SUMMARY OF CHANGES – Protocol

For Protocol Amendment # to: **"A Phase 1 Dose-Escalation and Exploratory Dose Expansion Study of KRT-232 (AMG 232) in Combination with Carfilzomib, Lenalidomide, and Dexamethasone in Relapsed and/or Refractory Myeloma."**

NCI Protocol #: 10076
Local Protocol #: NCI10076

NCI Version Date: 01/15/2024
Protocol Date: 01/15/2024

THIS AMENDMENT IS BEING SUBMITTED IN RESPONSE TO REQUEST FOR RAPID AMENDMENT (RRA) FROM DR. LORRAINE PELOSOF (CTEP MEMO DATED ON 12/29/2023)

	Section	Change
1	Protocol Cover Page	Protocol version date has been updated from 01/24/2022 to 01/15/2024. No change in the content of the protocol.
2	Section 7.1.1. (Pages 58-60)	Inserted revised language as per KRT-232 CAEPR on Version 2.4, December 8, 2023 • Added New Risk: [redacted]

		[redacted]

THE FOLLOWING ARE PREVIOUS CTEP ADMINSTRTIVE AMMENDMENT RECOMMENDATIONS FROM PREVIOUS CTEP AMENDMENT APPROVAL MEMO DATED 03/23/2021

#	Section	Comments
1.	**Protocol Cover Page**	***Please revise the Corresponding Organization as indicated:*** ~~The~~ University of Texas MD Anderson Cancer Center LAO (LAO-TX035) ***Please revise the Participating Organizations table as indicated:*** **Participating Organizations** **LAO-CA043** / City of Hope Comprehensive Cancer Center LAO LAO-11030 / University Health Network Princess Margaret Cancer Center LAO LAO-CT018 / Yale University Cancer Center LAO LAO-MA036 / Dana Farber – Harvard Cancer Center LAO LAO-MD017 / JHU Sidney Kimmel Comprehensive Cancer LAO ~~LAO-NC010 / Duke University – Duke Cancer Institute~~ LAO-OH007 / Ohio State University Comprehensive Cancer Center LAO LAO-PA015 / UPMC Hillman Cancer Center LAO ~~University of Pittsburg Cancer Institute~~

#	Section	Comments
		LAO-TX035 / University of Texas MD Anderson Cancer Center LAO LAO-NCI / National Cancer Institute LAO **PI Response: Completed**
2.	**4.1** **Page 35**	***Please revise the excerpt below as indicated.*** Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) ~~(i.e., clinical site staff requiring write access to Oncology Patient Enrollment Network (OPEN), Rave, or acting as a primary site contact)~~ must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr. RCR utilizes five person registration types. • IVR: MD, DO, or international equivalent, • NPIVR: advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD), • AP: clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System (RUMS), OPEN, Rave, acting as a primary site contact, or with consenting privileges, ~~(e.g., Roster Update Management System [RUMS], OPEN, Rave,),~~ • Associate (A): other clinical site staff involved in the conduct of NCI-sponsored trials, and • Associate Basic (AB): individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems. **PI Response: Completed**
3.	**4.1** **Page 36**	***Please revise the excerpt below as indicated.*** RCR requires the following registration documents:

#	Section	Comments

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✔	✔			
Financial Disclosure Form	✔	✔	✔		
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔		
GCP training	✔	✔	✔		
Agent Shipment Form (if applicable)	✔				
CV (optional)	✔	✔	✔		

~~Documentation Required~~	~~I V 1.1.~~	~~1.1.1~~	~~A 1.1.~~	~~1.1~~	~~A B~~
~~FDA Form 1572~~	~~✔~~	~~✔~~			
~~Financial Disclosure Form~~	~~✔~~	~~✔~~	~~✔~~		
~~NCI Biosketch (education, training, employment, license, and certification)~~	~~✔~~	~~✔~~	~~✔~~		
~~GCP training~~	~~✔~~	~~✔~~	~~✔~~		
~~Agent Shipment Form (if applicable)~~	~~✔~~				
~~CV (optional)~~	~~✔~~	~~✔~~	~~✔~~		

