KZR-261-101

A PHASE 1 STUDY OF KZR-261, A SMALL MOLECULE SEC61 INHIBITOR, IN SUBJECTS WITH ADVANCED SOLID MALIGNANCIES

Clinicaltrials.gov Identifier	*NCT05047536*
Date of protocol:	*02 October 2023*

CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 1 Study of KZR-261, a Small Molecule Sec61 Inhibitor, in Subjects with Advanced Solid Malignancies
Protocol Number:	KZR-261-101
Investigational Product:	KZR-261
Indication:	Advanced solid malignancies
Development Phase:	Phase 1
[redacted]	[redacted]
Sponsor:	Kezar Life Sciences, Inc. 4000 Shoreline Court, Suite 300 South San Francisco, CA 94080
Original Protocol Date:	29 April 2021
Version / Date:	Version 1.0 / 29 April 2021 Version 2.0 / 08 September 2021 Version 3.0 / 05 December 2022 Version 4.0 / 27 March 2023 Version 5.0 / 02 October 2023

Confidentiality Statement

Compliance Statement

This study will be conducted in accordance with this protocol, the International Council for Harmonisation (ICH), Guideline for Good Clinical Practice (GCP), and the applicable country and regional (local) regulatory requirements.

PROTOCOL ACCEPTANCE PAGE

Protocol Title: **A Phase 1 Study of KZR-261, a Small Molecule Sec61 Inhibitor, in Subjects with Advanced Solid Malignancies**

Protocol Number: **KZR-261-101**

Confidentiality and Current Good Clinical Practice (cGCP) Compliance Statement

I, the undersigned, have reviewed this protocol (and amendments), including appendices. I am aware of my responsibilities as an Investigator under the International Council for Harmonisation (ICH) Guideline for cGCP, the Declaration of Helsinki, all local, regional, and national regulatory requirements (including the Code of Federal Regulations [CFR] Title 21 for United States Investigators), requirements of the applicable Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and the clinical trial protocol. I agree to conduct the trial according to these regulations and guidelines, to appropriately direct and assist the staff under my control that will be involved in the trial, and to ensure that all staff members are aware of their clinical trial responsibilities.

Once the protocol has been approved by the IEC/IRB, I will not modify this protocol without obtaining prior approval of Kezar Life Sciences and of the IEC/IRB. I will submit the protocol amendments and/or any Informed Consent Form (ICF) modifications to Kezar Life Sciences and IEC/IRB, and approval will be obtained before any amendments are implemented.

I understand that all information obtained during the conduct of the study with regard to the subjects' state of health will be regarded as confidential. No subjects' names will be disclosed. All subjects will be identified by assigned numbers on all electronic case report forms (eCRFs), laboratory samples, or source documents forwarded to the Sponsor. Clinical information may be reviewed by the Sponsor or its agents or regulatory agencies. Agreement must be obtained from the subject before disclosure of subject information to a third party.

Information developed in this clinical study may be disclosed by Kezar Life Sciences, to other clinical Investigators, regulatory agencies, or other health authority or government agencies as required.

Investigator's Name: _____

Name of Institution/Site: _____

Signature: _____

Date: _____

STUDY PERSONNEL

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SAE Reporting Details (to be used for submitting the SAE forms):

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PROTOCOL SYNOPSIS

INVESTIGATIONAL PRODUCT (IP)	
Name of IP	KZR-261
[redacted]	[redacted]
Protocol ID	KZR-261-101
Protocol Title	A Phase 1 Study of KZR-261, a Small Molecule Sec61 Inhibitor, in Subjects with Advanced Solid Malignancies
Short Title	A Phase 1 Study of KZR-261 in Subjects with Advanced Solid Malignancies
Study Phase	Phase 1
CLINICAL CONDITION(S)/INDICATION(S)	
Dose Escalation (Part 1) • Advanced/metastatic solid malignancies (~70 subjects). **Dose Expansion (Part 2A)** • Tumor-specific cohorts (15 subjects, may increase up to 35 subjects as determined by prespecified futility criteria in Stage 1 and if the tumor type is not selected for investigation in Part 2B). o Malignant melanoma (including uveal melanoma) o Malignant mesothelioma o Metastatic castration-resistant prostate cancer (mCRPC) o Metastatic colorectal carcinoma (mCRC) • All-Tumors cohort (up to 35 biopsy-evaluable subjects) o Other advanced solid malignancies with tumor tissue at baseline (fresh biopsy required) **Dose Optimization (Part 2B)** • Up to 4 tumor types from Dose Expansion (~30 subjects per tumor type [~15 subjects/dose level]). Additional (or different) tumor types may be investigated at the Sponsor's discretion in Part 2 if evidence of anti-tumor activity of KZR-261 during Part 1 or in the All-Tumors cohort in Part 2 supports further evaluation.	
STUDY DESIGN	
Study Type	Interventional
Allocation	Multicenter, United States
Blinding/Masking	Open-label
Primary Purpose	Phase 1, first-in-human
Planned Duration of Subject Participation	Approximately 20 months: 4-week Screening Period, 24-week Treatment Period (6 cycles, 4 weeks each), 30-day Safety Follow-Up Period, 12-month Long Term Follow-up Period (after last dose of study treatment).

Overview of Study Design

This first-in-human, open-label, multicenter, Phase 1 study of KZR-261 is designed to assess the safety and tolerability, preliminary anti-tumor activity, and pharmacokinetics (PK) of KZR-261, as well as identify the recommended Phase 2 dose (RP2D). KZR-261 will be administered as a 30- to 60-minute intravenous (IV) infusion via a central line on Days 1, 8, and 15 of a 4-week (28-day) treatment cycle. Eligible subjects will have locally advanced or metastatic solid malignancies and no approved therapies, or refused such therapies if available.

Subjects will receive KZR-261 for up to 6 cycles. Upon completion of Cycle 6, a subject who is deriving clinical benefit may continue treatment at the discretion of the Investigator and with agreement of the Medical Monitor. Study treatment will be discontinued at any time for unacceptable adverse events (AEs), progressive disease, voluntary study withdrawal by the subject, another discontinuation criterion is met, or study closure by the Sponsor (Section 8.1.2). Safety assessments will be collected via safety laboratory monitoring, as well as changes from baseline in physical examinations, electrocardiogram (ECG) findings, vital sign (VS) measurements, and slit lamp and visual acuity exams. AEs will be assessed for severity using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0. Dose-limiting toxicity (DLTs) will be assessed during Part 1 as defined by pre-specified AE criteria detailed in Section 3.2.3.

Anti-tumor activity will be assessed in accordance with the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1). Subjects with mCRPC will be assessed per the Prostate Cancer Working Group 3 (PCWG3) guidelines.

Efforts will be made to follow subjects for up to 12 months after the last dose of KZR-261 to assess disease status and/or survival.

The study will be conducted in 2 parts: Part 1 (Dose Escalation), and Part 2 (Part 2A – Dose Expansion and Part 2B – Dose Optimization).

Part 1: Dose Escalation

In Part 1, increasing doses of KZR-261 will be administered in an "i3+3" design to approximately 70 subjects to evaluate the safety and tolerability, PK, and pharmacodynamics of KZR-261, including identifying the maximum tolerated dose (MTD) or maximum administered dose (MAD).

Dose-escalation decisions for KZR-261 will be guided by the i3+3 design (Zhou and Ji, 2020; Liu et al., 2020) as described in Section 3.2.1, with the targeted DLT rate p_T=0.3 and the equivalence interval (EI) = [0.25, 0.35]. The starting dose is 1.8 mg/m^2. During the DLT assessment period (Cycle 1), doses may be held up to 7 days for resolution of non-DLT toxicity.

A minimum of 2 subjects will be enrolled at each dose level of KZR-261. The number of subjects that will be enrolled at each dose level varies, with a typical cohort size of 2-4, and with 6 to approximately 12 subjects dosed at the putative MTD/MAD.

Intra-subject Dose Escalation

Intra-subject dose escalation will be permitted after consultation with the Medical Monitor and in the following circumstance only:

- Subject must have completed at least two 28-day cycles of treatment (Cycles 1 and 2).
- Subject may have experienced an AE* ≤Grade 3 with resolution to Grade 1 or baseline in the setting of a documented tumor response or stable disease over 2 consecutive assessment timepoints. For subjects who experienced a Grade 3 AE, the Investigator and Medical Monitor should come to an unequivocal consensus that the potential benefit of an increase in dose will outweigh the risk of future AEs.

- Subject must not have experienced a DLT.
- Subject must not have experienced a dose reduction for purposes of managing AEs and/or laboratory abnormalities.
- The higher dose cohort to which the subject would be escalated has been deemed by the Safety Review Committee (SRC) to be safe and adequately tolerated.

**Note: AEs must be assessed as unrelated to study treatment, such as intercurrent illness or concomitant medication. AEs that are assessed as related to study treatment would disqualify a patient from dose escalation.*

Definition of DLT

Toxicities will be assessed by the Investigator using NCI CTCAE v5.0. The attribution of an AE to KZR-261 is to be assessed by the Investigator. DLTs are defined in Section 3.2.3.

Definition of MTD and MAD

The estimated MTD is the dose level associated with approximately 30% of DLT-evaluable subjects experiencing a DLT. The target interval for the DLT rate is 25%-35%. Due to the discreteness of the dose levels and in the interest of the safety of subjects, the estimated MTD is the highest tested dose level with a DLT rate ≤35% in at least 6-12 DLT-evaluable subjects.

The MAD is declared without an MTD based on the highest dose level evaluated with an observed DLT rate <25% (the lower bound of the MTD range) and where sufficient safety and efficacy signals have been observed.

Subject Replacement

Subjects enrolled in Part 1 (Dose Escalation) who discontinue from study treatment for reasons other than a DLT may be replaced. However, any subject discontinued due to a DLT during Part 1 Cycle 1 (Dose Escalation) will not be replaced.

Part 2A: Dose Expansion

The Dose Expansion phase will commence following determination of the MTD/MAD and a review of the totality of safety data from Part 1. Part 2A will further characterize the safety profile of KZR-261 at the MTD or MAD and evaluate the anti-tumor activity of KZR-261 in subjects who have select malignancies. Up to 175 subjects may be enrolled in up to 4 tumor-specific cohorts (such as malignant melanoma [including uveal melanoma], mesothelioma, mCRPC, and mCRC) and 1 “All-Tumors” cohort. Additional or different tumor-specific cohorts may be investigated at the Sponsor’s discretion. Each tumor-specific cohort will enroll 15 subjects during Stage 1, expanding up to 35 subjects (Stage 2) as defined by a prespecified futility analysis and if the tumor type is not selected for investigation in Part 2B. If futility is not rejected after Stage 1 (ie, prespecified criteria for futility are met), subsequent enrollment to that Part 2A cohort will cease. The All-Tumors cohort may enroll up to 35 biopsy-evaluable subjects.

Part 2B: Dose Optimization

Dose optimization in tumor-specific cohorts may be initiated at the Sponsor's discretion based on the totality of data after the MTD/MAD has been determined. The Sponsor may also choose to cease enrollment in Part 2A and initiate enrollment of that tumor type in Part 2B. Approximately 30 subjects within each tumor-specific cohort will be randomized in a 1:1 ratio to receive KZR-261 at the MTD/MAD or a lower clinically active dose of KZR-261. Based on additional safety data from Part 2A, the Sponsor may convene an SRC meeting to determine whether a lower dose than the MTD/MAD as determined in Part 1 should be evaluated in Part 2B. Part 2B will further characterize the safety profile of KZR-261 to support determination of the RP2D and further evaluate the anti-tumor activity of KZR-261 in subjects with select malignancies. The number of tumor-specific cohorts to be investigated in Part 2B will be at the Sponsor's discretion.

Safety Review Committee (SRC)

The KZR-261 SRC will monitor the dose escalation (Part 1) portion of the study. The SRC will be convened periodically and evaluate safety data from each dose escalation cohort as well as review the totality of the safety data before proceeding to the dose expansion (Part 2A) or dose optimization (Part 2B) phases. The SRC will continue to periodically monitor the trial through the dose expansion and dose optimization portions of the study. The SRC will include the Medical Monitor (or designate), other Kezar representative(s), and participating Investigators. The SRC Charter defines the responsibilities of the committee for dose escalation and dose expansion/dose optimization.

Definition of RP2D

The RP2D is the dose chosen for further study based on assessment of a favorable benefit-risk profile across the totality of Phase 1 study results, including both Parts 1 and 2.

Tumor Specimens for Biomarkers

Tumor-specific Cohorts

Tumor biopsies (fresh [preferred] or archived) will be requested pre-treatment. For any subject who provides a tumor sample pre-treatment, an additional biopsy of accessible tumor tissue will be requested at either the end of Cycle 2 or at PD, whichever comes first.

All-Tumors Cohort

Pre-treatment tumor biopsies (fresh only) will be required for subjects enrolled in the All-Tumors cohort (exceptions to this requirement may be considered after discussion with the Medical Monitor); an additional biopsy of accessible tumor tissue will be required at either the end of Cycle 2 or at PD, whichever comes first.

Study Objectives	**Endpoints**
Primary objective for Part 1: • To evaluate the safety, tolerability, and PK of KZR-261 and identify the MTD or MAD.	**Safety:** DLTs, AEs and SAEs, deaths, dose reductions, treatment interruptions and discontinuations due to toxicity, clinical laboratory parameters, physical examination, ECG, and ocular examination findings, and VS measurements. Identification of the MTD or MAD. **PK parameters:** Maximal plasma concentration (C_{max}), area under the plasma concentration time curve (AUC), elimination half-life ($t_{½}$), clearance (CL), and volume of distribution (V_z).

Primary objective for Parts 2A and 2B: • To further characterize the safety profile of KZR-261 and identify the RP2D	**Safety**: AEs and SAEs, deaths, dose reductions, treatment interruptions and discontinuations due to toxicity, clinical laboratory abnormalities, physical examination, ECG, and ocular examination findings, and VS measurements. Identification of the RP2D.
Secondary objectives: • To detect evidence of anti-tumor activity of KZR-261. • To further characterize the PK of KZR-261 (Part 2A and 2B only).	**Anti-tumor activity:** Objective response rate (ORR) defined as the rate of partial responses (PRs) plus complete responses (CRs) according to RECIST v1.1, duration of response (DOR), progression-free survival (PFS), overall survival (OS), and clinical benefit rate (CBR). Subjects with mCRPC will be assessed per PCWG3 guidelines. **PK parameters:** KZR-261 plasma concentrations.
Exploratory objectives: • To evaluate potential pharmacodynamic biomarkers in peripheral blood based on gene expression and proteomic changes. • To explore and identify potential predictive biomarkers in tissue (including tumor) samples based on gene expression at baseline. • To evaluate changes in potential predictive biomarkers during treatment.	**Exploratory endpoints** • Serum biomarker levels including cytokines and other circulating proteins. • Whole blood gene expression changes. • Protein profiling of peripheral blood mononuclear cells (PBMCs). • Circulating tumor-associated proteins. • Changes in circulating tumor DNA. • Baseline gene and/or protein expression in pre- and on-treatment (post-Cycle 2) tumor biopsies to identify a potential predictive biomarker(s).
INVESTIGATIONAL PRODUCT(S), DOSE, AND MODE OF ADMINISTRATION	
Active Product	**Dosage form:** • KZR-261 will be supplied in single-use glass vials delivering 75 mg of KZR-261 and packaged in single vial cartons. Each vial is reconstituted with sterile Water for Injection prior to administration. **Dose and dose frequency:** • Escalating doses until MTD or MAD. • Starting dose: 1.8 mg/m^2 infused IV via a central line over 30 to 60 minutes on Days 1, 8, and 15 every 28 days. An infusion pump or syringe pump will be used for all infusions.
SUBJECT SELECTION	
Targeted Accrual	Dose Escalation (Part 1): ~70 subjects Dose Expansion (Part 2A): up to 175 subjects Dose Optimization (Part 2B): up to 120 subjects
Planned Number of Sites	Dose Escalation (Part 1): ~8 sites Dose Expansion and Dose Optimization (Part 2): ~12 additional sites

Inclusion Criteria

1. Age ≥18 years.
2. Willing and able to sign informed consent before initiation of any study-specific procedures or treatment.
3. Histologic or cytologic evidence of a malignant solid tumor (except primary central nervous system [CNS] neoplasms), either metastatic or locally advanced and not amenable to surgical resection or other locoregional therapies.
4. Disease that is resistant to or relapsed following available standard systemic therapy, or for which there is no standard systemic therapy, or refused such therapies if available. Documentation of the reason must be provided for subjects who have not received a standard therapy likely to result in clinical benefit.
5. Eastern Cooperative Oncology Group Performance Status score of 0 or 1.
6. Adequate baseline hematologic function:
   a. Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L. Myeloid growth factors must not have been administered within 7 days before the first dose of KZR-261.
   b. Hemoglobin ≥8 g/dL and no red blood cell (RBC) transfusions during the 14 days before the first dose of KZR-261.
   c. Platelet (PLT) count $\geq 100 \times 10^9$/L and no platelet transfusions during the 14 days before the first dose of KZR-261.
7. Adequate baseline organ function, as demonstrated by the following:
   a. Serum creatinine ≤1.5 × upper limit of normal (ULN) (local institution) or calculated creatinine clearance ≥60 mL/min by the Cockcroft-Gault formula.
   b. Serum albumin ≥2.5 g/dL.
   c. Bilirubin ≤1.5 × ULN (local institution).
   d. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 × ULN (local institution). Subjects with hepatic metastases may have ALT and AST ≤5 × ULN.
8. Serum amylase and lipase values <1.5 × ULN (local institution).
9. Fasting blood sugar <200 mg/dL.
10. Fasting triglycerides <300 mg/dL.
11. International normalized ratio (INR) ≤1.5 or prothrombin time (PT) ≤1.5 × ULN (local institution); and either partial thromboplastin time (PTT) or activated partial thromboplastin time (aPTT) ≤1.5 × ULN. Exceptions are allowed for patients receiving therapeutic anticoagulation for a history of thrombosis. Note: Anticoagulation with warfarin is exclusionary.
12. Female subjects must have negative serum β-human chorionic gonadotropin (β-hCG) test results during Screening and negative serum or urine pregnancy test results, whichever is preferred, at Baseline if the subject is a woman of childbearing potential (WOCBP), defined as a woman who has not undergone a hysterectomy or bilateral oophorectomy or has not been naturally postmenopausal for at least 24 consecutive months.
13. Subjects who are WOCBP must agree to use highly effective contraceptive methods or abstinence for the duration of time on the study and continue to use acceptable contraceptive methods for 3 months after administration of the last dose of study treatment. Highly effective contraception is

defined as use of the 2-barrier method (eg, female diaphragm and male condom) or 1 barrier method with spermicide, intrauterine device, or hormonal contraceptives (eg, implant or oral). If the subject is using a hormonal form of contraception, use must have been stable for at least 4 weeks prior to Screening. Abstinence will be acceptable only if it is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation) and withdrawal are not acceptable methods of contraception.

14. Male subjects with female partners of childbearing potential must be congenitally or surgically sterile (vasectomy with confirmation of aspermia) or agree to use 2 effective methods of contraception including one barrier method (eg, condom with spermicide) and contraception by the female partner for the duration of time on the study and for 3 months after administration of the last dose of study treatment. Use of a condom is required by men during intercourse with a male or female partner to prevent potential delivery of the drug via seminal fluid during the study until the End of Treatment visit.
15. The subject agrees to, and is capable of, adhering to the study visit schedule and other protocol requirements, including follow-up for survival.
16. Willing and able to comply with the requirements of the protocol.
17. Disease that is measurable by standard imaging techniques according to RECIST v1.1 (Eisenhauer et al., 2009). For subjects with prior radiation therapy, measurable lesions must be outside of any prior radiation field(s), unless disease progression has been documented following radiation to the site.

Additional Inclusion Criteria for Parts 2A and 2B (Dose Expansion and Dose Optimization)

All subjects considered for enrollment into Part 2 of the study must meet the following criteria in addition to the criteria listed above.

18. Subjects who agree to submit fresh or archived tumor tissue must do so during the Screening period.
19. For subjects who have **cutaneous melanoma**
    a. Must have histologic or cytologic evidence of disease that is locally advanced or metastatic (American Joint Committee on Cancer [AJCC] Stage 3 or 4).
    b. Must have relapsed or be refractory to treatment with currently approved therapies, including an immune checkpoint inhibitor(s), or unable to tolerate approved therapy(ies).
    c. For subjects with a RAF V600 mutation, the subject may have received therapy with a small molecule RAF V600 inhibitor with or without a small molecule MEK inhibitor.
20. For subjects who have **uveal melanoma**
    a. Must have histologic or cytologic evidence of locally advanced unresectable or metastatic uveal melanoma.
    b. Disease must be treatment naive or have progressed (radiologically or clinically) on most recent therapy.
21. For subjects who have **malignant mesothelioma of the peritoneum or pleura**
    a. Must have histologic or cytologic evidence of malignant mesothelioma that is either metastatic or locally advanced and not amenable to surgical resection or treatment with localized therapies.
    b. Must have been previously treated with an acceptable platinum-based regimen (eg, cisplatin or carboplatin combined with pemetrexed).
    c. The subject may have received Tumor Treating Fields (TTFields).

d. Has previously received treatment with an approved immunotherapy unless the subject is not a candidate for immunotherapy.

