572 or similar forms, correspondence, laboratory documentation (including accreditation documents, reference ranges, and manuals), Delegation of Authority Log (documenting procedures delegated by the Investigator to be performed by study staff), ME-401 study product records (including receipt, storage, dispensing, and return records), source documents (including clinic charts, medical records, laboratory results, radiographic reports), training records, screening/enrollment logs, monitoring visit logs, and study procedure manuals.

Should the Investigator leave the institution or otherwise withdraw from the investigation, or should there be any changes in the archival arrangements for the study records, the Sponsor will be notified. The Sponsor will be notified of the identity of any individual assuming responsibility for maintaining the study records and the location of their storage. If no other individual at the investigational site is willing to assume this responsibility, the Sponsor will assume responsibility for maintaining the study records.

14. AMENDMENTS TO THE PROTOCOL

Amendments will be originated and documented by the Sponsor. Individual study sites should communicate requests for protocol amendments directly to the Sponsor or its designee. The

Sponsor may be required to discuss potential protocol amendments with the appropriate regulatory agencies. Amendments shall only be implemented following the required regulatory and ethical review and approval. Protocol amendments also may require changes to the ICF.

15. PUBLICATION POLICY

The Sponsor intends to publish the results of this trial as soon as possible following completion of data analysis. Data derived from the trial are the exclusive property of the Sponsor. Authorship (both inclusion and sequence) will be determined by mutual agreement. In the event of a disagreement on authorship, the Sponsor will serve as adjudicator.

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APPENDIX 1. SCHEDULE OF ASSESSMENTS

Assessment/Procedure	Screening [b]	Cycle 1			Cycle 2		Cycle 3	Cycle 4		Cycle 5	Cycle 6		Cycle 7	Cycles 10, 13, 16, 19, 22, 25 [d]…	EOT/30-Day Safety Follow-up [e]	Post-Treatment Long-Term Follow-up
Day(s) of Cycle	**-28 to -1**	**1 [c]**	**8**	**15**	**1**	**15**	**1**	**1**	**7**	**1**	**1**	**7**	**1**	**1**	**30 (± 3) days post last dose or treatment discontinuation**	**Every 3 Months**
Study Day(s)	**-28 to -1**	**1**	**8**	**15**	**29**	**43**	**57**	**85**	**91**	**113**	**141**	**147**	**169**	**253, 337, 421, 505, 589…**		
Visit Window (days) [a]			**±3**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7 [a]**		
Informed consent form (ICF)	X															
Medical history[f]	X															
Physical examination	X	X			X		X	X		X	X		X	X	X	
Symptom-directed exam [g]			X	X		X										
Vital signs [h]	X	X	X	X	X	X	X	X		X	X		X	X	X	
Height	X															
Weight	X	X			X		X	X		X	X		X	X	X	
ECOG performance status	X	X			X		X	X		X	X		X	X	X	
Pregnancy test [i]	X	X			X		X	X		X	X		X	X	X	
HIV testing [j]	X															
Hepatitis B and C testing [k]	X															
Adverse events [l]		X	X	X	X	X	X	X		X	X		X	X	X	
Concomitant medication [m]	X	X	X	X	X	X	X	X		X	X		X	X	X	
ECG [n]	X	X					X				X			X	X	
CBC with differential [o]	X	X	X	X	X	X	X	X		X	X		X	X	X	
Serum chemistry [p]	X	X	X	X	X	X	X	X		X	X		X	X	X	
Coagulation [q]	X	X			X		X			X			X	X	X	
PCR test for CMV	X	X			X		X	X		X	X		X	X		
Urinalysis (Dipstick) [r]	X	X			X		X	X		X	X		X	X	X	
COVID-19 test[s]	X															

Assessment/Procedure	Screening [b]	Cycle 1			Cycle 2		Cycle 3	Cycle 4		Cycle 5	Cycle 6		Cycle 7	Cycles 10, 13, 16, 19, 22, 25 [d]…	EOT/30-Day Safety Follow-up [e]	Post-Treatment Long-Term Follow-up
Day(s) of Cycle	**-28 to -1**	**1 [c]**	**8**	**15**	**1**	**15**	**1**	**1**	**7**	**1**	**1**	**7**	**1**	**1**	**30 (± 3) days post last dose or treatment discontinuation**	**Every 3 Months**
Study Day(s)	**-28 to -1**	**1**	**8**	**15**	**29**	**43**	**57**	**85**	**91**	**113**	**141**	**147**	**169**	**253, 337, 421, 505, 589…**		
Visit Window (days) [a]			**±3**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7 [a]**		
Issue and assess compliance diary [t]		X			X		X	X		X	X		X	X		
Dispense study drug [u]		X			X		X	X		X	X		X	X		
PK Sampling [v]		X		X[w]	X				X			X				
Echocardiogram or MUGA [x]	X														X	
Correlative immune study (pre-dose) [y]		X		X	X		X			X			X	X	X	
Opportunistic infection monitoring [z]		X			X		X	X		X	X		X	X	X	
Post-Treatment Follow-up procedures [aa]																X

Response Assessment [,bb,cc]	Screening	Every 2 Months for the First 6 Months			Every 3 Months for the Next 12 Months (through 18 Months)				Every 6 Months Thereafter
Study Day		**61**	**121**	**182**	**274**	**365**	**456**	**547**	**730, 912, 1095…**
Visit Window (days)		**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±14**
CT neck/chest/abdomen/pelvis [dd]	X	X	X	X	X	X	X	X	X
FDG-PET scan [ee]	X		X			X			
Bone marrow biopsy/aspirate [ff]	X								
Endoscopy with biopsy [gg]	X								