PI Response: Completed

#	Section	Comments
4.	**4.1** **Page 37**	***Please revise the excerpt below as indicated.*** In addition, all investigators act as the Site-Protocol PI (Investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the Clinical Investigator (CI) on the DTL must be rostered at the enrolling site with a participating organization. ~~, consenting/treating/drug shipment, or as the CI on the DTL must be rostered at the enrolling site with a participating organization (i.e., Alliance).~~ **PI Response: Completed**
5.	**4.2** **Page 38**	***Please revise the following bullet point as specified.*** An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO), and **PI Response: Completed**
6.	**4.2.1** **Page 38**	***Please revise the excerpt below as indicated.*** Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a PO ~~Participating Organization~~ on the protocol. One way to search for a protocol is listed below. • Log on to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password, • Click on Protocols in the upper left of your screen o Enter the protocol number in the search field at the top of the protocol tree, or o Click on the By Lead Organization folder to expand, then select LAO-TX035, and protocol number 10076, • Click on Documents, select Site Registration, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load automatically to the CTSU ~~as described above~~.) Protocol Specific Requirements For 10076 Site Registration • Specimen Tracking System Training Requirement: o All data entry users (Clinical Research Associate role) at each participating site will need to complete the Theradex-led training. o Theradex will provide a certificate of completion, which will need to be submitted to the CTSU through the Regulatory Submission Portal.

#	Section	Comments
		o The training is a one-time only requirement per individual. If an individual has previously completed the training for another ETCTN study, the training does not need to be completed again nor does the certificate of completion need to be resubmitted to the CTSU. However, new versions of the Specimen Tracking System may require new training. o This training will need to be completed before the first patient enrollment at a given site. o Please contact STS Support at Theradex for the training (STS.Support@theradex.com, Theradex phone: 609-799-7580). ~~o Peter Clark and Diana Vulih are the main points of contact at Theradex for the training (PClark@theradex.com and DVulih@theradex.com, Theradex phone: 609-799-7580).~~ **PI Response: Completed**
7.	**4.2.2** **Page 39**	***Please revise the excerpt below as indicated.*** Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal on the CTSU website. To access the Regulatory Submission Portal, log on to the CTSU members' website, go to the Regulatory section, and select Regulatory Submission. ~~→ Regulatory →□Regulatory Submission.~~ Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support. Checking Site Registration Status Site's registration status may be verified on the CTSU website. • Click on *Regulatory* at the top of the screen, • Click on *Site Registration*, and • Enter the site's 5-character CTEP Institution Code and click on Go. o Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type. Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks. ~~Checking Site Registration Status~~

#	Section	Comments
		~~You can verify your site's registration status on the members' side of the CTSU website.~~ ~~• Log on to the CTSU members' website~~ ~~• Click on *Regulatory* at the top of your screen~~ ~~• Click on *Site Registration*~~ ~~• Enter your 5-character CTEP Institution Code and click on Go~~ ~~Note: The status shown only reflects institutional compliance with site registration requirements as outlined above. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.~~ **PI Response: Completed**
8.	**4.3.1** **Page 40**	***Please delete the information within this subsection and replace with the following language.*** 4.3.1 OPEN / IWRS The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN or IWRS will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave. Requirements for OPEN access: • A valid CTEP-IAM account. • To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or PO roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type. • If a DTL is required for the study, the registrar must hold the OPEN Registrar task on the DTL for the site. • Have an approved site registration for the protocol prior to patient enrollment. To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