22. For subjects who have **mCRPC**

a. Must have histologically or cytologically documented, locally advanced unresectable or metastatic adenocarcinoma of the prostate.

b. Must have disease progression despite castration by orchiectomy or ongoing luteinizing hormone-releasing hormone (LHRH) analogue.

c. Must have disease that progressed on or after treatment with androgen inhibitors.

d. Must have prior treatment with a taxane or not be a candidate for treatment with a taxane.

e. Must have prior treatment with an inhibitor of poly ADP-ribose polymerase (PARP) if the subject has a deleterious germline or somatic BRCA 1/2 mutation or another homologous recombination repair gene mutation.

f. Must have progressive disease as defined by PCWG3 criteria (Scher et al., 2016). Note: Patients with biochemical progression (ie. rising PSA levels) only are not eligible.

g. Must have measurable or evaluable disease. Eligible subjects must have at least 1 measurable lesion per RECIST v1.1 and/or evidence of relapse/progression in bone per PCWG3.

23. For subjects who have **mCRC**

a. Must have histologic or cytologic evidence of colorectal carcinoma that is locally advanced and unresectable or metastatic.

b. Must have received or demonstrated intolerance to, appropriate therapy consisting of a fluoropyrimidine-based regimen with oxaliplatin and/or irinotecan with or without a therapeutic targeting vascular endothelial growth factor (VEGF), and with a monoclonal antibody (mAb) targeting epidermal growth factor receptor (EGFR), if their tumor lacks a KRAS mutation.

c. If the subject has a tumor with a RAF V600 mutation, the subject must have received, or demonstrated intolerance to, appropriate therapy targeting RAF V600 with or without a small molecule MEK inhibitor plus a mAb targeting EGFR.

d. If the subject has a tumor that is microsatellite instability high (MSI-H), the subject must have received or demonstrated intolerance to therapy targeting PD-1.

e. Must have received no more than 4 prior lines of therapy for mCRC (adjuvant therapy does not count as a line of treatment).

24. For subjects who have relapsed or refractory solid tumors in the All-Tumors cohort (Part 2A), excluding primary CNS malignancies

a. Must be able to submit fresh tumor tissue during the Screening period. Exceptions to this requirement may be considered after discussion with the Medical Monitor.

b. Appendix C includes a list of prioritized tumor types.

Exclusion Criteria

Subjects who meet any of the following criteria at Screening will not be enrolled in the study:

1. Subjects who have participated in Part 1 dose escalation are not eligible to enroll in Part 2A dose expansion or Part 2B dose optimization.

2. Persistent clinically significant toxicities (≥Grade 2 per NCI CTCAE version 5.0) from previous anticancer therapy (excluding alopecia).
3. Treatment with any systemic anti-cancer therapy within 14 days or treatment with a biologic within 28 days before the first dose of KZR-261.
4. Treatment with an investigational drug within 14 days or treatment with a biologic within 28 days before the first dose of KZR-261.
5. Radiation therapy within 14 days before the first dose of KZR-261.
6. History of prior radiation to the pancreas.
7. History of diabetes that is not well-controlled.
8. History of symptomatic gallstones *not* treated with cholecystectomy within 5 years of Screening. For patients with a history of gallstones treated *with* cholecystectomy, diagnosis of bile duct stones within 3 years of Screening.
9. Major surgical procedure within 28 days before the first dose of KZR-261. Interventional procedures such as percutaneous catheters for drainage of an effusion or central line placement may be permitted following consultation with the Medical Monitor, unless the central line placement is for study treatment.
10. A history of familial hypertriglyceridemia.
11. A personal or family history of acute or chronic pancreatitis from any cause.
12. A diagnosis of Sjogren's syndrome.
13. Heavy alcohol use as defined by the Centers for Disease Control and Prevention: ≥15 alcoholic drinks for males or ≥8 alcoholic drinks for females per week.
14. Additional active malignancy that may confound assessment of the study endpoints. Subjects with the following concomitant malignancies are eligible: nonmelanoma skin cancer and carcinoma in situ (including transitional cell carcinoma, cervical cancer, anal carcinoma, and melanoma in situ). Subjects with a history of other secondary malignancies (ie, active malignancy within 2 years before study entry) with a low risk of recurrence may be discussed with the Sponsor for consideration of enrollment.
15. Clinically significant cardiovascular disease including, but not limited to, the following:
    a. Uncontrolled or any New York Heart Association Class III or IV congestive heart failure.
    b. History of myocardial infarction, unstable angina, or stroke within 6 months before study entry.
16. Hypertension or clinically significant arrhythmias not adequately controlled by medication.
17. Corrected QT (QTc) interval by Fridericia's formula (QTcF) on resting ECG at Screening or Baseline >470 msec.
18. History of risk factors for Torsades de pointes (eg, heart failure, hypokalemia, family history of long QT syndrome).
19. Uncontrolled, clinically significant pulmonary disease (eg, chronic obstructive pulmonary disease, pulmonary hypertension) that, in the opinion of the Investigator, would put the subject at significant risk for pulmonary complications during the study (subject must not require supplemental oxygen).
20. Active, symptomatic CNS metastases. Any surgery or radiation therapy administered for the treatment of CNS metastases must have been completed at least 28 days prior to the date of informed consent with a follow-up magnetic resonance imaging (MRI) demonstrating no

progression of previously active lesions. Patients requiring corticosteroids must be on a stable or decreasing dose for 4 or more weeks prior to the first dose of KZR-261.

21. Primary CNS malignancy.
22. Condition requiring systemic treatment with either corticosteroids (>20 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days before the first dose of KZR-261. Inhaled or topical steroids and adrenal replacement doses ≤20 mg daily prednisone equivalents are permitted.
23. Uncontrolled intercurrent illness including, but not limited to, medical illness that has the potential to prevent the patient from completing the first response assessment at the end of Cycle 2 as well as psychiatric illness, or social situations that would limit compliance with study requirements.
24. Known positive status for human immunodeficiency virus (screening is not required).
25. History of active or chronic hepatitis B or C. Subjects who are HBsAg negative and hepatitis B core antibody positive with no detectable HBV DNA at Screening will be allowed into the study and will require regular monitoring for hepatitis B virus DNA. Subjects with a history of hepatitis C should have received curative treatment and exhibit absence of detectable HCV RNA at Screening.
26. Any medical condition that, in the opinion of the Investigator, places the subject at unacceptably high risk.
27. Treatment with warfarin.
28. Concomitant medications that would need to be taken during the course of the study as defined in Section 6.2.2.
29. Women who are pregnant, lactating, or discontinued lactation less than 12 weeks prior to Screening, or who plan to become pregnant or initiate lactation during the study.
30. Unable to comply with the protocol in the Investigator's or Sponsor's opinion.

STATISTICAL METHODS

A detailed Statistical Analysis Plan will be prepared by the Sponsor and finalized prior to database lock.

Sample Size Estimates

Approximately 70 subjects will be enrolled and treated with KZR-261 in Part 1 (Dose Escalation) in an "i3+3" design.

In Part 2A (Dose Expansion), up to 175 subjects will be enrolled based on interim futility analyses for up to 4 tumor-specific expansion cohorts and 1 All-Tumors cohort. The tumor-specific cohorts (n = 15 at interim) may be increased up to 35 subjects per cohort to more precisely estimate the anti-tumor activity of KZR-261, if there is a sufficient efficacy signal in the interim analyses and if the tumor type is not selected for investigation in Part 2B (dose optimization). Note: Outcomes (ie, presence or absence of clinical benefit) for subjects enrolled in Part 1 with the same tumor type and who received the same dose of KZR-261 as evaluated in the corresponding Part 2A, tumor-specific cohort may be included among the initial 15 subjects at the interim analysis.

The All-Tumors cohort may enroll up to 35 biopsy-evaluable subjects. In Part 2B (Dose Optimization), up to 120 subjects (~30 per tumor-specific cohort) may be enrolled.

Planned Statistical Analyses

Safety

Summaries and descriptive statistics will be generated for all safety data including DLTs, AEs, Grade 3, Grade 4, and Grade 5 AEs, SAEs, AEs resulting in dosing reductions, treatment interruptions, or treatment discontinuations, clinical laboratory data, vital signs, ECGs, and results of physical and ocular examinations. Deaths that occur after the first dose of study drug and through 30 days after the last dose of study drug will be considered "on treatment" deaths and will be summarized. All deaths will be listed.

Anti-tumor Activity

ORR is defined as the proportion of subjects achieving a best response of CR or PR according to RECIST v1.1. Clinical benefit rate is defined as the proportion of subjects achieving a best response of CR/PR or stable disease over a period of ≥2 consecutive response assessment time points. Subjects with mCRPC will be assessed for response/clinical benefit per PCWG3 guidelines. DOR is defined as the date from first occurrence of PR or CR to the date of documented progressive disease (PD) or death. In assessing DOR, a subject alive and without disease progression will be censored at the date of the last evaluable disease assessment. Progression-free survival is defined as the date of initiation of study treatment to the date of documented PD or death from any cause, whichever occurs first. Landmark estimates of progression-free survival rate at various time points (eg, 4 months, 6 months) may also be calculated. OS is defined as the date of initiation of study treatment to the date of death from any cause.

The 2-sided exact CI using the Clopper-Pearson method will be calculated for response/clinical benefit rates where applicable. Distributions for PFS, DOR, and OS will be estimated by Kaplan-Meier methodology.

Pharmacokinetics

Plasma concentrations of KZR-261 will be analyzed using noncompartmental methods. PK parameters to be calculated (if adequate data are available for estimation) will include, but are not limited to, C_{max}, AUC, $t_{½}$, CL, and V_z. Concentrations and PK parameters of KZR-261 will be summarized for each dose level using descriptive statistics.

Exploratory Assessments

Assessments of various pharmacodynamic study readouts as a function of dose and time post-administration will be described and related to anticancer activity, PK, and safety parameters.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
β-hCG	β-human chorionic gonadotropin
BUN	blood urea nitrogen
CBR	clinical benefit rate
CCLE	Cancer Cell Line Encyclopedia
CEA	carcinoembryonic antigen
CL	clearance
C_{max}	maximum plasma concentration
CNS	central nervous system
CR	complete response
CRC	colorectal carcinoma
CRO	contract research organization
CRPC	castration-resistant prostate cancer
CT	computed tomography
CYP	cytochrome p450
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECOG PS	Eastern Cooperative Oncology Performance Status
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EOT	end of treatment
ER	endoplasmic reticulum
FBS	fasting blood sugar

FDA	Food and Drug Administration
FIH	first-in-human
FOB	functional observation battery
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HCC	hepatocellular carcinoma
HCO_3	bicarbonate
hERG	human ether-à-go-go-related gene
HNSCC	head and neck squamous cell carcinoma
HNSTD	highest non-severely toxic dose
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
INR	international normalized ratio
IP	investigational product
IRB	Institutional Review Board
IV	intravenous(ly)
LFT	liver function test
LHRH	luteinizing hormone-releasing hormone
mAb	monoclonal antibody
MAD	maximum administered dose
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
mCRC	metastatic colorectal carcinoma
mCRPC	metastatic castration-resistant prostate cancer
MedDRA	medical dictionary for regulatory activities
MRI	magnetic resonance imaging
MSI-H	microsatellite instability high
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell

PCWG3	Prostate Cancer Working Group 3
PD	progressive disease
PD-1	programmed death receptor-1
PET	positron emission tomography
PFS	progression-free survival
PFS4	progression-free survival at 4 months
PFS6	progression-free survival at 6 months
PLT	platelet
PK	pharmacokinetic
PO_4	phosphate
PR	partial response
PSA	prostate-specific antigen
PT	prothrombin time
PTT	partial thromboplastin time
QTc	corrected QT
QTcF	corrected QT by Fridericia's formula
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SRC	Safety Review Committee
STD_{10}	severely toxic dose to 10% of animals
SUSAR	suspected unexpected serious adverse reaction
t½	half-life
TCGA	The Cancer Genome Atlas
TTFields	Tumor Treating Fields
ULN	upper limit of normal
V_z	volume of distribution
VEGF	vascular endothelial growth factor
VEGFR2	vascular endothelial growth factor receptor-2
VS	vital signs
WBC	white blood cell
WOCBP	women of childbearing potential

1. BACKGROUND INFORMATION

1.1. Protein Secretion and Sec61

Proteins destined for extracellular secretion or cell membrane display require additional processing and targeting. For nearly all such proteins (~30% of all expressed genes (Uhlén et al., 2015), this requires translocation from the cytosol to the endoplasmic reticulum (ER) in a process termed co-translational translocation (Dudek et al., 2015).

Co-translational translocation initiates with translation of short, ribosomal-emergent peptide signal sequences unique to each secreted/transmembrane protein. Recruitment machinery generically recognizes signal sequences, stalls translation, then localizes the ribosomal-nascent protein complex to the translocon, a collection of proteins at the surface of the ER that mediates translocation of the translating protein. The core component of the translocon and key arbiter of co-translational translocation is an evolutionarily conserved heterotrimeric protein channel embedded in the ER membrane known as Sec61. Transmembrane helices of the central Sec61α subunit form a clam shell-like channel affording lateral and axial entrance to the ER which enables translocation of translating proteins to the ER bilipid membrane and lumen, respectively (Lang et al., 2017; Voorhees and Hegde, 2016). Recognition and opening of the lateral gate by signal sequences afford entrance of translocating transmembrane proteins toward the ER membrane lipid bilayer. Lateral gate opening also widens the pore ring and destabilizes an ER lumen-side plug thus allowing axial entrance of translating proteins into the lumen of the ER.

Protein secretion is especially important in cancer cells that depend on secreted proteins, such as growth factors that confer proliferative advantages by influencing the growth, survival, metastasis, and cell surface proteins that mediate immunosuppression. Considering the fundamental role Sec61 plays as a channel-like protein complex in the membrane of the ER through which nearly all secreted and transmembrane proteins must pass during protein secretion, Sec61 represents a novel therapeutic target for an anticancer therapy.

1.2. KZR-261 Background

KZR-261 is a first-in-class small molecule targeting the protein secretion pathway by affecting the function of Sec61. Effective targeting of the protein secretion pathway is relevant to multiple cancer indications including solid and hematologic malignancies.

By targeting Sec61, KZR-261 inhibits the secretion of many types of secreted and transmembrane proteins that are involved in tumorigenesis and tumor growth. These include oncogenic receptor tyrosine kinases (eg, epidermal growth factor receptor [EGFR]), growth factors, vascularization (eg, vascular endothelial growth factor [VEGF] and VEGF receptor-2 [VEGFR2]), and tumor-induced immune suppression (eg, programmed death receptor-1 [PD-1]). In nonclinical studies, inhibition of Sec61 resulted in broad anti-tumor activity in a wide range of solid and hematologic malignancies, and induced cellular stress, causing cell death via apoptosis. KZR-261 and other members of its chemical class produce relevant anticancer activity in a wide range of xenografts and syngeneic models of both solid and hematologic malignancies. Furthermore, KZR-261 was determined to be well tolerated at doses in repeat-dose toxicity studies in rats and monkeys considered relevant for clinical evaluation.

1.2.1. Bioinformatics Approach to Tumor Selection for the Expansion Cohorts

Tumors selected for inclusion in the expansion cohorts were chosen based in part on bioinformatic analysis of cancer cell line profiling and publicly available gene expression databases. Cancer cell lines were tested in vitro for sensitivity to Sec61 inhibition, revealing broad activity against a wide range of malignancies. The correlation between sensitivity to treatment and gene expression levels of these cell lines was evaluated by gene set enrichment analysis using transcriptomic data from the Cancer Cell Line Encyclopedia (CCLE).
This analysis identified 7 groups of genes related to processes such as metabolism, transcription, translation, protein secretion, and ER stress which are predicted to correlate with sensitivity to KZR-261. Expression levels of the 7 gene sets were then profiled in the primary tissue sample gene expression database of The Cancer Genome Atlas (TCGA) to identify primary tumor types predicted to be sensitive to KZR-261 relative to other tumors or normal tissues. These methods identified melanoma, uveal melanoma, mesothelioma, prostate cancer, colorectal cancer, urothelial carcinoma, soft tissue sarcoma, head and neck squamous cell carcinoma (HNSCC), and hepatocellular carcinoma (HCC), among others, as indications with gene expression patterns matching those predicted to be sensitive to KZR-261.

1.2.2. Clinical Indications

This first-in-human (FIH) study is designed to assess the safety and tolerability of KZR-261 in subjects with advanced solid malignancies (locally advanced or metastatic solid malignancies) and no approved therapies, or refused such therapies if available.

The tumors identified for the expansion part of the study were identified by a combination of nonclinical data, a bioinformatics analysis (Section 1.2.1), and assessment of clinical unmet need. The treatment for cutaneous melanoma has changed dramatically in the last decade with the approval of checkpoint inhibitors (eg, anti-PD-1 monoclonal antibodies) and targeted therapy to BRAF mutations. However, although the response rate to the newer therapies is high, resistance is acquired within 3 years in approximately 40% of patients. Contributing to the unmet need is the rising incidence of melanoma in the US (SEER, 2021). Uveal melanoma is a rare subset which has limited treatment options. Similarly, despite advances in screening, colorectal cancers are rising in incidence especially among young people. Colorectal cancer is the fourth most common diagnosed cancer in the US, and the second leading cancer-related cause of death (SEER, 2021). Outcomes for metastatic castrate-resistant prostate cancer (mCRPC) have improved with next-generation androgen inhibitors such as abiraterone and enzalutamide. Although there is clinical impact in the metastatic setting, many patients are receiving these agents early in the disease course. Therefore, options for mCRPC in patients who have received androgen inhibitors only include taxanes (docetaxel and carbezitaxel), radium 223, and sipuleucil-T for general treatment (NCCN, 2021). Metastatic mesothelioma has a <10% 5-year survival rate (ACS, 2020) due to lack of beneficial systemic therapies. In addition to the diseases that will be targeted for enrollment in the expansion phase, subjects with other tumor types will be eligible to enroll in the dose escalation phase and into the All-Tumors cohort of the expansion phase. Other tumor types which are of interest based on the bioinformatics approach are urothelial carcinoma, soft tissue sarcoma, HNSCC, and HCC.

1.2.3. Summary of Nonclinical Study Findings

1.2.3.1. Toxicology

Good Laboratory Practice (GLP)-compliant repeat-dose toxicity studies were conducted in rats and monkeys. After 4 weeks of weekly intravenous (IV) bolus administration, the severely toxic dose to 10% of the animals (STD_{10}) was determined to be 3 mg/kg (18 mg/m^2) in rats and the highest non-severely toxic dose (HNSTD) was determined to be 1.25 mg/kg (15 mg/m^2) in monkeys.

In rats, KZR-261-related gross and organ weight findings and correlative effects were found in several secretory organs, including the glandular parenchyma of reproductive (prostate and seminal vesicle), respiratory (trachea), special sense (exorbital lacrimal gland), and gastrointestinal (stomach, exocrine pancreas, and submandibular and sublingual salivary gland) organs. In monkeys, KZR-261-related effects were found in the pancreas (acinar atrophy and islet vacuolation), salivary gland (secretory depletion), and the eye (lens degeneration correlating to cataracts on ophthalmologic examination).

In both rats and monkeys, changes in histopathology of the pancreas were partially reversible following a 2-week recovery period. Histologic changes in rats correlated with alterations in amylase levels but hyperglycemia was not observed at any dose level in the rats. Pancreas histology changes in monkeys correlated with increased amylase levels, hyperglycemia, glucose and ketones in the urine, and increased triglycerides.

Cataracts were noted following repeat dosing in monkeys. Bilateral, diffuse anterior and posterior cortical cataracts (opacity) were observed in 9/28 animals at ≥2.5 mg/kg (30 mg/m^2) on Day 19/20 prior to the last dose. The incidence and severity of the cataracts progressed following a 2-week recovery period. The presence of cataracts correlated with increased serum and urine glucose; however, there was no correlation in total exposure in the animals and no difference in the frequency of cataracts between the mid and high dose. No ocular findings were observed in the rat study.

Reproductive system macroscopic and microscopic findings were noted in male and female rats. Adverse histologic findings in the prostate gland and seminal vesicles of males were not fully reversible. The prostate and seminal vesicular changes in male rats at ≥3.0 mg/kg would be expected to alter sperm number and vitality. No histological findings in the prostate or seminal vesicles were observed in monkeys at doses up to 5 mg/kg (60 mg/m^2). In female rats, mild to marked atrophy of the uterus, cervix, and vagina were considered secondary to stress and decreases in body weight and were not fully reversible. No histological findings in female reproductive organs were noted in monkeys at doses up to 5 mg/kg (60 mg/m^2).

Pancreas, salivary gland, reproductive organs (prostate, seminal vesicles, ovary, and uterus), stomach, lungs, bone marrow, and eye (lens) are all secretory organs with high Sec61 expression (Uhlén et al., 2015). In addition to the findings described above, lymphodepletion and/or decreased cellularity of the thymus and bone marrow and indications of altered liver function (increased liver enzymes and decreased albumin and globulin) were noted in both rats and monkeys at or above the STD_{10}/HNSTD.

KZR-261 was found to have no inhibitory effect on the human ether-à-go-go-related gene (hERG) with an IC_{50} >1 µM. When assessed for off-target profiling in a panel of 111 receptors

and enzymes, KZR-261 showed >50% inhibition of the sodium channel at 10 μM. Sodium channel antagonists may be antiepileptic and antiarrhythmic as well as proarrhythmic; agonists may also cause cardiac arrhythmia. No signs of cardiovascular effects were observed in any of the GLP monkey studies. In monkeys, there were no changes in electrocardiogram (ECG) morphology, QT, PR, and QRS intervals, or QTc, to KZR-261 at doses up to 5 mg/kg (60 mg/m^2). In the repeat-dose rat study, IV doses of 5/4 mg/kg (non-tolerated) were associated with several changes in functional observation battery (FOB) in females, which consisted of hunched body and lower grip strength of hind and forelimbs in the 5/4 mg/kg females; lower body temperature and weights were noted in both the 3 mg/kg and 5/4 mg/kg females. All FOBs recovered following a 2-week recovery period. The effects noted in FOB assessments most likely reflect the general toxicity of KZR-261. There were no KZR-261-related effects on respiratory or neurological assessments in monkeys at doses up to 5 mg/kg (60 mg/m^2).