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; ANC = absolute neutrophil count; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BP = blood pressure; BUN = blood urea nitrogen; CBC = complete blood count; CMV = cytomegalovirus; CMR = complete metabolic response; CO_2 = carbon dioxide; CR = complete response; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FDG-PET = ^{18}F-fluorodeoxyglucose positron emission tomography; HcT = hematocrit; HGB = hemoglobin; HIV = human immunodeficiency virus; HR = heart rate; ICF = informed consent form; INR = international normalized ratio; LDH = lactate dehydrogenase; MCH = mean corpuscular hemoglobin; MUGA = multigated acquisition scan; PCR = polymerase chain reaction; PK = pharmacokinetic; PT = prothrombin time; RBC = red blood cell; SOC = standard of care; WBC = white blood cell

[a.] **Study Assessment Day(s)** – There is ±3-day window allowable for each clinic visit for Cycle 1 Day 8 and Cycle 1 Day 15. For Cycles 2 through 25, the allowable window is ±7 days. After Cycle 25, the allowable window is ±1 month for each clinic visit and its associated assessments.

[b.] **Screening –** Screening assessments are to be performed within 28 days prior to enrollment. Upon confirmation of meeting eligibility criteria, subjects should be treated within a reasonable time frame (within 5 days). If there are >7 days between screening laboratory assessments and expected Cycle 1 Day 1 dosing, then the laboratory assessments should be repeated and reviewed prior to the first dose of ME-401. Some tests performed prior to obtaining ICF (e.g., CT scan, bone marrow biopsy) may not need to be repeated for the study as long as they were performed within the allowed screening window: refer to Appendix 5.

[c.] **Cycle 1 Day 1** – Physical examination need not be repeated on Cycle 1 Day 1 if performed within 7 days prior to start of treatment. Laboratory assessments (CBC with differential, serum chemistry, coagulation, urinalysis) need not be repeated on Cycle 1 Day 1 if performed within 7 days prior to start of treatment.

[d.] **Cycle 25+ –** Subjects who remain on study after 25 cycles (approximately 2 years) will visit the clinic every 3 months (±1 month), with a response assessment performed every 6 months as per standard of care.

[e.] **EOT/30-Day Safety Follow-up –** Visit will be completed 30 (±3) days post last dose of study drug administration (or prior to starting a new treatment if urgent treatment is required) or from study drug discontinuation.

[f.] If known, record in the medical history information on COVID-19 vaccination administered at any time prior to subject consent to participate in the study.

[g.] **Symptom-directed exam –** Performed on Cycle 1 Day 8, Cycle 1 Day 15, and Cycle 2 Day 15, only as needed/indicated, based on interim history.

[h.] **Vital signs** – BP, HR, temperature.

[i.] **Pregnancy test** – The screening serum pregnancy test in females of childbearing potential must be completed within 28 days prior to Cycle 1 Day 1. Urine or serum pregnancy test must be performed on study Day 1. For women of childbearing potential, a monthly serum or urine pregnancy test will be conducted every dosing cycle and 30 days after discontinuation of dosing.

[j.] **HIV testing** – HIV antibody is required.

[k.] **Hepatitis B and C testing** – Hepatitis B core antibody, Hepatitis B surface antigen, and hepatitis C antibody are required. Hepatitis B PCR is required if hepatitis B core antibody and/or surface antigen is positive. Hepatitis C PCR is required if hepatitis C antibody is positive.

[l.] **Adverse events** – Recorded from the time of the first dose of study drug on Cycle 1 Day 1 and continues until 30 days after the last dose of study drug or start of new anti-cancer treatment.

[m.] **Concomitant medications** – Recorded from 28 days prior to Cycle 1 Day 1 until the EOT/30-Day Safety Follow-up visit, or start of new anti-cancer treatment. Please, record information about COVID-19 vaccination, if performed.

[n.] **ECG** – 12-lead ECGs performed at screening; Cycle 1 Day 1 pre-dose (unless the Screening visit is within 3 days prior to Day 1); pre-dose on Day 1 of Cycles 3, 6, 13, 19, and 25, and every 6 months thereafter; at the EOT/30-Day Safety Follow-up visit, and as clinically indicated. ECGs should be performed pre-dose. For Cycle 1 Day 1 and Cycle 3 Day 1, ECGs should be taken pre-dose and at expected C_{max} (3–5 hours after dosing).

[o.] **CBC with differential** – WBC, ANC, RBC, HGB, HcT, lymphocytes, eosinophils, monocytes, basophils, platelets, and MCH. Screening labs must be repeated if performed >7 days prior to Cycle 1 Day 1.

[p.] **Serum chemistry** – Glucose, BUN or urea, creatinine, sodium, potassium, chloride, calcium, ALP, AST, ALT, total bilirubin, total protein, albumin, LDH, and phosphorous. Screening labs must be repeated if performed >7 days prior to Cycle 1 Day 1.

[q.] **Coagulation** – aPTT, PT/INR. Screening labs must be repeated if performed >7 days prior to Cycle 1 Day 1.

[r.] **Urinalysis** – Dipstick or urine test (pH, specific gravity, glucose, ketones, blood, and protein). Screening labs must be repeated if performed >7 days prior to Cycle 1 Day 1.

[s.] **COVID-19 test results –** Please record COVID-19 test results in the AE CRF page, if positive.

[t.] **Issue and Assess Compliance Diary** – Compliance diary to record daily study drug administration. Returned diaries are to be assessed for study product compliance. New compliance diary is to be issued with each dispensing of ME-401.

