[redacted]

A Phase 2 Basket Study of Milademetan in Advanced/Metastatic Solid Tumors (MANTRA-2)

Sponsor:	Rain Therapeutics Inc. 8000 Jarvis Avenue Suite 204 Newark, CA 94560 USA
Sponsor Protocol No.:	RAIN-3202
[redacted]	[redacted]
EU CT No.:	2022-502564-20-00
Investigational Drug Name:	Milademetan (RAIN-32)
Phase:	2
Date of Protocol:	21 November 2022
Version Number:	2.0
Version History/Date:	Version 1.0 (16 June 2021)

This study will be conducted according to the protocol and in compliance with Good Clinical Practice, the Declaration of Helsinki, and other applicable regulatory requirements.

STATEMENT OF THE SPONSOR

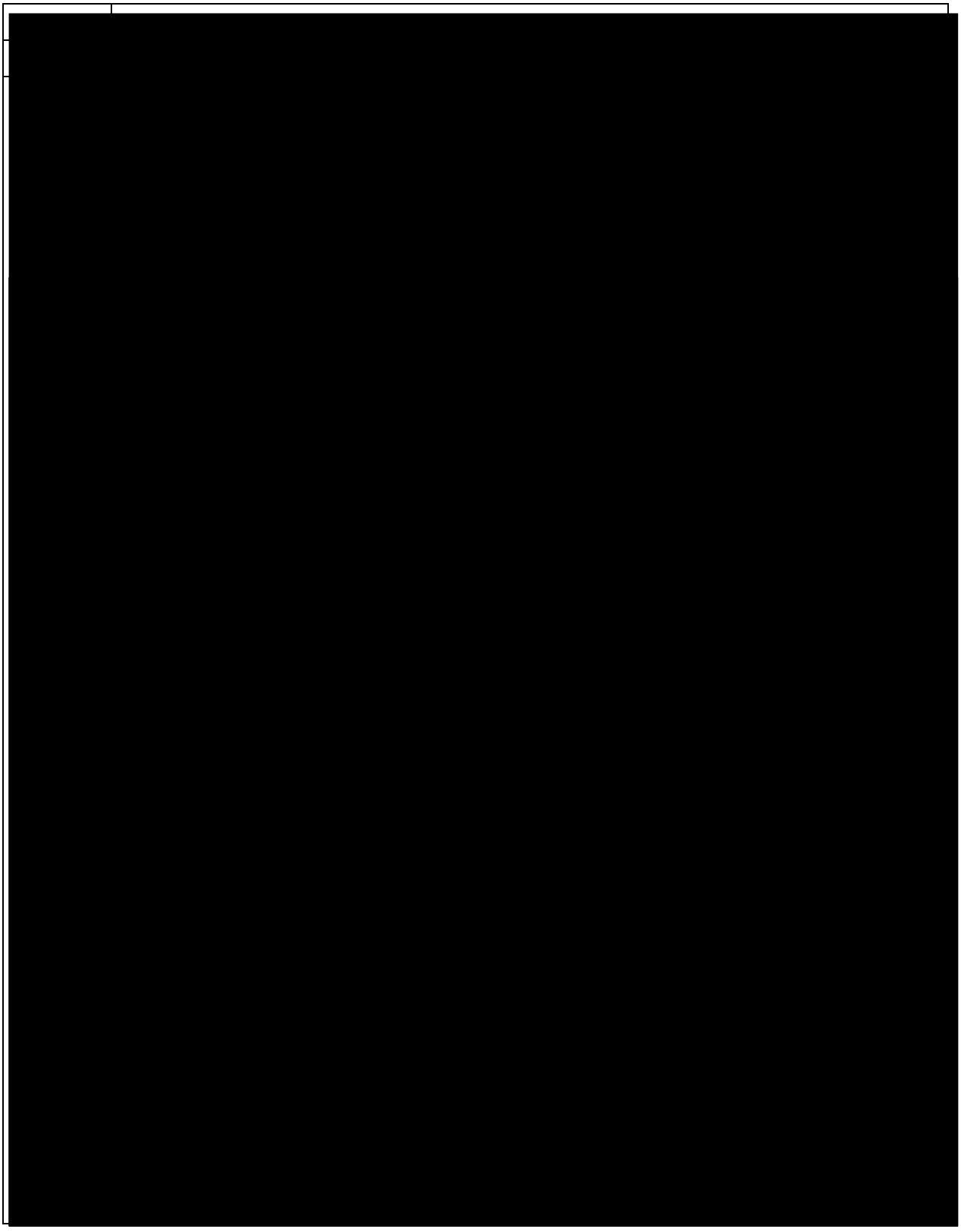
Protocol Title: **A Phase 2 Basket Study of Milademetan in Advanced/Metastatic Solid Tumors**

This study was designed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and is consistent with Good Clinical Practice and applicable regulatory requirements. Foreseeable risks and inconveniences have been weighed against the anticipated benefit for the individual study patient and society. Review of the available nonclinical and clinical information supports this study, and the anticipated benefits justify the risks.

The rights, safety, and well-being of the study patients are the most important consideration. While foreseeable risks have been identified, strategies are included to help mitigate both anticipated and unanticipated risks.

This clinical study is scientifically sound, and the study design is clearly described in this document.

PROTOCOL VERSION HISTORY

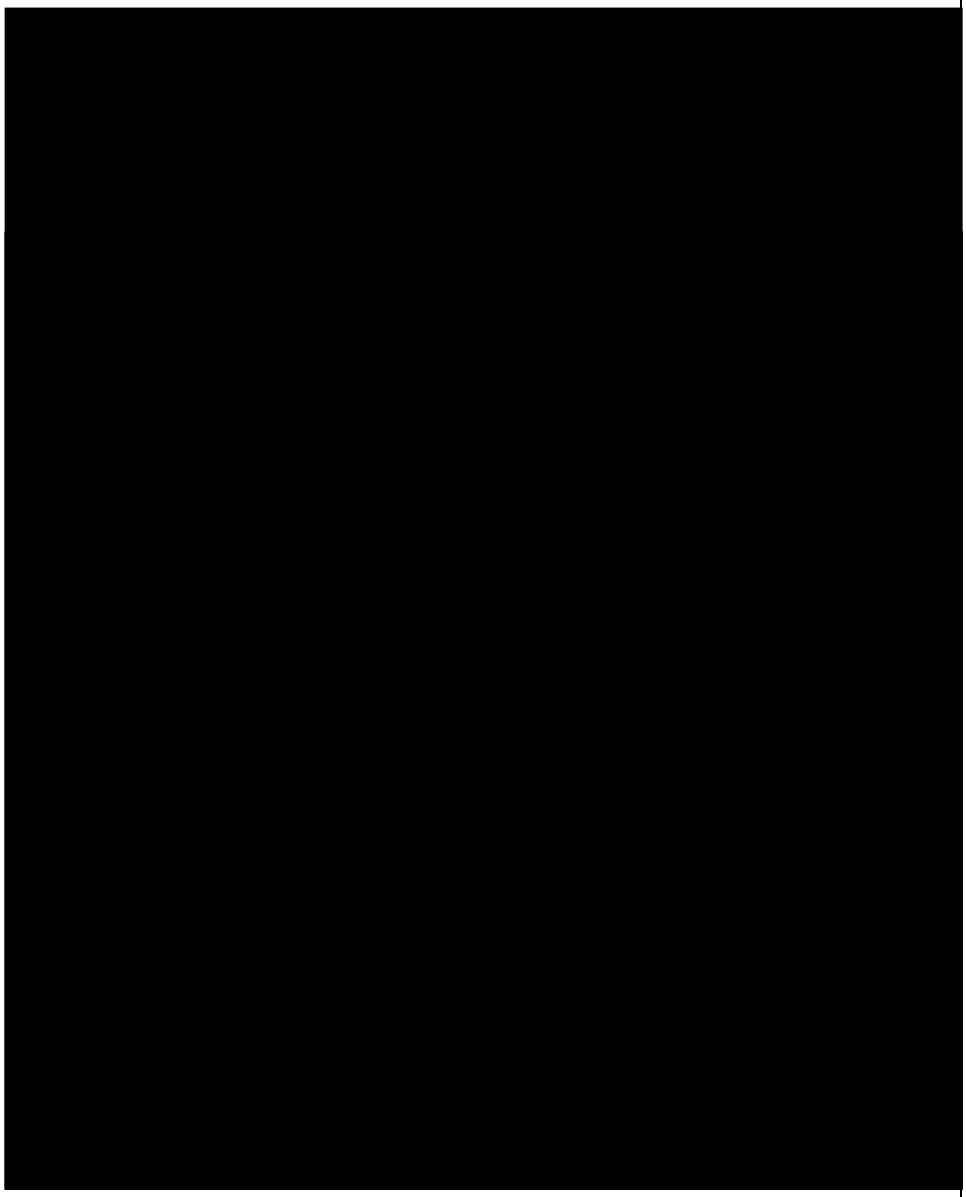


	[redacted]

SYNOPSIS

Study Number	**RAIN-3202**
Sponsor	Rain Therapeutics Inc.
Phase	2
Study Duration	Estimated to be 3 years
Objectives	Primary Objective The primary objective is to determine the objective response rate (ORR) of treatment with milademetan in patients with advanced/metastatic solid tumors with murine double minute 2 (*MDM2*) gene amplification. Secondary Objectives • To assess treatment with milademetan for the following efficacy parameters: o Duration of response (DOR) o Progression-free survival (PFS) o Growth modulation index (GMI) o Disease control rate (DCR) o Overall survival (OS) • To assess the safety profile of milademetan • To evaluate patient-reported health-related quality of life with the European Organisation for Research and Treatment of Cancer Quality-of Life Questionnaire, Core 30 (QLQ-C30) Exploratory Objectives [redacted]-1)
Study Design	This is a Phase 2, multicenter, single-arm, open-label basket study designed to evaluate the safety and efficacy of milademetan in patients with advanced or metastatic solid tumors refractory or intolerant to standard-of-care therapy that exhibit wild-type (WT) tumor protein 53 (*TP53*) gene and *MDM2* copy number (CN) ≥ 8 using prespecified biomarker criteria. Approximately 65 patients will be enrolled to receive milademetan. Patients will receive the study drug until reaching unequivocal disease progression (per Response Evaluation Criteria in Solid Tumors [RECIST] version [v]1.1), as determined by the Investigator; experiencing unmanageable toxicity; or until other treatment discontinuation criteria are met. Patients may be treated beyond tumor progression if

	they are experiencing clinical benefit based on the assessment of the Investigator in discussion with the Sponsor's Medical Monitor. All patients will be followed for documentation of disease progression and survival information (i.e., date and cause of death). Long-term follow-up will continue every 12 weeks (± 7 days) until the endpoint of death, the patient is lost to follow-up, or for 24 months after the first dose of study drug for the last patient, whichever comes first.
Investigational Treatment (Milademetan)	[redacted] **Dose and Mode of Administration:** 260 mg administered orally once daily (QD) on Days 1 to 3 and Days 15 to 17 of each 28-day cycle. [redacted]
Eligibility	**Inclusion Criteria** Each patient must meet all of the following criteria to be enrolled in the study: 1. Is a patient ≥ 18 years old 2. Has signed and dated an informed consent form prior to the start of any study-specific qualification procedures 3. Has histologically and/or cytologically confirmed diagnosis of a cancer that is a locally advanced or metastatic solid tumor 4. Has measurable tumor lesion(s) in accordance with RECIST v1.1 5. Must have received all standard therapy appropriate for their tumor type and stage of disease or, in the opinion of the Investigator, would be unlikely to tolerate or derive clinically meaningful benefit from appropriate standard-of-care therapy [redacted]

	6. Has resolution of any clinically relevant toxic effects of prior chemotherapy, surgery, radiotherapy, or hormonal therapy  8. Has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 9. Has adequate bone marrow function, defined as: a. Platelet count ≥ 100×10^9/L b. Hemoglobin ≥ 9.0 g/dL c. Absolute neutrophil count ≥ 1.5×10^9/L 10. Has adequate renal function, defined as creatinine clearance ≥ 30 mL/min, as calculated using the modified Cockcroft-Gault equation (or equivalent glomerular filtration rate calculated using the Chronic Kidney Disease Epidemiology Collaboration formula) 11. Has adequate hepatic function, defined as:

a. Alanine aminotransferase and aspartate aminotransferase ≤ 3 × the upper limit of normal (ULN) if no liver metastases are present or ≤ 5 × ULN if liver metastases are present
b. Total bilirubin ≤ 1.5 × ULN or ≤ 3 × ULN in the presence of liver metastases. Patients with Gilbert's disease who have serum bilirubin levels > 3 × ULN may be enrolled

12. Is willing and able to comply with the protocol requirements
13. If requiring anticoagulation medication, should be on a stable regimen, defined as being on the same dose for at least 4 weeks
14. If a woman of childbearing potential (WOCBP), they must have a negative serum pregnancy test at Screening and a negative urine pregnancy test on Cycle 1 Day 1 before receiving the first dose of study drug

[redacted]

15. If a male patient, is surgically sterile, willing to use a condom, or remain abstinent upon enrollment through the Treatment Period and until at least 90 days after the final dose of the study drug

[redacted]

Exclusion Criteria

A patient who meets any of the following criteria will not be eligible to participate in the study:

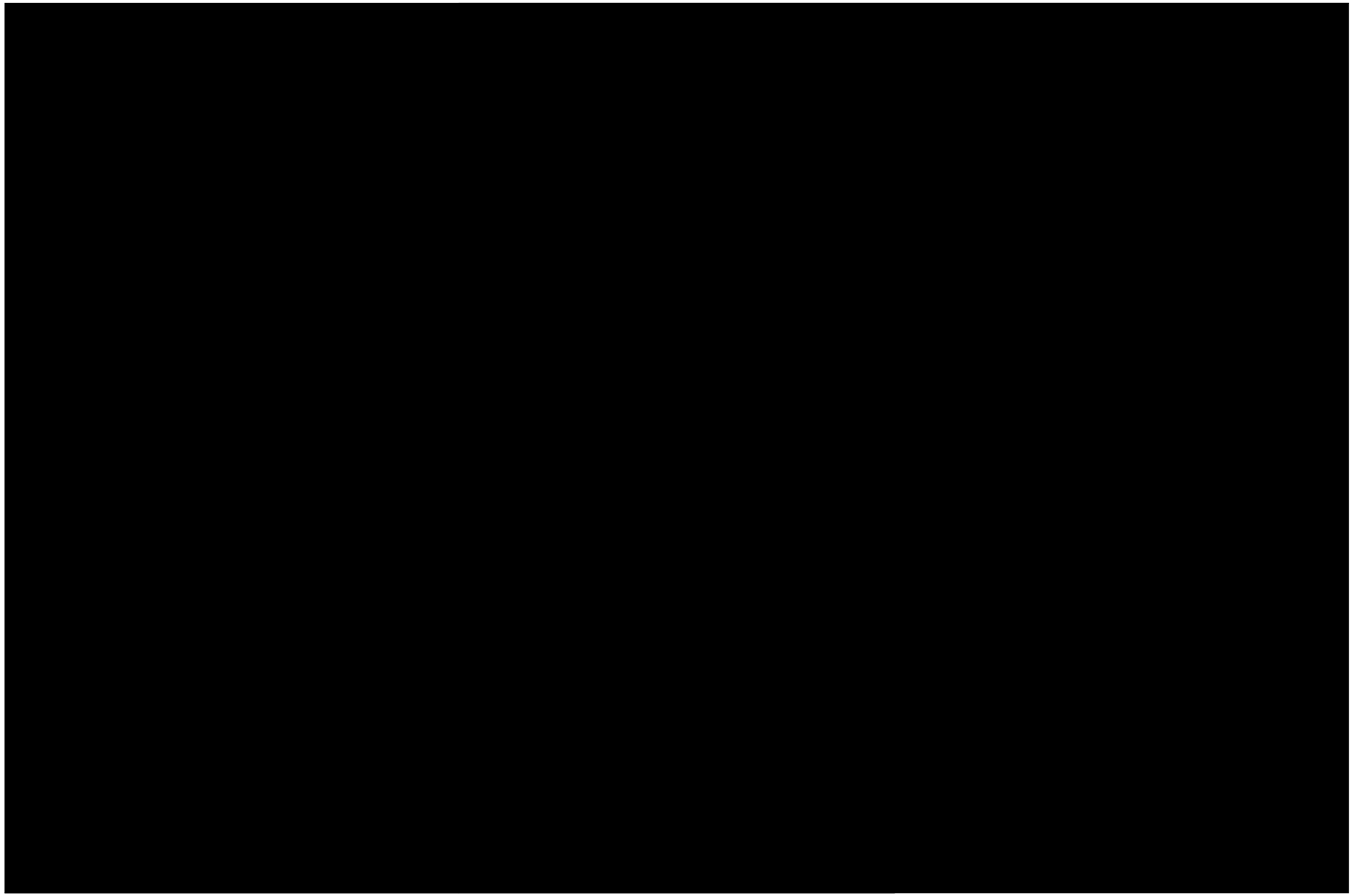
1. Has had prior treatment with an MDM2 inhibitor [redacted]
2. Has well-differentiated/dedifferentiated liposarcoma or intimal sarcoma/cardiac sarcoma
3. Has other primary malignancies that required systemic antineoplastic treatment within the previous 2 years, except for localized cancers that have apparently been cured (e.g., nonmelanoma skin cancer, superficial bladder cancer, or carcinoma in situ of the cervix or breast) and will not interfere with the study outcomes
4. Has a primary malignant brain tumor of any grade or histology
5. Has untreated brain metastases