KZR-261 was not genotoxic when tested in the in vitro mutagenicity (Ames) test, in vitro chromosomal aberration assay, and in vivo micronucleus assay in rats.

To further understand the effect of KZR-261 on fasting glucose levels, non-GLP repeat-dose studies were conducted in monkeys in which the rate and schedule of administration was varied. Increased hyperglycemia did not appear to correlate with increased exposure but did correlate with decreased food-induced insulin secretion. Administration of KZR-261 as a 30-minute IV infusion rather than an IV bolus reduced elevations in glucose, triglycerides, lipase, pancreatic elastase 1, and amylase levels. Hyperglycemia observed with weekly dosing was also attenuated when the same dose was administered biweekly (Q2W). These findings suggest that pancreatic toxicity can potentially be attenuated by delivering KZR-261 via a 30-minute infusion, thus lowering the maximum plasma concentration (C_{max}), or by decreasing the frequency of the dose administration.

In summary, KZR-261 showed minimal off-target activity, no inhibition of hERG, and did not induce cardiovascular or respiratory toxicity in vivo. The starting dose for this Phase 1 human study is 1.8 mg/m^2 (1/10th of the STD_{10} in rats, the most sensitive species) infused over 30 minutes.

1.2.3.2. KZR-261 Absorption, Distribution, Metabolism, and Excretion (ADME)

After single IV bolus and infusion administration of KZR-261 to mice, rats, and monkeys, KZR-261 was slowly cleared with clearance values less than hepatic blood flow in all species. Terminal half-life ($t_{½}$) values were 5–17 hours, and drug was still measurable at 24 or 36 hours after dosing in all species. Exposure to KZR-261 increased dose proportionally in rats and monkeys across the dose ranges tested. No accumulation was observed upon multiple administrations of KZR-261 in rats. However, modest accumulation and higher inter-animal variability was observed in monkeys at doses above the HNSTD. After an IV bolus or 30-minute infusion to mice or rats, KZR-261 was widely distributed to tissues except brain.

Metabolic profiling using hepatocyte suspensions from rats, monkeys, and humans reveal that a single *N*-demethylation metabolite was the major metabolic pathway. Levels of this metabolite were determined to be <5% of parent in rat and monkey plasma, indicating minimal exposure.

KZR-261 strongly bound to plasma proteins with an overall bound fraction of approximately 99.984%, 99.986%, 99.998%, and 99.996%, in mouse, rat, dog, and human, respectively.

KZR-261 showed time-dependent inhibitory effects on cytochrome P450 (CYP) 3A4, and its inhibition was quasi-irreversible. Exposures to KZR-261 at concentrations up to 10 μM did not induce CYP1A2 or CYP2B6 and resulted in minimal induction of CYP3A4. CYP3A4 plays a minor role in the clearance of KZR-261.

KZR-261 had poor permeability in Caco-2 cells, was not an inhibitor of P-gp, BCRP, OATP1B1, OAT1, OCT2, OAT3, and MATE2K, and was a weak inhibitor of OCT1 and MATE1. KZR-261 showed no substrate potential for OATP1B1, OAT1, OCT1, OAT3, MATE1, and MATE2K.

1.3. Study Rationale

The heterotrimeric, ER membrane protein complex Sec61 offers an untapped potential therapeutic target for a broad spectrum of malignancies. KZR-261 is a novel inhibitor of Sec61 that potently blocks expression of secreted and membrane proteins and has shown potent anti-tumor effect in nonclinical models. The nonclinical toxicology profile of KZR-261 is consistent with other potent antineoplastic agents.

Part 1 of this FIH study of KZR-261 is designed to assess the safety, tolerability, and pharmacokinetics (PK) of KZR-261 in a standard i3+3 dose escalation design and to inform the dose and schedule of KZR-261 for additional investigation in Part 2A (Dose Expansion), Part 2B (Dose Optimization), and subsequent Phase 2 studies. The study also seeks to detect preliminary anticancer activity in subjects with solid malignancies with an expansion in select malignancies such as malignant melanoma (including uveal melanoma), mesothelioma, mCRPC, and metastatic colorectal carcinoma (mCRC). The study will also explore protein changes (eg, specific Sec61 cargo proteins) in peripheral blood and/or tumor biopsy samples and their relationship to KZR-261 treatment and genomic (eg, mutations and translocations) and transcriptomic (gene expression) markers in tumors at baseline as predictors of tumor response.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objective for Part 1 (Dose Escalation)

- To evaluate the safety, tolerability, and PK of KZR-261 and identify the maximum tolerated dose (MTD) or maximum administered dose (MAD).

2.1.2. Primary Objective for Parts 2A and 2B (Dose Expansion and Dose Optimization)

- To further characterize the safety profile of KZR-261 and identify the recommended Phase 2 dose (RP2D).

2.1.3. Secondary Objectives

- To detect evidence of anti-tumor activity of KZR-261.
- To further characterize the PK of KZR-261 (Part 2A and 2B only).

2.1.4. Exploratory Objectives

- To evaluate potential pharmacodynamic biomarkers in peripheral blood based on gene expression and proteomic changes.
- To explore and identify potential predictive biomarkers in tissue (including tumor) samples based on gene expression at baseline.
- To evaluate changes in potential predictive biomarkers during treatment.

2.2. Study Endpoints

2.2.1. Primary Endpoints

2.2.1.1. Safety – Part 1

Safety endpoints include the following:

- Incidence of dose-limiting toxicities (DLTs) during the DLT assessment period. DLTs will be assessed during Part 1 using pre-specified AE criteria detailed in Section 3.2.3.
- Type, incidence, and severity of adverse events (AEs) and serious adverse events (SAEs), deaths, dose reductions, treatment interruptions and discontinuations due to toxicity, and changes from baseline in clinical laboratory parameters. Adverse events will be graded for severity per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0.
- Changes from baseline in physical examination, ECG, and ocular examination findings.

- Changes from baseline in vital sign (VS) measurements and pulse oximetry.
- Identification of the MTD or MAD.

2.2.1.2. Safety – Parts 2A and 2B

Safety endpoints include the following:

- Type, incidence, and severity of AEs and SAEs, deaths, dose reductions, treatment interruptions and discontinuations due to toxicity, and changes from baseline in clinical laboratory parameters.
- Changes from baseline in physical examination, ECG, and ocular examination findings.
- Changes from baseline in VS measurements and pulse oximetry.
- Identification of the RP2D.

2.2.1.3. Pharmacokinetic

PK endpoints (if applicable) include the following:

- Plasma concentrations, including maximal plasma concentration (C_{max}).
- Area under the plasma concentration-time curve (AUC).
- Elimination half-life ($t_{½}$).
- Clearance (CL).
- Volume of distribution (V_z).

2.2.2. Secondary Endpoints

2.2.2.1. Anti-tumor Activity

The anti-tumor activity of KZR-261 will be measured by the following:

- Objective response rate (ORR) defined as the rate of partial responses (PRs) plus complete responses (CRs) according to the revised Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) guidelines (Eisenhauer et al., 2009). Subjects with mCRPC will be assessed per Prostate Cancer Working Group 3 (PCWG3) guidelines (Scher et al., 2016).
- Clinical benefit rate (CBR), defined as the proportion of subjects achieving a best response of CR/PR or SD over at least 2 consecutive response assessment time points.
- Duration of response (DOR).
- Progression-free survival (PFS).
- Overall survival (OS).

2.2.3. Exploratory Endpoints

2.2.3.1. Exploratory Biomarker Endpoints

Exploratory endpoints include the following:

- Serum biomarker levels including cytokines and other circulating proteins.
- Whole blood gene expression changes.
- Protein profiling of peripheral blood mononuclear cells (PBMCs).
- Circulating tumor-associated proteins.
- Changes in circulating tumor DNA.
- Baseline gene and/or protein expression in pre- and on-treatment (post-Cycle 2) tumor biopsies to identify a potential predictive biomarker(s).

3. STUDY DESIGN

3.1. Overview of Study Design

This FIH, open-label, multicenter, Phase 1 study is designed to assess the safety and tolerability, preliminary anti-tumor activity, and the PK characteristics of KZR-261, as well as identify the RP2D. KZR-261 will be administered as a 30- to 60-minute IV infusion via a central line on Days 1, 8, and 15 of a 4-week (28-day) treatment cycle. (Doses may be held up to 7 days for resolution of non-DLT toxicity.) Eligible subjects will have locally advanced or metastatic solid malignancies and no approved therapies, or refused such therapies if available.

The study will be conducted in 2 parts: Part 1 (Dose Escalation) and Part 2 (Part 2A –Dose Expansion and Part 2B – Dose Optimization).

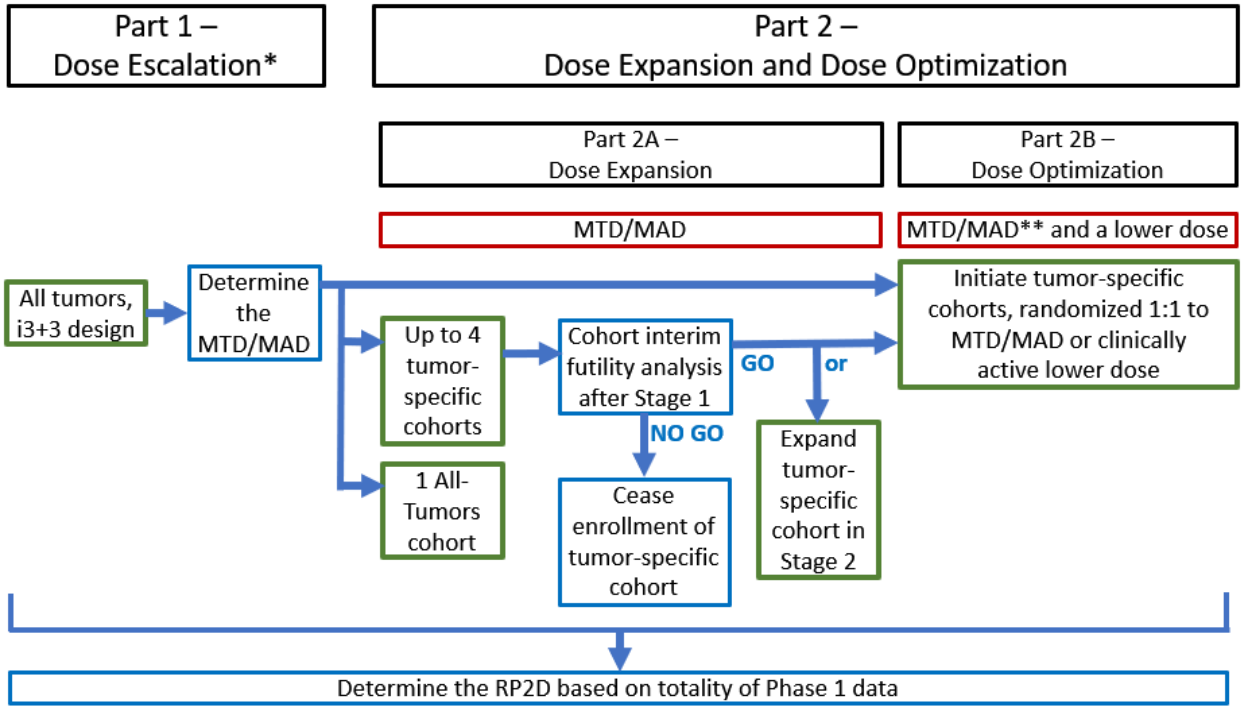
In Part 1, increasing doses of KZR-261 will be administered in an "i3+3" design to approximately 70 subjects to evaluate the safety and tolerability, PK, and pharmacodynamics of KZR-261, including identifying the MTD or MAD.

The Dose Expansion phase will commence following determination of the MTD/MAD and a review of the totality of safety data from Part 1. Part 2A will further characterize the safety profile of KZR-261 at the MTD or MAD and evaluate the anti-tumor activity of KZR-261 in subjects who have select malignancies. Up to 175 subjects may be enrolled in up to 4 tumor-specific cohorts (such as malignant melanoma [including uveal melanoma], mesothelioma, mCRPC, and mCRC) and 1 "All-Tumors" cohort. Additional or different tumor-specific cohorts may be investigated at the Sponsor's discretion. Each tumor-specific cohort will enroll 15 subjects during Stage 1, expanding up to 35 subjects (Stage 2) as defined by a prespecified futility analysis and if the tumor type is not selected for investigation in Part 2B (see below). If futility is not rejected after Stage 1 (ie, prespecified criteria for futility are met), subsequent enrollment to that Part 2A cohort will cease. The All-Tumors cohort may enroll up to 35 biopsy-evaluable subjects.

Dose optimization in tumor-specific cohorts may be initiated at the Sponsor's discretion based on the totality of data after the MTD/MAD has been determined. The Sponsor may choose to cease enrollment in Part 2A and initiate enrollment of that tumor type in Part 2B. Approximately 30 subjects within each tumor-specific cohort will be randomized in a 1:1 ratio to receive KZR-261 at the MTD/MAD or a lower clinically active dose of KZR-261 in Part 2B. Based on additional safety data from Part 2A, the Sponsor may convene an SRC meeting to determine whether a lower dose than the MTD/MAD as determined in Part 1 should be evaluated in Part 2B. Part 2B will further characterize the safety profile of KZR-261 to support determination of the RP2D and further evaluate the anti-tumor activity of KZR-261 in subjects with select malignancies. The number of tumor-specific cohorts to be investigated in Part 2B will be at the Sponsor's discretion.

A schematic representation of the study design is presented in Figure 1.

Figure 1: Study Schematic



MAD=maximum administered dose; MTD=maximum tolerated dose; RP2D=recommended Phase 2 dose
*Backfilling of a cohort may occur during dose escalation.
**Based on additional safety data from Part 2A, the Sponsor may convene an SRC meeting to determine whether a lower dose than the MTD/MAD as determined in Part 1 should be evaluated in Part 2B.

For each subject, written informed consent must be obtained prior to initiating any study procedure, including screening assessments for study eligibility (Section 4.2), unless the procedure or assessment is consistent with the standard of care for the underlying malignancy. Screening assessments must be completed within 28 days prior to the first dose of study treatment. Subjects who meet all eligibility criteria will be enrolled in the study and receive their first dose of study treatment on Cycle 1 Day 1.

During the Treatment Period, study assessments will be performed as detailed in the Schedule of Events (Appendix A and Appendix B). All study visits will be conducted on an outpatient basis.

Subjects will receive KZR-261 for up to 6 cycles. Upon completion of Cycle 6, a subject who is deriving clinical benefit may continue treatment at the discretion of the Investigator and with agreement of the Medical Monitor. Study treatment will be discontinued at any time for unacceptable AEs, progressive disease, voluntary withdrawal by the subject, another discontinuation criterion is met, or study closure by the Sponsor (Section 8.1.2).

Following discontinuation of study treatment, subjects will complete an End of Treatment (EOT) visit as soon as possible after their last dose of study treatment (Section 8.3). Safety follow-up will be conducted by telephone 30 days after the subject's last dose of study treatment (Section 9.1.5). If AEs have not resolved at that time, additional safety follow ups will occur approximately every 30 days until resolution of AEs or until, in the opinion of the Investigator, the event is stabilized or determined to be chronic.

Subjects who discontinue study treatment for reasons other than progressive disease (PD) will be contacted by telephone approximately every 90 days for 12 months after last study treatment for evidence of PD, collection of information about subsequent anti-tumor therapy, and assessment of survival status. Subjects who discontinue study treatment for PD will be contacted by telephone approximately every 90 days for 12 months after last study treatment for assessment of survival status.

Safety will be assessed as described in Section 2.2.1.1.

Anti-tumor activity will be assessed as described in Section 2.2.2.1, with assessments of response conducted after every 2 treatment cycles.

3.2. Part 1: Dose Escalation

3.2.1. Cohort Dose Escalation

Dose-escalation decisions for KZR-261 will be guided by the i3+3 design (Zhou and Ji, 2020; Liu et al., 2020) with the targeted DLT rate p_T=0.3 and the equivalence interval (EI) = [0.25, 0.35]. The number of subjects that will be enrolled at each dose level varies, with a minimum of 2 subjects, a typical cohort size of 2-4, and 6 to approximately 12 subjects dosed at the putative MTD or MAD. Table 1, generated using [redacted], lists the decisions for up to 12 subjects treated at a given dose.

The columns in Table 1 represent the number of subjects enrolled at a given dose, and the row represents the number of DLTs at the same dose. The dose-escalation decisions are as follows: E: Escalate to the next higher dose; S: Stay at the current dose; D: De-escalate to a lower dose; DU: De-escalate to a lower dose, the current dose may not be used again pending advice of the Safety Review Committee (SRC). The determination of the dose escalation or dose de-escalation will be based on the algorithm as described in Table 1. Safety data from all subjects enrolled in each cohort will be reviewed to confirm occurrence of any DLTs experienced during the first cycle (DLT assessment period) to determine whether to expand the current cohort or to initiate enrollment into the next cohort. Note that if 2 out of 2 subjects have DLTs when treated at the lowest dose level the Sponsor, based on recommendations from the SRC, may choose to enroll one more subject, amend the study to allow a revised dose regimen (ie, enroll subjects at a lower dose or modify the dosing schedule), or terminate the study.

Table 1: Decision Table in i3+3 Design for up to 12 Subjects Treated at a Given Dose with the Targeted DLT Rate p_T=0.3 and the Equivalence Interval (EI) = [0.25, 0.35]

Number of Subjects with DLTs	Number of Subjects											
	1	2	3	4	5	6	7	8	9	10	11	12
0	E	E	E	E	E	E	E	E	E	E	E	E
1	S	S	S	S	E	E	E	E	E	E	E	E
2		DU*	D	D	S	S	S	S	E	E	E	E
3			DU	DU	D	D	D	D	S	S	S	S
4				DU	DU	DU	D	D	D	D	D	S
5					DU	DU	DU	DU	DU	D	D	D
6						DU	DU	DU	DU	DU	DU	D
7							DU	DU	DU	DU	DU	DU
8								DU	DU	DU	DU	DU
9									DU	DU	DU	DU
10										DU	DU	DU
11											DU	DU
12												DU

E: Escalate to the next higher dose; S: Stay at the same dose; D: De-escalate to a lower dose; DU: De-escalate to a lower dose, the current dose may not be used again pending advice of the Safety Review Committee. The dose level for de-escalation will be selected by the SRC.

* If at the first dose level, Sponsor can choose to enroll one more subject, amend the study to allow a revised dose regimen (ie, enroll subjects at a lower dose or modify the dosing schedule), or terminate the study based on their discretion and in consultation with the SRC.

Source: (Liu et al., 2020)

3.2.1.1. Dose Level Escalation for Each Cohort (X+1)

Increments in dose escalation or whether to de-escalate will be based on review of emerging safety data by a SRC composed of study Investigators and Sponsor representatives (Section 3.5). At a minimum, the SRC will convene upon completion of each successive cohort. The SRC will review safety and available PK data from subjects enrolled to the most recently completed dose cohort who have completed the DLT assessment period. Dose increments for the next cohort will be determined based on the following criteria:

Up to a 100% dose increment may occur if:

- no subject in the most recent cohort required dose reduction for purposes of managing AEs and/or laboratory abnormalities;
- no subject experienced AEs greater than Grade 2 in severity;
- no subject exhibited one or more treatment-emergent serum amylase or lipase >1.5× the upper limit of normal (ULN) lasting longer than 72 hours after dosing;

- no subject exhibited fasting blood sugar (FBS) >200 mg/dL on 2 consecutive measures over a 72-hour period after dosing; or
- no subject exhibited FBS >160 mg/dL three or more times over a 72-hour period after dosing.

Up to a 50% dose increment may occur if:

- no subject in the most recent cohort required dose reduction for purposes of managing AEs and/or laboratory abnormalities;
- there is resolution of any ≥ Grade 3 AE to Grade 1 or baseline in ≤10 days

Up to a 33% dose increment may occur if:

- no subject in the most recent cohort required dose reduction for purposes of managing AEs and/or laboratory abnormalities;
- there is no resolution of any ≥ Grade 3 AE to Grade 1 or baseline within 10 days.

AEs for dose increment decisions must be treatment-emergent and considered at least possibly related to KZR-261.

Lower dose increases (ie, 25% increase or *1.25 × current dose)* may be considered based on the frequency and severity of AEs not described above that are at least possibly related to KZR-261.

If a DLT necessitates enrollment of additional subjects into a cohort, all safety data for that cohort will be reviewed after the additional subjects have completed the DLT assessment period. Based on evaluation of the data, the SRC and/or Sponsor may decide to enroll subjects at a KZR-261 dose level that is intermediate between the previous and the next higher planned dose.

If a slot within the current dose escalation cohort is not available, additional subjects may be treated at a lower dose level deemed by the SRC to be safe and adequately tolerated. Subjects with malignant melanoma, malignant mesothelioma, mCRPC, or mCRC are preferred but not required for backfilling.

The SRC can recommend enrollment of additional subjects at the putative MTD or MAD dose level to further assess safety at this dose.

3.2.2. Intra-subject Dose Escalation

Intra-subject dose escalation will be permitted after consultation with the Medical Monitor and in the following circumstance only:

- Subject must have completed at least two 28-day cycles of treatment (Cycles 1 and 2).
- Subject who experienced an AE* ≤Grade 3 with resolution to Grade 1 or baseline in the setting of a documented tumor response or stable disease over 2 consecutive assessment timepoints. For subjects who experienced a Grade 3 AE, the Investigator and Medical Monitor should come to an unequivocal consensus that the potential benefit of an increase in dose is likely to outweigh the risks.
- Subject must not have experienced a DLT.