[u.] **Dispense Study Drug** – Study drug is to be taken orally once a day on an empty stomach at least 1 hour prior to food intake or 2 hours after food intake at the same time each day. On days of PK sampling, instruct subjects to not take study drug until after the pre-dose PK sample is drawn. Compliance diary and count of returned capsules are performed on each day of dispensing study drug.

[v.] **PK sampling** – Pre-dose PK samples are to be obtained within 1 hour before study drug administration on Cycle 1 Day 1, Cycle 2 Day 1, Cycle 4 Day 7, and Cycle 6 Day 7. Pre-dose PK samples collected after Cycle 1 Day 1 are to be obtained within ±60 minutes of the scheduled time, which is based on the Cycle 1 Day 1 dosing time.

[w.] **PK Sampling** – **Cycle 1 Day 15**: pre-dose and 3 hours (±30 min) post intake of study drug. Collect data regarding food and drink intake 4 hours prior to study drug intake.

[x.] **Echocardiogram or MUGA** – Performed at screening, EOT/30-Day Safety Follow-up visit, and as clinically indicated. The same methodology (echocardiogram or MUGA) should be used throughout the study.

[y.] **Correlative Sample Study** – US Sites only. Samples will be obtained pre-dose on Day 1 of Cycle 1, and then pre-dose on the following visits: Day 15 of Cycle 1; Day 1 of Cycles 2, 3, 5, 7, 10; then every 3 cycles thereafter; and at the EOT/30-Day Safety Follow-up visit. Fresh blood samples will be collected and shipped overnight to a central laboratory for analysis. Samples may be shipped only Monday to Thursday. Samples may not be shipped for delivery on weekends or holidays. If possible, a sample will also be obtained when a subject develops a late onset Grade 2 AE of diarrhea/colitis, rash/mucositis, transaminase elevation, or non-infectious pneumonitis, or when a subject discontinues study drug permanently for another reason. Samples will be collected at the first visit of the adverse event, at the time when treatment is held, and at the time when treatment is resumed.

[z.] **Opportunistic Infection Monitoring** – Prior to start of every cycle of treatment with ME-401, monitoring will be conducted, and for subjects with identified risk factors and those who developed an OI while on study treatment, additional assessments should include: CD4 and CD8 count and ratio, c-reactive protein, blood cultures, any additional laboratory and diagnostic methods according to local SOC reported as unscheduled laboratory and diagnostic methods of assessment, radiological imaging (i.e., chest X-ray or CT scans). Note: Treatment of the OI that started while on study should be based on local SOC.

[aa.] **Post-treatment Follow-up Procedures** –Every 3 months from the last dose of study drug to obtain data regarding changes in efficacy assessments, death or subsequent therapy based on standard of care assessments. Imaging tests to assess disease status will be performed at least once every 6 months or earlier as indicated per standard of care. Any AE that has not returned to baseline or Grade ≤2 should be followed until it has returned to baseline or better, the event is assessed as stable by the Investigator, the subject is lost to follow up, or the subject withdraws consent. Survival follow-up will continue for up to 3 years after the last subject is enrolled in the study.

[bb.] **Response assessment** – Imaging scans, physical examination, bone marrow aspirate/biopsy (if applicable), and laboratory evaluation as appropriate for individual subjects.

[cc.] **Response assessment at the EOT/30-Day Safety Follow-up visit** – Perform imaging test (CT scan or PET/CT scan) only if last imaging tests outside the window noted for CT scan or PET-CT.

[dd.] **CT Scan** – CT of the neck, chest, abdomen, and pelvis must be obtained at screening (within 6 weeks prior to Cycle 1 Day 1). CT scans must be performed using IV contrast. For subjects who are intolerant to contrast agents, the CT scan will be performed with oral contrast or MRI scans will be used.

[ee.] **PET/CT** – FDG-PET scan must be obtained at screening (within 6 weeks prior to Cycle 1 Day 1), as indicated, and to confirm CR/CMR. PET/CT imaging is no longer needed once a CMR has been achieved and a CT scan is an appropriate imaging test.

[ff.] **Bone marrow biopsy/aspirate** – Bone marrow biopsy/aspirate is obtained at screening and to confirm CR if PET scans were not performed or were not evaluable to assess bone marrow involvement. In addition, it can be performed as clinically indicated at the discretion of the Investigator.

[gg.] **Endoscopy with biopsy** – For subjects with gastric MZL, endoscopy with biopsy to be performed to confirm CR.

APPENDIX 2. COCKCROFT-GAULT EQUATION FOR ESTIMATED CREATININE CLEARANCE

Estimate the subject's creatinine clearance using the serum creatinine value provided by the local laboratory, actual body weight, and the appropriate Cockcroft-Gault formula (if necessary, convert serum creatinine values from µmol/L to mg/dL by dividing by 88.4; for example, 100 µmol/L divided by 88.4 equals 1.131 mg/dL):

Estimated Creatinine Clearance (C_{Cr}) by the Cockcroft-Gault Equation:
$$C_{Cr} = \frac{(140 - age\ in\ years)\ \times\ (weight\ in\ kg)}{72\ \times (serum\ creatinine\ in\ mg/dL)} \times (0.85\ if\ female)$$

Abbreviations: CCr = creatinine clearance (in mL/minute)

APPENDIX 3. SKIN ASSESSMENT

In the event of cutaneous or mucosal disease, the following assessments are required:

Date Rash or Mucosal Disease Began _____

Date Resolved _____

Date of Consultation _____

Event date as related to the study Cycle 1 Day 1 _____

RASH SYMPTOMS		
Skin Pain/Tenderness	Y	N
Pruritus	Y	N
Blistering/sloughing/epidermal detachment	Y	N
If yes, please estimate total body surface area (TBSA) of blistered/detached skin _____%		
Pustules	Y	N
Facial/ear edema	Y	N
Other, Please specify _____		
Please estimate TBSA of all skin involvement _____%		

MUCOSAL INVOLVEMENT		
Ocular symptoms	Y	N
Oral Symptoms	Y	N

SYSTEMIC INVOLVEMENT		
Elevated AST, ALT, Alk Phos, and/or Tbili	Y	N
Elevated total number of eosinophils: ≥500/µL	Y	N
≥1500/µL	Y	N

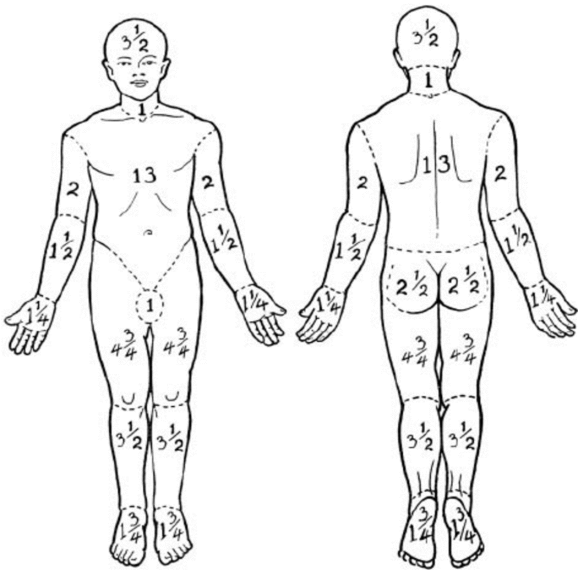
HISTORY

Please circle Y for yes, N for no, or UNK for Unknown

Allergies to medicine	Y	N	UNK
Specify: _____			
Skin Problems	Y	N	UNK
Specify: _____			

TREATMENT FOR SKIN/MUCOSAL DISEASE		
High dose steroids ≥1 mg/kg prednisone (or equivalent)	Y	N
If yes, dated began: _____		
Low dose steroids <1 mg/kg prednisone (or equivalent)	Y	N
If yes, dated began: _____		
Topical steroids of any potency	Y	N
Other, please specify _____		
Other, please specify _____		

PROCEDURE		
Did the subject undergo skin biopsy	Y	N
Results: _____		
_____		
_____		
Did disease resolve in ≥15 days?	Y	N
Do you think this was a drug reaction?	Y	N
If yes, what do you think is/are the likely culprit drug(s)? _____		
_____		



APPENDIX 4. GUIDELINES FOR WOMEN OF CHILDBEARING POTENTIAL AND FERTILE MALE SUBJECTS

For females of childbearing potential, defined as all premenopausal women capable of becoming pregnant, must agree to use a medically effective contraceptive method (has a failure rate of <1% per year) starting with the first dose of study drug through 6 months and 1 week (i.e., 25 weeks) after study drug discontinuation.

Postmenopausal women are defined as no menstrual periods for at least 12 consecutive months OR follicle-stimulating hormone (FSH) greater than 40 IU/L on at least two occasions.

Fertile male subjects, defined as all males physiologically capable of conceiving offspring, must agree to use a medically effective contraceptive method starting with the first dose of study drug through 3 months and a week (i.e., 13 weeks) after study drug discontinuation. This requirement applies to fertile male subjects who are sexually active with a female partner of child-bearing potential. Male subjects must also refrain from donating sperm during their participation in the study until 90 days after completing the study.

Acceptable Contraception Methods:

Highly effective contraception is defined as:

True Abstinence	When this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
Sterilization	When a woman of childbearing potential has had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks prior to study entry. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment.
Male Partner Sterilization	When the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate.
Use of a combination of any two of the following (one from a *and* one from b):	a) Placement of an intrauterine device (IUD) or intrauterine system (IUS) or established use of oral, injected, or implanted hormonal methods of contraception b) Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.

Unacceptable Contraception Methods:

Unacceptable contraception methods for women of childbearing potential include:

- IUD progesterone T
- Female condom
- Natural family planning (rhythm method) or breastfeeding
- Fertility awareness
- Withdrawal
- Cervical shield

APPENDIX 5. LYMPHOMA RESPONSE CRITERIA: MODIFIED LUGANO CLASSIFICATION

SELECTION OF TARGET LESIONS

Up to six of the largest dominant nodes or tumor masses selected according to all of the following:

1. Clearly measurable in two diameters (longest diameter [LDi] and shortest diameter) at baseline
    a. All nodal lesions must measure >1.5 cm in longest diameter regardless of short axis measurement
    b. All measurable extranodal lesions should have a longest tumor diameter >1.0 cm
2. All other lesions (including nodal, extranodal, and assessable disease) should be followed as nontarget lesions
3. If possible, the lesions should be from disparate regions of the body
4. Should include mediastinal and retroperitoneal areas of disease whenever these sites are involved

SELECTION OF NON-TARGET LESIONS

Non-target lesions will be qualitatively assessed at each subsequent timepoint. All of the sites of disease present at baseline and not classified as target lesions will be classified as non-target lesions, including any measurable lesions that were not chosen as target lesions.