	[redacted] 6. Has gastrointestinal conditions that could affect the absorption of milademetan, in the opinion of the Investigator [redacted] 7. Has a clinically significant uncontrolled infection within the last 7 days requiring intravenous antibiotics, antivirals, or antifungals 8. Has known HIV infection or active hepatitis B or C infection 9. Has not met the minimum washout period before enrollment, defined as: a. Cytochrome P450 (CYP)3A4 isozyme strong inhibitor: 5 elimination half-lives of the inhibitor b. CYP3A4 strong or moderate inducers (e.g., St. John's wort and modafinil): 4 weeks c. Systemic anticancer therapy (chemotherapy; small molecules, including antibody drug therapy; retinoid therapy; or hormonal therapy) or investigational therapy: 3 weeks or 5 half-lives, whichever is shorter d. Immunotherapy with a checkpoint inhibitor: 4 weeks 10. Has had major surgery ≤ 3 weeks from Cycle 1 Day 1 11. Has had curative-intent radiation therapy ≤ 4 weeks or palliative radiation therapy, defined as ≤ 30 Gy in ≤ 10 fractions (e.g., 20 Gy in 5 fractions or 8 Gy in 1 fraction), ≤ 2 weeks from Cycle 1 Day 1 12. Has uncontrolled or significant cardiovascular disease, including: a. Corrected QTc interval as calculated according to Fridericia's formula (QTcF) at rest, where the mean QTcF interval is > 480 ms (average of triplicate 12-lead electrocardiograms [ECGs]) in the absence of an offending medication that can be safely discontinued b. Myocardial infarction within 6 months prior to Screening c. Uncontrolled angina pectoris within 6 months prior to Screening d. New York Heart Association Class 3 or 4 congestive heart failure e. Uncontrolled hypertension (resting systolic blood pressure > 150 mm Hg or diastolic blood pressure > 100 mm Hg) on repeat measurements and despite adequate medical management 13. Is a woman who is pregnant or breastfeeding or intends to become pregnant during the study 14. Has a concomitant medical condition that would interfere with the assessment of efficacy or increase the risk of toxicity, in the opinion of the Investigator or Sponsor
Criteria for Efficacy Evaluation	The primary efficacy endpoint is ORR, and the secondary efficacy endpoints are DOR, PFS, GMI, DCR, and OS. Health-related quality-of-life evaluations include the QLQ-C30.

	The ORR is defined as the percentage of patients who have achieved a confirmed complete response (CR) or partial response (PR). Tumor assessments via imaging (computed tomography scans or magnetic resonance imaging) will be performed by the Investigator; the evaluation of tumor response will be based on RECIST v1.1. Tumor response evaluations will be performed at Screening and then every 8 weeks (± 7 days) while the patient remains on the study drug, and any other time during the study as clinically indicated. In accordance with RECIST version 1.1, response (PR and CR) must be confirmed by a subsequent tumor assessment at least 4 weeks after the initial observed response. The secondary efficacy endpoints DOR, PFS, GMI, DCR, and OS are defined as: • The DOR is defined as the time from the date of first response to the date of disease progression or death • The PFS is defined as the time from the date of first dose to the earliest date of the first objective documentation of radiographic disease progression or death due to any cause • The GMI will be determined using the ratio of time to progression (TTP) with nth line of therapy (TTP_n; here defined as milademetan) to the most recent prior line of therapy (TTP_{n-1}) • The DCR is defined as the percentage of patients who have achieved confirmed CR, PR, or stable disease (SD) lasting for ≥ 16 weeks • OS, as measured from the date of the first dose of the study drug to the date of death due to any cause Health-related quality-of-life endpoints include QLQ-C30.
Criteria for Safety Evaluation	Safety endpoints include the incidence of treatment-emergent AEs (TEAEs); including serious AEs, TEAEs leading to dose reductions, TEAEs leading to discontinuation of the study drug, and TEAEs leading to study withdrawal); changes in clinical laboratory parameters (hematology, serum or plasma chemistry, and urine pregnancy test), deaths, vital signs, and ECG parameters (especially QT intervals); physical examination results; and use of concomitant medications.
Criteria for Pharmacokinetic Evaluation	[redacted]
Exploratory Evaluations	[redacted]

	[redacted]
Statistical Methods	[redacted]

	[redacted]



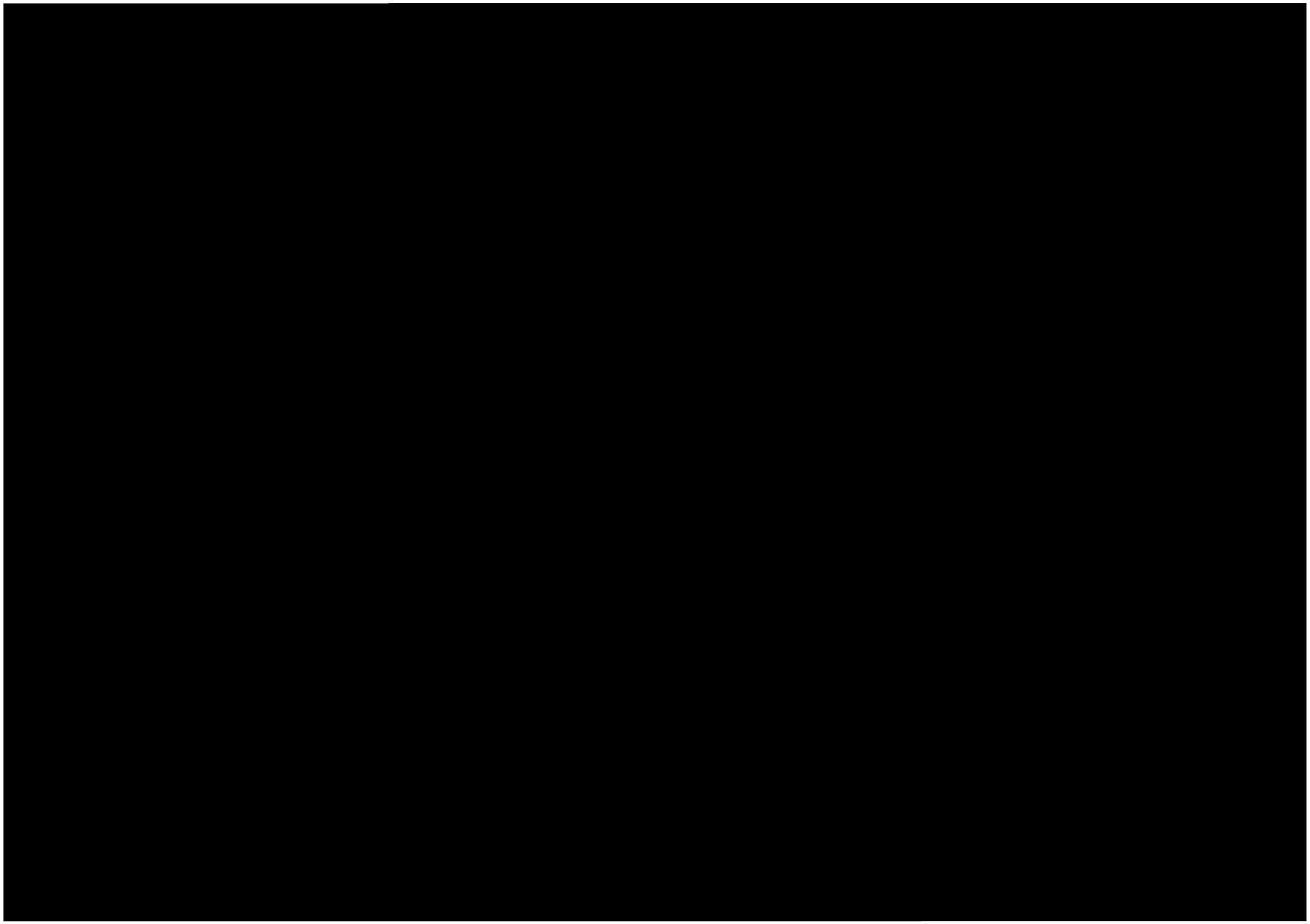


TABLE OF CONTENTS

LIST OF TABLES

[redacted]

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation or Specialist Term	Definition
(3/14 × 2)	3 days on, 11 days off every 2 weeks
AE	adverse event
AUC	area under the curve
BCRP	breast cancer resistance protein
CCP	Centrally Confirmed Population
CFU-GM	colony-forming unit granulocyte/macrophage
CI	confidence interval
C_{max}	maximum peak plasma concentration
C_{min}	minimum plasma concentration
CN	copy number
CR	complete response
CRF	case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
CYP	cytochrome p450
DCR	disease control rate
DOR	duration of response
EC_{50}	half-maximal response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EIU	exposure in utero
EOT	end of treatment
FAP	Full Analysis Population
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FSH	follicle-stimulating hormone
GMI	growth modulation index
HNSTD	highest non severely toxic dose
IB	Investigator's Brochure
IC_{50}	concentration causing 50% inhibition
ICH	International Council for Harmonisation
IEC	independent ethics committee
IRB	institutional review board
MDM2	murine double minute 2 gene

Abbreviation or Specialist Term	Definition
MDM2	murine double minute 2
MedDRA	Medical Dictionary for Regulatory Activities
MIC-1	macrophage inhibitory cytokine-1
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NOAEL	no-observed-adverse-effect level
ORR	objective response rate
OS	overall survival
p21	cyclin-dependent kinase inhibitor 1
p53	Tumor suppressor protein 53
P-gp	P-glycoprotein
PD	progressive disease
PDX	patient-derived xenograft
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PUMA	p53 upregulated modulator of apoptosis
QD	once daily
QLQ-C30	European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire, Core 30
QTc	corrected QT interval
QTcF	corrected QTc interval as calculated according to Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SJSA-1	osteosarcoma cell line
TEAE	treatment-emergent adverse event
TP53	tumor protein p53 gene
TTP	time to progression
TTP_n	time to progression with the nth line of therapy
TTP_{n-1}	time to progression to the most recent prior line of therapy
ULN	upper limit of normal
US	United States
v	version
WHO	World Health Organization
WOCBP	women of childbearing potential
WT	wild type

1. INTRODUCTION

The tumor suppressor protein p53 plays an essential role in preventing neoplasia by inducing cell cycle arrest or apoptosis in cells undergoing various types of physiological stress. However, inactivation of TP53 by mutation occurs in a significant percentage of human tumors, resulting in a loss of tumor suppressor activity and thereby removing a pivotal barrier to neoplastic development. In human tumors that retain WT p53 protein, its activity is frequently inhibited by intermolecular interactions between p53 and MDM2. MDM2 and p53 form a regulatory feedback loop in which MDM2 maintains low levels of p53 activity in normal, unstressed cells by promoting export of p53 out of the nucleus and proteasome-mediated degradation of p53 through its E3 ubiquitination ligase activity (Shangary 2009). In the presence of stress, p53 becomes activated and subsequently acts as a transcription factor that modulates the expression of a variety of genes, including MDM2 (Levine 2009). The MDM2 binding domain on p53 overlaps with the transcriptional activation domain of p53, thereby inhibiting the activity of p53. Thus, in human tumors, disruption of MDM2/p53 balance through overexpression and/or oncogenic activation of MDM2 allows tumorigenesis and tumor growth by preventing p53 function.

In patients with cancers that do not harbor TP53 mutations, MDM2 gene amplification or increased MDM2 activity represent an alternate path for loss of p53 function. Alterations, such as gene amplification, are associated with tumorigenic potential (Fakharzadeh 1991) and thus, may serve as a predictive biomarker of antitumor activity with MDM2 inhibitors. MDM2 gene amplification is found across solid tumors at varying frequencies and with varying levels of gene amplification. Pharmacologic inhibition of the interaction between MDM2 and WT p53 in tumor cells could result in sustained increases in p53 activity and subsequent antitumor effects (Vassilev 2004, Shangary 2008). Therefore, pharmacologic restoration of the p53 pathway could be an effective strategy for cancer therapy targeting the wide array of human cancers that retain WT p53 (Vassilev 2007).

Milademetan (RAIN-32) is a small-molecule inhibitor of MDM2 that disrupts the interactions between MDM2 and the tumor suppressor protein p53 (Noguchi 2019). MDM2 expression and/or activity can be upregulated by multiple mechanisms in cancer cells including *MDM2* gene amplification (Tirunagaru 2021), cyclin-dependent kinase inhibitor 2A gene (*CDKN2A)* loss (Sherr 2000), and Merkel cell polyomavirus-encoded small T antigen (Park 2021) among other mechanisms, leading to potential MDM2-dependency and sensitivity to milademetan.