- Subject must not have experienced a dose reduction for purposes of managing AEs and/or laboratory abnormalities.
- The higher dose cohort to which the subject would be escalated has been deemed by the SRC to be safe and adequately tolerated.

** AEs must be assessed as unrelated to study treatment, such as intercurrent illness or concomitant medication. AEs that are assessed as related to study treatment would disqualify a patient from dose escalation.*

3.2.3. Definition of Dose-Limiting Toxicity for Part 1

A DLT is defined as an AE or abnormal laboratory value that occurs during the first 28 days of treatment (Cycle 1) and meets the criteria listed below, unless it is assessed to be related to the disease under study, intercurrent illness, or concomitant medications.

Toxicities will be assessed by the Investigator using the NCI CTCAE v5.0. AEs that are not listed in the NCI CTCAE are to be assessed using the criteria in Section 9.1.2. The attribution of an AE is to be assessed by the Investigator using the criteria in Section 9.1.3.

Subjects who experience a DLT in Part 1, Cycle 1 must be withdrawn from study treatment and will not be replaced. Subjects enrolled in Part 1 who discontinue from study treatment for reasons other than a DLT prior to completion of the DLT assessment period (Section 3.2.3) may be replaced. AEs that meet the definition of a DLT that are reported after Cycle 1 will be taken into consideration for dose escalation decisions and to help determine the dose for further investigation in Part 2.

Subjects who do not experience a DLT in Part 1, Cycle 1 (Dose Escalation) must receive all of their scheduled doses (Days 1, 8, and 15) with completed follow-up data available through 28 days of Cycle 1 to be eligible for DLT assessment. Subjects in Part 1, Cycle 1 who miss a dose for non-AE-related reasons will be replaced.

Both hematologic and non-hematologic DLTs include the following:

- Any AE that prevents the subject from receiving all planned doses during Cycle 1 (Doses may be held up to 7 days for resolution of non-DLT toxicity).
- Any AE that delays the initiation of Cycle 2 by >7 days because the AE has not resolved per criteria required for initiation of a new cycle (Section 6.1.2 and Section 6.1.4).

Hematologic DLTs include the following:

- Grade 3 or 4 neutropenia (absolute neutrophil count [ANC] $<1.0 \times 10^9$/L) with a single temperature of >101°F (38.3°C), or microbiologically or radiographically documented infection.
- Grade 4 neutropenia (ANC $<0.5 \times 10^9$/L) in the absence of fever or infection lasting >7 consecutive days (complete blood count with differential must be measured every 2 to 3 days until recovery of ANC to ≤Grade 2).

- Grade 4 thrombocytopenia (platelet [PLT] count $<25 \times 10^9$/L) lasting >7 days (platelet counts must be measured every 2 to 3 days until recovery to ≤Grade 2 thrombocytopenia).
- Grade 3 or 4 thrombocytopenia (PLT count $<50 \times 10^9$/L) associated with clinically significant bleeding requiring platelet transfusion.

Non-hematologic DLTs include the following:

- Any non-hematologic AE ≥Grade 3, except the following:
  - Nausea, vomiting, diarrhea, electrolyte/metabolic abnormalities, constipation, fever, fatigue, or skin rash that resolves to ≤Grade 2 within 72 hours in the setting of optimal supportive care.
  - Grade 3 elevation in amylase or lipase without clinical or imaging manifestations of acute pancreatitis. In contrast, Grade 4 elevation in amylase or lipase and symptomatic Grade 3 lipase or amylase elevation are considered DLTs.
- Clinical signs and symptoms of acute pancreatitis.
- Drug-induced liver injury (Hy's law), including all of the following: greater than 3 × ULN elevation in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT), total bilirubin >2 × ULN in the absence of findings of cholestasis (ie, absence of alkaline phosphatase elevation to >2 × ULN) AND no other etiology to explain the combination of increased ALT/AST and total bilirubin.
- FBS >200 mg/dL on 2 consecutive measurements, at least 24 hours apart, over a 7-day period. In the DLT assessment period, subjects who experience FBS >200 mg/dL must have testing repeated within 7 days.

3.2.4. Definition of Maximum Tolerated Dose, Maximum Administered Dose, and Recommended Phase 2 Dose

The estimated MTD is the dose level associated with approximately 30% of DLT-evaluable subjects experiencing a DLT. The target interval for the DLT rate is 25%-35%. Due to the discreteness of the dose levels and in the interest of the safety of subjects, the estimated MTD is the highest tested dose level with a DLT rate ≤35% in at least 6-12 DLT-evaluable subjects. In general, the highest dose in Part 1 that provides an acceptable safety profile (MTD or MAD) will also be the highest dose tested in Part 2 unless one or more of the following suggest that an alternate (ie, lower) dose would be preferable:

- Clinically significant anti-tumor effects observed at a lower dose.
- The frequent occurrence of late and relevant AEs that occur after the DLT period.

The MAD is declared without an MTD based on the highest dose level with an observed DLT rate <25% (the lower bound of the MTD range) and where sufficient safety and efficacy signals have been observed.

The RP2D is the dose chosen for further study based on assessment of a favorable benefit-risk profile across the totality of Phase 1 study results, including both Parts 1 and 2. The RP2D will

take into account late and relevant toxicities that occur after the DLT assessment period in Part 1 and/or the safety/tolerability of multiple cycles of treatment.

3.3. Part 2A: Dose Expansion

Following determination of the MTD/MAD, separate tumor-specific cohorts of subjects will be treated with KZR-261. For all subjects enrolled in a tumor-specific cohort, tumor biopsies (fresh [preferred] or archived) will be requested pre-treatment. For any subject who provides a tumor sample pre-treatment, an additional biopsy of accessible tumor tissue will be requested at either the end of Cycle 2 or at PD, whichever comes first. Pre-treatment tumor biopsies (fresh) will be required for subjects enrolled in the All-Tumors expansion cohort (exceptions to this requirement may be considered after discussion with the Medical Monitor); an additional biopsy of accessible tumor tissue will be required at either the end of Cycle 2 or at PD, whichever comes first.

Fifteen subjects will be enrolled in each tumor-specific cohort (Stage 1), which may be increased up to 35 subjects in total as determined by prespecified futility criteria in Stage 1 (Section 10.6) and if the tumor type is not selected for investigation in Part 2B. Up to 35 biopsy-evaluable subjects may be enrolled in the All-Tumors cohort.

The following distinct dose expansion cohorts may be evaluated, as depicted in Figure 1.

Tumor-Specific Cohorts

- **Malignant melanoma**—histologically or cytologically confirmed, locally advanced unresectable or metastatic cutaneous or uveal melanomas (Section 4.2).
- **Malignant mesothelioma**—histologically or cytologically confirmed that is either metastatic or locally advanced and not amenable to surgical resection or local therapies (Section 4.2).
- **mCRPC**—histologically or cytologically confirmed, locally advanced unresectable or metastatic adenocarcinoma of the prostate that is castration (physical or chemical) resistant(Section 4.2).
- **mCRC**—histologically or cytologically confirmed, metastatic or locally advanced unresectable colorectal carcinoma (Section 4.2).

All-Tumors Cohort

- **All-Tumors**—any relapsed or refractory solid tumors that are amenable to tumor biopsies (Section 4.2).

Additional (or different) tumor types may be investigated at the Sponsor's discretion in Part 2 if evidence of anti-tumor activity of KZR-261 during Part 1 or in the All-Tumors cohort in Part 2 supports further evaluation.

3.4. Part 2B: Dose Optimization

Dose optimization in tumor-specific cohorts may be initiated at the Sponsor's discretion based on the totality of data after the MTD/MAD has been determined. The Sponsor may also choose to cease enrollment in Part 2A and initiate enrollment of that tumor type in Part 2B. Approximately 30 subjects in each Part 2B cohort will be randomized 1:1 to treatment with

KZR-261 at the MTD/MAD or a lower clinically active dose. Based on additional safety data from Part 2A, the sponsor may convene an SRC meeting to determine whether a lower dose than the MTD/MAD as determined in Part 1 should be evaluated in Part 2B.

As in Part 2A, subjects enrolled in Part 2B will be requested to provide pre-treatment tumor tissue (fresh [preferred] or archived). For subjects who provide a tumor sample pre-treatment, a biopsy of accessible tumor tissue will be requested at either the end of Cycle 2 or at PD, whichever comes first.

3.5. Safety Review Committee (Parts 1, 2A, and 2B)

The SRC will consist of the Medical Monitor (or designate), other Kezar representative(s), and participating Investigators. All Investigators who enroll subjects in the cohort under review will be consulted prior to the SRC meeting if they are unable to attend the scheduled meeting.

During Part 1, the committee will review safety data from the current cohort and previous cohorts before deciding on escalation to the next dose level. Dose escalation may occur only after the SRC has agreed (Section 3.2.1.1).

The totality of safety data from Part 1 will be reviewed prior to a declaration of the MTD/MAD. Available PK data may also be reviewed.

During Parts 2A and 2B, the SRC will periodically monitor safety data through the end of the study.

In Part 2, the study will be halted if there is one Grade 5 or two Grade 4 AEs in different subjects that are considered at least possibly related to KZR-261. Exceptions to the halting criteria include asymptomatic Grade 4 laboratory abnormalities (eg, neutropenia) that resolve either with or without routine supportive care measures and without sequelae. If this scenario occurs, a formal safety analysis will be conducted, and the findings will be submitted to the IND for the FDA to review prior to enrolling additional subjects.

A separate SRC Charter will describe the responsibilities of this committee for both dose escalation and dose expansion/dose optimization.

3.6. Planned Duration of Subject Participation (Parts 1, 2A, and 2B)

The study comprises a 4-week Screening Period, a Treatment Period lasting approximately 24 weeks (6 cycles, 4 weeks each), a 30-day Safety Follow-up Period, and a 12-month Long Term Follow-up Period (after last dose of study treatment), for a total study duration of approximately 20 months. Upon completion of Cycle 6, a subject who is deriving clinical benefit may continue treatment at the discretion of the Investigator and with agreement of the Medical Monitor.

3.7. Number of Planned Sites

Approximately 8 sites are planned for the Dose Escalation part of the study (Part 1), up to approximately 12 additional sites may participate in Dose Expansion and Dose Optimization (Part 2).

4. SUBJECT SELECTION

4.1. Number of Planned Subjects

Approximately 70 subjects will be enrolled and treated in Part 1 (Dose Escalation) of KZR-261. The principal determinants of the total number of subjects will depend on the number of dose levels of KZR-261, the number of subjects per dose level, and the number of subjects treated at the MTD or the MAD(s). In Part 2A (Dose Expansion), up to 175 subjects will be enrolled (Section 3.3). In Part 2B (Dose Optimization), up to 120 subjects (30 per tumor-specific cohort [15 per dose level]) will be enrolled into up to 4 tumor-specific cohorts (Section 3.4).

4.1.1. Subject Screening

Study participation begins once written informed consent is obtained (see Section 11.3 for details). The Investigator will ensure that each subject has provided written informed consent before performing any study-related assessments unless the procedure or assessment is consistent with the standard of care for the underlying malignancy.

Once informed consent is obtained, each subject will be assigned a sequential identification number and undergo screening evaluations to assess study eligibility (inclusion/exclusion criteria). The subject identification number will be used to identify the subject during the screening process and throughout study participation.

Screening assessments for this study should be performed between Day –28 and Day –1 (see the Schedule of Events, Appendix A). All subjects will be reviewed and approved by the Medical Monitor prior to enrollment. Subjects may be re-screened one time, if needed, with the Sponsor's approval. Subjects who have failed 1 or more screening assessments may be re-tested for that assessment(s) within the designated 28-day time frame for final eligibility determination. Screening data will be captured in the electronic case report form (eCRF).

4.2. Inclusion and Exclusion Criteria

Only patients who fulfill all the inclusion criteria and none of the exclusion criteria may be enrolled into the study. For enrollment in Parts 2A or 2B (Dose Expansion or Dose Optimization), subjects must meet additional tumor-specific criteria outlined in Section 4.2.2 to be considered eligible for study participation.

4.2.1. Inclusion Criteria

1. Age ≥18 years.
2. Willing and able to sign informed consent before initiation of any study-specific procedures or treatment.
3. Histologic or cytologic evidence of a malignant solid tumor (except primary central nervous system [CNS] neoplasms), either metastatic or locally advanced and not amenable to surgical resection or other locoregional therapies.
4. Disease that is resistant to or relapsed following available standard systemic therapy, or for which there is no standard systemic therapy, or refused such therapies if available.

Documentation of the reason must be provided for subjects who have not received a standard therapy likely to result in clinical benefit.

5. ECOG PS score of 0 or 1.
6. Adequate baseline hematologic function:
   a. ANC $\geq 1.5 \times 10^9$/L. Myeloid growth factors must not have been administered within 7 days before the first dose of KZR-261.
   b. Hemoglobin ≥8 g/dL and no red blood cell (RBC) transfusions during the 14 days before the first dose of KZR-261.
   c. PLT count $\geq 100 \times 10^9$/L and no platelet transfusions during the 14 days before the first dose of KZR-261.
7. Adequate baseline organ function, as demonstrated by the following:
   a. Serum creatinine ≤1.5 × ULN (local institution) or calculated creatinine clearance ≥60 mL/min by the Cockcroft-Gault formula.
   b. Serum albumin ≥2.5 g/dL.
   c. Bilirubin ≤1.5 × ULN (local institution).
   d. AST and ALT ≤2.5 × ULN (local institution). Subjects with hepatic metastases may have ALT and AST ≤5 × ULN.
8. Serum amylase and lipase values <1.5 × ULN (local institution).
9. FBS <200 mg/dL.
10. Fasting triglycerides <300 mg/dL.
11. International normalized ratio (INR) ≤1.5 or prothrombin time (PT) ≤1.5 × ULN (local institution); and either partial thromboplastin time (PTT) or activated partial thromboplastin time (aPTT) ≤1.5 × ULN. Exceptions are allowed for patients receiving therapeutic anticoagulation for a history of thrombosis. Note: Anticoagulation with warfarin is exclusionary.
12. Female subjects must have negative serum β-human chorionic gonadotropin (β-hCG) test results during Screening and negative serum or urine pregnancy test results, whichever is preferred, at Baseline if the subject is a woman of childbearing potential (WOCBP), defined as a woman who has not undergone a hysterectomy or bilateral oophorectomy or has not been naturally postmenopausal for at least 24 consecutive months.
13. Subjects who are WOCBP must agree to use highly effective contraceptive methods or abstinence for the duration of time on the study and continue to use acceptable contraceptive methods for 3 months after administration of the last dose of study treatment. Highly effective contraception is defined as use of the 2-barrier method (eg, female diaphragm and male condom) or 1 barrier method with spermicide, intrauterine device, or hormonal contraceptives (eg, implant or oral). If the subject is using a hormonal form of contraception, use must have been stable for at least 4 weeks prior to Screening. Abstinence will be acceptable only if it is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation) and withdrawal are not acceptable methods of contraception.

14. Male subjects with female partners of childbearing potential must be congenitally or surgically sterile (vasectomy with confirmation of aspermia) or agree to use 2 effective methods of contraception including one barrier method (eg, condom with spermicide) and contraception by the female partner for the duration of time on the study and for 3 months after administration of the last dose of study treatment. Use of a condom is required by men during intercourse with a male or female partner to prevent potential delivery of the drug via seminal fluid during the study until the End of Treatment visit.
15. The subject agrees to, and is capable of, adhering to the study visit schedule and other protocol requirements, including follow-up for survival.
16. Willing and able to comply with the requirements of the protocol.
17. Disease that is measurable by standard imaging techniques according to RECIST v1.1 (Eisenhauer et al., 2009). For subjects with prior radiation therapy, measurable lesions must be outside of any prior radiation field(s), unless disease progression has been documented following radiation to the site.

4.2.2. Additional Inclusion Criteria for Parts 2A and 2B (Dose Expansion and Dose Optimization)

All subjects considered for enrollment into Part 2 of the study must meet the following criteria in addition to the criteria listed in Section 4.2.1:

18. Subjects who agree to submit fresh or archived tumor tissue must do so during the Screening period tissue.
19. For subjects who have **cutaneous melanoma**:
    a. Must have histologic or cytologic evidence of disease that is locally advanced or metastatic (American Joint Committee on Cancer [AJCC] Stage 3 or 4).
    b. Must have relapsed or be refractory to treatment with currently approved therapies, including an immune checkpoint inhibitor(s), or unable to tolerate approved therapy(ies).
    c. For subjects with a RAF V600 mutation, the subject may have received therapy with a small molecule RAF V600 inhibitor with or without a small molecule MEK inhibitor.
20. For subjects who have **uveal melanoma**:
    a. Must have histologic or cytologic evidence of locally advanced unresectable or metastatic uveal melanoma.
    b. Disease must be treatment naive or have progressed (radiologically or clinically) on most recent therapy.
21. For subjects who have malignant mesothelioma of the peritoneum or pleura:
    a. Must have histologic or cytologic evidence of malignant mesothelioma that is either metastatic or locally advanced and not amenable to surgical resection or treatment with localized therapies.
    b. Must have been previously treated with an acceptable platinum-based regimen (eg, cisplatin or carboplatin combined with pemetrexed).

c. The subject may have received Tumor Treating Fields (TTFields).
d. Has previously received treatment with an approved immunotherapy unless the subject is not a candidate for immunotherapy.

22. For subjects who have **mCRPC**:

a. Must have histologically or cytologically documented, locally advanced unresectable or metastatic adenocarcinoma of the prostate.
b. Must have disease progression despite castration by orchiectomy or ongoing luteinizing hormone-releasing hormone (LHRH) analogue.
c. Must have disease that progressed on or after treatment with androgen inhibitors.
d. Must have prior treatment with a taxane or not be a candidate for treatment with a taxane.
e. Must have prior treatment with an inhibitor of poly ADP-ribose polymerase (PARP) if the subject has a deleterious germline or somatic BRCA 1/2 mutation or another homologous recombination repair gene mutation.
f. Must have progressive disease as defined by PCWG3 criteria (Scher et al., 2016). Note: Patients with biochemical progression (ie, rising PSA levels) only are not eligible.
g. Must have measurable or evaluable disease. Eligible subjects must have at least one measurable lesion per RECIST v1.1 and/or evidence of relapse/progression in bone per PCWG3.

23. For subjects who have **mCRC**:

a. Must have histologic or cytologic evidence of CRC that is locally advanced and unresectable or metastatic.
b. Must have received or demonstrated intolerance to, appropriate therapy consisting of a fluoropyrimidine-based regimen with oxaliplatin and/or irinotecan with or without a therapeutic targeting VEGF, and with a monoclonal antibody (mAb) targeting EGFR, if their tumor lacks a KRAS mutation.
c. If the subject has a tumor with a RAF V600 mutation, the subject must have received, or demonstrated intolerance to, appropriate therapy targeting RAF V600 with or without a small molecule MEK inhibitor plus a mAb targeting EGFR.
d. If the subject has a tumor that is microsatellite instability high (MSI-H), the subject must have received or demonstrated intolerance to therapy targeting PD-1.
e. Must have received no more than 4 prior lines of therapy for mCRC (adjuvant therapy does not count as a line of treatment).

24. For subjects who have relapsed or refractory solid tumors in the All-Tumors cohort (Part 2A), excluding primary CNS malignancies.

a. Must be able to submit fresh tumor tissue during the Screening period. Exceptions to this requirement may be considered after discussion with the Medical Monitor.
b. Appendix C includes a list of prioritized tumor types.

4.2.3. Exclusion Criteria

Subjects who meet any of the following criteria at Screening will not be enrolled in the study:

1. Subjects who have participated in Part 1 dose escalation are not eligible to enroll in Part 2A dose expansion or Part 2B dose optimization.
2. Persistent clinically significant toxicities (≥Grade 2 per NCI CTCAE version 5.0) from previous anticancer therapy (excluding alopecia).
3. Treatment with any systemic anti-cancer therapy within 14 days or treatment with a biologic within 28 days before the first dose of KZR-261.
4. Treatment with an investigational drug within 14 days or treatment with a biologic within 28 days before the first dose of KZR-261.
5. Radiation therapy within 14 days before the first dose of KZR-261.
6. History of prior radiation to the pancreas.
7. History of diabetes that is not well-controlled.
8. History of symptomatic gallstones *not* treated with cholecystectomy within 5 years of Screening. For patients with a history of gallstones treated with cholecystectomy, diagnosis of bile duct stones within 3 years of Screening.
9. Major surgical procedure within 28 days before the first dose of KZR-261. Interventional procedures such as percutaneous catheters for drainage of an effusion or central line placement may be permitted following consultation with the Medical Monitor, unless the central line placement is for study treatment.
10. A history of familial hypertriglyceridemia.
11. A personal or family history of acute or chronic pancreatitis from any cause.
12. A diagnosis of Sjogren's syndrome.
13. Heavy alcohol use as defined by the Centers for Disease Control and Prevention: ≥15 alcoholic drinks for males or ≥8 alcoholic drinks for females per week.
14. Additional active malignancy that may confound assessment of the study endpoints. Subjects with the following concomitant malignancies are eligible: nonmelanoma skin cancer and carcinoma in situ (including transitional cell carcinoma, cervical cancer, anal carcinoma, and melanoma in situ). Subjects with a history of other secondary malignancies (ie, active malignancy within 2 years before study entry) with a low risk of recurrence may be discussed with the Sponsor for consideration of enrollment.
15. Clinically significant cardiovascular disease including, but not limited to, the following:
    a. Uncontrolled or any New York Heart Association Class III or IV congestive heart failure.
    b. History of myocardial infarction, unstable angina, or stroke within 6 months before study entry.
16. Hypertension or clinically significant arrhythmias not adequately controlled by medication.
17. Corrected QT (QTc) interval by Fridericia's formula (QTcF) on resting ECG at Screening or Baseline >470 msec.