Examples of non-target lesions include:

1. All bone lesions, irrespective of the modality used to assess them
2. Lymphangitis of the skin or lung
3. Cystic lesions
4. Irradiated lesions
5. Measurable lesions beyond the maximum number of 6
6. Groups of lesions that are small and numerous
7. Pleural/pericardial effusions and/or ascites
    a. Effusions, ascites, or other fluid collections will be followed as non-target lesions
    b. At each assessment point, radiologists will check for the presence or absence of effusions/ascites. If there is a significant volume increase in the absence of a benign etiology, progression can be assessed
    c. Significant new effusions, ascites, or other fluid collections, which are radiographically suggestive of malignancy should be recorded as new lesions and should be assessed

Response should be determined on the basis of radiographic and clinical evidence of disease. For subjects who achieve a CR by CT criteria, an FDG-PET will be performed. Assessment by PET should follow the criteria described by Cheson 2014 which is summarized in Table 7.

- Overall response should be determined based upon the Modified Lugano response criteria (Table 8).

Spleen Involvement

- Splenomegaly defined as enlargement of spleen measured by vertical (cranial or caudal) length of >13 cm. Nodal measurable lesions can be followed as target, non-target, or new extra-nodal lesions.

Liver Involvement

- CT measurements used for qualitative assessment of liver involvement, and FDG-PET used for assessment of response (e.g., new uptake indicative of disease progression). Nodal measurable lesions followed as target, non-target, or new extra-nodal lesions.

Table 7: Revised Criteria for Response Assessment from Cheson et al. 2014

Response Site	PET/CT—Based Response	CT-Based Response
Complete Response	**Complete metabolic response**	**Complete radiologic response (all of the following)**
Lymph nodes and extralymphatic sites	• Score 1, 2, or 3 [a] with or without a residual mass on 5PS [b] • It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake.	• Target nodes/nodal masses must regress to ≤1.5 cm in LDi • No extralymphatic sites of disease
Nonmeasured lesions	• Not applicable	• Absent
Organ enlargement	• Not applicable	• Regress to normal
New lesions	• None	• None
Bone marrow	• No evidence of FDG-avid disease in marrow	• Normal by morphology; if indeterminate, IHC-negative
Partial Response	**Partial metabolic response**	**Partial remission (all of the following):**
Lymph nodes and extralymphatic sites	• Score 4 or 5b with reduced uptake compared with baseline and residual mass(es) of any size. • At interim, these findings suggest responding disease. • At end of treatment, these findings indicate residual disease.	• ≥50% decrease in SPD of up to 6 target measurable nodes and extranodal sites • When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value • When no longer visible, 0 × 0 mm • For a node >5 mm × 5 mm, but smaller than normal; use actual measurement for calculation
Nonmeasured lesions	• Not applicable	• Absent/normal, regressed, but no increase
Organ enlargement	• Not applicable	• Spleen must have regressed by >50% in length beyond normal
New lesions	• None	• None

Table 7: Revised Criteria for Response Assessment from Cheson et al. 2014 (Continued)

Response Site	PET/CT—Based Response	CT-Based Response
Bone marrow	• Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan.	• Not applicable
No Response or Stable Disease	**No metabolic response**	**Stable disease**
Target nodes/nodal masses, extranodal lesions	• Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	• <50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	• Not applicable	• No increase consistent with progression
Organ enlargement	• Not applicable	• No increase consistent with progression
New lesions	• None	• None
Bone marrow	• No change from baseline	• Not applicable
Progressive Disease	**Progressive metabolic disease**	**Progressive disease requires at least one of the following**
Individual target nodes/nodal masses	• Score 4 or 5 with an increase in intensity of uptake from baseline and/or	• PPD progression:

Extranodal lesions	• New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	• An individual node/lesion must be abnormal with
		• LDi >1.5 cm and
		• Increase by ≥50% from PPD nadir and
		• An increase in LDi or SDi from nadir
		  ○ 0.5 cm for lesions ≤2 cm
		  ○ 1.0 cm for lesions >2 cm
		• In the setting of splenomegaly, the splenic length must increase by >50% of the extent of its prior increase beyond baseline (e.g., a 15 cm spleen must increase to >16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline. New or recurrent splenomegaly

Table 7: Revised Criteria for Response Assessment from Cheson et al. 2014 (Continued)

Response Site	PET/CT—Based Response	CT-Based Response
Nonmeasured lesions	• None	• New or clear progression of pre-existing nonmeasured lesions
New Lesions	• New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered.	• Regrowth of previously resolved lesions • A new node >1.5 cm in any axis • A new extranodal site >1.0 cm in any axis; if <1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma • Assessable disease of any size unequivocally attributable to lymphoma
Bone Marrow	• New or recurrent FDG-avid foci	• New or recurrent involvement

Abbreviations: 5PS = 5-point scale; CT = computed tomography; FDG = ^{18}F-fluorodeoxyglucose; GI = gastrointestinal; IHC = immunohistochemistry; LDi = longest transverse diameter of a lesion; MRI = magnetic resonance imaging; PET = positron emission tomography; PPD = cross product of the LDi and perpendicular diameter; SDi = shortest axis perpendicular to the LDi; SPD = sum of the product of the perpendicular diameters for multiple lesions.

[a.] Measured dominant lesions: up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (e.g., liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (e.g., GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (e.g., with marrow activation as a result of chemotherapy or myeloid growth factors).