#	Section	Comments
		Prior to accessing OPEN, site staff should verify the following: • Patient has met all eligibility criteria within the protocol stated timeframes, and • All patients have signed an appropriate consent form and HIPAA authorization form (if applicable). Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. IWRS system also sends an email confirmation of the registration. You may print this confirmation for your records. Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com. Patient enrollment for this study will be facilitated using the Slot Reservation System in conjunction with the registration system in OPEN. Prior to discussing protocol entry with the patient, all site staff must use the CTSU OPEN Slot Reservation System or the IWRS Slot Reservation System to ensure that a slot on the protocol is available to the patient. Once a slot reservation confirmation is obtained, site staff may then proceed to CTSU OPEN Step 1 to enroll the patient to this study. This Study will use the ETCTN Specimen Tracking System (STS). • All biospecimens collected for this trial must be submitted using the ETCTN Specimen Tracking System (STS) unless otherwise noted. • The system is accessed through Rave user roles: "Rave CRA" and "Rave CRA (Labadmin)" for data entry at the treating institutions and "Biorepository" for users receiving the specimens for processing and storage at reference labs and the NCI Early-Phase and Experimental Clinical Trials Biospecimen Bank (EET Biobank, formerly known as the ETCTN Biorepository). • Please refer to the Medidata Account Activation and Study Invitation Acceptance link on the CTSU website in the Data Management section under the Rave Home tab and then under Rave Resource Materials. • **Important: Failure to complete required fields in STS may result in a delay in sample processing.** Any case reimbursements associated with sample submissions will not be credited if samples requiring STS submission are not logged into STS. Detailed instructions on use of the STS can be found in Section **Error! R eference source not found.**. **PI Response: Completed**

#	Section	Comments
9.	**4.3.3** **Page 43**	***Please revise the Theradex Helpdesk number as indicated below.*** Theradex has developed a Slot Reservations and Cohort Management User Guide, which is available on the Theradex website: http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11 This link to the Theradex website is also on the CTSU website OPEN tab. For questions about the use of IWRS for slot reservations, contact the Theradex Helpdesk at 855-828-6113 ~~609-619-7802~~ or Theradex main number 609-799-7580; CTMSSupport@theradex.com. **PI Response: Completed**
10.	**5.2** **Page 44**	Based on the recent PK data, KRT-232 (AMG-232) can now be taken with or without food. Please revise the administration guidance to **take with a glass of water with or without food.** **PI Response: Completed**
11.	**Appendix E** **Pages 117-118**	[redacted] **PI Response: Completed**

NCI Protocol #: **10076**

Local Protocol #: NCI10076

ClinicalTrials.gov Identifier: NCT03031730

TITLE: A PHASE 1 DOSE-ESCALATION AND EXPLORATORY DOSE EXPANSION STUDY OF KRT-232 (AMG 232) IN COMBINATION WITH CARFILZOMIB, LENALIDOMIDE, AND DEXAMETHASONE IN RELAPSED AND/OR REFRACTORY MYELOMA

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Participating Organizations

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LAO-11030 / University Health Network Princess Margaret Cancer Center LAO
LAO-CT018 / Yale University Cancer Center LAO
LAO-MA036 / Dana Farber – Harvard Cancer Center LAO
LAO-MD017 / JHU Sidney Kimmel Comprehensive Cancer LAO
LAO-OH007 / Ohio State University Comprehensive Cancer Center LAO
LAO-PA015 / UPMC Hillman Cancer Center LAO
LAO-TX035 / University of Texas MD Anderson Cancer Center LAO
LAO-NCI / National Cancer Institute LAO

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NCI-Supplied Agent: KRT-232 (AMG 232) (NSC 789723)

Other Agent(s): Carfilzomib (NSC 756640, Commercial)
Lenalidomide (NSC 703813, Commercial)
Dexamethasone (NSC 34521, Commercial)