18. History of risk factors for Torsades de pointes (eg, heart failure, hypokalemia, family history of long QT syndrome).
19. Uncontrolled, clinically significant pulmonary disease (eg, chronic obstructive pulmonary disease, pulmonary hypertension) that, in the opinion of the Investigator, would put the subject at significant risk for pulmonary complications during the study (subject must not require supplemental oxygen).
20. Active, symptomatic CNS metastases. Any surgery or radiation therapy administered for the treatment of CNS metastases must have been completed at least 28 days the date of informed consent with a follow-up magnetic resonance imaging (MRI) demonstrating no progression of previously active lesions. Patients requiring corticosteroids must be on a stable or decreasing dose for 4 or more weeks prior to the first dose of KZR-261.
21. Primary CNS malignancy.
22. Condition requiring systemic treatment with either corticosteroids (>20 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days before the first dose of KZR-261. Inhaled or topical steroids and adrenal replacement doses ≤20 mg daily prednisone equivalents are permitted.
23. Uncontrolled intercurrent illness including, but not limited to, medical illness that has the potential to prevent the patient from completing the first response assessment at the end of Cycle 2 as well as psychiatric illness, or social situations that would limit compliance with study requirements.
24. Known positive status for human immunodeficiency virus (screening is not required).
25. History of active or chronic hepatitis B or C. Subjects who are HBsAg negative and hepatitis B core antibody positive with no detectable HBV DNA at Screening will be allowed into the study and will require regular monitoring for hepatitis B virus DNA. Subjects with a history of hepatitis C should have received curative treatment and exhibit absence of detectable HCV RNA at Screening.
26. Any medical condition that, in the opinion of the Investigator, places the subject at unacceptably high risk.
27. Treatment with warfarin.
28. Concomitant medications that would need to be taken during the course of the study as defined in Section 6.2.2.
29. Women who are pregnant, lactating, or discontinued lactation less than 12 weeks prior to Screening, or who plan to become pregnant or initiate lactation during the study.
30. Unable to comply with the protocol in the Investigator's or Sponsor's opinion.

5. STUDY DRUG

Instructions for the receipt, inspection, storage, preparation, administration, and disposal of KZR-261 will be provided in a separate Pharmacy Manual to each clinical site.

5.1. KZR-261

5.1.1. Physical Description of KZR-261

KZR-261 is a small molecule protein secretion inhibitor formulated for clinical use as [redacted] KZR-261 for Injection is a lyophilized drug product that is supplied in vials delivering 75 mg of KZR-261 [redacted]. Each vial is reconstituted with sterile Water for Injection prior to administration.

5.1.2. Packaging and Labeling of KZR-261

The drug product will be supplied in a single-use glass vial delivering 75 mg of KZR-261 and packaged in single vial cartons.

The Sponsor or its representatives will be responsible for labeling according to local regulatory requirements.

All packaging and labeling operations will be performed according to Good Manufacturing Practice for Medicinal Products (GMP) and the relevant regulatory requirements.

5.1.3. Supply, Dispensing, Storage, and Study Drug Accountability for KZR-261

Refer to the Pharmacy Manual for storage conditions of KZR-261. The Sponsor or its representatives will supply KZR-261 to the investigational sites. The study drug supplies provided for this study will be manufactured under current GMPs, will be subject to release, and will be suitable for human use.

The Investigator (or designate) must confirm that appropriate temperature conditions have been maintained during transit for all investigational product received and any discrepancies have been reported and resolved before use of the investigational drug product.

Only subjects enrolled in the study may receive study drug, and only authorized site staff may supply or administer study drug. All study drug should be stored in an environmentally controlled and monitored (manual or automated) area in accordance with the labeled storage conditions. Access to study drug must be limited to the Investigator and authorized site staff. Further information on the storage, preparation, and administration of study drug will be provided in the Pharmacy Manual.

On receipt of the study drug, the Investigator (or designate) will conduct an inventory of the supplies and verify that study drug supplies are received intact and in the correct amounts. The study monitor may check the study supplies at each study center at any time during the study.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study drug accountability, reconciliation, and record maintenance (such as receipt, reconciliation, and final disposition records).

It is the responsibility of the study monitor to ensure that the Investigator (or designate) has correctly documented the amount of the study drug received, dispensed, and returned on the dispensing log that will be provided. A full drug accountability log will be maintained at the study center at all times. The study monitor will perform an inventory of study drug at the closeout visit to the study center. All discrepancies must be accounted for and documented.

6. DOSAGE AND TREATMENT ADMINISTRATION

6.1. Treatment Administration

For all subjects, KZR-261 will be administered as a 30- to 60-minute IV infusion via a central line on Days 1, 8, and 15 of a 4-week (28-day) treatment cycle. An IV infusion pump or syringe pump will be used for all infusions.

Further details regarding drug product formulation, preparation, and administration of KZR-261 will be provided in a separate Pharmacy Manual.

6.1.1. Monitoring of Dose Administration

Study treatment will be administered on an outpatient basis. Subjects should remain at the study site for observation for 6 hours following the first cycle, first dose (Cycle 1 Day 1) and for 2 hours following study treatment administration for the rest of Cycle 1 (Cycle 1 Days 8 and 15). For Cycle 2, subjects will be under observation for 1 hour following study treatment. For Cycle 3 and beyond, there is no required post-infusion monitoring.

This is a FIH study; therefore, treatment modifications for AEs may change as data are accrued. Subjects experiencing unacceptable AEs should have their treatment interrupted until resolution (Section 6.1.2 and Section 6.1.4). Treatment with KZR-261 can then be reinitiated after consultation with the Medical Monitor.

6.1.2. Criteria for Interrupting Treatment During a Treatment Cycle

Within a treatment cycle, KZR-261 should be withheld on any scheduled treatment day if, during the previous 24 hours, the subject experiences any of the following events:

- ≥Grade 2 diarrhea, despite optimal anti-diarrheal therapy
- ≥Grade 2 vomiting, despite optimal anti-emetic therapy
- ≥Grade 3 fatigue that is not relieved by rest and limits self-care activities
- ≥Grade 3 transaminase elevation
- ≥Grade 2 amylase
- FBS ≥200 mg/dL
- PLT count $<50 \times 10^9$/L
- ANC $<0.5 \times 10^9$/L
- Average QTcF >500 msec
- No resolution to ≤Grade 2 or baseline of previously reported Grade 3 or 4 events

6.1.3. Criteria for Initiation of a New Cycle

To commence treatment in Cycle 2 and beyond, subjects must meet the following criteria:

- ANC $\geq 1.25 \times 10^9$/L
- Hemoglobin ≥8 g/dL
- PLT count $\geq 75 \times 10^9$/L
- Serum creatinine ≤1.5 × ULN (local institution) or calculated creatinine clearance >60 mL/min by the Cockcroft-Gault formula
- Total bilirubin ≤1.5 × ULN (local institution)
- AST and ALT ≤3 × ULN (local institution) or ALT and AST ≤5 × ULN if the subject has hepatic metastases
- FBS <200 mg/dL
- Serum amylase and lipase values ≤1.5 × ULN (local institution)
- Average QTcF <470 msec
- Resolution to ≤Grade 2 or baseline of any previously reported Grade 3 or 4 event

6.1.4. Dose Modification Guidelines for KZR-261

Dose reductions are not permitted during Cycle 1 (DLT assessment period) of Part 1 (Dose Escalation). If a subject experiences an event that qualifies as a DLT, as defined in Section 3.2.3, the subject must be discontinued from study treatment and followed for resolution of AEs as described in Section 9.1.5. Doses may be withheld or reduced for specific AEs and/or laboratory abnormalities in Cycles 2+ for subjects participating in Part 1 and in all cycles for subjects in Part 2 (Section 6.1.4.2).

Withheld doses should not be made up (Section 6.1.5).

6.1.4.1. Dose Interruptions

Subjects who experience an AE at any time during the study may interrupt study treatment per Section 8.1. Subjects must continue to fulfill all criteria outlined in Section 6.1.3 and not fulfill any of the criteria outlined in Section 6.1.2 prior to each dose.

6.1.4.2. Dose Modifications for Toxicity

Outside the DLT assessment period, dose modifications are to be discussed with the Medical Monitor prior to implementation to determine whether a dose modification is recommended. If KZR-261 is withheld for any toxicity within a treatment cycle, KZR-261 may be resumed **within that cycle** pending fulfillment of the criteria in Section 6.1.2 to Grade 1 or baseline, platelet counts to Grade 2 without clinical bleeding, or absolute neutrophil counts to Grade 2 prior to the next scheduled treatment.

Table 2 through Table 7 summarize guidelines for KZR-261 treatment modifications for various potential toxicities encountered. The dose modifications detailed in these tables are based on toxicities encountered within a cycle to determine the most appropriate dose for initiation of a

subsequent treatment cycle (assuming that all the retreatment criteria for a new cycle as summarized in Section 6.1.3 are met). Any dose reductions should be discussed with the Medical Monitor and documented in the source file and the eCRF.

Table 2: Dose Modifications for Isolated Transaminase Elevations

NCI-CTC AE Grade	Dose Adjustment
First episode of ≥Grade 3 (>5× baseline). Check transaminases at least twice per week until peak levels are reached, and then no less than weekly.	Withhold dose Resume dosing when elevations resolve to ≤Grade 2 and: • Reduce KZR-261 dose by one level if within a cycle • Subsequent cycles will begin at the reduced dose level
Second episode of ≥Grade 3 (>5× baseline). Check transaminases at least twice per week until peak levels are reached, and then no less than weekly.	Withhold dose Resume dosing at the subject's baseline grade and: • Reduce KZR-261 dose by one more level if within a cycle • Subsequent cycles will begin at the reduced dose level
Third episode of ≥Grade 3 (>5× baseline). Check transaminases at least twice per week until peak levels are reached, and then no less than weekly.	Discontinue KZR-261. Subject is not eligible to resume treatment.

Abbreviations: NCI CTCAE=Common Terminology Criteria for Adverse Events
Toxicity grades are per CTCAE v5.

Table 3: Dose Modifications for Thrombocytopenia

NCI CTCAE Grade	Dose Adjustment
Grade 3 thrombocytopenia with resolution to ≤Grade 2 within 1 week	No dose adjustment for subsequent cycles
Grade 3 thrombocytopenia without resolution to ≤Grade 2 within 1 week	Withhold dose until resolution to ≤Grade 2; no dose adjustment for subsequent cycles
Grade 4 thrombocytopenia or Grade 3 thrombocytopenia accompanied by clinically significant bleeding	Withhold dose until resolution of bleeding and/or thrombocytopenia to ≤Grade 2: • Dose reduce KZR-261 by one level if within a cycle • Subsequent cycles will begin at the reduced dose level

Abbreviations: NCI CTCAE=Common Terminology Criteria for Adverse Events

Table 4: Dose Modifications for Neutropenia

NCI CTCAE Grade	Dose Adjustment
≤Grade 3 neutropenia	No dose adjustment for subsequent cycles
Grade 4 neutropenia (duration <7 days) with resolution to ≤Grade 2 within 1 week	No dose adjustment for subsequent cycles
Grade 4 neutropenia (duration ≥7 days)	• Withhold dose until ≤Grade 2 • Reduce dose by one level if within a cycle, and begin subsequent cycles at the reduced dose level
Second episode of Grade 4 neutropenia (duration ≥7 days)	• Withhold dose until ≤Grade 2 • Reduce dose by one additional level if within a cycle, and begin subsequent cycles at the reduced dose level
Grade 3 or 4 neutropenia accompanied by fever (≥38.3°C)	• Withhold dose until afebrile with resolution of neutropenia to ≤Grade 2 within 1 week; resume dosing without dose reduction. • For a second episode of febrile neutropenia, reduce dose by one level if within a cycle, and begin subsequent cycles at the reduced dose level.

Abbreviations: NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events

Table 5: Dose Modifications for Pancreatic Toxicity

NCI CTCAE Grade	Dose Adjustment
Amylase or lipase ≥Grade 3	Discontinue KZR-261
Hyperglycemia ≤Grade 1; amylase, lipase Grade 1 or Grade 2 without any symptoms.	No dose adjustment for subsequent cycles
Hyperglycemia ≥Grade 2 (ie, requiring treatment)	Withhold dose until ≤Grade 1, then: • Resume KZR-261 at the same dose or dose reduce one level if within a cycle • Begin subsequent cycles at the same or reduced dose level

Abbreviations: NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events

Table 6: Dose Modifications for Ocular Toxicity

NCI CTCAE Grade	Dose Adjustment
Cataract ≤Grade 2 or baseline; any other ocular toxicity ≤Grade 1 or baseline	No dose adjustment if within a cycle or for subsequent cycles unless slit-lamp examination reveals treatment-emergent progression of incidental, asymptomatic cataract that is considered at least possibly related to study drug. If progression occurred, reduce dose by one level.

Abbreviations: NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events

Table 7: Dose Modifications for Other Toxicity

NCI CTCAE Grade	Dose Adjustment
≥Grade 3 with resolution to ≤Grade 2 or baseline within 1 week	Withhold dose until ≤Grade 1 or baseline, then: • Resume KZR-261 at the same dose or reduce dose by one level if within a cycle • Begin subsequent cycles at the same or reduced dose level
≥Grade 3 lasting ≥1 week	• Withold dose until ≤Grade 1 or baseline • Reduce dose by one level if within a cycle, and begin subsequent cycles at a reduced dose level

Abbreviations: NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events

Note:

- In the setting of Grade 2 toxicities not referenced above, including (but not limited to) nausea, vomiting, diarrhea, or fatigue that recur in successive cycles or are persistently debilitating in the opinion of the subject or Investigator, dose reduction by one level may be considered if within a cycle and for subsequent cycles and should be discussed with the Medical Monitor.

6.1.5. Missed Doses

Study treatment should be administered within the visit windows as per the Schedule of Events (Appendix A and Appendix B), with an exception for delays in dosing for up to 7 days duration for resolution of toxicity. Missed doses as a result of patient non-compliance will be considered protocol deviations.

Subjects who do not fulfill treatment interruption criteria (Section 6.1.2) or meet Individual Subject Stopping Rules (Section 8.1.2) may miss up to 2 consecutive doses or up to 6 doses in total over the first 6 cycles for any reason (eg, AE, scheduling, emergency). Subjects who require more than two dose reductions, or who miss one entire cycle because of an AE(s) must permanently discontinue KZR-261. Missed doses due to implementation of Study Stopping Rules (Section 8.1.1) should be discussed with the Medical Monitor to evaluate whether KZR-261 should be discontinued.

6.2. Prior and Concomitant Medications

A concomitant therapy is any therapy that may be administered (eg, transfusions, physical therapy, radiotherapy, surgery, medications). A concomitant medication is any prescription or over-the-counter preparation, including vitamins and supplements. All concomitant therapies must be recorded on the eCRF. Except as described below, prior medications used will be recorded for the 60 days prior to Screening until the first dose of study treatment. Concomitant medications will be recorded from first dose of study medication through 30 days after the last dose.

All prior anticancer treatments will be recorded on a separate, dedicated eCRF.

6.2.1. Permitted Concomitant Medications

6.2.1.1. Concurrent Supportive Care

Hematopoietic growth factors (eg, thrombopoietic agents such as romiplostim and eltrombopag, erythropoiesis stimulating agents, or granulocyte colony stimulating factors such as filgrastim and pegfilgrastim) are not permitted during Cycle 1 (the DLT assessment period, Section 3.2.3) for subjects in Part 1 (Dose Escalation) unless they are required for treatment of a DLT. In Cycles 2 and beyond, hematopoietic growth factors are permitted and may be used as clinically warranted and following institutional policies and recommendations. In case of severe or febrile neutropenia, growth factors may be used until neutrophil count recovery. In Part 2, hematopoietic growth factors may be used in Cycle 1 based on agreement between the Investigator and the Medical Monitor and in Cycles 2+ as per the aforementioned guidelines for Part 1.

Comprehensive supportive care is permitted during the study, including but not limited to anti-emetic and anti-diarrheal agents, appetite stimulants, stimulants with wakefulness-promoting properties (eg, modafinil), anticachexia therapy (eg, fish oil supplements), antidepressants, opiate and non-opiate analgesics, antibiotics, selective use of corticosteroids (≤20 mg daily prednisone or prednisone equivalent), therapies for diabetes mellitus, and platelet/neutrophil growth factors as indicated above. Anticoagulants except warfarin are also permitted.

Subjects with mCRPC are expected to continue on LHRH analogues if ongoing at Screening.

6.2.1.2. Other Concomitant Medications

Hormonal contraception is allowed. If using a hormonal form of contraception, use must have been stable for at least 4 weeks prior to Screening (Section 4.2.1). The same hormonal contraception should be continued for the duration of the study. If hormonal contraception is discontinued for safety reasons, the Investigator should ensure that the subject is using another acceptable form of contraception.

KZR-261 may affect medications that are substrates of CYP3A4. Administration of sensitive substrates of CYP3A4, or narrow therapeutic index drugs that are metabolized by CYP3A4 is not recommended from 14 days prior to the first dose of KZR-261 and during study treatment. If no alternative is available, please refer to the respective prescribing labels for dosing instructions. Medications that are sensitive substrates of CYP3A4, defined as those whose exposure may increase >5-fold in the presence of CYP3A4 inhibition, are listed in Appendix D.

6.2.2. Prohibited Concurrent Medications/Therapies

While receiving treatment with KZR-261, enrolled subjects may not receive investigational or approved anticancer agents including cytotoxic chemotherapy, targeted therapies, or therapeutic monoclonal antibodies.

Palliative radiation is permitted only for symptom management and with a narrow radiation port (eg, solitary bone lesion). Sponsor review and approval is required before administration of palliative radiation while on study treatment.

7. STUDY PROCEDURES

7.1. Schedule of Study Procedures

Schedules of study procedures for the Screening Period, Treatment Period, and the Follow-up Period (including visit windows) are presented in the Schedule of Events (Appendix A and Appendix B).

Details regarding the specific blood draw requirements for each visit are outlined in the Laboratory Manual provided to each study site.

7.2. Description of Study Procedures

Prior to undergoing any study-specific procedures/assessments (except those consistent with standard of care for management of the underlying malignancy), all potential subjects must sign an informed consent form (ICF) describing the study with sufficient information for subjects to make an informed decision regarding their participation per Section 11.3.

The following sections provide details of the procedures to be performed.

7.2.1. Medical History

Documentation of the subject's medical history should contain the subject's full medical history including prior and concomitant illnesses/diseases, concomitant medications, and demographic data. Historical cancer data and diagnostic information, including tumor mutational profile if known, will be captured in the eCRF. Prior imaging reports may be requested.

7.2.2. Physical Examination

A complete physical examination including collection of body weight will be conducted at Screening and Baseline and should include assessments of at least the following systems: head and neck, dermatological, respiratory, cardiovascular, abdomen, extremities, neurological, and musculoskeletal. Height will be collected at the Screening visit only.

A symptom-directed abbreviated physical examination including collection of body weight will be conducted at all other study visits indicated in the Schedule of Events (Appendix A and Appendix B).

Subjects will be asked at each visit that includes a physical examination about mouth dryness, salivary gland pain and sensitivity, and urinary and ejaculation issues. Treatment-emergent, medically significant changes from baseline in physical examination will be recorded as AEs.

7.2.3. Pregnancy Testing and Reproduction Precautions

Women of childbearing potential must have a negative serum β-hCG pregnancy test result at Screening. Negative serum or urine pregnancy tests will be required at all other visits indicated in the Schedule of Events (Appendix A and Appendix B). The Screening visit test should be performed within 2 weeks prior to initiation of study treatment or in closer proximity to the treatment start-date as required by local/institutional regulations. A positive urine pregnancy test result should be confirmed by a serum pregnancy test.

The subject must agree to use highly effective contraceptive methods or abstinence for the duration of time on the study and continue to use acceptable contraceptive methods for 3 months after administration of the last dose of study treatment. Highly effective contraception is defined as the use of 2-barrier methods (eg, female diaphragm and male condom) or 1 barrier method with spermicide, intrauterine device, or hormonal contraceptives (eg, implant or oral). If the subject is using a hormonal form of contraception, use must have been stable for at least 4 weeks prior to Screening, and if using concomitant mycophenolate, the subject must use another nonhormonal form of highly effective contraception. Abstinence will be acceptable only if it is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation) and withdrawal are not acceptable methods of contraception.

Male subjects with female partners of childbearing potential must be congenitally sterile or surgically sterile (vasectomy with confirmation of aspermia) or agree to use 2 effective methods of contraception including one barrier method (eg, condom with spermicide and contraception by female partner) for the duration of time on the study and for 3 months after administration of the last dose of study treatment. Use of a condom is required by men during intercourse with a male or female partner to prevent potential delivery of the drug via seminal fluid during the study until the EOT visit.

7.2.4. Electrocardiogram

ECGs will be performed at the timepoints indicated in the Schedule of Events (Appendix A and Appendix B). Note that some study visits have pre-treatment and multiple post-treatment ECG timepoints. Additional ECGs are required during Cycle 4 (Appendix B).

Vital sign measurements should be performed per institutional guidelines, preferably prior to ECGs. A 12-lead ECG is performed 10 minutes after the subject has been in the supine position. The Investigator or qualified designate will review and indicate if the ECG is normal or abnormal, and if abnormal, whether clinically significant. Any medically significant changes from the Screening ECG will be recorded as an AE.

7.2.5. Vital Sign Measurements and Oxygen Saturation

Vital signs measurements (including systolic and diastolic blood pressure, pulse rate, respiration rate, and body temperature) and oxygen saturation will be collected at all study visits. Blood pressure and pulse should be collected after the subject has had at least 5 minutes of rest in the seated position. If blood pressure is elevated on the first measurement at Screening or Baseline, it should be repeated after an additional 5 minutes of rest. It is recommended that blood pressure is measured using the same arm at each assessment. When the time of vital signs measurement coincides with a blood sample collection, vital signs will be measured per institutional guidelines.