[b.] PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

Table 8: Modified Lugano Response Criteria

Morphologic Response	Metabolic Response	Bone Marrow Biopsy	Prior Combined Response	Lugano Combined Response
NE/No CT	CMR			CR
	PMR			SD unless the previous CT scan indicated CR or PR, then combined response is PR*
	NMR			SD
	PMD			PD
	NE/No PET			NE
PD	CMR			PD
	PMR			PD
	NMR			PD
	PMD			PD
	NE/No PET			PD
SD	CMR			CR
	PMR			SD*
	NMR			SD
	PMD			PD
	NE/No PET***			SD
PR	CMR			CR
	PMR			PR
	NMR			PR*
	PMD			PD
	NE/No PET***			PR
CR	CMR			CR
	PMR			PR
	NMR			PR
	PMD			PD
	NE/No PET		No prior PET response	PR
	NE/No PET		No prior response and prior PET was negative	CR
	NE/No PET		SD	PR
	NE/No PET		PR	PR
	NE/No PET		CR	CR
	NE/No PET		PD and prior evaluable PET was not PMD	PR
	NE/No PET***		PD and prior PET was PMD	NE
	NE/No PET	CR**		CR

Abbreviations: BMB = bone marrow biopsy; CMR = complete metabolic response; CR = complete response; CT = computed tomography; NE = not evaluated; NMR = no metabolic response; PD = progressive disease; PET = positron emission tomography; PMD = progressive metabolic disease; PMR = partial metabolic response; PR = partial response; SD = stable disease

* Lugano combine response criteria for this response combination has been modified per FDA request.

** When a PET scan is not acquired or not evaluable, a bone marrow biopsy (BMB) is required to confirm a CR by CT. If no BMB is taken (and no PET can be acquired for this time point), the best possible overall response is a PR unless the prior overall response meets either criteria: prior overall response was CR or there was no prior overall response and the baseline/prior PET was negative.

*** When a timepoint does not have an evaluable PET scan, the morphologic response is not PD, and the most recent evaluable PET scan indicated a metabolic response of PMD, then the combined response will be NE. An improved combined response without evidence that the findings in the prior PET scan have resolved isn't justified. However, there is not PET-based evidence that the subject has continuing PD, so the response is designated as NE.

APPENDIX 6. ECOG PERFORMANCE STATUS CRITERIA

Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., 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	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

References: Oken 1982.

APPENDIX 7. LIST OF CYP2C8 INHIBITORS AND INDUCERS

Following is a table of known inducers and inhibitors of CYP2C8.

Inhibitors of CYP2C8 can be classified by their potency, such as:

- **Strong inhibitor** being one that causes at least a 5-fold increase in the plasma AUC values, or more than 80% decrease in clearance.
- **Moderate inhibitor** being one that causes at least a 2-fold increase in the plasma AUC values, or 50–80% decrease in clearance.
- **Weak inhibitor** being one that causes at least a 1.25-fold but less than 2-fold increase in the plasma AUC values, or 20–50% decrease in clearance.

Inhibitors	Inducers
Strong inhibitor gemfibrozil **Moderate inhibitor** trimethoprim glitazones montelukast quercetin	**Unspecified potency** rifampin

Note: Medicines on this list must be reviewed by Principal Investigators on an ongoing basis to assure updates.

Please note the following: This is not an exhaustive list. For an updated list, see the following links:

- http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#4
- http://medicine.iupui.edu/clinpharm/ddis/main-table/

APPENDIX 8. LIST OF CYP3A INHIBITORS AND INDUCERS

Strong CYP3A Inhibitors
Antibiotics: clarithromycin, telithromycin, troleandomycin
Antifungals: itraconazole, ketoconazole, posaconazole, voriconazole
Antivirals: boceprevir, telaprevir
Other: cobicistat, conivaptan, elvitegravir, mibefradil, nefazodone
Protease inhibitors: indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir
Moderate CYP3A Inhibitors
CYP3A4, CYP3A5, CYP3A7
Antibiotics: ciprofloxacin, erythromycin
Antifungals: fluconazole, clotrimazole
Protease inhibitors: amprenavir, atazanavir, darunavir/ritonavir, fosamprenavir
Calcium channel blockers: diltiazem, verapamil
Tyrosine kinase inhibitors (anticancer): imatinib, crizotinib
Food products: grapefruit juice (*citrus paradisi* juice)
Herbal medications: Schisandra sphenanthera
Others: amiodarone, aprepitant, casopitant, cimetidine, cyclosporine, dronedarone, tofisopam
Strong/Moderate CYP3A Inducers*
Avasimibe, bosentan, **carbamazepine**, efavirenz, **enzalutamide**, etravirine, **phenytoin**, **rifampin (rifampicin)**, **St. John's wort (hypericum perforatum), mitotane** modafinil, phenobarbital, rifabutin

Abbreviation: CYP = cytochrome P450.
Note: The list of drugs in this table is not exhaustive. Please refer to the prescribing information of concomitant medication to check for CYP3A inhibition or induction risks or contact the medical monitor of the protocol.
Source: Food and Drug Administration Drug Development and Drug Interactions: Table of Substrates, Drug Development and Drug Interactions and Inducers. Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine.
http://medicine.iupui.edu/flockhart/table.htm.
* Strong inducers of CYP3A are shown in bold.

APPENDIX 9. LIST OF DRUGS KNOWN TO PROLONG QT/QTC INTERVAL

The table below includes a list of drugs known to prolong QT/QTc interval from https://www.cpsbc.ca/files/pdf/Methadone-Drugs-QT-Interval-Prolongation.pdf.

Note: Medicines on this list must be reviewed by Principal Investigators on an ongoing basis to assure updates.