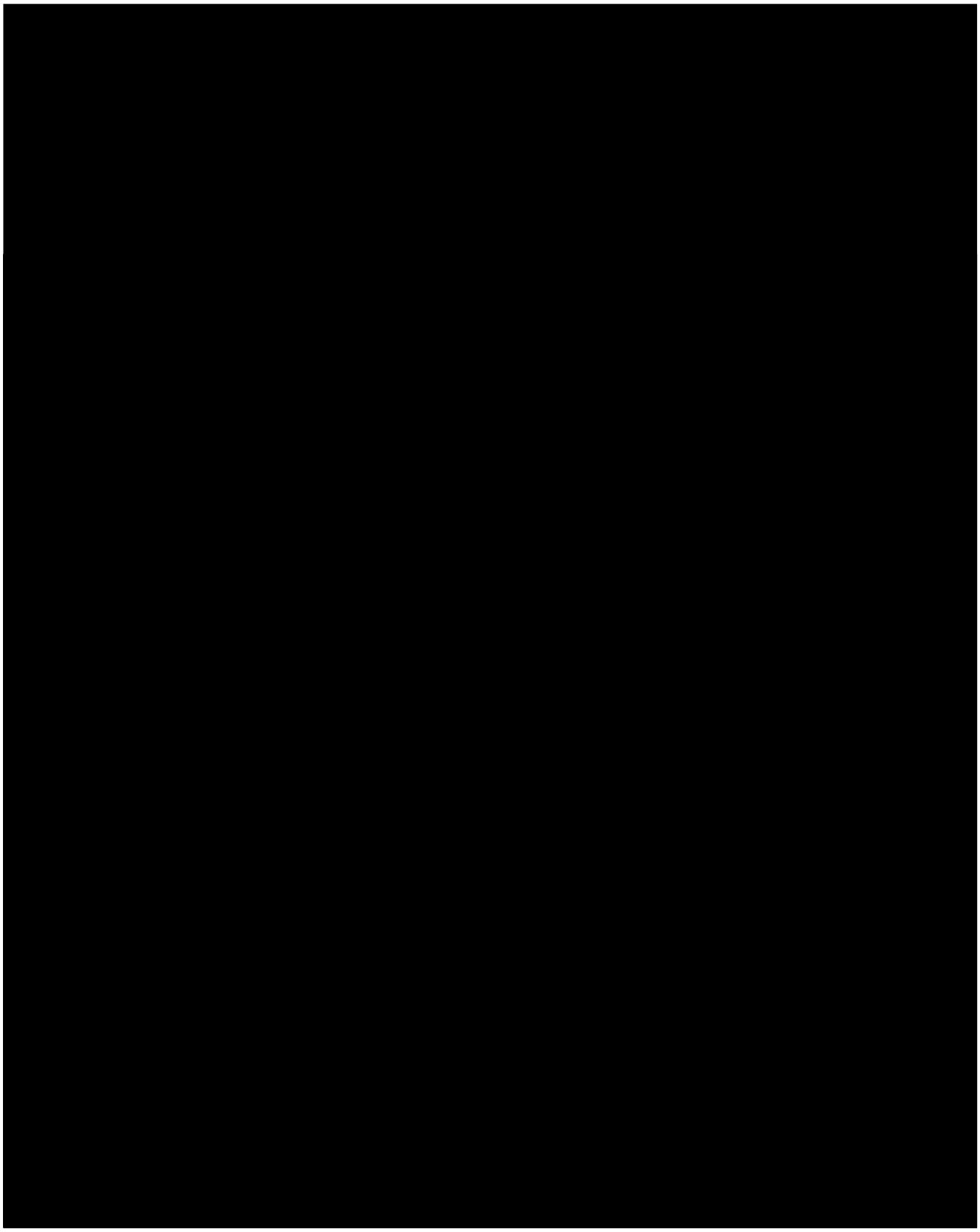
This is a Phase 2 multicenter, single-arm, open-label basket study designed to evaluate the safety and efficacy of milademetan in patients with advanced or metastatic solid tumors refractory or intolerant to standard-of-care therapy and that exhibit WT *TP53* and *MDM2* CN $\geq$ 8 using prespecified biomarker criteria. The primary objective of the study is to determine the ORR of treatment with milademetan in these patients.

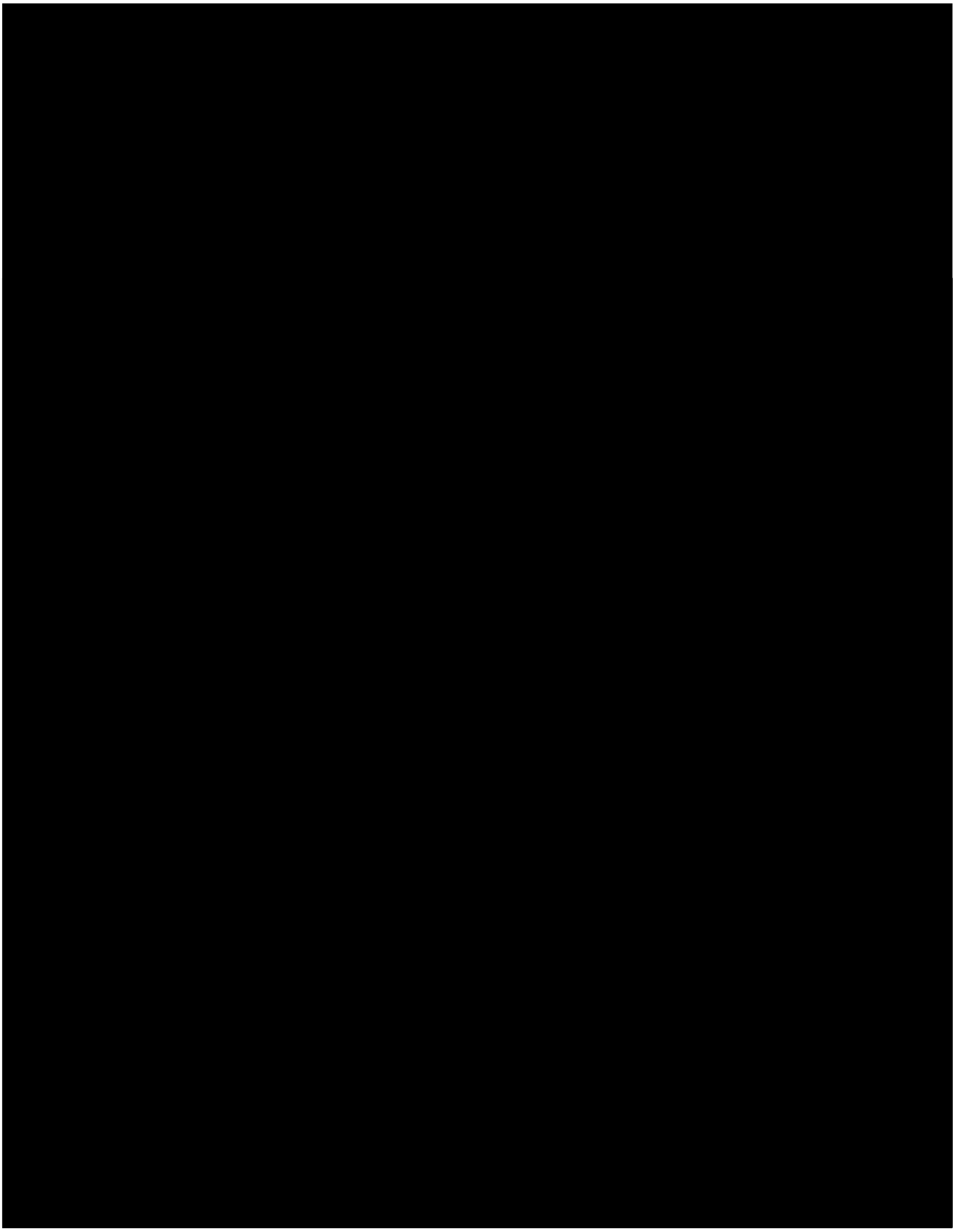
2. BACKGROUND INFORMATION

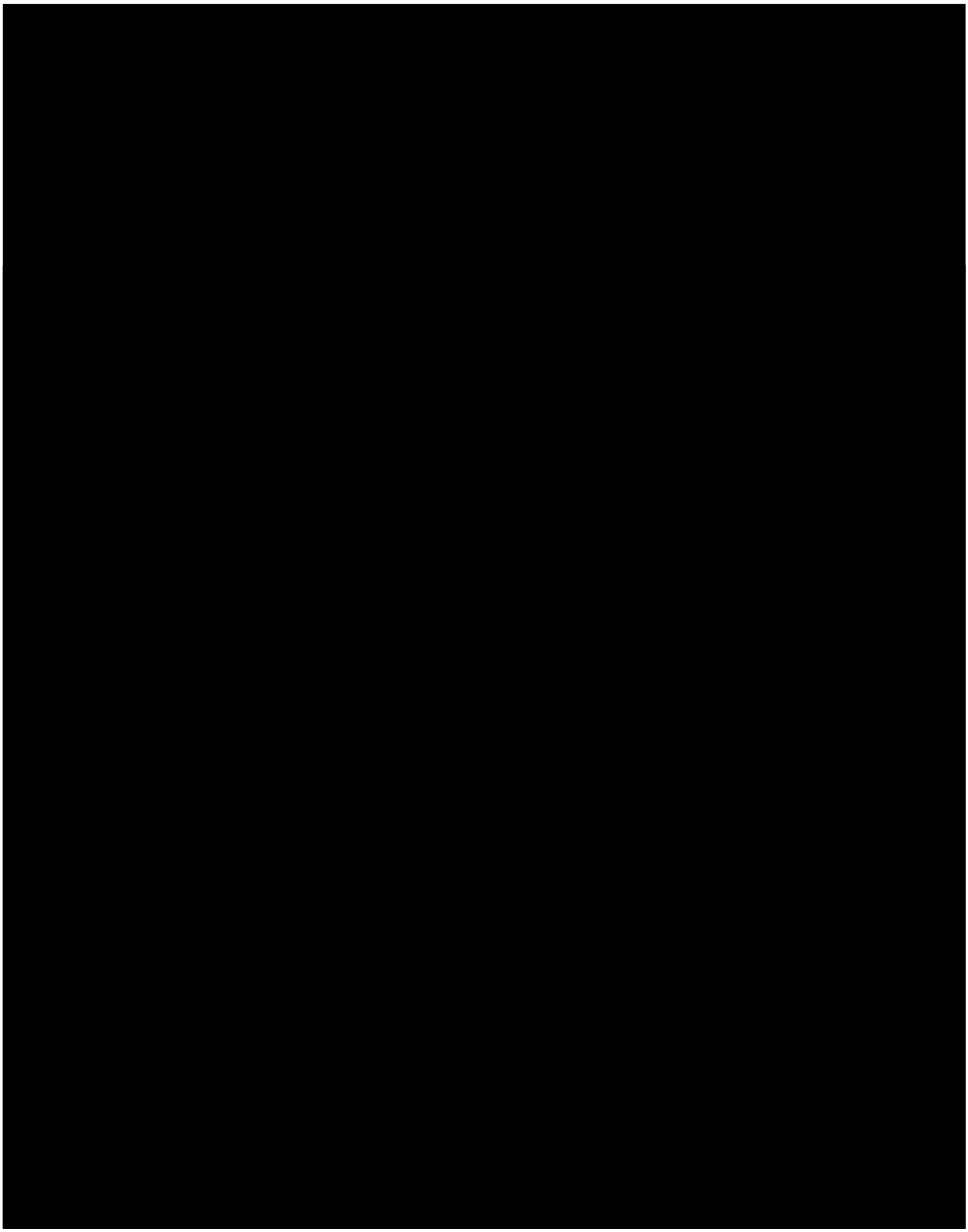
2.1. Milademetan

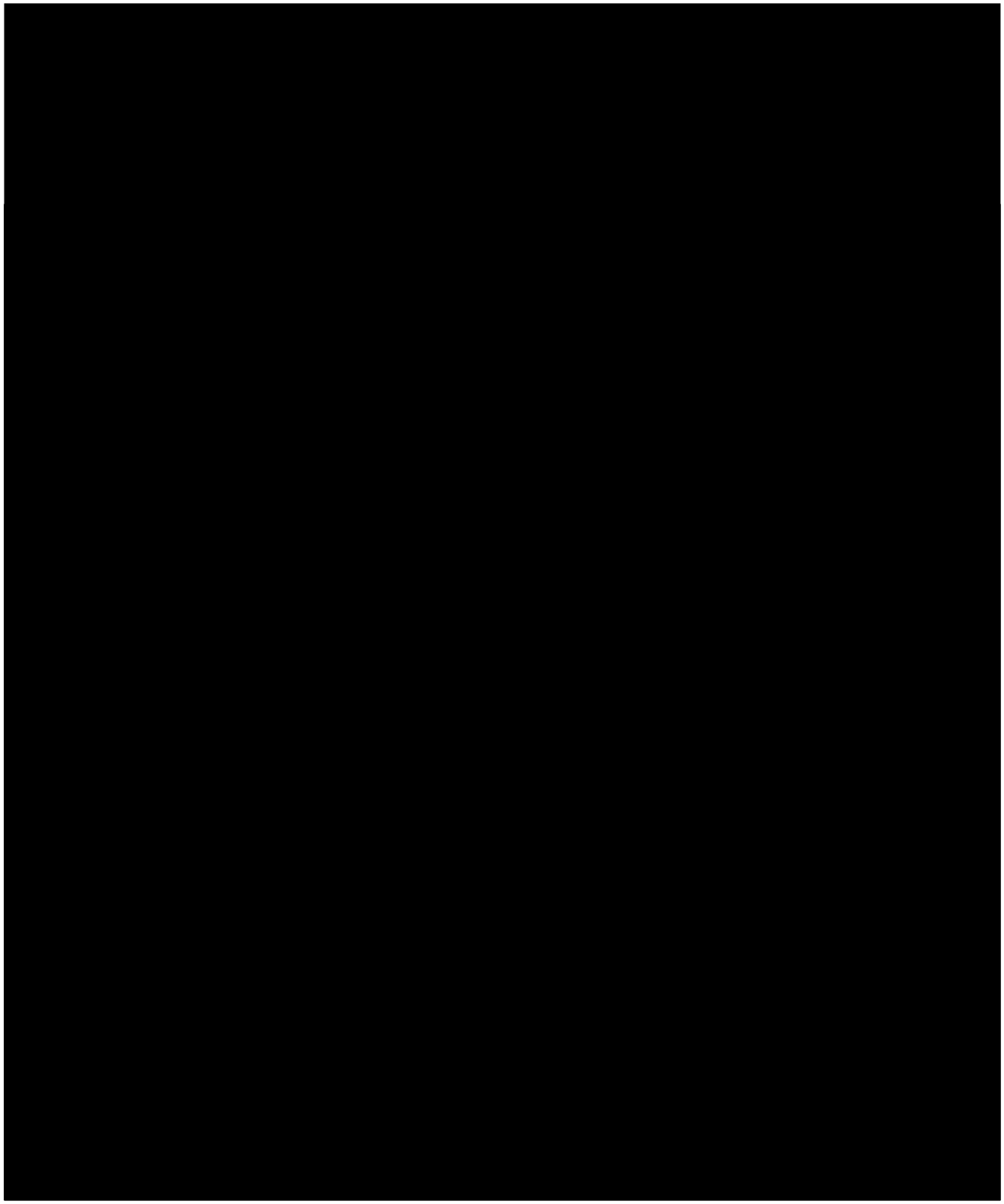
Milademetan is a novel, specific, small-molecule inhibitor of MDM2 that disrupts the interactions between MDM2 and the tumor suppressor protein p53 in tumor cells, preventing excessive degradation of p53 (Noguchi 2019). In normal cells, the balance of MDM2 and p53 levels are maintained by a feedback mechanism in which p53 induces MDM2 expression, and the MDM2-p53 interaction promotes nuclear export of p53 and its proteasome-mediated degradation through the E3 ubiquitin ligase activity of MDM2 (Vassilev 2004). Mutational inactivation of p53 occurs in a significant percentage of human tumors, resulting in the loss of tumor suppressor activity in tumor cells. In human tumors that harbor WT *TP53*, MDM2 levels or activity are frequently elevated by *MDM2* gene amplification or other mechanisms of overexpression, resulting in increased MDM2-p53 interaction and loss of p53 tumor suppressor function due to its degradation. Pharmacologic disruption of the interaction between MDM2 and p53 by milademetan in animal models of tumors that harbor WT *TP53* have demonstrated sustained increases in p53 activity with a resultant antitumor effect (Vassilev 2007).

2.1.1.1. In Vitro Pharmacology Studies









2.4. Rationale for Dose Selection

2.5. Benefit/Risk Assessment

Current evidence supports the continued study of milademetan in clinical studies.