7.2.6. Ocular Examination

Slit lamp and visual acuity examinations will be conducted to monitor for cataracts and should be reviewed prior to administration of KZR-261 at the beginning of each cycle where an eye examination is required (Appendix A and Appendix B). Any medically significant changes from the Screening evaluation will be recorded as an AE.

7.2.7. Tumor Specimens for Biomarkers

Tumor biopsies will be requested pre-treatment. Although a fresh sample is preferred, submission of an adequate tumor specimen (paraffin block) collected within 1 year before the subject's first dose of KZR-261 will be acceptable for subjects where a fresh sample cannot be obtained. If a paraffin block is not available, a minimum of 10 and up to 20 5-µm unstained slides should be provided. For any subject who provided a tumor sample pre-treatment, a biopsy of accessible tumor tissue will be requested at either the end of Cycle 2 (Days 21-28 of Cycle 2) or at PD, whichever comes first.

Pre-treatment tumor biopsies (fresh only) will be required for subjects enrolled in the All-Tumors expansion cohort in Part 2A (exceptions to this requirement may be considered after discussion with the Medical Monitor); an additional biopsy of accessible tumor tissue will be required at either the end of Cycle 2 (Days 21-28 of Cycle 2) or at PD, whichever comes first.

7.2.8. Clinical Laboratory Evaluations

Collection of blood and urine samples for clinical laboratory evaluations are outlined in the Schedule of Events for Cycles 1 and 2 (Appendix A) and Cycle 3+ (Appendix B).

Clinical laboratory tests for safety (hematology, serum chemistries, urinalyses, coagulation tests, serum pregnancy) and other tests during scheduled visits will be performed at the clinical trial site or an alternative, licensed local testing facility. Pregnancy tests, urine or serum, may be performed at the study site using a licensed test. Abnormal safety laboratory results that are considered clinically significant should be repeated as soon as possible (preferably within 24–48 hours).

Subjects who are HBsAg negative and hepatitis B core antibody positive with no detectable DNA at Screening will require regular monitoring of hepatitis B virus DNA at the discretion of the Investigator.

Unscheduled or additional laboratory tests with results reported by local laboratories may be performed if immediate results are necessary for management of treatment-emergent AEs or dosing determination. Unless otherwise noted, when scheduled simultaneously with a dosing visit, results of laboratory evaluations should be reviewed prior to administration of study drug.

Detailed instructions for sample collection, processing, storage, and shipment will be provided in the Laboratory Manual. It is recommended that the smallest appropriate sampling tubes be used for local laboratory sample collection to curtail blood loss due to phlebotomy.

7.2.8.1. Hematology

Blood samples for hematology testing will be collected at timepoints detailed in the Schedule of Events (Appendix A and Appendix B). Hematology parameters shown in Table 8 will be analyzed according to standard methods at a local laboratory.

Table 8: Hematology Tests

Hematology Tests
• Hemoglobin • Hematocrit • White blood cell (WBC) count (total and differential) • Red blood cell (RBC) count • Platelet (PLT) count • Mean corpuscular volume (MCV) • Mean corpuscular hemoglobin (MCH) • Mean corpuscular hemoglobin concentration (MCHC)

7.2.8.2. Serum Chemistry

Blood samples for serum chemistry testing will be collected at timepoints detailed in the Schedule of Events (Appendix A and Appendix B) while the subject is in a fasting state (no food or caloric drinks after an overnight fast or other fasting period lasting at least 6 hours). Clinical chemistry parameters shown in Table 9 will be analyzed according to standard methods at a local laboratory.

Table 9: Clinical Chemistry Tests

Serum Chemistry Tests (Fasting)	
• Creatinine • Blood urea nitrogen (BUN) • Aspartate aminotransferase (AST) • Alanine aminotransferase (ALT) • Alkaline phosphatase (AP) • Total bilirubin • Serum albumin • Serum total protein • Sodium	• Bicarbonate (HCO_3) • Potassium • Chloride • Glucose • Phosphate (PO_4) • Calcium • Amylase • Lipase • Triglycerides

7.2.8.3. Urinalysis

Urinalysis testing will be performed according to standard methods at a local laboratory. Dipstick testing is acceptable.

7.2.8.4. Coagulation Parameters

Blood samples for analysis of coagulation parameters will be collected at timepoints detailed in the Schedule of Events (Appendix A and Appendix B). Coagulation parameters to be analyzed are presented in Table 10. For coagulation parameter tests, either PT or INR may be measured, and either PTT or aPTT, depending on institutional standards. Blood samples for coagulation parameter tests must be collected within 24 hours prior to all biopsy procedures.

Table 10: Coagulation Tests

Coagulation Tests
• International normalized ratio (INR) or prothrombin time (PT) • Partial thromboplastin time (PTT) or activated partial thromboplastin time (aPTT)

7.2.8.5. Hemoglobin A1c (HgbA1c)

Blood samples for quantitation of HgbA1c will be collected at timepoints shown in the Schedule of Events (Appendix A and Appendix B).

7.2.9. Tumor Markers

If tumor markers in blood (eg, PSA, CA-125, carcinoembryonic antigen [CEA], CA-15.3, CA-19.9) are known to be elevated, they should be measured at timepoints shown in the Schedule of Events (Appendix A and Appendix B).

7.2.10. Response Assessments

Assessments of response and progression will occur in accordance with RECIST v1.1 (Eisenhauer et al., 2009) at timepoints shown in the Schedule of Events (Appendix A and Appendix B). Subjects with mCRPC will be assessed per PCWG3 guidelines (Scher et al., 2016).

All subjects must have contrast-enhanced imaging studies of chest, abdomen, and pelvis as well as other areas of suspected disease within 28 days prior to their first dose of study treatment. The preferred imaging modality is contrast-enhanced computed tomography (CT). In subjects for whom IV contrast for CT is contraindicated, perform contrast-enhanced magnetic resonance imaging (MRI) scanning of the aforementioned anatomic regions with non-contrast enhanced CT of the chest. Subjects known to have flurodeoxyglucose (FDG)-avid tumors are required to undergo positron emission tomography (PET) scanning along with the CT scan at Screening. Subjects whose tumors demonstrate FDG update at Screening should undergo follow-up PET scanning post-Cycle 6, post-Cycle 12, and every 6 cycles thereafter (see below). Subjects with skin, subcutaneous or lymph node metastases may also have evaluations of measurable lesions (including measurements, with a ruler or calipers) by means of physical examination.

Subjects with mCRPC must have a baseline PSA and bone scan in addition to the aforementioned imaging studies. (Note: A rising PSA as the sole indicator of disease activity will not lead to a determination of disease progression.) On-treatment bone scans will be performed at the same time points as CT/MRI scans. As a rule, the same imaging modality (ie, CT or MRI or combined CT/PET scans) should be used for all scheduled tumor assessments and measurements.

Imaging studies should be repeated prior to Cycle 3 (ie, end of Cycle 2) and every 2 cycles thereafter (ie, end of Cycles 4, 6, 8, etc). There is a 7-day window for imaging procedures to allow time for availability of results prior to the next cycle. If an imaging procedure must be scheduled to occur outside the 7-day window, this should be discussed with the Medical Monitor for approval prior to the procedure.

Response assessments, including imaging studies, are to be performed at the EOT visit, if PD has not already been established and the last response assessment was conducted >4 weeks prior to EOT.

Subjects who discontinue study treatment for reasons other than PD will be contacted by telephone approximately every 90 days for 12 months after last study treatment for evidence of PD, collection of information about subsequent anti-tumor therapy, and assessment of survival status. Subjects who discontinue study treatment for PD will be contacted by telephone approximately every 90 days for 12 months after last study treatment for assessment of survival status.

7.3. Pharmacokinetic Measurements

Blood samples for assessment of plasma PK parameters for KZR-261 will be collected according to the Schedule of Events (Appendix A).

7.4. Exploratory Assessments

Samples for assessment of pharmacodynamic and other exploratory biomarkers will be collected during Cycles 1 and 2 from all subjects according to the Schedule of Events (Appendix A).

7.4.1. Pharmacodynamic and Biomarker Measurements

Whole blood samples will be collected for pharmacodynamic analyses according to the Schedule of Events (Appendix A and Appendix B). Pharmacodynamic analyses may include the monitoring of circulating proteins and/or proteins expressed in peripheral blood mononuclear cells.

Whole blood and tumor biopsy samples will be collected according to the Schedule of Events (Appendix A and Appendix B) to study circulating and tumor-derived biomarkers of drug activity, such as can be found in the DNA, RNA, and protein components of these samples. RNA-based biomarkers of gene expression may be particularly relevant. Selection of the tumor types targeted for the expansion cohorts was guided, in part, by an analysis of gene modules (eg, modules encoding Sec61 clients, ribosomal proteins, and constituents of Golgi vesicles) whose expression is both associated with sensitivity to Sec61 inhibition in vitro and found to be frequently perturbed in the selected tumor types. Pre-treatment tumor biopsies will be evaluated for expression of these gene modules, and the results will be correlated with KZR-261 response in an exploratory fashion. In subjects for whom both an on-treatment and baseline sample are available, a paired analysis of changes in the expression of these modules will be performed to better understand KZR-261's mechanism of action.

Additional information regarding sample collection and handling will be outlined in the Laboratory Manual.

7.5. Sample Management/Future Research

All samples will be coded with the subject number. Samples and any data generated can be linked back to the subject as detailed in Section 4.1.1.

Samples collected for future research may be retained by the Sponsor or its designate for up to 5 years after study completion or as permitted by the applicable laws and regulations in the relevant country in which the study is conducted. Additional consent for storage of samples will be requested as a separate approval line on the ICF. Remaining de-identified unused clinical samples (blood/urine) will be retained by the Sponsor and used for the Sponsor's future research,

including, but not limited to, the evaluation of additional targets for novel therapeutic agents and to identify biomarkers for response and/or safety.

If additional written consent is not provided, any remaining biological samples will be destroyed by the Sponsor or its designate following study completion.

8. STUDY DISCONTINUATION

8.1. Stopping Rules for Safety

8.1.1. Study Stopping Rules

If any of the following events occur, the accumulated safety data will be reviewed by the SRC.

- Death of any subject due to an AE, unless the Grade 5 event is a complication of disease progression or intercurrent illness.
- Unexpected life-threatening event in 2 subjects, unless due to a complication of disease progression or intercurrent illness.
- Any event that contraindicates further enrollment of additional subjects as assessed by either the SRC or a regulatory authority.

In Part 2, the study will be halted if there is one Grade 5 or two Grade 4 AEs in different subjects considered at least possibly related to KZR-261. Exceptions include asymptomatic Grade 4 laboratory abnormalities (eg, neutropenia) that resolve either with or without routine supportive care measures and without sequelae.

Based on its review of any of the aforementioned scenarios, the SRC will have the ability to recommend the study be continued as is, continued with modification, or discontinued. Modifications could include implementation of additional monitoring measures or a reduction of KZR-261 dose.

If any of these scenarios occurs, a formal safety analysis will be conducted, and the findings will be submitted to the IND for FDA review prior to enrolling additional subjects.

8.1.2. Individual Subject Stopping Rules

If any of the following events occur in an individual subject, administration of study drug should be held until a review of the accumulated safety data is undertaken by the Medical Monitor.

- Any scenario that fulfills criteria for Study Stopping Rules (per Section 8.1.1).
- Any scenario that, in the opinion of the Investigator or Medical Monitor contraindicates further dosing (eg, acute phase-like systemic drug reaction).

After such a review, the Medical Monitor in conjunction with the Investigator may recommend the subject resume dosing, including consideration for any prophylactic interventions (as per Section 6.1.1), or discontinue dosing. Alternatively, the Medical Monitor may request that the SRC review all accumulated safety data prior to issuing a recommendation whether to resume or discontinue dosing.

If any of the following events occur, administration of study drug to an individual subject should be discontinued:

- Intolerable toxicity unresponsive to appropriate supportive interventions
- Requirement for more than two dose reductions, or missed one entire treatment cycle
- PD

- Voluntary withdrawal by the subject from the study
- Requirement for a prohibited medication without a suitable alternative (including non-protocol anticancer therapy)
- DLT in Part 1, Cycle 1
- Pregnancy
- Physician's decision
- Closure of the study by the Sponsor (Section 8.3.2).

Subjects discontinuing study treatment must complete EOT assessments, particularly safety evaluations. The primary reason for study treatment discontinuation will be identified and recorded on the appropriate eCRF, along with the date of discontinuation.

8.2. Early Withdrawal of Subjects from Study

In accordance with applicable regulations, a subject has the right to withdraw from the study, at any time and for any reason, without prejudice to future medical care.

Subjects must be withdrawn from the study for any of the following reasons:

- Subject request/withdraw consent for any reason

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

- Use of non-permitted concurrent therapy
- Non-compliance with the study drug or study schedule
- Lost to follow-up
- Occurrence of AEs not compatible with the continuation of subject participation in the study, in the Investigator's or Sponsor's opinion, or unacceptable to the subject to continue
- Investigator request
- Sponsor request

The reason(s) for study withdrawal, if available, will be documented in the eCRF. If a subject withdraws consent, all samples obtained will be retained for analysis unless the subject confirms in writing that he or she wishes the samples to be discarded.

Reasonable efforts should be made to contact subjects who are lost to follow-up (defined as at least 3 unsuccessful contact attempts including 1 certified mail attempt). These efforts must be documented.

8.3. End of Treatment and End of Study

8.3.1. End of Treatment (or Early Withdrawal) Visit

The EOT / Early Withdrawal Visit will take place as soon as possible after permanent treatment discontinuation and prior to initiation of follow-on anticancer therapy (Appendix B). The following procedures will be performed at the EOT / Early Withdrawal Visit:

- Record any AEs that have occurred since the last visit and any changes in concomitant medication
- Record vital signs
- Record any clinically significant changes from baseline in physical examination as AEs
- Collect samples for hematology, clinical chemistry, and urinalysis.
- Perform assessments of response, if the subject stops study treatment for reasons other than PD and the last response assessment was performed >4 weeks before the EOT visit.

8.3.2. End of Study

At End of Study (EOS) for each subject, disposition will be recorded. EOS will occur at the earliest of the following:

- Long-term follow-up is complete
- Voluntary withdrawal by the subject from the study
- Subject death
- Closure of the study by the Sponsor

Completion of the conduct of the study is defined as the date of the last visit of the last subject.

8.4. Study Termination

The Sponsor has the right to terminate the study at any time if judged necessary for safety, regulatory, or other reasons consistent with applicable laws, regulations, and Good Clinical Practice (GCP). In this event, the Investigator(s) will be informed of the reason for study termination. Should this occur, all data available will also be recorded in the eCRFs. The Investigator should notify the relevant Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) in writing of the study's completion or early discontinuation.

9. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

9.1. Adverse Event Reporting

9.1.1. Definitions

An AE is defined as any untoward medical occurrence in a clinical study subject administered a medicinal product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, disease, or medical condition temporally associated with the use of a medicinal (investigational) product, whether or not it is related to the medicinal (investigational) product. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, or drug interaction. Anticipated fluctuations of pre-existing conditions, including the disease under study, that do not represent a clinically significant exacerbation or worsening need not be considered AEs.

Progression of the underlying malignancy that is clearly consistent with the progression as defined by RECIST v1.1 criteria (or PCWG3 criteria in the setting of mCRPC), or other protocol defined criteria, is not considered an AE. Hospitalization due solely to progression of the underlying malignancy should not be reported as an SAE.

If signs, symptoms and/or physical findings cannot be determined as exclusively due to progression of the underlying malignancy or do not fit the expected pattern of progression, these clinical symptoms should be reported as AEs or SAEs.

If there is any uncertainty regarding an AE or SAE being due to progression of malignancy, these should be reported as AEs or SAEs.

Signs and symptoms associated with overdose of KZR-261 must be reported as AEs.

It is the responsibility of the Investigator to document all AEs that occur during the study. AEs will be elicited by asking the subject a nonleading question, for example, “Have you experienced any new or changed symptoms since we last asked/since your last visit?” AEs should be reported on the appropriate page of the eCRF.

9.1.2. Assessment of Severity

Severity of AEs will be graded according to NCI CTCAE v5.0. If there is a change in severity of an AE, it must be recorded as a separate event. For AEs not listed in the NCI CTCAE, the Investigator should determine the severity of the AE according to the criteria in Table 11.

Table 11: Adverse Event Severity Assessment

Grade 1 (Mild)	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2 (Moderate)	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
Grade 3 (Severe)	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
Grade 4 (Life-threatening)	Life-threatening consequences; urgent intervention indicated.
Grade 5 (Death)	Death related to the adverse event.

9.1.3. Assessment of Causality

The Investigator will assess the causal relationship between study drug and an AE. AEs will be deemed related to study drug unless irrefutably determined to be related to the disease under study or another non-study drug cause.

The causal relationship between the study drug and the AE will be assessed using 1 of the following 2 categories:

Unrelated: An AE is not associated with study drug if any of the following is true:

- A temporal relationship is lacking (ie, the event did not occur within a reasonable time frame after administration of the study drug)
- Other causative factors more likely explain the event (eg, intercurrent illness, concomitant treatments, traumatic event).
- The AE did not reoccur upon re-administration of the study drug (if applicable)

Related: An AE is attributed to the study drug if any of the following is true:

- There is a positive temporal relationship (ie, the event occurred within a reasonable time frame after administration of study drug)
- The AE is more likely explained by the study drug than by another cause and cannot be clearly assessed as “unrelated”

Reporting of unexpected adverse reactions is described in Section 9.5.

9.1.4. Action Taken

The Investigator will describe the action taken with study drug in the appropriate section of the eCRF, as follows:

- None
- Study drug stopped
- Study drug temporarily interrupted
- Study dose modification
- Other, specify

9.1.5. Follow-up of Adverse Events

AEs are intended to be collected according to the procedures outlined above from the time of ICF and are to continue for 30 days following the last dose of study drug.

All Investigators should follow up with subjects with AEs until the event is resolved or until, in the opinion of the Investigator, the event is stabilized or determined to be chronic. Details of AE resolution must be documented in the eCRF.

9.1.6. Documentation and Reporting of Adverse Events

AEs (including SAEs) should be reported and documented in accordance with the procedures outlined below. All AEs occurring during the study must be documented on the relevant eCRF pages. The following data should be documented for each AE:

- Diagnosis or description of the symptom if diagnosis is not established
- Classification of 'serious' or 'not serious'
- Severity
- Date of first occurrence and date of resolution (if applicable)
- Action taken with study drug
- Causal relationship with study drug
- Whether medication or therapy was given
- Outcome of event (unknown, recovered, not yet recovered, recovered with sequelae, death [with date and cause reported])

9.2. Serious Adverse Events

9.2.1. Serious Adverse Events Definition

An SAE is any untoward medical occurrence or affect that, at any dose:

- Results in death
- Is life-threatening (an AE is life-threatening if the subject was at immediate risk of death from the event as it occurred, ie, it does not include a reaction that might have caused death if it had occurred in a more serious form)
- Requires or prolongs inpatient hospitalization. (Complications occurring during hospitalization are AEs and are SAEs if they cause prolongation of the current hospitalization. Hospitalization for elective treatment of a pre-existing non-worsening condition is not, however, considered an AE. The details of such hospitalizations must be recorded on the medical history or physical examination page of the eCRF)
- Results in persistent or significant disability/incapacity. (An AE is incapacitating or disabling if it results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions)

- Results in a congenital anomaly/birth defect
- Is an important medical event that requires medical and scientific judgement to decide if prompt notification is required in situations other than those defined for SAEs above. This may include any event that the Investigator regards as serious that did not strictly meet the criteria above but may have jeopardized the subject and may require medical or surgical intervention to prevent one of the other outcomes listed above.

9.2.2. Serious Adverse Event Reporting and Documentation Requirements

Any SAE must be reported as detailed in Section 9.1.6 by the Investigator if it occurs from the time of signed consent through 30 days after the last dose of study drug, whether or not the SAE is considered to be related to the investigational product. All Investigators should follow up with subjects with SAEs until the event is resolved or until, in the opinion of the Investigator, the event is stabilized or determined to be chronic. Details of SAE resolution must be documented.

An SAE report consists of the SAE form, provided separately. If considered necessary, additional redacted source documents regarding an SAE may be requested.

Redacted source documents (ie, medical records) should not be provided in lieu of a completed SAE report form.

SAEs that occur during the reporting period must be reported by the Investigator to the [redacted] Safety Reporting e-mail address [redacted], or dedicated fax [redacted] (see also Study Personnel page at the front of this protocol) and entered into electronic data capture (EDC) within 24 hours from the point in time when the Investigator becomes aware of the SAE.

The Investigator should not wait to receive additional information to fully document the event before notification of a SAE, though additional information may be requested. Where applicable, information from relevant laboratory results, hospital case records, and autopsy reports should be obtained.

Instances of death, congenital abnormality, or an event that is of such clinical concern as to influence the overall assessment of safety, if brought to the attention of the Investigator at any time after cessation of study drug administration and considered by the Investigator to be related to participation in this study, should be reported to the study monitor.

The Sponsor and/or the Contract Research Organization (CRO) will promptly notify all relevant Investigators and the regulatory authorities of findings that could adversely affect the safety of subjects, impact the conduct of the study or alter the IEC/IRB approval/favorable opinion of the study. In addition, the CRO and the Sponsor will expedite the reporting to all concerned Investigators, to the IECs/IRBs, where required, and to the regulatory authorities of all adverse reactions that are both serious and unexpected (Section 9.5.1).