IND #: 134935
IND Sponsor: DCTD, NCI

Protocol Type / Version # / Version Date:
Original/Version Date: 12/1/2016
Revision/Version Date: 01/31/2017
Revision/Version Date: 03/23/2017
Revision/Version Date: 06/09/2017
Revision/Version Date: 06/26/2017
Revision/Version Date: 07/11/2017
Revision/Version Date: 10/12/2017
Revision/Version Date: 02/08/2018
Revision/Version Date: 06/07/2018
Revision/Version Date: 08/03/2018
Revision/Version Date: 08/17/2018
Revision/Version Date: 11/06/2018
Revision/Version Date: 05/23/2019
Revision/Version Date: 07/30/2019
Revision/Version Date: 09/23/2019
Revision/Version Date: 02/06/2020
Revision/Version Date: 07/02/2020
Revision/Version Date: 08/04/2020
Revision/Version Date: 02/23/2021
Revision/Version Date: 12/07/2021
Revision/Version Date: 01/24/2022

PROTOCOL SYNOPSIS

Study Title:	Phase 1 Dose-Escalation and Exploratory Dose Expansion Study of KRT-232 (AMG 232) in Combination with Carfilzomib, Lenalidomide, and Dexamethasone (KRd) in Relapsed and/or Refractory Multiple Myeloma
IND Number:	134935
Investigational Product:	KRT-232 (AMG 232)
Study Phase:	Phase 1
Study Sponsor:	Cancer Therapy Evaluation Program (CTEP)
Indication:	Relapsed or refractory multiple myeloma with one to three lines of prior therapy
Study Objectives:	**Part A: Dose-escalation** **Primary Objectives:** 1) Evaluate safety and tolerability of KRT-232 (AMG 232) in combination with carfilzomib, lenalidomide, and dexamethasone (KRd). 2) Determine the Maximum Tolerated Dose (MTD) and Recommended Phase 2 Dose (RP2D) of KRT-232 (AMG 232) in combination with carfilzomib, lenalidomide, and dexamethasone (KRd). **Secondary Objectives:** 1) Evaluate PD effects of KRT-232 (AMG 232) through serum MIC-1 levels. 2) Assess KRT-232 (AMG 232) exposure-response relationships (PD, toxicity, and efficacy) **Exploratory Objectives:** 1) Evaluate the overall response rate of KRT-232 (AMG 232) in combination with carfilzomib, lenalidomide, and dexamethasone (KRd) in relapsed/refractory myeloma by International Myeloma Working Group (IMWG) criteria (Kumar et al., 2016). 2) Evaluate RNA expression levels of relevant genes in the *TP53* pathway that may predict response to therapy using pre- and post-treatment bone marrow biopsies. **Part B: Dose-expansion** **Primary Objectives:** 1) Confirm the safety and tolerability of KRT-232 (AMG 232) in combination with carfilzomib, lenalidomide, and dexamethasone (KRd) at MTD/tentative RP2D in a goal of 10 subjects with relapsed and/or refractory myeloma **Secondary Objectives:** 1) Evaluate the overall response rate of KRT-232 (AMG 232) in combination with carfilzomib, lenalidomide, and dexamethasone (KRd) in relapsed/refractory myeloma by International Myeloma Working Group (IMWG) criteria (Kumar et al., 2016). 2) Evaluate PD effects of KRT-232 (AMG 232) through serum MIC-1 levels. 3) Assess KRT-232 (AMG 232) exposure-response relationships (PD, toxicity, and efficacy)