Preclinical and preliminary clinical data support the development of milademetan in patients with advanced or metastatic solid tumors that are refractory or intolerant to standard-of-care therapy and exhibit WT *TP53* and *MDM2* CN $\geq$ 8. The mechanism of action of milademetan, the inhibition of MDM2 which increases p53 activity with a resultant antitumor effect, suggests a potential benefit in this patient population.

Overall, milademetan was generally well tolerated, with an acceptable benefit/risk assessment.

3. STUDY OBJECTIVES AND PURPOSE

The purpose of the study is to evaluate the safety and efficacy of milademetan in patients with advanced/metastatic solid tumors with WT *TP53* and *MDM2* gene amplification. To be eligible, patients must have progressed on 1 or more prior systemic therapies.

3.1. Primary Objective

The primary objective of the study is to determine the ORR of treatment with milademetan in patients with advanced/metastatic solid tumors with *MDM2* gene amplification.

3.2. Secondary Objectives

The secondary objectives of the study are:

- To assess treatment with milademetan for the following efficacy parameters:
  - DOR
  - PFS
  - GMI
  - DCR
  - OS
- To assess the safety profile of milademetan
- To evaluate patient-reported quality-of-life questionnaire (QLQ-C30)

4. STUDY DESIGN

4.1. Study Design Overview

This is a Phase 2, multicenter, single-arm, open-label basket study designed to evaluate the safety and efficacy of milademetan in patients with advanced or metastatic solid tumors refractory or intolerant to standard-of-care therapy that exhibit WT *TP53* and *MDM2* CN $\geq$ 8 using prespecified biomarker criteria. Local lab results for determination of *TP53* mutation status

and *MDM2* amplification may be used for eligibility; verification of *MDM2* CN should be performed using a central laboratory as outlined under Section 5.1 Inclusion Criteria.

Approximately 65 patients will be enrolled to receive milademetan.

Patients will receive the study drug until reaching unequivocal disease progression (per RECIST v1.1), as determined by the Investigator; experiencing unmanageable toxicity; or until other treatment discontinuation criteria are met. Patients may be treated beyond tumor progression if patients are experiencing clinical benefit based on the assessment of the Investigator in discussion with the Sponsor's Medical Monitor.

All patients will be followed for documentation of disease progression and survival information (i.e., date and cause of death). Long-term follow-up (LTFU) will continue every 12 weeks (± 7 days) until the endpoint of death, the patient is lost to follow-up, or for 24 months after the first dose of the study drug for the last patient, whichever comes first.

4.2. Endpoints and Criteria for Evaluation

4.2.1. Primary Endpoint

The primary efficacy endpoint is ORR. The ORR is defined as the percentage of patients who have achieved a confirmed CR or PR. Tumor response will be assessed in accordance with RECIST v1.1.

4.2.2. Secondary Endpoints

Secondary efficacy endpoints include:

- The DOR, defined as the time from the date of first response to the date of disease progression or death
- The PFS, defined as the time from the date of first dose to the earliest date of the first objective documentation of radiographic disease progression or death due to any cause
- The GMI will be determined using the ratio of TTP with TTP_n (here defined as milademetan) to TTP_{n-1}
- The DCR, defined as the percentage of patients who have achieved confirmed CR, PR, or SD for ≥ 16 weeks
- OS, as measured from the date of the first dose of the study drug to the date of death due to any cause

Health-related quality-of-life endpoints include the QLQ-C30.

Safety endpoints include the incidence of TEAEs (including SAEs, TEAEs leading to dose reductions, TEAEs leading to discontinuation of study drug, and TEAEs leading to study withdrawal); changes in clinical laboratory parameters (hematology, serum or plasma chemistry, and urine pregnancy test), deaths, vital signs, and ECG parameters (especially QT intervals); physical examination results; and use of concomitant medications.

4.3. Measures Taken to Minimize/Avoid Bias

If a patient withdraws from the study, the data (including tested and untested samples) collected to the point of withdrawal will remain part of the study database and will not be removed.

Response criteria are based on objective measurements, as defined in RECIST v1.1, by site radiologists. All responses will be source verified; copies of tumor assessment scans will be collected and stored for future potential evaluation.

4.4. Duration of Study Treatment

Patients will continue to receive the study drug until reaching unequivocal disease progression (per RECIST v1.1), as determined by the Investigator, or experiencing unmanageable toxicity. See Section 6.4 for treatment beyond progression.

5. SELECTION AND WITHDRAWAL OF PATIENTS

5.1. Inclusion Criteria

Each patient must meet all of the following criteria to be enrolled in the study:

1. Is ≥ 18 years of age at the time of signing informed consent
2. Has signed and dated an informed consent form prior to the start of any study-specific qualification procedures
3. Has histologically and/or cytologically confirmed diagnosis of a cancer that is a locally advanced or metastatic solid tumor
4. Has measurable tumor lesion(s) in accordance with RECIST v1.1
5. Must have received all standard therapy appropriate for their tumor type and stage of disease or, in the opinion of the Investigator, would be unlikely to tolerate or derive clinically meaningful benefit from appropriate standard-of-care therapy

6. Has resolution of any clinically relevant toxic effects of prior chemotherapy, surgery, radiotherapy, or hormonal therapy

[redacted]

7. Presence of WT *TP53* and *MDM2* gene amplification by tumor tissue/blood testing, defined as:
   a. ≥ 8 copies in tumor tissue by central laboratory or
   b. ≥ 8 copies or 4-fold increase in tumor tissue or blood by local testing

[redacted]

8. Has an ECOG performance status of 0 or 1
9. Has adequate bone marrow function, defined as:
   a. Platelet count ≥ 100×10^9/L
   b. Hemoglobin ≥ 9.0 g/dL
   c. Absolute neutrophil count ≥ 1.5×10^9/L
10. Has adequate renal function, defined as creatinine clearance ≥ 30 mL/min, as calculated using the modified Cockcroft-Gault equation (or equivalent glomerular filtration rate calculated using the Chronic Kidney Disease Epidemiology Collaboration formula)
11. Has adequate hepatic function, defined as:

a. Alanine aminotransferase and aspartate aminotransferase ≤ 3 × the ULN if no liver metastases are present or ≤ 5 × ULN if liver metastases are present
b. Total bilirubin ≤ 1.5 × ULN or ≤ 3 ×ULN in the presence of liver metastases. Patients with Gilbert's disease who have serum bilirubin levels of > 3 × ULN may be enrolled

12. Is willing and able to comply with the protocol requirements
13. If requiring anticoagulation medication, should be on a stable regimen, defined as being on the same dose for at least 4 weeks
14. If a WOCBP, they must have a negative serum pregnancy test at Screening and a negative urine pregnancy test on Cycle 1 Day 1 before receiving the first dose of study drug or within 72 hours of the first dose of study drug

[redacted]

15. If a male patient is surgically sterile and willing to use a condom or remain abstinent upon enrollment through the Treatment Period and until at least 90 days after the final dose of the study drug

[redacted]

5.2. Exclusion Criteria

A patient who meets any of the following criteria will not be eligible to participate in the study:

1. Has had prior treatment with a murine double minute 2 (MDM2) inhibitor [redacted]
2. Has well-differentiated/dedifferentiated liposarcoma or intimal sarcoma/cardiac sarcoma
3. Has other primary malignancies that required systemic antineoplastic treatment within the previous 2 years, except for localized cancers that have apparently been cured (e.g., nonmelanoma skin cancer, superficial bladder cancer, or carcinoma in situ of the cervix or breast) and will not interfere with the study outcomes
4. Has a primary malignant brain tumor of any grade or histology
5. Has untreated brain metastases

[redacted]

6. Has gastrointestinal conditions that could affect the absorption of milademetan, in the opinion of the Investigator.

[redacted]

7. Has a clinically significant uncontrolled infection within the last 7 days requiring intravenous antibiotics, antivirals, or antifungals
8. Has known HIV infection or active hepatitis B or C infection
9. Has not met the minimum washout period before enrollment, defined as:
    a. CYP3A4 isozyme strong inhibitor: 5 elimination half-lives of the inhibitor
    b. CYP3A4 strong or moderate inducers (e.g., St. John's wort and modafinil): 4 weeks
    c. Systemic anticancer therapy (chemotherapy; small molecules, including antibody drug therapy; retinoid therapy; or hormonal therapy) or investigational therapy: 3 weeks or 5 half-lives, whichever is shorter
    d. Immunotherapy with a checkpoint inhibitor: 4 weeks
10. Has had major surgery ≤ 3 weeks from Cycle 1 Day 1
11. Has had curative-intent radiation therapy ≤ 4 weeks or palliative radiation therapy, defined as ≤ 30 Gy in ≤ 10 fractions (e.g., 20 Gy in 5 fractions or 8 Gy in 1 fraction), ≤ 2 weeks from Cycle 1 Day 1
12. Has uncontrolled or significant cardiovascular disease, including:
    a. QTcF at rest, where the mean QTcF interval is > 480 ms (average of triplicate 12-lead ECGs) in the absence of an offending medication that can be safely discontinued
    b. Myocardial infarction within 6 months prior to Screening
    c. Uncontrolled angina pectoris within 6 months prior to Screening
    d. New York Heart Association Class 3 or 4 congestive heart failure
    e. Uncontrolled hypertension (resting systolic blood pressure > 150 mm Hg or diastolic blood pressure > 100 mm Hg) on repeat measurements and despite adequate medical management
13. Is a woman who is pregnant or breastfeeding or intends to become pregnant during the study
14. Has a concomitant medical condition that would interfere with the assessment of efficacy or increase the risk of toxicity, in the opinion of the Investigator or Sponsor

5.3. Patient Withdrawal Criteria

All patients are free to discontinue the study drug or withdraw from the study at any time. All patients wishing to discontinue from the study drug or withdraw from the study will be queried to determine the reason for withdrawal while respecting the privacy of the patient. The reason a patient decided to withdraw from study drug will be recorded.

In the event of withdrawal of consent, the Investigator should make every effort to ensure that the patient is followed for AEs for a minimum of 30 days after their last dose of the study drug or until the initiation of a new anticancer treatment, whichever comes first, with documented patient agreement.

Patients will be discontinued from the study drug if any of the following events occur:

- PD according to RECIST v1.1 at any time during the study (unless approved by the Sponsor's Medical Monitor [see Section 6.4])
- Clinical progression (e.g., symptomatic deterioration) not meeting the RECIST v1.1 criterion for PD but considered by the Investigator to require discontinuation of the study drug
- Patient is unable to tolerate dosing after dose reductions per Table 4
- Significant deviation from the protocol or eligibility criteria. These patients may continue dosing with the study drug after discussion and agreement between the Investigator and Sponsor's Medical Monitor and subsequent approval by the IRB or IEC.
- Pregnancy
- Patient withdrawal of consent and/or election to discontinue the study drug
- Termination of the study by the Sponsor
- Any other reason which, in the opinion of the Investigator, would justify discontinuing the patient from the study drug

A patient may also be discontinued from the study drug by the Sponsor, Regulatory Authorities, or IECs/IRBs.

If a patient discontinues from the study drug due to the ongoing COVID-19 global pandemic, information should be captured in the eCRF so this information can be summarized in the clinical study report at the end of the study. The reason for discontinuation should be recorded in the eCRF as COVID-19, if applicable, and include as many details as possible. For example, specific reasons may include, but are not limited to:

- The patient exhibits symptoms consistent with COVID-19
- The patient has a positive test result for COVID-19
- The patient has neither symptoms nor a positive test for COVID-19 but has decided to discontinue the study drug due to personal choice related to COVID-19 concerns

Patients who are discontinued from the study drug for reasons other than PD by RECIST v1.1 should undergo scans for tumor assessments according to the original tumor assessment schedule (every 8 weeks [± 7 days] from Cycle 1 Day 1) until any of the following occur, whichever comes first:

- PD by RECIST v1.1
- Initiation of new anticancer treatment
- Discontinuation from the study (death, withdrawal of consent, or loss to follow-up)

After discontinuation from study drug, all patients will have an EOT Visit. The EOT Visit will occur 30 days (±7 days) after the last dose of the study drug administration or before starting new anticancer therapy. If the patient begins another form of anticancer therapy before the end of the 30-day period, every effort will be made to complete all EOT Visit assessments prior to commencing the new anticancer therapy. If there is an AE in need of monitoring beyond the EOT Visit, patients will be followed until resolution or confirmed stability of the AE. Long-term follow-up visits, to obtain survival information after the EOT Visit, will be performed every 12 weeks (± 7 days) until the endpoint of death, the patient is lost to follow-up, or for 24 months after the first dose of study drug for the last patient, whichever comes first.

Withdrawal from the study should be in a stepwise fashion. As mentioned above, patients may discontinue or be discontinued from the study drug. Any patient who discontinues or is discontinued from the study drug should be encouraged to complete all planned safety and follow-up assessments. If the patient wishes to withdraw from all study assessments, permission should be requested to contact the patient, a designated contact person, or the patient's primary care provider for long-term survival follow-up. If the patient does not wish to have any direct follow-up, permission should be requested to conduct periodic medical record review and/or contact the patient's medical care provider for LTFU. If the patient withdraws from the study and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. Where allowed by local regulations, public records may still be consulted for the patient's survival status.

6. TREATMENT OF PATIENTS

6.1. Patient Enrollment

Selected patients may require central verification of *TP53* mutation status and /or *MDM2* amplification which can be performed under prescreening consent as outlined in the inclusion section.

Prior to any study-related assessments, all potential patients will provide written informed consent. After written informed consent has been obtained and eligibility has been confirmed, the study site will obtain the patient's identification number from the Interactive Response Technology System. Once a patient identification number has been assigned, it will be used to identify the patient throughout the study, and it cannot be reassigned to another patient.

Investigational sites will provide the Sponsor's Medical Monitor with a completed Eligibility Checklist for Sponsor review. Patients who meet the eligibility criteria may be enrolled. Patients will be considered enrolled upon their first dose of the study drug.

Patients who cannot complete the procedures within the Screening window or are not initially eligible may be rescreened. In this situation, a new patient identification number will be assigned. For rescreening within the original Screening window, certain Screening procedures may not need to be repeated. Reconsent is required for rescreening outside the original Screening window.

An Investigational Drug Accountability Log must be used for drug accountability. For additional details on investigational study drug management, please refer to the Pharmacy Manual. Patients will be provided with a patient diary to record study drug administration and compliance.