9.3. Pregnancy Reporting

Pregnancy occurring in a subject or partner of a subject during a clinical investigation must be reported within 24 hours on a Pregnancy Monitoring Form. The outcome of a pregnancy should be followed up carefully and any abnormal outcome of the mother or the child should be reported. This also applies to pregnancies following the administration of the investigational

product to the father prior to sexual intercourse. Infants should be followed for a minimum of 8 weeks, and all findings should be reported to the Sponsor. Study drug is to be discontinued immediately upon Investigator knowledge of pregnancy in a subject.

If the outcome of the pregnancy meets a criterion for immediate classification as an SAE-spontaneous abortion (any congenital anomaly detected in an aborted fetus is to be documented), stillbirth, neonatal death, or congenital anomaly–the Investigator should repeat the procedures for expedited reporting of SAEs (Section 9.2.2).

Full details will be recorded on the withdrawal page of the eCRF, or an SAE report will be completed if the subject has completed the study.

9.4. Adverse Events of Special Interest

There are no identified AEs of special interest for this FIH study that require expedited reporting.

9.5. Unexpected Adverse Reactions

9.5.1. Unexpected Adverse Reaction Definition

An unexpected adverse reaction is any untoward or unintended response that is related to the administration of the study drug at any dose that is not consistent with the applicable product information (eg, not listed in the Reference Safety Information section of the Investigator's Brochure or prescribing information or not listed at the specificity or severity it has been observed).

All suspected unexpected serious adverse reactions (SUSARs) will be subject to expedited reporting. The Sponsor and/or the CRO shall ensure that all relevant information about a SUSAR that is fatal or life-threatening is reported to the relevant competent authorities and IEC/IRB within 7 days after knowledge by the Sponsor of such a case and that relevant follow-up information is communicated within an additional 8 days. All other SUSARs will be reported to the relevant competent authorities and IEC/IRB within 15 days after knowledge by the Sponsor of such a case. Also, all Investigators that are involved in the current study and any study with KZR-261 will be informed regarding a SUSAR occurrence.

All Investigators should follow up SUSARs until the event is resolved or until, in the opinion of the Investigator, the event is stabilized or determined to be chronic. Post-study SUSARs that occur after the subject has completed the clinical study must be reported by the Investigator to the Sponsor in the same manner.

10. STATISTICAL ANALYSES

A detailed Statistical Analysis Plan will be prepared by the Sponsor and finalized prior to database lock.

10.1. Sample Size Estimates

10.1.1. Part 1

The sample size for Part 1 will be approximately 70 subjects, but the actual sample size will depend on the number of dose levels of KZR-261, number of subjects per dose level, and the number of subjects treated at the MTD or the MAD(s) of KZR-261.

Dose escalation will continue accruing until one of the three stopping conditions below is triggered:

- The maximum sample size has been achieved,
- MTD/MAD has been identified with sufficient accuracy: data from 6 to approximately 12 subjects have been accumulated at a dose that is deemed to be the MTD/MAD, or
- All doses explored appear to be overly toxic and the MTD cannot be determined.

Due to binomial data variability in small samples, DLTs may be observed in a first cohort(s) by chance even when the true probability (DLT) is fairly low. This could result in the estimated posterior DLT rate exceeding the targeted 30% very early in the trial, triggering an early stop when very few subjects (2-4) have been treated. To prevent stopping the trial prematurely in such cases, a step-down option with a lower dose of 0.9 mg/m^2 is added to the dose grid. This dose will be explored only if a high DLT rate occurs in the first cohort assigned to 1.8 mg/m^2, ie, it will not be used as a starting dose and the algorithm will always assign the first cohort of subjects to a dose of 1.8 mg/m^2.

10.1.2. Part 2A

The sample size in Part 2A is based on clinical and statistical considerations. Upon identification of the MTD/MAD at the conclusion of Part 1, the study will continue with up to 4 tumor-specific expansion cohorts and 1 All-Tumors cohort in Part 2A. The tumor-specific cohorts (n = 15 at interim) may be increased up to 35 subjects per cohort to more precisely estimate the anti-tumor activity of KZR-261, if there is a sufficient efficacy signal at the interim analyses (Section 10.6) and if the tumor type is not selected for investigation in Part 2B (dose optimization). The All-Tumors cohort may enroll up to 35 biopsy-evaluable subjects.

10.1.3. Part 2B

In Part 2B (Dose Optimization), up to 120 subjects (30 per each tumor-specific cohort [15 per dose level]) may be enrolled into up to 4 tumor-specific cohorts based on the totality of data after the MTD/MAD has been determined. The sample size for Part 2B is based on clinical considerations.

10.2. Analysis Populations

Three (3) analysis populations are planned for the study as follows:

- The Safety Population consists of all subjects who receive at least 1 dose of study treatment (KZR-261) and will be used for the safety analyses.
- The Response Evaluable Population is defined as all subjects who receive at least 1 dose of study treatment (KZR-261) and who have a baseline and at least 1 post-baseline anti-tumor response assessment using RECIST v1.1.
- The PK Analysis Population consists of all subjects who receive at least 1 dose of KZR-261 and who have at least one post-dose PK sample with measurable concentration of KZR-261. Any protocol deviations affecting PK analyses may result in exclusion from summaries for individual time point concentrations, complete profiles, and/or PK parameters. These exclusions will be reviewed before database lock and confirmed with the Sponsor before implementation.

Unless otherwise specified, all data will be summarized by dose level and overall for Part 1 (Dose Escalation), tumor-specific cohort for Part 2A (Dose Expansion), and dose and tumor-specific cohort for Part 2B (Dose Optimization).

10.3. Demographics, Disposition, and Baseline Characteristics

Subject enrollment and disposition, including reasons for early discontinuation from treatment and the study, will be summarized.

Baseline demographic (including sex, age, race, ethnicity, weight, height, body mass index) and disease characteristics will be summarized.

10.4. Methods of Analysis

In general, descriptive statistics, including numbers and percentages for categorical variables and numbers, means, standard deviations, medians, minimums, and maximums for continuous variables will be provided.

10.5. Statistical Analyses

10.5.1. Dose Escalation Algorithm

In Part 1, the dose escalation algorithm for the i3+3 design is rule-based and implemented by escalate (E), stay at the current dose (S) and de-escalate (D or DU), according to observed toxicities (Liu et al., 2020). Suppose dose d is the dose currently used to treat subjects, n_d is the number of subjects who have been treated at dose d, and x_d is the number of subjects who have experienced DLTs at dose d. The i3+3 design can be summarized as follows: at the current dose d, calculate two quantities x_d / n_d and $(x_d - 1) / n_d$. The decision rules compare these two quantities to the equivalence interval (EI), and depending on the comparison outcome, decide the next dose level for enrolling subjects.

- If x_d / n_d is below the EI, escalate (E) and enroll subjects at the next higher dose (d + 1);
  - else, if x_d / n_d is inside the EI, stay (S) and continue to enroll subjects at the current dose d;
  - else, if x_d / n_d is above the EI, there are two scenarios:
    1. if (x_d -1) / n_d is below the EI, stay (S) and continue to enroll subjects at the current dose d,
    2. else, de-escalate (D or DU) and enroll subjects at a lower dose (d − 1).

When d is the highest dose or the lowest dose, the above rules need to be modified as special cases.

- If the current dose is the highest dose, and x_d / n_d is below the EI, stay (S) instead of escalate (E) and continue to enroll subjects at the current dose. This is because there is no dose to escalate to.
- If the current dose is the lowest dose, and x_d / n_d is above the EI, stay (S) instead of potentially de-escalating (D or DU) and continue to enroll subjects at the current dose. This is because there is no dose to de-escalate to.

Following the mTPI and mTPI-2 designs, two safety rules are added as ethical constraints to avoid excessive toxicity:

- Safety rule 1 (early termination due to excessive toxicity at the lowest dose). In the special case of cohorts of size 1, this early stopping rule should not be applied until three or more patients have been evaluated at a dose.
  - The term, excessive toxicity at the lowest dose (dose 1) can be expressed mathematically as follows: assume $n_1 > 0$, if $Pr(p_1 > p_T \mid x_1, n_1) > \xi$, for a large probability ξ, say 0.95 has occurred. Where Pr is probability and p_1, p_T, x_1, and n_1 represent "DLT rate at dose 1", "target DLT rate", "# of DLT at dose 1" and "cohort size at dose 1" respectively.
- Safety rule 2 (dose exclusion): Suppose that the decision is to escalate from dose d to dose (d + 1). If there is a high probability that there is an excessive toxicity at dose (d + 1), ie, $Pr(p_{d+1} > p_T \mid x_{d+1}, n_{d+1}) > \xi$ for $\xi = 0.95$, then treat the next cohort of patients at dose d instead of (d + 1), and dose (d + 1) and higher doses will be removed from the trial. These doses will be marked as "DU" to indicate that they are Unacceptable to use in the trial anymore.

Under the i3+3 design, a trial is terminated either when a prespecified sample size is reached or according to Safety rule 1. Table 1 provides a decision table in i3+3 design for up to 12 patients treated at a given dose with the targeted DLT rate p_T=0.3 and the equivalence interval (EI) = [0.25, 0.35].

10.5.2. Estimation of MTD

At the end of Part 1, the MTD selection under the i3+3 design follows the same procedure as in the mTPI and mTPI-2 designs (Liu et al., 2020). The MTD should be the dose that KZR-261's

DLT rate is closest to the prespecified target DLT rate and within the equivalence interval (EI); to select the dose as the estimated MTD with the smallest difference: $|\hat{p}^*_d - p_T|$ among all the doses d for which $n_d > 0$ and $Pr(p_d > p_T | x_d, n_d) < \xi$. Here $\hat{p}^*_d$ is the isotonically transformed posterior mean of p_d, the same as that in the mTPI design (Zhou and Ji, 2020). If two or more doses tie for the smallest difference, perform the following rule. Let p^* denote the transformed posterior mean $\hat{p}^*_d$ of the tied doses.

- If $p^* < p_T$, choose the highest dose among the tied doses.
- If $p^* > p_T$, choose the lowest dose among the tied doses.

10.5.3. Simulations and Operating Characteristics of the i3+3 Design

Other than the slightly different decision tables (see (Liu et al., 2020) [Figure A1 in Appendix D]), the i3+3, mTPI, and mTPI-2 designs use the same safety rules and same inference to select the MTD. Because the mTPI and mTPI-2 designs have been well established in the literature with desirable performance, as indicated by the authors (Liu et al., 2020), there is no need to conduct more and larger simulations, such as a simulation study with 1,000 random scenarios, to further evaluate the operating characteristics of the i3+3 design. The i3+3 design is expected to perform at a similar level as the mTPI and mTPI-2 designs due to its similar but slightly improved decision table, which puts i3+3 in par with other major model-based designs.

10.5.4. Safety Analysis

Safety analyses will be performed for all subjects who received at least 1 dose of study drug.

Prior and concomitant medications will be coded using the WHO Drug dictionary (version March 2023 or later). Verbatim AE terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) (version 26.0 or later). All AEs that occur after administration of the first dose of study drug and through 30 days after last dose of study drug will be considered treatment-emergent adverse events and will be summarized by MedDRA system organ class and preferred term. The incidences (percentages) of subjects experiencing each AE preferred term will be summarized. AEs will also be summarized by severity in accordance with NCI CTCAE v5.0 and by causality (relationship to study treatment). DLTs, AEs, Grade 3, Grade 4, and Grade 5 AEs, SAEs, and AEs resulting in dose reductions, treatment interruptions, or treatment discontinuation will be summarized by MedDRA preferred terms. Deaths that occur after the first dose of study drug and through 30 days after the last dose of study drug will be considered “on treatment” deaths and will be summarized. All deaths will be listed.

Clinical laboratory, vital sign measurements, and ECG data will be summarized descriptively (means, medians, standard deviations, and minimum and maximum values) by dose/treatment group and overall and at protocol-specified time points along with a summary of change from baseline at each protocol-specified time point.

Incidences of clinical laboratory abnormalities will be summarized with descriptive statistics. Vital signs and physical examination results will be summarized with descriptive statistics. Changes from baseline in physical and ocular examination findings will be listed and described for each subject.

10.5.5. Anti-tumor Activity

ORR is defined as the proportion of subjects achieving a best response of CR or PR according to RECIST v1.1. CBR is defined as the proportion of subjects achieving a best response of CR/PR or stable disease over a period of ≥2 consecutive response assessment time points. Subjects with mCRPC will be assessed for response/clinical benefit per PCWG3 guidelines. DOR is defined as the date from first occurrence of CR or PR to the date of documented PD or death. In assessing DOR, a subject alive and without disease progression will be censored at the date of the last evaluable disease assessment. PFS is defined as the date of initiation of study treatment to the date of documented PD or death from any cause, whichever occurs first. OS is defined as the date of initiation of study treatment to the date of death from any cause.

The 2-sided exact CI using the Clopper-Pearson method will be calculated for response/clinical benefit rates where applicable (Clopper and Pearson, 1934). Distributions for PFS, DOR, and OS will be estimated by Kaplan-Meier methodology.

The CBR will be summarized by response assessment timepoints (ie, every 2 cycles).

Summary tables of best ORR, PFS, and OS will be provided overall and by malignancy if necessary. Efficacy listings will be provided that include best response, first CR/PR date, last date with CR or PR, most recent date without progression, progression date, death date, and last tumor assessment date, etc. The definition of each response category is provided in RECIST v1.1.

Table 12 provides an overview of the planned efficacy analysis.

Table 12: Anti-tumor Assessments

Endpoint	Analysis Sets	Statistical Method
Objective response rate (ORR)	Dose Expansion and Optimization cohorts	Exact CI
Progression-free survival (PFS)	Dose Expansion and Optimization cohorts	Kaplan-Meier
Duration of response (DOR)	Dose Expansion and Optimization cohorts	Kaplan-Meier
Overall survival (OS)	Dose Expansion and Optimization cohorts	Kaplan-Meier
Clinical benefit rate (CBR)	Dose Expansion and Optimization cohorts	Exact CI

CI=confidence interval.
Note: Anti-tumor analyses may include patients in dose escalation phase.

10.5.6. Pharmacokinetics

PK parameters will be calculated from measurements of KZR-261 plasma concentrations at prespecified timepoints pre- and post-infusion using noncompartmental methods. Other approaches, such as population PK analyses may be considered, if appropriate. PK parameters to be calculated (if adequate data are available for estimation) will include, but not be limited to, C_{max}, AUC, $t_{½}$, CL, and V_z. Concentrations and PK parameters of KZR-261 will be summarized for each dose level by cycle and day in Part 1 using descriptive statistics.

10.5.7. Exploratory Assessments

Assessments of various pharmacodynamic study readouts as a function of dose and time post-administration will be described and related to anticancer activity, PK, and safety parameters (Section 7.4.1).

10.5.8. Handling of Missing Data

Subjects discontinue study treatment and/or the study for any reason will be included in all analyses regardless of the duration of treatment. There will be no imputation for missing data, unless otherwise specified in the Statistical Analysis Plan.

10.6. Interim Analyses

The Go/No-Go futility analysis for each tumor-specific cohort in Part 2A will be based on CBR as the primary outcome measurement (as defined in Section 10.5.5) after Stage 1 enrollment of 15 subjects. Each of the expansion cohorts is based on the following assumptions:

- Each expansion cohort has a maximum sample size of 35 with one interim futility analysis at 15 subjects. At the interim analysis, if there is 1 or no subject with CBR (ie, CBR rate <7%), further enrollment into the cohort will be stopped for futility. If futility is rejected at the interim analysis (ie, 2 or more of 15 subjects with clinical benefit), the final analysis will be based on a total 35 subjects (ie, 20 additional subjects evaluable for CBR). Note: Outcomes (ie, presence or absence of clinical benefit) for subjects enrolled in Part 1 with the same tumor type and who received the same dose of KZR-261 as evaluated in the corresponding Part 2A, tumor-specific cohort may be included among the initial 15 subjects at the interim analysis, as described above.

The operating characteristics of this design are presented in Table 13. If the true CBR is less than 5%, there is a reasonable chance to reach the futility criterion at interim. On the other hand, if the true CBR is 20% or higher, the probability to stop for futility is moderately low (<20%).

Table 13: Operating Characteristics of Dose Expansion Phase (Part 2A)

	Interim Analysis (N=15)	Final Analysis (N=35)		
True CBR	Pr(Futility*)	Pr(obs. CBR ≥15% 6 or more subjects with CBR)	Pr(obs. CBR ≥20% 7 or more subjects with CBR)	Pr(obs. CBR ≥25% 9 or more subjects with CBR)
5%	83%	<1%	<1%	<1%
10%	55%	11%	5%	<1%
15%	32%	39%	25%	7%
20%	17%	67%	54%	25%
25%	8%	86%	78%	52%
30%	4%	95%	92%	76%
35%	1%	98%	97%	91%

CBR=clinical benefit rate; obs.=observed; Pr=probability
* 1 or fewer subjects with CBR among the first 15 subjects.

11. ETHICAL AND ADMINISTRATIVE CONSIDERATIONS

11.1. Compliance Statement

The Investigator(s) and all parties involved in this study should conduct the study in adherence to the ethical principles based on the Declaration of Helsinki, International Council for Harmonisation (ICH) guidelines for current GCP, and the applicable national and local laws and regulatory requirements.

Relevant study documentation will be submitted to the regulatory authorities of the participating countries, according to local/national requirements, for review and approval before the beginning of the study. On completion of the study, the regulatory authorities will be notified that the study has ended.

11.2. Institutional Review Board or Independent Ethics Committee

Before initiation of the study at each study center, the protocol, the ICF, other written material given to the subjects, and any other relevant study documentation will be submitted to the appropriate IEC/IRB. Written approval of the study and all relevant study information must be obtained before the study center can be initiated or the study drug is released to the Investigator. Any necessary extensions or renewals of IEC/IRB approval must be obtained for changes to the study (ie, amendments to the protocol, the ICF, or other study documentation). The written approval of the IEC/IRB together with the approved ICF must be filed in the study files.

The Investigator will promptly report to the IEC/IRB any new information that may adversely affect the safety of the subjects or the conduct of the study. The Investigator will submit written summaries of the study status to the IEC/IRB as required. On completion of the study, the IEC/IRB will be notified that the study has ended.

11.3. Informed Consent and Human Subject Protection

The process of obtaining informed consent must be in accordance with applicable regulatory requirement(s) and must adhere to current GCPs.

Subjects will provide written informed consent before any study-related procedures are performed unless the procedure or assessment is consistent with the standard of care for the underlying malignancy.

The Investigator is responsible for ensuring that no subject undergoes any study-related examination or activity before that subject has given written informed consent to participate in the study unless the procedure or assessment is consistent with the standard of care for the underlying malignancy.

The Investigator or designated personnel will inform the subject of the objectives, methods, anticipated benefits, potential risks, and inconveniences of the study. The subject should be given every opportunity to ask for clarification of any points s/he does not understand and, if necessary, ask for more information. At the end of the interview, the subject will be given ample time to consider the study. Subjects will be required to sign and date the ICF. After signatures are obtained, the ICF will be kept and archived by the Investigator in the Investigator's study file. A signed and dated copy of the subject ICF will be provided to the subject.

It should be emphasized that the subject may refuse to enter the study or to withdraw from the study at any time, without consequences for their further care or penalty or loss of benefits to which the subject is otherwise entitled. Subjects who refuse to give or who withdraw written informed consent should not be included or continue in the study.

If new information becomes available that may be relevant to the subject's willingness to continue participation in the study, a new ICF will be approved by the IEC(s)/IRB(s) (and regulatory authorities, if required). The study subjects will be informed about this new information and reconsent will be obtained.

11.4. Direct Access to Source Data, Source Documents, and Study Records

The Sponsor or its representatives may periodically check a sample of the subject data recorded against source documents at the study site. The study may be audited by the Sponsor and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

The Investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the Investigator will provide the Sponsor, applicable regulatory agencies, and applicable review boards with direct access to the original source documents.

11.5. Data Collection and Handling

An EDC system will be used in this study. The study site must define and retain all source records and must maintain a record of any data where source data are directly entered into the data capture system.

Data systems used for the study will have controls and requirements in accordance with local data protection law.

The purpose and use of subject personal information collected will be provided in a written document to the subject by the Sponsor.

11.6. Confidentiality

Monitors, auditors, and other authorized agents of the Sponsor and/or its designate, the IEC(s)/IRB(s) approving this research, and the FDA, as well as that of any other applicable agency(ies), will be granted direct access to the study subjects' original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subjects to the extent permitted by the law and regulations. In any presentations of the results of this study or in publications, the subjects' identity will remain confidential.

All personal data collected and processed for the purposes of this study should be managed by the Investigator and his/her staff with adequate precautions to ensure confidentiality of those data, and in accordance with the Health Insurance Portability and Accountability Act, applicable to national and/or local laws and regulations on personal data protection.

11.7. Financing and Insurance

Financing and insurance of this study will be outlined in a separate agreement between the CRO and the Sponsor.

11.8. Audit and Inspection

Study centers and study documentation may be subject to Quality Assurance audit during the course of the study by the Sponsor or its nominated representative. In addition, inspections may be conducted by regulatory authorities at their discretion.

11.9. Monitoring

Data for each subject will be recorded on an eCRF. Data collection must be completed for each subject who signs an ICF.

In accordance with current GCP and ICH guidelines, the study monitor will carry out source document verification at regular intervals to ensure that the data collected in the eCRF are accurate and reliable.

The Investigator must permit the monitor, the IEC/IRB, the Sponsor's internal auditors, and representatives from regulatory authorities' direct access to all study-related documents and pertinent hospital or medical records for confirmation of data contained within the eCRFs.

11.10. Quality Control and Quality Assurance

All aspects of the study will be carefully monitored by the Sponsor or its authorized representative(s) for compliance with applicable government regulations with respect to current GCP and Standard Operating Procedures.