Generic Name	Brand Names (Partial List)
Alfuzosin	Uroxatral®
Amantadine	Symmetrel®, Symadine®
Amiodarone	Cordarone®, Pacerone®, Nexterone®
Amisulpride (Only on Non US Market)	Solian®, Supitac®, Soltus®, Amitrex®, Amazeo®
Amitriptyline	Elavil® (Discontinued 6/13), Tryptomer®, Tryptizol®, Laroxyl®, Saroten®, Sarotex® Lentizol®, Endep®
Anagrelide	Agrylin®, Xagrid®
Apomorphine	Apokyn®, Ixense®, Spontane®, Uprima®
Aripiprazole	Abilify®, Aripiprex®
Arsenic trioxide	Trisenox®
Artenimol+piperaquine	Eurartesim®
Asenapine	Saphris®, Sycrest®
Astemizole (Removed from Market)	Hismanal®
Atazanavir	Reyataz®
Atomoxetine	Strattera®
Azithromycin	Zithromax®, Zmax®
Bedaquiline	Sirturo®
Bepridil (Removed from Market)	Vascor®
Bortezomib	Velcade®, Bortecad®
Bosutinib	Bosulif®
Ceritinib	Zykadia®
Chloral hydrate	Aquachloral®, Novo-Chlorhydrate®, Somnos®, Noctec®, Somnote®
Chloroquine	Aralen®
Chlorpromazine	Thorazine®, Largactil®, Megaphen®
Cilostazol	Pletal®
Ciprofloxacin	Cipro®, Cipro-XR®, Neofloxin®
Cisapride (Removed from Market)	Propulsid®
Citalopram	Celexa®, Cipramil®
Clarithromycin	Biaxin®, Prevpac®
Clomipramine	Anafranil®
Clozapine	Clozaril®, Fazaclo®, Versacloz®
Cocaine	Cocaine

Generic Name	Brand Names (Partial List)
Crizotinib	Xalkori®
Cyamemazine (cyamepromazine) (Only on Non-US Market)	Tercian®
Dabrafenib	Tafinlar®
Dasatinib	Sprycel®
Degarelix	Firmagon®
Delamanid (Only on Non-US Market)	Deltyba®
Desipramine	Pertofrane®, Norpramine®
Dexmedetomidine	Precedex®, Dexdor®, Dexdomitor®
Diphenhydramine	Benadryl®, Nytol®, Unisom®, Sominex®, Dimedrol®, Daedalon®
Disopyramide	Norpace®
Dofetilide	Tikosyn®
Dolasetron	Anzemet®
Domperidone (Only on Non-US Market)	Motilium®, Motillium®, Motinorm Costi®, Nomit®
Donepezil	Aricept®
Doxepin	Sinequan®, Silenor®, Aponal®, Adapine®, Doxal®, Deptran®, Sinquan®
Dronedarone	Multaq®
Droperidol	Inapsine®, Droleptan®, Dridol®, Xomolix®
Eribulin mesylate	Halaven®
Erythromycin	E.E.S.®, Robimycin®, EMycin®, Erymax®, Ery-Tab®, Eryc Ranbaxy®, Erypar®, Eryped®, Erythrocin Stearate Filmtab®, Erythrocot®, E-Base®, Erythroped®, Ilosone®, MY-E®, Pediamycin®, Zineryt®, Abboticin®, Abboticin-ES®, Erycin®, PCE Dispertab®, Stiemycine®, Acnasol®, Tiloryth®
Escitalopram	Cipralex®, Lexapro®, Nexito®, Anxiset-E® (India), Exodus® (Brazil), Esto® (Israel), Seroplex®, Elicea®, Lexamil®, Lexam®, Entact® (Greece), Losita® (Bangladesh), Reposil® (Chile), Animaxen® (Colombia), Esitalo® (Australia), Lexamil® (South Africa)
Famotidine	Pepcid®, Fluxid®, Quamatel®
Felbamate	Felbatol®
Fingolimod	Gilenya®
Flecainide	Tambocor®, Almarytm®, Apocard®, Ecrinal®, Flécaine®
Fluconazole	Diflucan®, Trican®
Fluoxetine	Prozac®, Sarafem®, Fontex®
Foscarnet	Foscavir®
Furosemide (frusemide)	Lasix®, Fusid®, Frumex®
Galantamine	Reminyl®, Nivalin®, Razadyne-ER®,
Gatifloxacin (Removed from Market)	Tequin®
Gemifloxacin	Factive®

Generic Name	Brand Names (Partial List)
Granisetron	Kytril®, Sancuso®, Granisol®
Grepafloxacin	Raxar®
Halofantrine	Halfan®
Haloperidol	Haldol® (US & UK), Aloperidin®, Bioperidolo®, Brotopon®, Dozic®, Duraperidol® (Germany), Einalon S®, Eukystol®, Halosten®, Keselan®, Linton®, Peluces®, Serenace®, Serenase®, Sigaperidol®
Hydrochlorothiazide	Apo-Hydro®, Aquazide H®, BP Zide®, Dichlotride®, Hydrodiuril®, HydroSaluric®, Hydrochlorot®, Microzide®, Esidrex®, Oretic®
Hydrocodone - ER	Hysingla™ ER, Zohydro ER
Hydroxychloroquine	Plaquenil®, Quineprox®
Hydroxyzine	Atarax®, Vistaril®, Aterax®, Alamon®, Durrax®, Equipose®, Masmoran®, Orgatrax®, Paxistil® Quiess®, Tran-Q®, Tranquizine®
Ibutilide	Corvert®
Iloperidone	Fanapt®, Fanapta®, Zomaril®
Imipramine (melipramine)	Tofranil®
Indapamide	Lozol®, Natrilix®, Insig®
Isradipine	Dynacirc®
Itraconazole	Sporanox®, Onmel®
Ivabradine	Procoralan®, Coralan®, Corlentor®, Coraxan®, Ivabid®, Bradia®
Ketoconazole	Nizoral®, Sebizole®, Ketomed®, Keton®
Lapatinib	Tykerb®, Tyverb®
Lenvatinib	Lenvima®
Leuprolide	Lupron®, Eligard®, Viadur®, Carcinil®, Enanton®, Leuplin®, Lucrin®, Procren®, Prostap® and others
Levofloxacin	Levaquin®, Tavanic®
Levomepromazine (Only on Non-US Market)	Nosinan®, Nozinan®, Levoprome®
Levomethadyl (Removed from Market)	Orlaam®
Lithium	Eskalith®, Lithobid®
Mesoridazine (Removed from Market)	Serentil®
Methadone	Dolophine®, Symoron®, Amidone®, Methadose®, Physeptone®, Heptadon®
Metoclopramide	Reglan®, Afipran®, Maxolon®, Cerucal®, Clopamon®, Clopra®, Maxeran®, Maxolon®, Metozolv®, Plasil®, Pramin®, Primperan®, Perinorm®
Metronidazole	Flagyl® and many others
Mifepristone	Korlym®, Mifeprex®
Mirabegron	Myrbetriq®
Mirtazapine	Remeron
Moexipril/HCTZ	Uniretic®, Univasc®