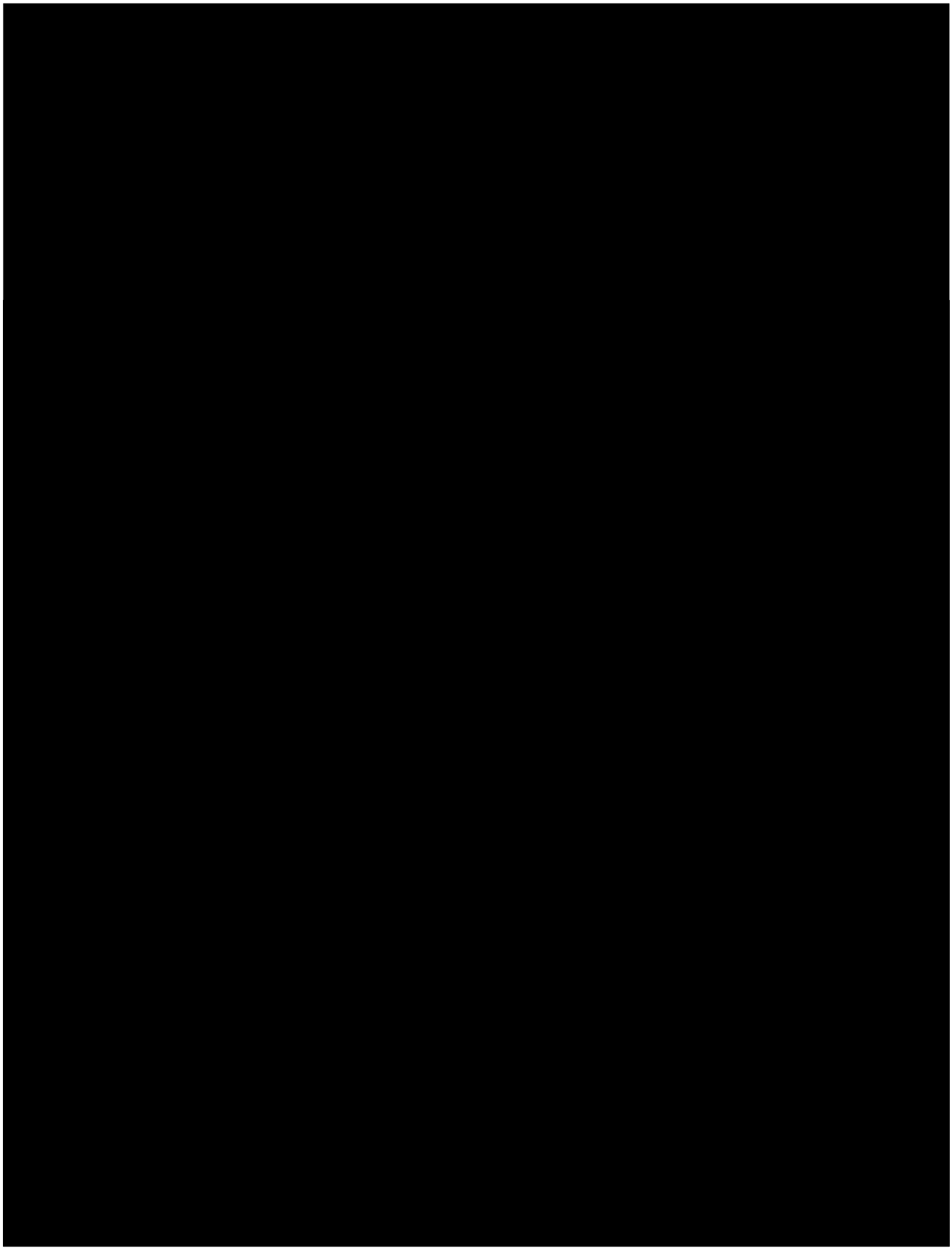
6.2. Milademetan Administration

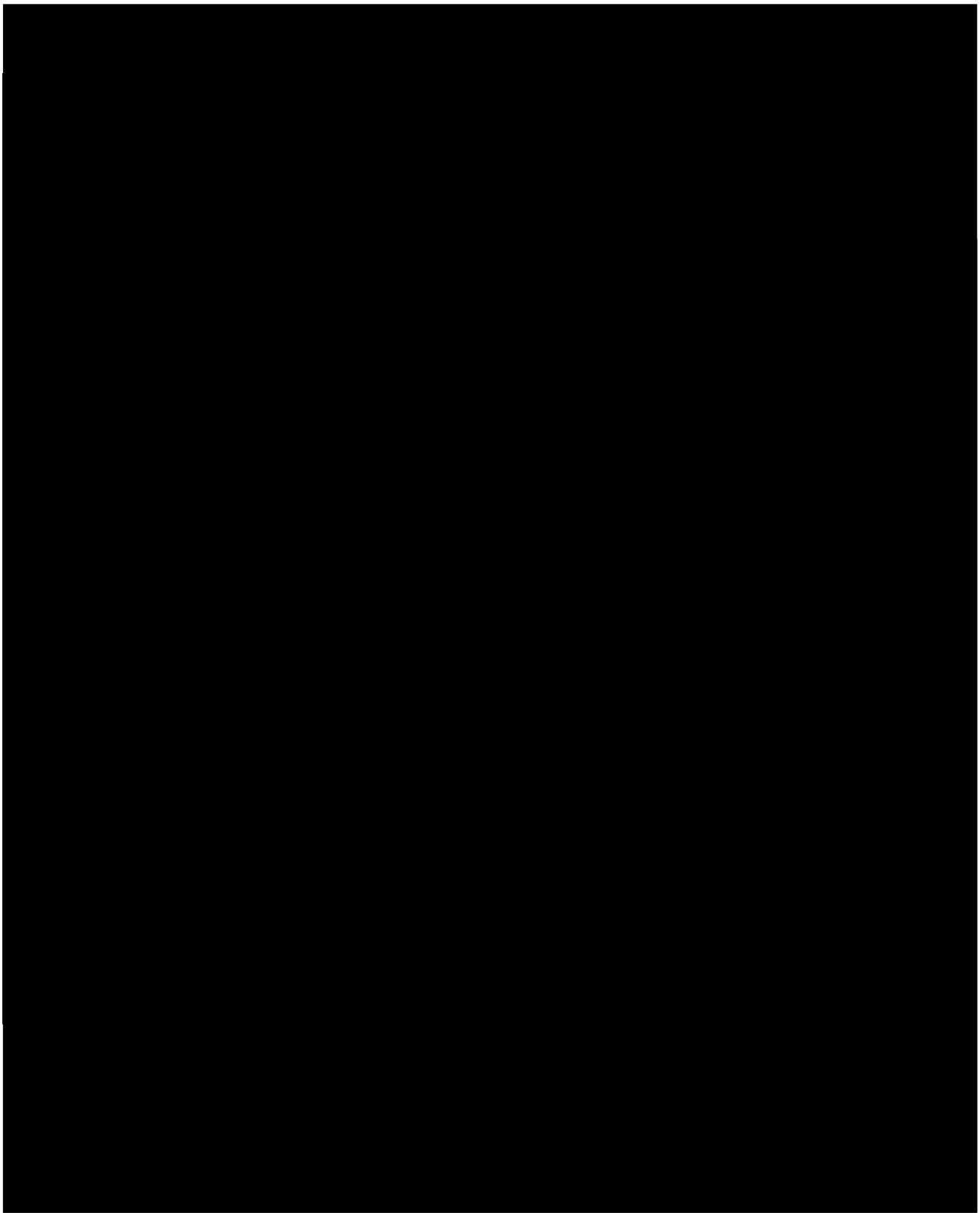
Refer to the Pharmacy Manual for milademetan packaging, labeling, and storage instructions.

Milademetan 260 mg QD will be administered orally QD on Days 1 to 3 and Days 15 to 17 of each 28-day cycle after all predose procedures have been performed. Clinical laboratory assessments must be resulted and evaluated prior to administration of study drug on the day of

day.

6.3. Milademetan Dose Modifications





6.4. Treatment Beyond Progression

Patients with PD who meet the following criteria may continue to receive the study drug if, in the opinion of the Investigator, the patient is still benefiting (e.g., asymptomatic systemic progression or local symptomatic progression), after discussion with and approval by the Sponsor's Medical Monitor (or designee):

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status
- Absence of symptomatic rapid disease progression requiring urgent medical intervention (e.g., symptomatic pleural effusion or spinal cord compression)

The Investigator should periodically discuss ongoing treatment with the study drug with the Sponsor's Medical Monitor. Where applicable, the IRB/IEC will be notified of any planned treatment beyond progression. Patients may receive palliative radiation to disease sites of progression, including brain metastases, after discussion with and approval by the Sponsor's Medical Monitor (or designee).

At the time of radiographic progression of disease, patients should be informed of treatments with known clinical benefit they may be foregoing in order to continue receiving the study drug.

6.5. Compliance

Investigators are required to conduct the study in compliance with the protocol. Compliance with the protocol will be closely monitored. Important aspects of compliance with this clinical study include:

- Eligibility
- Study drug administration, including dose modification
- Performance of protocol-specified assessments
- ECG monitoring
- AE reporting

Protocol deviations are defined as any departure from the protocol or associated instructions and will be monitored. Deviations from the protocol, including violations of the eligibility criteria, will be assessed as "minor" or "major". Protocol deviations at investigational sites will be discussed with the Investigator, and additional training will be provided as needed to secure Investigator compliance.

If a deviation impacts the safety of a patient, the Investigator must contact the Sponsor immediately. The Investigator will also ensure that deviations meeting IRB/IEC and applicable regulatory authorities' criteria are documented and communicated appropriately. All documentation and communications to the IRB/IEC and applicable regulatory authorities may be provided to the Sponsor and maintained within the Trial Master File.

Study staff will receive additional training as needed to prevent noncompliance.

6.6. Study Visits

Protocol-required assessments scheduled for each study visit are summarized in the Schedule of Events (Table 1) and described in the following sections. In exceptional circumstances with prior Sponsor approval, study visits may be performed by a local provider.

6.7. Prescreening

Potential patients who meet any of the criteria on local testing specified in Inclusion Criterion #7 (Section 5.1) may be asked to consent to prescreening.

During prescreening the patient will authorize the study personnel to obtain previously collected tumor tissue and have it processed at a central laboratory. Prescreening eligibility does not guarantee study enrollment and the patient must consent to the main study before any Screening activities may commence.

6.8. Screening Period/Baseline Assessments

Patients may be screened at any time during the 21 days prior to the first dose of the study drug. Unless otherwise specified, Screening/baseline assessments may be done any time after consent and prior to the first dose of the study drug. Physical examination, ECOG, and clinical laboratory assessments on Cycle 1 Day 1 can be performed within 72 hours before the first dose of study drug. Patients who are determined not to meet eligibility criteria at any time prior to the first dose of the study drug will not be enrolled. The following will be assessed or measured at Screening/baseline:

- Informed consent

- Eligibility (including tumor assessment)
- Medical/disease history
- Smoking history: Smoking history should be documented on the eCRF page as "never," "former" (with quit date), or "current" (document pack years)
- Demographics
- Physical examination focused on major organ systems that are clinically relevant as determined by the Investigator and including symptom directed findings and vital signs (taken 5 minutes after sitting), including height and weight
- ECOG Performance Status Scale
- ECG (12-lead) in triplicate
- Blood samples for laboratory assessments (see Table 1); ensure a serum pregnancy test is conducted for WOCBP
- Patient-reported outcomes: QLQ-C30
- Tissue as newly obtained biopsy or archived tissue ≤ 5 years old for central diagnostic laboratory verification of WT *TP53* and *MDM2* CN. Tissue may be submitted as either:
  - FFPE block, or
  - at least 15 unstained, unbaked, positively charged slides with ≥20% tumor tissue in 5-micron sections per slide as confirmed by a local pathologist

  Note: Patients who have central testing of *TP53* and *MDM2* gene status performed under prescreening consent can forego this tissue submission requirement.
- In patients who provide consent to the optional procedure:
  - Tumor biopsy consisting of sufficient tissue to generate at least 15 slides of adequate quality
- Prior and concomitant medications:
  - Record all concomitant medication use after 21 days prior to Cycle 1 Day 1
  - Special attention should be accorded to medications that are known to cause prolongation of QTc or deplete potassium
- Baseline radiographic tumor assessment per RECIST v1.1:
  - Perform according to institutional practice and/or disease type; include CT or MRI of the chest and abdomen; baseline radiographic tumor assessment is required within 28 days prior to the first dose of study drug.
  - Baseline brain scan to exclude occult central nervous system metastases is required for all patients with lung cancer, breast cancer, melanoma, testicular cancer, or renal cell cancer and is strongly recommended in other appropriate

clinical settings at the discretion of the Investigator. Brain scans do not need to be repeated for patients without central nervous system metastases at baseline. Patients with a history of brain metastasis should be followed per standard institutional practice.

- Bone scan during baseline radiographic tumor assessment is only required for patients with a primary tumor diagnosis in the prostate, breast, kidney, lung, or thyroid. Additional tumor types may have baseline bone scans at the discretion of the Principal Investigator if there is suspicion of bone metastasis.
- For patients where baseline brain and/or bone scans are required, the tumor assessment must be performed within 28 days prior to the first dose of study drug.
- Brain and bone scans do not need to be repeated for patients with no brain or bone metastases at baseline, unless clinically indicated.
- If brain and/or bone metastases are identified at the baseline visit, brain, and/or bone scans must be repeated and aligned with the protocol-specified tumor assessment schedule. These lesions should be followed per RECIST v1.1 guideline using the same modalities at each assessment.

6.9. Treatment Period

See the Schedule of Events for the timing of procedures during the Treatment Period (Table 1).

[redacted] Please refer to the Pharmacy Manual for further information on treatment continuation after dose holds.

Physical and radiographic tumor assessments will be performed every 8 weeks (± 7 days) while the patient remains on the study drug and any other time during the study as clinically indicated. In accordance with RECIST v1.1, response (PR and CR) must be confirmed by a subsequent tumor assessment at least 4 weeks after the initial observed response. The same imaging modality used for baseline imaging (i.e., CT or MRI) must be used for subsequent radiographic tumor assessments. Any dose interruption after starting study treatment will not cause adjustment to the tumor assessment schedule. Additional tumor assessments may be performed as clinically indicated (e.g., if disease progression is suspected).

6.10. EOT Visit

The EOT Visit will occur 30 days (± 7 days) after the last dose of the study drug administration or before starting a new anticancer therapy. If the patient begins another anticancer therapy before the end of the 30-day period, every effort will be made to complete all the EOT Visit assessments prior to commencing the new anticancer therapy. If there is an AE in need of monitoring beyond the EOT Visit, patients will be followed until resolution or confirmed stability of the AE. The following will be assessed or measured at the EOT Visit:

- ECOG Performance Status Scale
- Physical examination focused on major organ systems that are clinically relevant as determined by the Investigator and including symptom directed findings, and vital signs, including weight
- Urine pregnancy test for WOCBP
- Record AEs
- Record concomitant medications
- Patient-reported outcomes: QLQ-C30
- Blood samples for laboratory assessments (see Table 1)
- Serum samples for exploratory biomarkers
- In patients who provide consent to the optional procedure: tumor biopsy consisting of sufficient tissue to generate an FFPE block or at least ≥ 15 slides of adequate quality
- Survival follow-up

6.11. Long-Term Follow-up

Once a patient has completed the EOT Visit, they will enter the follow-up phase. All patients will be followed for documentation of disease progression and survival information (i.e., the date and cause of death) and subsequent treatment information (i.e., the date/duration of treatment, response, and subsequent disease progression). Long-term follow-up will continue every 12 weeks (± 7 days) until the endpoint of death, the patient is lost to follow-up, or for 24 months after the first dose of study drug for the last patient, whichever comes first. Unless the patient withdraws consent, all patients enrolled in the study will be followed for LTFU assessments after EOT.