11.11. Data Management and Coding

The Sponsor or the CRO will be responsible for activities associated with the data management of this study. This will include setting up a relevant database and data transfer mechanisms, along with appropriate validation of data and resolution of queries. Data generated within this clinical study will be handled according to the relevant standard operating procedures of the data management and biostatistics departments of Sponsor or the CRO.

Study centers will enter data directly into an EDC system by completing the eCRF via a secure internet connection. Data entered into the eCRF must be verifiable against source documents at the study center. Data to be recorded directly on the eCRF will be identified and the eCRF will be considered the source document. Any changes to the data entered into the EDC system will be recorded in the audit trail and will be FDA CFR 21 Part 11 compliant.

Medical coding will use MedDRA for concomitant diseases and AEs with World Health Organization drug classifications being used for medications.

Missing or inconsistent data will be queried in writing to the Investigator for clarification. Subsequent modifications to the database will be documented.

11.12. Reporting and Publication, Including Archiving

Essential documents are those documents that individually and collectively permit evaluation of the study and quality of the data produced. After completion of the study (end of study defined as the date of the last visit of the last subject), all documents and data relating to the study will be kept in an orderly manner by the Investigator in a secure study file. This file will be available for

inspection by the Sponsor or its representatives. Essential documents should be retained for 2 years after the final marketing approval in a region, for at least 2 years since the discontinuation of clinical development of the investigational product, or according to local requirements, whichever is longer. It is the responsibility of the Sponsor to inform the study center when these documents no longer need to be retained. The Investigator must contact the Sponsor before destroying any study-related documentation. In addition, all subject medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice.

The Sponsor must review and approve any results of the study or abstracts for professional meetings prepared by the Investigator(s). Published data must not compromise the objectives of the study. Data from individual study centers in multicenter studies must not be published separately.

12. REFERENCES

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13. APPENDICES

APPENDIX A. SCHEDULE OF EVENTS FOR SCREENING AND CYCLES 1 & 2

Study Period	Screening[a]	Pre-Treatment (Baseline)	Treatment Period									Treatment Period								
Cycle			Cycle 1 [q]									Cycle 2 [q]								
Day	D-28 to D-1	D0 to D1	D1	D2	D3[t]	D5[t]	D8	D15	D16	D22	D28[p]	D1[p]	D2	D3[t]	D5[t]	D8	D15	D16	D22	D28[p]
Visit Window (days)					+1	+1	±1	±3		±3	+3	+1		+1	+1	±1	±3		±3	+3
Informed consent form	X																			
Inclusion/exclusion criteria	X																			
Hepatitis B and C testing	X																			
Medical history	X																			
ECOG PS	X	X									X	X								X
Physical examination [b]	X	X					X	X		X	X	X				X	X		X	X
Slit lamp exam and visual acuity [s]	X										X	X								X
Pregnancy test [c]	X	X									X	X								X
Vital sign measurement and oxygen saturation [d]	X	X	X	X			X	X	X	X	X	X	X			X	X	X	X	X
12-lead ECG [e]	X	X	X	X			X	X	X		X	X	X			X	X	X		X
Hematology (Table 8)	X	X					X	X		X	X	X				X	X		X	X
Serum chemistry (fasting) [g] (Table 9)	X	X					X	X		X	X	X				X	X		X	X
HgbA1c [r]		X																		
Coagulation parameters [g] (Table 10)	X										X	X								X
Urinalysis [h]	X										X	X								X
PSA [i]		X									X	X								X
Tumor markers [j]	X										X	X								X
Tumor imaging and measurements [k]	X																			X
PK [l]																				

Study Period	Screening[a]	Pre-Treatment (Baseline)	Treatment Period									Treatment Period								
Cycle			Cycle 1 [q]									Cycle 2 [q]								
Day	D-28 to D-1	D0 to D1	D1	D2	D3[t]	D5[t]	D8	D15	D16	D22	D28[p]	D1[p]	D2	D3[t]	D5[t]	D8	D15	D16	D22	D28[p]
Visit Window (days)					+1	+1	±1	±3		±3	+3	+1		+1	+1	±1	±3		±3	+3
Part 1			X	X	X	X	X	X	X			X	X	X	X	X	X	X		
Part 2			X	X			X	X												
Pharmacodynamic & biological studies [m]			X	X			X	X	X		X	X								X
Circulating tumor DNA [n]			X								X	X								X
Tumor biopsy or submission of tumor specimen [f]	X																		X	
KZR-261 treatment [o]			X				X	X				X				X	X			
Concomitant medications		X	X	X			X	X	X	X	X	X	X			X	X	X	X	X
AE and SAEs		X	AEs collected through 30 days after last KZR-261 dose.																	

Abbreviations: AE=adverse event; aPTT=activated partial thromboplastin time; β-hCG=β-human chorionic gonadotropin; CA=cancer antigen; CEA=carcinoembryonic antigen; CT=computed tomography; DNA=deoxyribonucleic acid; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group Performance Status; EOT=End of Treatment; INR=internal normalized ratio; mCRPC=metastatic castration-resistant prostate cancer; MRI=magnetic resonance imaging; PBMC=peripheral blood mononuclear cell; PCWG3= Prostate Cancer Working Group 3; PD= progressive disease; PK=pharmacokinetics; PSA=prostate-specific antigen; PT=prothrombin time; PTT=partial thromboplastin time; RECIST=Response Evaluation Criteria in Solid Tumors; RNA=ribonucleic acid; SAE=serious adverse event; WOCBP=woman of childbearing potential

[a] All Screening procedures must be performed prior to the Day 0 or Day 1 visit. Eligibility for this study should be assessed only after signing of informed consent.

[b] A complete physical examination including measurement of body weight will be conducted at Screening and Baseline. Height will be measured at the Screening visit only. An abbreviated physical examination including measurement of body weight will be conducted at all other study visits indicated. Subjects with skin, subcutaneous, or lymph node metastases may also have tumor evaluations (including measurements, with a ruler or calipers) by means of physical examination. Patients will be asked at each visit about mouth dryness and salivary gland pain and sensitivity, and urinary and ejaculation issues.

[c] For WOCBP, a negative serum β-hCG pregnancy test is required at Screening and a negative pregnancy test, serum or urine, at all other visits indicated. The Screening visit test should be performed within 2 weeks prior to treatment and in closer proximity to treatment start date if required by local/institutional regulations. A positive urine pregnancy test result should be confirmed by a serum pregnancy test. Pregnancy testing may occur more frequently if required by local/institutional regulations.

[d] Vital signs and oxygen saturation will be measured at all visits except Days 3 and 5. Blood pressure and pulse should be measured after the subject has had at least 5 minutes of rest in the seated position. If blood pressure is elevated on the first measurement at Screening or Baseline, it should be repeated after an additional 5 minutes of rest. It is recommended that blood pressure be obtained from the same arm at each assessment.

[e] When performed at the same time point, vital sign measurements should be performed per institutional guidelines, preferably prior to ECGs. A 12-lead ECG is performed 10 minutes after the subject has been in the supine position. ECGs will be performed on Days 1 and 15 of Cycles 1 and 2 pre-treatment, 15 minutes after the start of the infusion, at the end of the infusion, and 5 and 30 minutes, and 2, 4, 6, and 24 hours (Day 2 and Day 16) post-infusion. Additional ECGs will be performed on Day 8, 30 minutes prior to infusion, and 5 and 15 minutes and 1-hour post-infusion. ECG time points during the infusion, at the end of the infusion, and ≤1 hour post-infusion have a ±2 minute window. ECG time points >1 hour post-infusion have a ±5 minute window; the 24-hour ECG has a ±60 minute window.

[f] Tumor biopsies (fresh [preferred] or archived) will be requested pre-treatment. Although a fresh sample is preferred, submission of an adequate tumor specimen (paraffin block) collected within one year before the subject's first dose of KZR-261 will be acceptable for subjects where a fresh sample cannot be obtained. If a paraffin block is not available, a minimum of 10 and up to 20 5-µm unstained slides should be provided. For any subject who provided a tumor sample pre-treatment, an additional biopsy of accessible tumor will be requested at either the end of Cycle 2 (Days 21-28 of Cycle 2) or at PD, whichever comes first.
Pre-treatment tumor biopsies (fresh only) will be required for subjects enrolled in the All-Tumors expansion cohort (exceptions to this requirement may be considered after discussion with the Medical Monitor); an additional biopsy of accessible tumor tissue will be required at either the end of Cycle 2 (Days 21-28 of Cycle 2) or at PD, whichever comes first. Blood samples for coagulation parameter tests must be collected within 24 hours prior to all biopsy procedures.

[g] Blood samples for serum chemistry tests must be collected with subject in a fasting state (ie, no food or caloric drinks for at least 6 hours before testing, or overnight). For coagulation parameter tests, either PT or INR may be measured, and either PTT or aPTT, depending on institutional standards. Blood samples for coagulation parameter tests must be collected within 24 hours prior to all biopsy procedures. It is recommended that the smallest appropriate sampling tubes be used for sample collection to curtail blood loss due to phlebotomy.

[h] Urinalysis dipstick testing is acceptable.

[i] Only subjects with mCRPC.

[j] If tumor markers in blood (eg, PSA, CA-125, CEA, CA-15.3, CA-19.9) are known to be elevated, they should be measured.

[k] All subjects must have Baseline imaging (CT scan of chest/abdomen/pelvis or MRI, as indicated) within 28 days prior to first dose of study treatment. Imaging should be repeated prior to Cycle 3 (ie, end of Cycle 2) There is a 7-day window around imaging procedures to allow time for result availability prior to the next cycle. If an imaging procedure must be scheduled to occur outside the 7-day window allowance, this should be discussed with the Medical Monitor for approval prior to the procedure. Response assessments will be conducted in accordance with RECIST 1.1 criteria. Subjects with mCRPC will be assessed per PCWG3 guidelines. All subjects with mCRPC will have bone scans at the same time points as the imaging procedures. Subjects with skin, subcutaneous, or lymph node metastases may also have tumor evaluations (including measurements, with a ruler or calipers) by means of physical examination.

[l] Plasma PK samples will be collected during Part 1 on Days 1 and 15 of Cycles 1 and 2 pre-treatment, 15 minutes post-start of infusion, end of infusion, 5 minutes, 15 minutes, 30 minutes, 1 hour, 2 hours, 4 hours, 6 hours, and 24 hours (ie, Day 2 and Day 16) post-infusion. An additional plasma sample will be obtained in Cycles 1 and 2 at 48 hours (Day 3) and 96 hours (Day 5) post-infusion and on Day 8 at pre-treatment (30 minutes prior to infusion), 15 minutes and 1 hour after completion of the infusion.
Plasma PK samples will be collected during Parts 2A and 2B on Day 1 of Cycle 1 at the end of infusion and 24 hours post-start of infusion (Day 2). An additional plasma sample will be obtained on Days 8 and 15 prior to infusion and Day 15 at the end of infusion.
Windows for PK sampling are provided in the laboratory manual.

[m] Whole blood samples will be collected for pharmacodynamic studies Cycle 1 Day 1 pre-treatment, 6 hours post-dose, 24 hours post-dose (Day 2), Cycle 1 Day 8 pre-treatment and Cycle 1 Day 15 pre-treatment, 6 hours post-dose, 24 hours post-dose (Day 16), and Cycle 2 Day 1 pre-treatment in a [redacted]

tube for RNAseq, in sodium heparin to be shipped to central laboratory for PBMC processing, and in sodium heparin processed onsite to plasma samples (as described in the laboratory manual). Samples will be collected on Cycle 1 Day 28 if treatment is halted and not proceeding to Cycle 2.

[n] Whole blood will be collected in a [redacted] tube and shipped to the central laboratory for processing to plasma samples (for circulating tumor DNA testing) and cell pellet (cellular genomic DNA) pre-treatment Day 1 of Cycle 1, pre-treatment Day 1 Cycle 2, or at time of disease progression.

[o] Subjects should remain at the study site for 6 hours following study treatment administration for observation for the first cycle, first dose (Cycle 1 Day 1) and for 2 hours for the rest of Cycle 1 dosing (Cycle 1 Days 8 and 15). For Cycle 2, subjects will be under observation for 1 hour following study treatment administration. For Cycle 3 and beyond, there will be no required monitoring following study treatment administration.

[p] Day 28 assessments of the prior cycle may be combined with Day 1 of the next cycle. Whenever possible, these evaluations should be referred to as the End of Cycle evaluation (for the earlier cycle) as opposed to the beginning of cycle evaluation for the subsequent cycle.

[q] For subjects who discontinue study treatment during or after Cycles 1 or 2, see EOT evaluations in Appendix B. Subsequent to discontinuation of study treatment, subjects will have an EOT visit as soon as possible following their last KZR-261 dose and prior to initiation of follow-on anticancer therapy. Safety follow-up by telephone will occur approximately 30 days following their last KZR-261 dose. Subjects who discontinue study treatment for reasons other than PD will be contacted by telephone approximately every 90 days for 12 months after last study treatment for evidence of PD, collection of information about subsequent anti-tumor therapy, and assessment of survival status. Subjects who discontinue study treatment for PD will be contacted by telephone approximately every 90 days for 12 months after last study treatment for assessment of survival status.

[r] HgbA1c to be measured at pre-treatment (baseline).

[s] Subjects will have monitoring for cataracts at Screening, at the end of Cycle 1 prior to the start of Cycle 2, and at the end of Cycle 2 prior to Cycle 3.

[t] Day 3 and Day 5 visits are for Part 1 only.

APPENDIX B. SCHEDULE OF EVENTS FOR CYCLE 3+

Study Period	Treatment Period					EOT/EW (as soon as possible after last dose of study treatment) [l]	Safety F/U 30 days after last dose of study treatment [l]	Long-Term F/U 12 months after last dose of study treatment [m]
Day	**D1 [k]**	**D8**	**D15**	**D22**	**D28 [k]**			
Visit Window (days)	**±3**	**±1**	**±3**	**±3**	**±3**			
ECOG PS	X				X	X		
Physical examination [a]	X				X	X		
Slit lamp exam and visual acuity [b]	X				X	X		
Pregnancy test [c]	X				X			
Vital sign measurement and oxygen saturation [d]	X	X	X	X	X	X		
12-lead ECG [e]	X	X [e]	X [e]		X	X		
Hematology (Table 8)	X	X	X	X	X	X		
Serum chemistry (fasting) [f] (Table 9)	X	X	X	X	X	X		
HgbA1c [o]	X				X			
Coagulation parameters [f] (Table 10)	X				X	X		
Urinalysis [g]	X				X	X		
PSA [h]	X				X			
Tumor markers [i]	X				X			
Tumor imaging and measurements [j]					X	X		
Circulating tumor DNA [n]	X				X	X		
KZR-261 Treatment	X	X	X					
Concomitant medications	Concomitant medications through 30 days after the last dose.						X	
AE and SAEs	AEs collected through 30 days after last KZR-261 dose.						X	
Disease/survival status						X		X

Abbreviations: AE=adverse event; aPTT=activated partial thromboplastin time; β-hCG=β-human chorionic gonadotropin; CA=cancer antigen; CEA=carcinoembryonic antigen; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group Performance Status; EOT=End of Treatment; EW=Early Withdrawal; F/U=Follow-Up; INR=internal normalized ratio; mCRPC=metastatic castration-resistant prostate cancer; PD=progressive disease;

PSA=prostate-specific antigen; PT=prothrombin time; PTT=partial thromboplastin time; RECIST=Response Evaluation Criteria in Solid Tumors; SAE=serious adverse event; WOCBP=woman of childbearing potential

[a] For Cycles 3+, an abbreviated physical examination including weight, is only required prior to the start of each cycle (Day 1) and at the EOT visit. Subjects with skin, subcutaneous, or lymph node metastases may also have tumor evaluations (including measurements, with a ruler or calipers) by means of physical examination. Patients will be asked at each visit about mouth dryness and salivary gland pain and sensitivity, and urinary and ejaculation issues.

[b] Subjects will have monitoring for cataracts at Cycle 4 Day 1 ±3 days, Cycle 6 Day 1 ±3 days. Slit lamp and visual acuity examinations should be conducted at EOT.

[c] For WOCBP, a negative serum or urine pregnancy test, whichever is preferred, is required at all visits indicated. A positive urine pregnancy test result should be confirmed by a serum pregnancy test. Pregnancy testing may occur more frequently if required by local/institutional regulations.

[d] Vital signs and oxygen saturation will be measured at all visits. Blood pressure and pulse should be measured after the subject has had at least 5 minutes of rest in the seated position. If blood pressure is elevated on the first measurement at Screening or Baseline, it should be repeated after an additional 5 minutes of rest. It is recommended that blood pressure be obtained from the same arm at each assessment.

[e] When performed at the same time point, vital sign measurements should be performed per institutional guidelines, preferably prior to ECGs. A 12-lead ECG is performed 10 minutes after the subject has been in the supine position. ECGs will be performed on Day 1 pre-treatment and at the end of infusion for all cycles. For Cycle 4 only, ECGs will be performed on Days 1 and 15 at pre-treatment, 15 minutes after the start of the infusion, at the end of the infusion, and 5 and 30 minutes, and 2, 4, and 6 hours post-infusion. Additional ECGs for Cycle 4 only will be performed on Day 8, 30 minutes prior to infusion, and 5 and 15 minutes and 1 hour post-infusion. ECG time points during the infusion, at the end of the infusion, and ≤1 hour post-infusion have a ±2 minute window. ECG time points >1 hour post-infusion have a ±5 minute window. ECG time points >1 hour post-infusion have a ±5 minute window.

[f] Blood samples for serum chemistry tests must be collected with subject in a fasting state (ie, no food or caloric drinks for at least 6 hours before testing, or overnight). For coagulation parameter tests, either PT or INR may be measured, and either PTT or aPTT, depending on institutional standards. It is recommended that the smallest appropriate sampling tubes be used for sample collection to curtail blood loss due to phlebotomy.

[g] Urinalysis dipstick testing is acceptable.

[h] Only subjects with mCRPC.

[i] If tumor markers in blood (eg, PSA, CA-125, CEA, CA-15.3, CA-19.9) are known to be elevated, they should be measured.

[j] Imaging should be repeated prior to Cycle 3, prior to Cycle 5 (ie, end of Cycle 4) and every 2 cycles thereafter (ie, end of Cycles 4, 6, 8 etc.). There is a 7-day window around imaging procedures to allow time for result availability prior to the next cycle. If an imaging procedure must be scheduled to occur outside the 7-day window allowance, this should be discussed with the Medical Monitor for approval prior to the procedure. Imaging should be repeated at EOT if the last response assessment was >4 weeks prior. Tumors will be measured according to RECIST v1.1. Subjects with mCRPC will be assessed per PCWG3 guidelines. All subjects with mCRPC will have bone scans at the same time points as the imaging procedures. Subjects with skin, subcutaneous, or lymph node metastases may also have tumor evaluations (including measurements, with a ruler or calipers) by means of physical examination.

[k] Day 28 assessments of the prior cycle may be combined with Day 1 of the next cycle. Whenever possible, these evaluations should be referred to as the End of Cycle evaluation (for the earlier cycle) as opposed to the beginning of cycle evaluation for the subsequent cycle.

[l] Subsequent to discontinuation of study treatment, subjects will have an EOT visit as soon as possible following their last KZR-261 dose and prior to initiation of follow-on anticancer therapy. Safety follow-up by telephone will occur approximately 30 days after the subject's last dose of study treatment. If AEs have not resolved at that time, additional safety follow-ups will occur approximately every 30 days until AE resolution or until, in the opinion of the Investigator, the event is stabilized or determined to be chronic.
If a subject attending a Day 28 or Day 1 visit meets criteria for EOT, the EOT visit assessments should be conducted instead of Day 28/Day 1 assessments.

[m] Subjects who discontinue study treatment for reasons other than PD will be contacted by telephone approximately every 90 days for 12 months after last study treatment for evidence of PD, collection of information about subsequent anti-tumor therapy, and assessment of survival status. Subjects who discontinue study treatment for PD will be contacted by telephone approximately every 90 days for 12 months after last study treatment for assessment of survival status.

[n] Whole blood will be collected in a [redacted] tube and shipped to the central laboratory for processing to plasma samples (for circulating tumor DNA testing) and cell pellet (cellular genomic DNA) pre-treatment Day 1 of Cycles 3-6. A circulating tumor DNA sample should be collected at EOT or at time of disease progression. This collection is not required for subjects who continue to receive treatment beyond Cycle 6.

[o] HgbA1c to be measured on Day 28 every 3 cycles (ie, end of Cycles 3, 6, 9, etc.) or at Day 1 prior to treatment of the following cycles (ie, Day 1 of cycles 4, 7, 10, etc.).

APPENDIX C. LIST OF PREFERRED TUMORS FOR THE ALL-TUMORS COHORT

Based on the bioinformatics study (Section 1.2.1) and the evaluation of KZR-261 in tumor xenograft models, the following tumor types are prioritized for inclusion in the All-Tumors cohort:

- Urothelial carcinoma
- Soft tissue sarcoma (except GIST)
- Head and neck carcinoma
- Small-cell lung cancer
- Hepatocellular carcinoma
- Pancreatic cancer

APPENDIX D. LIST OF SENSITIVE SUBSTRATES OF CYP3A4

The list below is available at https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers. See also https://drug-interactions.medicine.iu.edu/MainTable.aspx.

Note: This list contains examples and is not intended to be exhaustive.

Category	Drug Names
Sensitive substrates of CYP3A	alfentanil, avanafil, buspirone, conivaptan, darifenacin, darunavir, ebastine, everolimus, ibrutinib, lomitapide, lovastatin, midazolam, naloxegol, nisoldipine, saquinavir, simvastatin, sirolimus, tacrolimus, tipranavir, triazolam, vardenafil budesonide, dasatinib, dronedarone, eletriptan, eplerenone, felodipine, indinavir, lurasidone, maraviroc, quetiapine, sildenafil, ticagrelor, tolvaptan

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