Generic Name	Brand Names (Partial List)
Moxifloxacin	Avelox®, Avalox®, Avelon®
Nelfinavir	Viracept®
Nicardipine	Cardene®
Nilotinib	Tasigna®
Norfloxacin	Noroxin®, Ambigram®
Nortriptyline	Pamelor®, Sensoval®, Aventyl®, Norpress®, Allegron®, Noritren®, Nortrilen®
Ofloxacin	Floxin®
Olanzapine	Zyprexa®, Zydis®, Relprevv®
Ondansetron	Zofran®, Anset®, Ondemet®, Zuplenz®, Emetron®, Ondavell®, Emeset®, Ondisolv®, Setronax®
Osimertinib	Tagrisso®
Oxaliplatin	Eloxatin®
Oxytocin	Pitocin®, Syntocinon®
Paliperidone	Invega®, Xepilon®
Panobinostat	Farydak®
Pantoprazole	Protonix® and others
Papaverine HCl	none
Paroxetine	Paxil®, Aropax®, Pexeva®, Seroxat®, Sereupin®
Pasireotide	Signifor®
Pazopanib	Votrient®
Pentamidine	Pentam®
Perflutren lipid microspheres	Definity®
Pimozide	Orap®
Pipamperone (Only on Non-US Market)	Dipiperon (E.U), Propitan (Japan)
Posaconazole	Noxafil®, Posamol®
Probucol (Removed from Market)	Lorelco®
Procainamide	Pronestyl®, Procan®
Promethazine	Phenergan®
Propofol	Diprivan®, Propoven®
Quetiapine	Seroquel®
Quinidine	Quinaglute®, Duraquin®, Quinact®, Quinidex®, Cin-Quin®, Quinora®
Quinine sulfate	Qualaquin®
Ranolazine	Ranexa®, Ranozex®
Rilpivirine	Edurant®, Complera®, Eviplera®
Risperidone	Risperdal®
Ritonavir	Norvir®

Generic Name	Brand Names (Partial List)
Roxithromycin (Only on Non-US Market)	Rulide®, Xthrocin®, Roxl-150®, Roxo®, Surlid®, Rulide®, Biaxsig®, Roxar®, Roximycinv®, Roxomycin®, Rulid®, Tirabicin®, Coroxin®
Saquinavir	Invirase®(combo)
Sertindole (Only on Non-US Market)	Serdolect®, Serlect®
Sertraline	Zoloft®, Lustral®, Daxid®, Altruline®, Besitran®, Deprax®, Elrval®, Emergen®, Gladem®, Implicane®, Sedoran®, Sealdin®, SerivoLowfin®, Stimuloton®, Tresleen®, Sertralin Bluefish®
Sevoflurane	Ulane®, Sojourn®
Solifenacin	VESIcare®
Sorafenib	Nexavar®
Sotalol	Betapace®, Sotalex®, Sotacor®
Sparfloxacin (Removed from Market)	Zagam®
Sulpiride (Only on Non-US Market)	Dogmatil®, Dolmatil®, Eglonyl®, Espiride®, Modal®, Sulpor®
Sunitinib	Sutent®
Tacrolimus	Prograf®, Prograf®, Advagraf®, Protopic®
Tamoxifen	Nolvadex®(discontinued 6/13), Istubal®, Valodex®
Telaprevir	Incivo®
Telavancin	Vibativ®
Telithromycin	Ketek®
Terfenadine (Removed from Market)	Seldane®
Tetrabenazine	Nitoman®, Xenazine®
Thioridazine	Mellaril®, Novoridazine®, Thioril®
Tizanidine	Zanaflex®, Sirdalud®
Tolterodine	Detrol®, Detrusitol®
Toremifene	Fareston®
Torsemide	Demadex®, Diuver®, Examide®
Trazodone	Desyrel® (discontinued 6/13), Oleptro®, Beneficat®, Deprax®, Desirel®, Molipaxin®, Thombran®, Trazorel®, Trialodine®, Trittico®, Mesyrel®
Trimipramine	Surmontil®, Rhotrimine®, Stangyl®
Tropisetron (Only on Non-US Market)	Navoban®, Setrovel®
Vandetanib	Caprelsa®
Vardenafil	Levitra®
Vemurafenib	Zelboraf®
Venlafaxine	Effexor®, Efexor®
Voriconazole	VFend®
Vorinostat	Zolinza®
Ziprasidone	Geodon®, Zeldox®