6.12. Concomitant Medications and Treatments

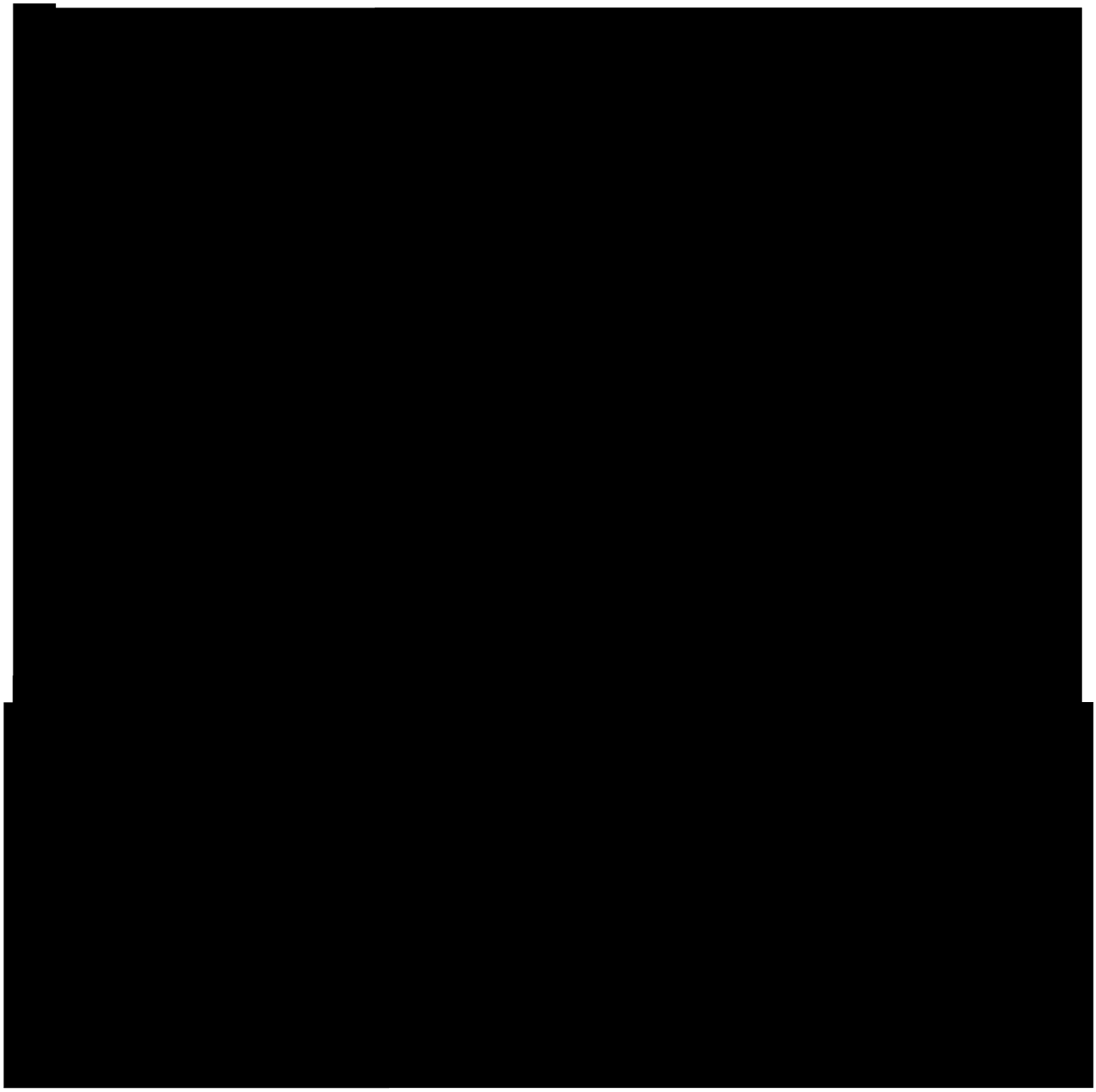
All concomitant medications (prescription and over-the-counter) and blood products taken from Screening until the EOT Visit will be recorded. The reason(s) for treatment, dose, and dates of treatment will be recorded. In addition, concomitant medications used to treat AEs occurring up to 30 days after the last dose of the study drug will be recorded.

See Appendix A for a list of prohibited medications and those medications that are permitted but should be used with caution during the study. Supportive care should be provided as appropriate to each patient to manage disease-related symptoms (e.g., antiemetics, antibiotics, transfusions, nutritional support, and pain control) according to institutional guidelines.

Use of filgrastim is allowed in accordance with ASCO/ESMO guidelines (Klastersky 2016, Smith 2015).

6.12.1. Prohibited Medications

[redacted]



7. ASSESSMENT OF EFFICACY

Tumor assessments via imaging (CT scans or MRIs) will be performed by the Investigator; the evaluation of tumor response will be based on RECIST v1.1. The primary objective is to determine the ORR of treatment with milademetan in patients with advanced/metastatic solid tumors with *MDM2* gene amplification. The decision to discontinue the study drug for disease progression will be determined locally by the Investigator.

Tumor response evaluations will be performed at Screening and then every 8 weeks (±7 days) while the patient remains on the study drug, and any other time during the study as clinically indicated.

In accordance with RECIST v1.1, response (PR and CR) must be confirmed by a subsequent tumor assessment at least 4 weeks after the initial observed response. The scheduling of subsequent tumor assessments may be adjusted based on the date of the most recent imaging. Investigators are instructed to ensure that original images (or high-quality copies) of all baseline and on-study scans are collected and filed for transmission to the Sponsor (or designee) for future independent review.

7.1. Primary Efficacy Endpoint

The primary efficacy endpoint is ORR, as determined by Investigator assessment.

7.2. Secondary Efficacy Endpoints

Secondary efficacy endpoints include the following according to the Investigator's assessment:

- DOR
- PFS
- GMI
- DCR
- OS

Health-related quality-of-life evaluations, including QLQ-C30, are additional secondary endpoints.

8. ASSESSMENT OF SAFETY AND EXPLORATORY VARIABLES

8.1. Definitions

8.1.1. Adverse Event Definitions

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug and does not imply any judgment about causality. An AE can arise with any use of the drug (e.g., off-label use or use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

8.1.1.1. Events Not Considered to Be AEs

AEs do not include the following events:

- Preexisting diseases, conditions, or laboratory abnormalities present or detected before the Screening Visit that do not worsen after the initiation of study drug

- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery or social and/or convenience admissions)
- Overdose without clinical sequelae. Overdose is a special situation that should be reported using the Special Situation Report Form.
- Any medical condition or clinically significant laboratory abnormality with an onset date on or after the informed consent form is signed but before the first dose of study drug and not related to a protocol-associated procedure. In this case, the medical condition or clinically significant laboratory abnormality is not an AE but should be considered preexisting and should be documented as medical history.
- An event that is part of the natural course of the disease under study (i.e., disease progression, death due to disease progression) should not be recorded as an AE or SAE; however, signs and symptoms of clinical sequelae resulting from disease progression will be reported if they fulfill the definition of AE or SAE. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an AE or SAE.

8.1.2. Serious Adverse Events

An AE is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- death
- is life-threatening (i.e., immediate risk of death at the time of event)
- inpatient hospitalization or prolongation of existing hospitalization
- persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- a congenital anomaly/birth defect

Based upon appropriate medical judgment, an AE that may jeopardize the patient or require medical or surgical intervention to prevent one of the aforesaid outcomes should be reported as an SAE. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency department or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.2. AE Reporting

8.2.1. AE Collection Period

After signing the informed consent, but before the initiation of study drug, an event must be collected and reported on the AE CRF, **IF** it is related to protocol-required procedures (e.g., biopsy); otherwise, the event must be reported as medical history.

After initiation of study drug, all AEs, regardless of causality, will be collected and entered on the AE CRF until 30 days after the last administration of study drug or until initiation of another anticancer therapy, whichever comes first.

All AEs should be followed until resolution or until the AE is stable, if possible. The Sponsor may request that certain AEs be followed beyond the protocol-defined follow-up period.

8.2.2. AE Term

AEs must be reported using standard medical terminology. The use of abbreviations (standard and nonstandard) should be avoided to help ensure a clear understanding of the event. An example of a standard abbreviation that may have several meanings is "MI," which could mean "myocardial infarction" or "mitral insufficiency". All AE terms will be coded using a standardized dictionary (i.e., Medical Dictionary for Regulatory Activities [MedDRA). Generally, when reporting a well-known and understood condition, it is preferable to report the overall diagnosis rather that the individual signs and symptoms. The term "intermittent" should be avoided as the duration and incidence of events helps in understanding the safety profile of the study drug.

8.2.3. AE Severity

AE severity will be graded according to NCI CTCAE v5.0. A copy of the document will be provided to investigational sites, and an electronic version is available at:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf.

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, according to the NCI CTCAE); the event itself may be of relatively minor medical significance (e.g., severe headache without any further findings).

Events not listed in NCI CTCAE will be graded according to the criteria described in Table 5.

Table 5: Severity Grading Guideline for AEs Not Listed in NCI CTCAE

AE Not Listed in NCI CTCAE v5.0	
Grade	**Description**
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 activities of daily living[a]
3	• Severe or medically significant but not immediately life threatening • Hospitalization or prolongation of hospitalization indicated • Disabling • Limiting selfcare activities of daily living[b]
4	• Life-threatening consequences • Urgent intervention indicated

5	• Death related to adverse event

Abbreviations: AE = adverse event; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; v = version.
Note: A semicolon indicates "or" within the description of the grade.
[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[b] Self-care activities of daily living refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

8.2.4. AE Duration

The start date (the date that the event/condition was first noticed or diagnosed) and end date (the date that the event/condition had completely resolved, returned to baseline, or changed in severity grade) will be recorded. If the exact date is not known, the best estimate should be reported.

All AEs will be followed until stabilization or resolution.

8.2.5. AE Causality

Where the determination of the relationship of the AE to the study drug rests on medical judgment, the determination must be made with the appropriate involvement of the Investigator or, if the Investigator is not a physician, a designated sub-Investigator who is a physician.

Using the following criteria, Investigators will assess whether there is a reasonable possibility that the study drug caused or contributed to the AE.

Related

- The time sequence between the onset of the AE and study drug administration is consistent with the event being related to the study drug; and/or
- There is a possible biologic mechanism for the study drug causing or contributing to the AE and the AE may or may not be attributed to concurrent/underlying illness, other drugs, or procedures.

Not Related

- Another cause of the AE is most likely; and/or
- The time sequence between the onset of the AE and study drug administration is inconsistent with a causal relationship; and/or
- A causal relationship is considered biologically unlikely.

8.3. SAE Reporting

Investigators must report all SAEs regardless of causality immediately (within 24 hours of awareness) on the AE CRF. If the EDC system is unavailable, SAEs must be reported by completing the back-up paper SAE report form and emailing the completed form to: [redacted]

An event that results in hospitalization or prolongs existing hospitalization will not be considered an SAE if the only reason for that hospitalization or prolongation is:

- To administer the study drug
- To conduct protocol-specified study procedures
- For placement of a permanent intravenous catheter
- Hospice placement due to PD
- Respite care

8.5. Reporting Disease Progression and Death

Progressive disease, also referred to as disease progression, and death due to disease progression are study endpoints, and information related to these events will be collected in eCRFs specifically designed to collect these data. These events will not be reported as AEs/SAEs unless the Investigator feels that they are accelerated, atypical, or related to the study drug. All deaths must be communicated as soon as possible to the appropriate IRB/IEC and reported in accordance with local laws and regulations.

If an autopsy is performed, a copy of the report will be requested and provided to the Sponsor, if available.

8.6. Special Situation Reporting

Special situations may require expedited reporting and/or safety evaluations. These include, but are not limited to:

- Overdose of the study drug – administration of a quantity of study drug above the recommended dose according to the protocol. In cases of a discrepancy in the drug accountability, overdose is established only when it is clear that the patient has taken additional doses or the Investigator has a reason to suspect that the patient has taken additional doses.
- Abuse of the study drug – persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.
- Misuse of a study drug – situations where the medicinal product is intentionally and inappropriately used in a way that is not in accordance with the protocol instructions or local prescribing information and may be accompanied by harmful physical and/or psychological effects.
- Medication error – unintentional error in the prescribing, dispensing, or administration of the medicinal product.

- Product complaint – any written, electronic, or oral communication alleging deficiencies related to the identity, quality, durability, reliability, safety, or effectiveness of a drug after it is released for distribution. This situation should be reported by completing the specific Product Complaint Form (see Pharmacy Manual forms for details). If also associated with an AE, report the AE on the AE CRF.

All special situations must be reported by completing the Special Situation Report form except for a product complaint (see above). The completed form should be sent via email to: [redacted] If the special situation is associated with an AE, the AE must also be recorded on the AE eCRF.

8.7. ECG Monitoring

Standard 12-lead ECGs will be performed locally using a calibrated digital ECG machine capable of providing automated measurements. All ECG tracings will be acquired with the patient in the supine position after the patient has been resting for at least approximately 10 minutes. ECG tracings will be measured and interpreted locally by a cardiologist or other qualified healthcare professional in accordance with institutional standard of care.

ECGs will be performed at the time points indicated in the Schedule of Events (Table 1). The Screening ECG will be performed in triplicate.

8.8. Vital Sign Assessments

The following vital signs will be assessed after the patient has been sitting for approximately 5 minutes. Vital signs will be obtained at each visit as indicated in the Schedule of Events (Table 1). Vital signs to be measured include:

- Blood pressure (systolic and diastolic; mmHg)
- Heart rate (beats per minute)
- Body temperature (°C)
- Respiration rate (breaths per minute)

8.9. Clinical Laboratory Assessments

Clinical laboratory assessments will be performed by each institution's local laboratory and must be resulted and evaluated prior to administration of the study drug. The laboratory variables in Table 6 will be collected in accordance with the Schedule of Events (Table 1).

Table 6: Clinical Laboratory Assessments

Serum or Plasma Chemistry:	Sodium Potassium Chloride Calcium Magnesium Phosphorous Glucose	Total Bilirubin Aspartate aminotransferase Alanine aminotransferase Alkaline phosphatase Albumin Total protein Creatinine
Hematology:	Red blood cell count Hemoglobin Hematocrit Platelet counts White blood cell count with differential (reported as absolute counts), where possible Total neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils	
Coagulation:	International normalized ratio Partial thromboplastin time Activated partial thromboplastin time	
Pregnancy Test:	In women of childbearing potential only: serum β-human chorionic gonadotropin pregnancy test, urine, or urine dipstick	

All clinically significant unscheduled laboratory results will be recorded, and all clinically significant laboratory results (scheduled and unscheduled) obtained during the study period will be reported as AEs (e.g., Grade ≥ 2 aspartate aminotransferase, alanine aminotransferase, or serum bilirubin).

8.10. Contraception, Pregnancy Testing and Reporting

Patients who are WOCBP will have a serum pregnancy test performed at Screening and urine pregnancy test performed on Day 1 (before dosing) of every cycle and the EOT Visit. If a patient's serum pregnancy test at Screening is within 72 hours of their first dose of study drug, a negative urine pregnancy test on Cycle 1 Day 1 is not required. Additional pregnancy testing may be performed according to institutional practice.

Patients who are WOCBP and male patients whose partners are WOCBP will be counseled on the importance of avoiding pregnancy. [redacted]

WOCBP participating in the study must use a highly effective method of contraception during the study [redacted] Highly effective contraceptive measures include, but are not limited to, the following:

- Combined (estrogen and progestogen containing) hormonal contraception (oral, etc.) associated with inhibition of ovulation
- Progestogen-only hormonal contraception (oral, etc.) associated with inhibition of ovulation
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner

If a female patient becomes pregnant, she should immediately discontinue the study drug and receive appropriate monitoring and care until the conclusion of the pregnancy.

[redacted]

Note: For this study, abstinence is defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. Periodic abstinence, withdrawal (coitus interrupts), or the use of spermicides only are not acceptable methods of contraception.

All patients will be instructed to report any suspected pregnancies in themselves or their female partners during the study within the timeline specified above after the last dose of study drug. The Investigator must report the pregnancy by completing the exposure in utero (EIU) form and emailing the completed form to [redacted] ithin 24 hours of awareness.

The Investigator must obtain permission from a patient's pregnant partner before collecting further information regarding the pregnancy.

The pregnancy itself is not considered an AE nor is an induced elective abortion to terminate a pregnancy without medical reasons. However, the pregnancy should be followed until the outcome is known. Once the outcome of the pregnancy is known, the EIU form should be completed within 24 hours of awareness and emailed to [redacted]

If the pregnancy outcome is spontaneous abortion, stillbirth, neonatal death, infant with congenital anomaly, or a postpartum complication, the Investigator must also report the outcome as an SAE by completing the required information on the AE eCRF.

8.11. Physical Examinations

Complete physical examinations focused on major organ systems that are clinically relevant as determined by the Investigator and including system directed findings, vital signs (taken 5 minutes after sitting), height and weight will be performed at the visits indicated in the Schedule of Events (Table 1). Height will be recorded at Screening. Weight will be recorded at all time

points indicated in the Schedule of Events. Clinically significant findings observed during the physical examination will be reported as medical history (pretreatment) or AEs (posttreatment).

8.12. ECOG Performance Status Scale

All patients will be assessed on Days 1 and 15 in Cycles 1 to 3, Day 1 only in Cycles 4 and beyond, and at the EOT Visit using the ECOG Performance Status Scale (Table 7). An ECOG performance score of 0 to 1 is required for study entry but is not a criterion for retreatment or study drug discontinuation.

Table 7: ECOG Performance Status Scale

ECOG Performance Status Scale	
Grade	**Description**
0	Fully active, able to continue 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 or office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about > 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair > 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

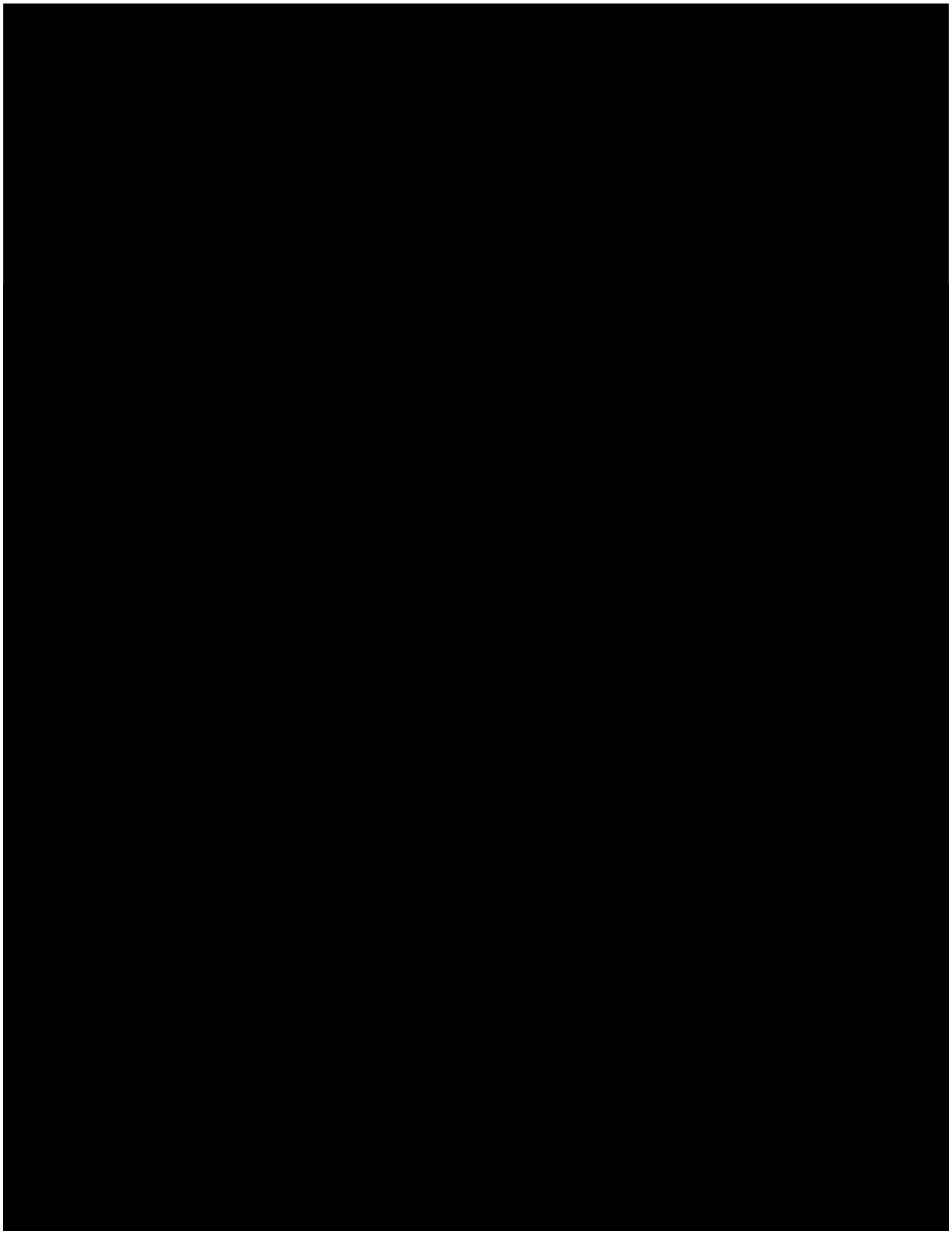
Abbreviation: ECOG = Eastern Cooperative Oncology Group.
Source: Oken 1982

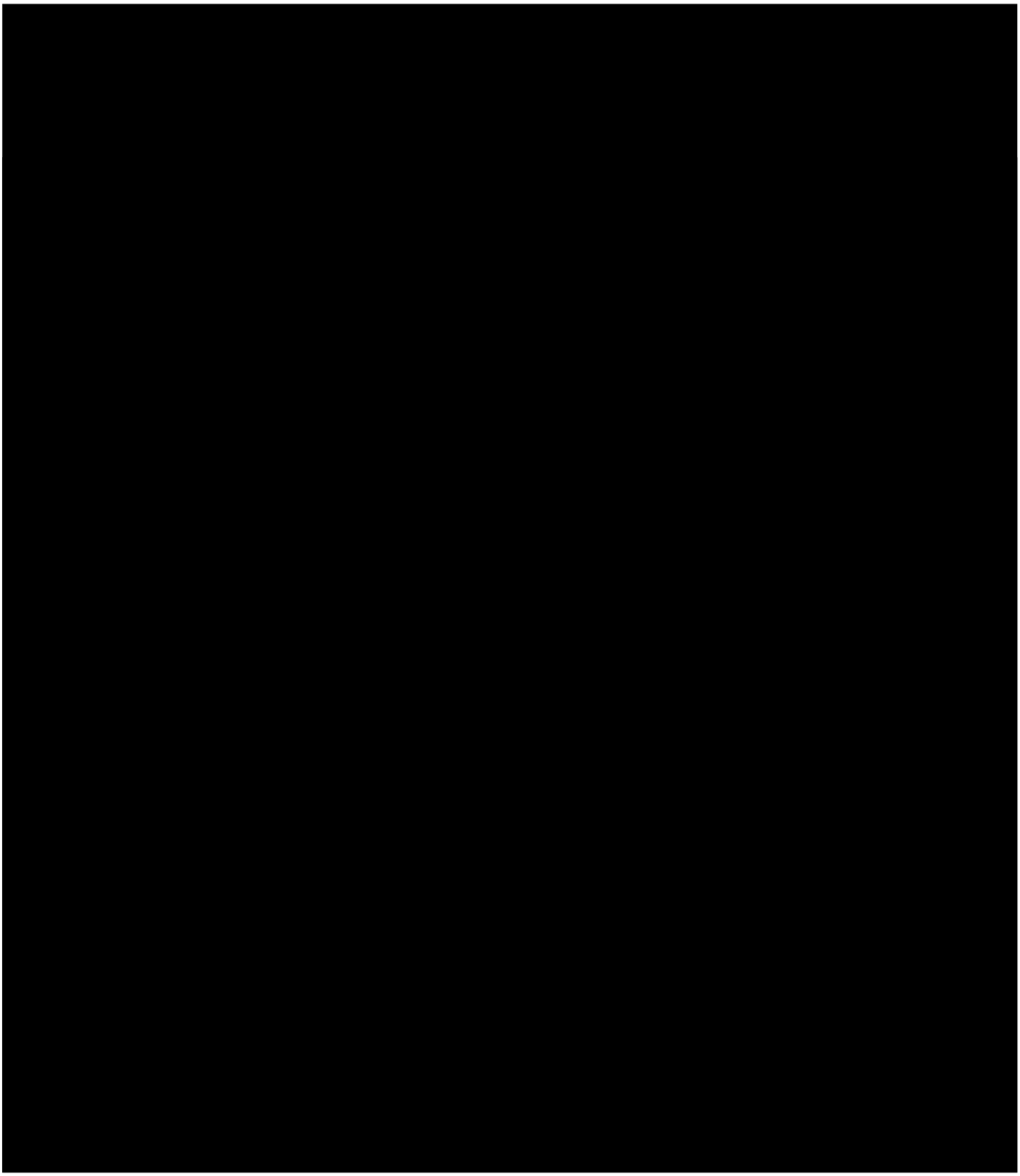
8.13. Pharmacokinetics

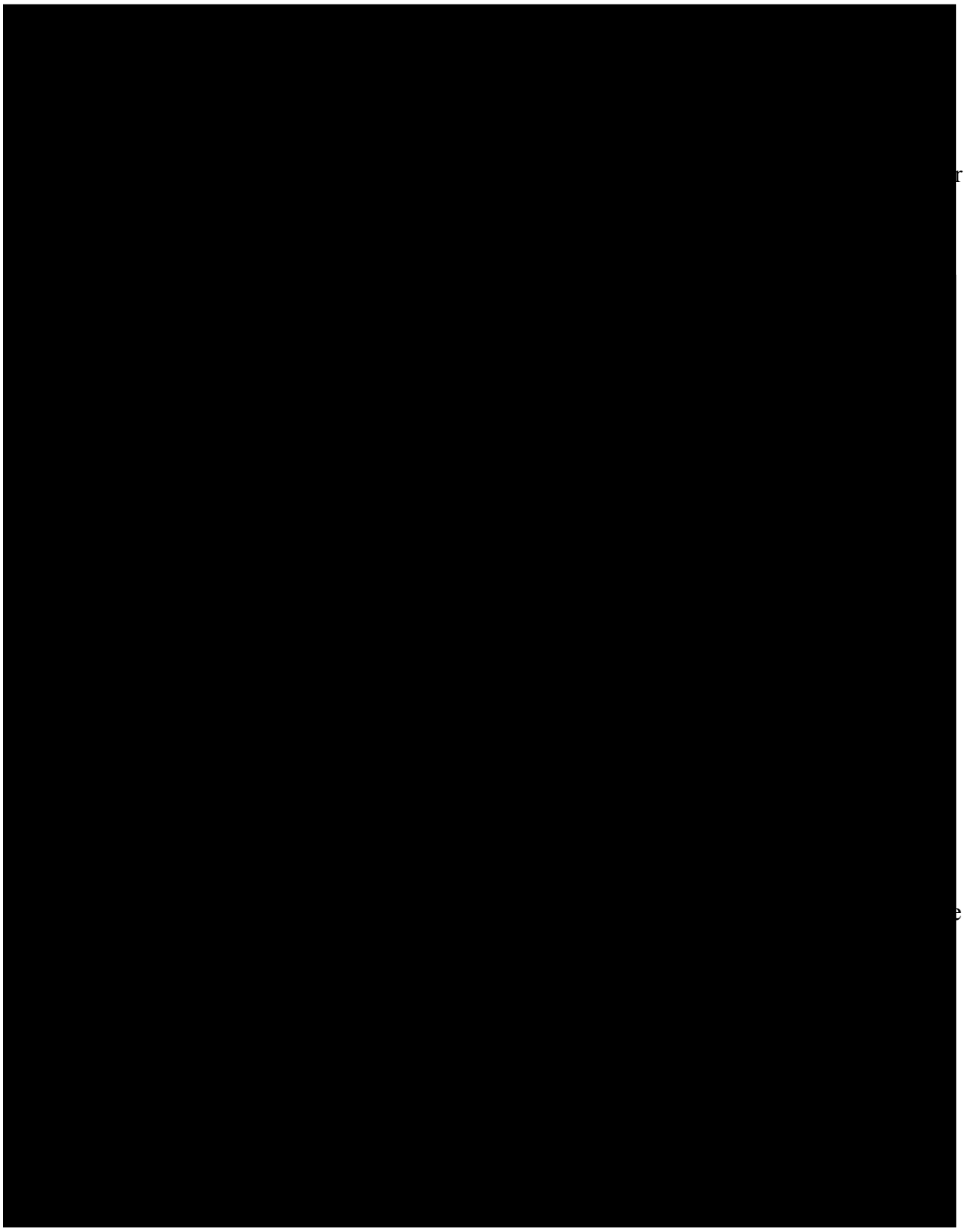
[redacted]

8.14. Tumor Tissue

[redacted]







10. QUALITY CONTROL AND QUALITY ASSURANCE

10.1. Data Quality Assurance

The Sponsor or Sponsor's designee will conduct a site visit to verify the qualifications of each Investigator, inspect the site facilities, and inform the Investigator of the responsibilities and procedures for ensuring adequate and correct documentation.

The Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study patient. All information recorded in the EDC system for the study must be consistent with the patients' source documentation (i.e., medical records).

10.1.1. Database Management and Quality Control

All data generated by the site personnel will be captured electronically at each study center using an EDC system. Data from external sources (such as laboratory data) will be entered into the database. Once the EDC clinical data have been submitted to the central server at the

independent data center, corrections to the data fields will be captured in an audit trail. The reason for change and name of the person who performed the change, together with the time and date, will be logged to provide an audit trail.

If additional corrections are needed, the responsible monitor or data manager will raise a query in the EDC application. The appropriate staff at the study site will answer queries sent to the Investigator. The name of the staff member responding to the query and time and date stamp will be captured to provide an audit trail. Once all source data verification is complete and all queries are closed, the monitor will freeze the EDC.

The specific procedures to be used for data entry and query resolution using the EDC system will be provided to study sites in a training manual. In addition, site personnel will receive training on the EDC system.

11. ETHICS

11.1. Prescreening Informed Consent

Potential patients who meet the any of the criteria on local testing specified in Inclusion Criteria #7 (Section 5.1) may be asked to consent to prescreening.

By signing the prescreening consent, the patient will authorize the study personnel to obtain archival tumor tissue and have it processed at a central laboratory. Prescreening eligibility does not guarantee study enrollment and the patient must consent to the main study before any Screening activities may commence. Patients who have central testing of *TP53* and *MDM2* gene status performed under prescreening consent may use the same tissue for submission requirement.

11.2. Informed Consent

Before each patient is admitted to the study, written informed consent will be obtained from the patient according to the regulatory and legal requirements of the participating country. This consent form must be dated and retained by the Investigator or designee (designee must be listed on the Delegation of Authority Log or equivalent) as part of the study records. The Investigator will not undertake any investigation specifically required only for the clinical study until valid consent has been obtained. The terms of the consent and when it was obtained must also be documented in the EDC system. A copy of each signed and dated informed consent form must be provided to the patient at the time it is signed by the patient.

Patients may elect to provide optional tumor biopsies for analysis and correlative studies. These samples will be collected only if the patient provides additional consent.

If a protocol amendment is required, the informed consent form may need to be revised to reflect the changes to the protocol. If the consent form is revised, it must be reviewed and approved by the appropriate IEC/IRB and signed by all patients subsequently enrolled in the study, as well as those currently enrolled in the study.

11.3. Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IEC/IRB/Competent Authorities, in accordance with local legal requirements. The Sponsor or Sponsor's designee must ensure that all ethical and legal requirements have been met before the first patient provides consent to participate in the study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IRB/IEC/Competent Authority approval prior to implementation (if appropriate).

Administrative changes (not affecting the patient benefit/risk ratio) may be made without the need for a formal amendment. All amendments will be distributed to all protocol recipients with appropriate instructions.

11.4. Duration of the Study

The total study duration is estimated to be 3 years, including approximately 12 months for accrual and approximately 5 months for follow--up after the last patient is enrolled. Patients are expected to receive up to 12 months of treatment. The end of the study is defined as the last patient visit or contact, including telephone contacts, for collection of any study-related data.

11.5. Premature Termination of the Study

If the Investigator, Sponsor, or Medical Monitor become aware of conditions or events that suggest a possible hazard to patients if the study continues, the study may be terminated after appropriate consultation between the relevant parties. The study may also be terminated early at the Sponsor's discretion in the absence of such a finding.

Conditions that may warrant termination include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study
- Failure to enroll patients at an acceptable rate
- A decision on the part of the Sponsor to suspend or discontinue development of the study drug

11.6. Confidentiality

All goods, materials, information (oral or written), and unpublished documentation provided to the Investigator (or any company acting on their behalf), inclusive of this protocol, the patient eCRFs, and the milademetan IB are the exclusive property of the Sponsor. Documents and information provided to the Investigator by the Sponsor may not be given or disclosed by the Investigator or by any person within his authority in part or in totality to any unauthorized person without the prior written formal consent of the Sponsor.

It is specified that the submission of this protocol and other necessary documentation to the IRB/IEC is expressly permitted, the IRB/IEC members having the same obligation of confidentiality.

The Investigator shall consider as confidential and take all necessary measures to ensure that there is no breach of confidentiality in respect of all information accumulated, acquired, or deduced during the study, other than that information to be disclosed to a third party mandated by applicable law.

Any language relating to these issues appearing in the Clinical Trial Agreement will supersede that outlined in this section.

The anonymity of participating patients must be maintained. Patients will be identified in the EDC system and other documents submitted to the Sponsor or Sponsor's designee by their patient number, initials, and/or birth date, not by name. Documents not to be submitted to the Sponsor or Sponsor's designee that identify the patient (e.g., the signed informed consent) must be maintained in confidence by the Investigator.

Information on maintaining patient confidentiality in accordance with individual local and national patient privacy regulations must be provided to each patient as part of the informed consent process either as part of the informed consent form or as a separate signed document (for example, in the US, a site-specific Health Insurance Portability and Accountability Act of 1996 consent may be used). The Investigator or designee must explain to each patient that for the evaluation of study results, the patient's protected health information obtained during the study may be shared with the Sponsor and its designees, regulatory agencies, and IRBs/research ethics boards/IECs. The study Sponsor will not use the patient's protected health information or disclose it to a third party without applicable authorization. It is the Investigators or designee's responsibility to obtain written permission to use protected health information from each patient. If a patient withdraws permission to use protected health information, it is the Investigator's responsibility to obtain the withdrawal request in writing from the patient and ensure that no further data will be collected from the patient. Any data collected on the patient before withdrawal will be used in the analysis of the study results.

During the review of source documents by the monitors or auditors, the confidentiality of the patient will be respected with strict adherence to professional standards and regulations.

12. DATA HANDLING AND RECORD KEEPING

12.1. CRFs and Source Documentation

All data obtained during the study should be entered in the EDC system promptly. All source documents from which EDC entries are derived should be placed in the patient's medical records. Measurements for which source documents are usually available include laboratory assessments, ECG recordings, CT scans, MRI, and X-rays. EDC entries may be checked against source documents at the study site or remotely by the Sponsor or Sponsor's designee site monitor. After review by the site monitor, completed EDC entries will be uploaded and forwarded to the Sponsor (or designee). Instances of missing or uninterpretable data will be discussed with the Investigator for resolution.

The specific procedures to be used for data entry and query resolution using the EDC system will be provided to study sites in a training manual. In addition, site personnel will receive training on the EDC system.

12.1.1. Data Collection

The Investigators (and appropriately authorized staff) will be given access to an online web-based EDC system that is compliant with the ICH guidelines for Good Clinical Practice (ICH E6). This system is specifically designed for the collection of clinical data in electronic format. Access and rights to the EDC system will be carefully controlled and configured according to everyone's role throughout the study. In general, only the Investigator and authorized staff will be able to enter data and make corrections in the eCRFs.

The eCRF should be completed for each patient included in the study and reflect the latest observations on the patient. Therefore, the eCRFs are to be completed as soon as possible during or immediately after the patient's visit or assessment. The Investigator must verify that all data entries in the eCRF are accurate and correct.

Computerized data--check programs and manual checks will identify any clinical data discrepancies for resolution. Corresponding queries will be loaded into the system, and the site will be informed about new issues to be resolved online. All discrepancies will be solved online directly by the Investigator or authorized staff. Offline edit checks will be done to examine relationships over time and across panels to facilitate quality data.

After completion, the Investigator will be required to electronically sign off the clinical data.

Data about all study drug dispensed or administered to the patient and any dosage changes will be tracked in the eCRF.

12.2. Access to Source Data

Patients are informed about who may have access to their medical records and study data. During the study, a monitor will make site visits or conduct remote monitoring to review protocol compliance, compare EDC entries and individual patient's medical records, and ensure that the study is being conducted according to pertinent regulatory requirements. EDC entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained. Appropriate access controls will be in place to ensure that access to confidential research information is restricted to those who need access.

Checking of EDC entries for completeness and clarity and cross-checking with source documents will be required to monitor the progress of the study. Moreover, Regulatory Authorities of certain countries, IRBs, IECs, and/or the Sponsor's Clinical Quality Assurance Group may wish to carry out such source data checks and/or on-site audit inspections. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and medical confidentiality. The Investigator assures the Sponsor (or designee) the necessary access at all times.

12.3. Data Processing

All data will be entered by site personnel into the EDC system. The data-review and data-handling document, to be developed during the initiation phase of the study, will include specifications for consistency and plausibility checks on data and will also include data-handling rules for obvious data errors. Query/correction sheets for unresolved queries will be sent to the

study monitors for resolution with the Investigator. The database will be updated based on signed corrections.

Concomitant medications will be coded using the WHO Drug Global dictionary, which employs the Anatomical Therapeutic Chemical classification system. Medical history, current medical conditions, and AEs will be coded using MedDRA terminology. The versions of the coding dictionaries will be provided in the clinical study report. When personal data is transferred electronically, data will be encrypted during transfer.

12.4. Archiving Study Records

The Investigator shall retain study drug disposition records and all source documentation (such as original ECG tracings and laboratory reports, in subject or office subject records) for the maximum period required by the country and institution where the study will be conducted or for the period specified by Rain, whichever is longer. The investigator must contact Rain prior to destroying any records associated with the study. If the investigator withdraws from the study (due to relocation, retirement, etc.), the records shall be transferred to a mutually agreed upon designee, such as another investigator or IRB/IEC. Notice of such transfer will be provided in writing to Rain.

Rain Therapeutics Inc. will maintain archive copies of all records for a period of no less than 25 years.

13. PUBLICATION POLICY

By signing the study protocol, the Investigator agrees with the use of results of the study for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. If necessary, Regulatory Authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement.

An Investigator shall not publish any data (poster, abstract, paper, etc.) without discussion with and approval by the Sponsor.

14. REFERENCES

Fakharzadeh SS, Trusko SP, George DL. Tumorigenic potential associated with enhanced expression of a gene that is amplified in a mouse tumor cell line. *EMBO J*. 1991;10(6):1565-9.

Flørenes VA, Maelandsmo GM, Forus A, et al. *MDM2* gene amplification and transcript levels in human sarcomas: relationship to *TP53* gene status. *J Natl Cancer Inst*. 1994;86(17):1297-302.

Klastersky J, de Naurois J, Rolston K, et al. Management of febrile neutropaenia: ESMO Clinical Practice Guidelines. Ann Oncol. 2016;27(suppl 5):v111-v118. doi:10.1093/annonc/mdw325

Levine AJ, Oren M. The first 30 years of p53: growing ever more complex. Nat Rev Cancer. 2009 Oct; 9(10):749-58.

National Cancer Institute. Genomic Data Commons Data Portal. https://portal.gdc.cancer.gov/

National Cancer Institute; Surveillance, Epidemiology, and End Results Program. Cancer Stat Facts. Cited November 2022. Available from: https://seer.cancer.gov/statfacts.

Noguchi S, Seki T, Adachi N, et al. PF225 Azacitidine (AZA) enhances antileukemic activity of the MDM2 inhibitor milademetan in TP53 wild-type acute myeloid leukemia (AML). *HemaSphere*. 2019;3(S1):65.

Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5(6):649-55.

Park SY, Doolittle-Amieva C, Moshiri Y, Akaike T, Parvathaneni U, Bhatia S, et al. How we treat Merkel cell carcinoma: within and beyond current guidelines. Future Oncol. 2021 Apr;17(11):1363-1377. doi: 10.2217/fon-2020-1036.

Pugh TJ, Bell JL, Bruce JP, et al. AACR Project GENIE: 100,000 Cases and Beyond. Cancer Discov. 2022;12(9):2044-2057. doi:10.1158/2159-8290.CD-21-1547

Shangary S, Qin D, McEachern D, Liu M, Miller RS, Qiu S, et al. Temporal activation of p53 by a specific MDM2 inhibitor is selectively toxic to tumors and leads to complete tumor growth inhibition. Proc Natl Acad Sci U S A. 2008 Mar 11;105(10):3933-8.

Shangary S, Wang S. Small-molecule inhibitors of the MDM2-p53 protein-protein interaction to reactivate p53 function: a novel approach for cancer therapy. *Annu Rev Pharmacol Toxicol*. 2009; 49:223-41.

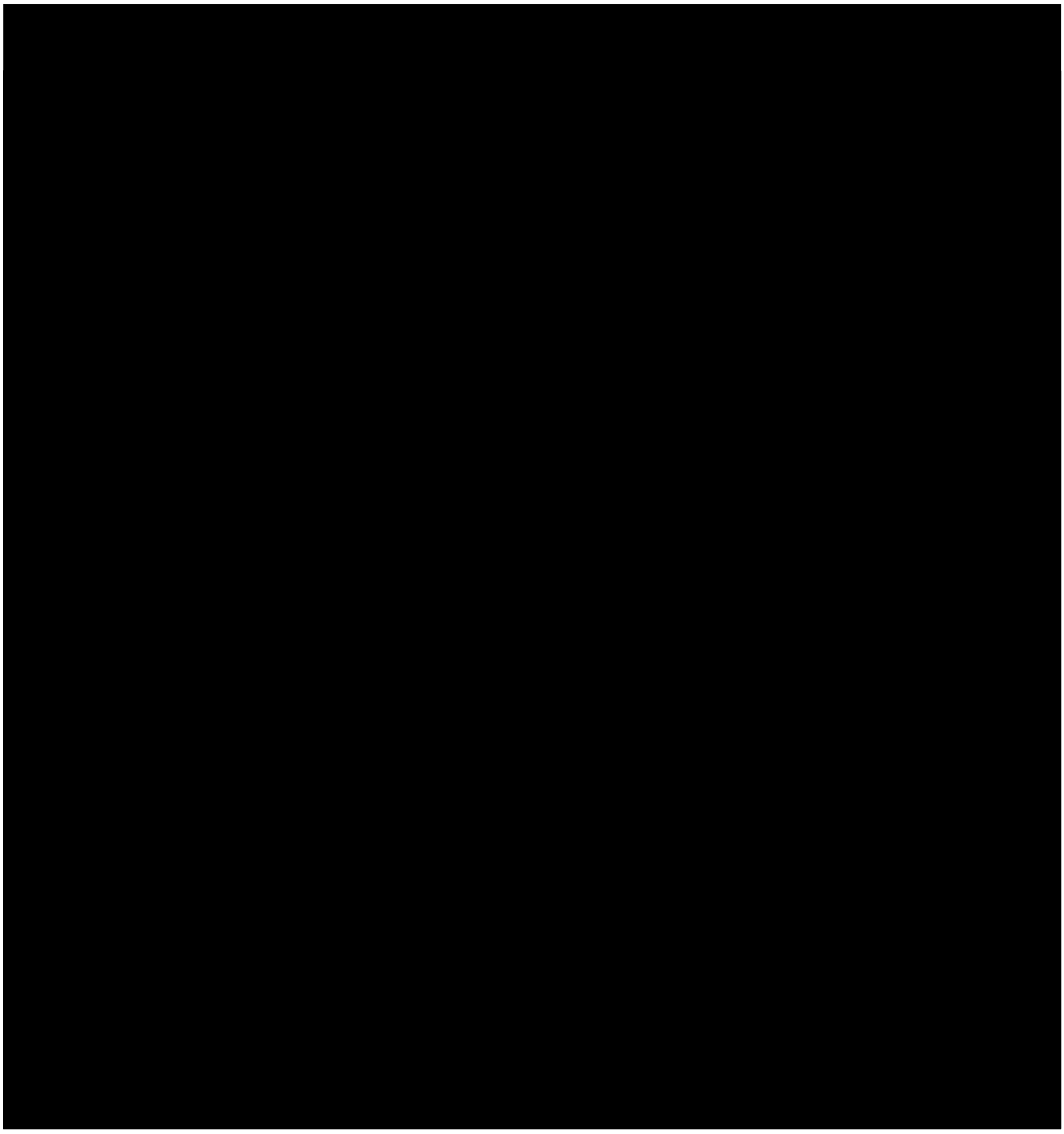
Sherr CJ, Weber JD. The ARF/p53 pathway. *Curr Opin Genet Dev*. 2000 Feb;10(1):94-9.

Smith TJ, Bohlke K, Lyman GH, et al. Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol*. 2015;33(28):3199-3212. doi:10.1200/JCO.2015.62.3488

Tirunagaru VG, Gounder MM, Kumar P, Hong D, Doebele RC. *MDM2* gene amplification as a predictive biomarker for the MDM2 inhibitor milademetan. Poster presented at: AACR-NCI-EORTC Virtual International Conference on Molecular Targets and Cancer Therapeutics; 2021 Oct 7-10.

Vassilev LT. MDM2 inhibitors for cancer therapy. *Trends Mol Med*. 2007;13(1):23-31.

Vassilev LT, Vu BT, Graves B, et al. In vivo activation of the p53 pathway by small-molecule antagonists of MDM2. *Science*. 2004;303(5659):844-8.



APPENDIX B. DECLARATION OF THE INVESTIGATOR

All documentation for the study that is supplied to me and has not been previously published will be kept in the strictest confidence. This documentation includes the study protocol, milademetan Investigator's Brochure, electronic data capture system, and other scientific data. I have read and understood and agree to abide by all the conditions and instructions contained in this protocol, including the following statements:

- I will conduct the study in accordance with the relevant current protocol and will only make changes in a protocol after notifying the Sponsor, except when necessary to protect the safety, rights, or welfare of patients.
- I will personally conduct or supervise the described investigation.
- I will inform any patients or any persons used as controls that the study drug is being used for investigational purposes, and I will ensure that the requirements relating to obtaining informed consent in Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and approval in the International Council for Harmonisation (ICH) Guidelines on Good Clinical Practice (ICH E6) and local requirements are met.
- I will report to the Sponsor adverse experiences that occur in the course of the investigation(s) in accordance with ICH E6 and local requirements. I have read and understand the information in the protocol and milademetan Investigator's Brochure, including the potential risks and side effects of the study drug.
- I will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
- I will maintain adequate and accurate records in accordance with the ICH E6 and local requirements, including making these records available for inspection.
- I will ensure that an IRB/IEC that complies with the requirements of ICH E6 and local requirements will be responsible for the initial and continuing review and approval of the clinical investigation. I will also promptly report to the IRB/IEC all changes in the research activity and all unanticipated problems involving risks to patients or others. Additionally, I will not make any changes in the research without IRB/IEC approval, except where necessary to eliminate apparent immediate hazards to patients.
- I will comply with all other requirements regarding the obligations of clinical Investigators and all other pertinent requirements in ICH E6 and local requirements.

I understand that before I publish any findings from this study in scientific journals or present these at scientific meetings, I must first provide the Sponsor with ample opportunity to review the intended use of the study data. The Sponsor must authorize the disclosure of study data for any proposed abstract, manuscript, or meeting materials prior to the submission

Responsible Investigator

Signature	Date
Name (Printed)	
Title (Printed)	