	Exploratory Objectives: 1) Evaluate RNA expression levels of relevant genes in the *TP53* pathway that may predict response to therapy using pre- and post-treatment bone marrow biopsies**.**
Study Design:	This will be a two-part Phase 1 dose-escalation and exploratory dose-expansion study of KRT-232 (AMG 232) in combination with carfilzomib, lenalidomide, and dexamethasone (KRd) in relapsed and/or refractory *TP53* WT myeloma subjects with 1-3 lines of prior therapy. Part A will consist of a dose-escalation phase of KRT-232 (AMG 232) to assess its safety and tolerability and identify an MTD/tentative RP2D in combination with KRd. After the MTD has been established, Part B of the study will involve an exploratory-dose expansion study of a goal of 10 additional subjects with relapsed and/or refractory myeloma who will be enrolled at the tentative RP2D. Due to the timely need to initiate treatment in relapsed myeloma, *TP53* mutation status at screening is NOT required prior to KRT-232 (AMG 232) dosing. However, subjects found to have *TP53* mutation and/or deletion from screening bone marrow biopsy will be removed from study after C1 and continue on standard-of-care KRd alone. Toxicity monitoring of such subjects removed from active therapy with KRT-232 (AMG 232) will continue as described in the Treatment Plan. During the dose-expansion phase, subjects removed from study after Cycle 1 based on the *TP53* mutation and/or deletion status will be replaced to ensure that a goal of 10 subjects with TP53 wild-type status are enrolled in the dose-expansion cohort. **Treatment Plan:** *Dose Regimen* KRT-232 (AMG 232) + carfilzomib, lenalidomide, and dexamethasone (KRd) will be administered per the following schedule: Cycles 1-12 (28 day cycle) • KRT-232 (AMG 232) once daily by mouth 7 out of 28 days • Carfilzomib 20 mg/m^2 IV on Days 1 and 2 of Cycle 1, escalating to 27 mg/m^2 IV on Days 8, 9, 15, 16 of Cycle 1 and continuing on Days 1, 2, 8, 9, 15, 16 of Cycles 2 through Cycle 12 • Lenalidomide 25 mg PO on Days 1-21 • Dexamethasone 40 mg PO or IV on Days 1, 8, 15, and 22 Cycles 13-18 (28 days each) • KRT-232 (AMG 232) once daily by mouth 7 out of 28 days • Carfilzomib 27 mg/m2 IV on Days 1, 2, 15, and 16 • Lenalidomide 25 mg PO on Days 1-21 • Dexamethasone 40 mg PO or IV on Days 1, 8, 15, and 22 Cycles 19+ (28 days each) • KRT-232 (AMG 232) once daily by mouth 7 out of 28 days • Lenalidomide 25 mg PO on Days 1-21 • Dexamethasone 40 mg PO or IV on Days 1, 8, 15, and 22 *Part A (Dose-escalation scheme)* The MTD is defined as the highest dose at which six subjects have been treated and less than two subjects experienced DLT within the first cycle of treatment in Phase I

of the trial. To determine the MTD, escalation for KRT-232 (AMG 232) will be conducted following the "3+3" design with de-escalation. A cohort of three subjects will be treated at the starting dose level and observed until the end of the first cycle (subjects non-evaluable for DLT will be replaced). The dose level will be escalated with each new cohort until at least one out of three subjects of a cohort experiences DLT. If one subject experiences a DLT, then three additional subjects will be treated at the same dose level; if none of the three additional subjects experiences a DLT, then the dose escalation will be continued by treating the next cohort of three subjects at the next higher dose level. If at least two out of up to six subjects at a dose level experience a DLT, the MTD will be considered to have been exceeded, and up to 3 more subjects will be treated at the next lower dose if there are less than 6 subjects already treated at that dose. The dose steps for escalation are displayed below:

Dose-Escalation Schedule	
Dose Level	**KRT-232 (AMG 232) Dose**
- 1	30 mg/day PO x 7 days out of 28 day cycle
+ 1	60 mg/day PO x 7 days out of 28 day cycle
+ 2	90 mg/day PO x 7 days out of 28 day cycle
+ 3	120 mg/day PO x 7 days out of 28 day cycle
+ 4	180 mg/day PO x 7 days out of 28 day cycle
+ 5	240 mg/day PO x 7 days out of 28 day cycle

If dose-de-escalation is needed for Dose level 1, Dose level -1 is defined as 30 mg/day x 7 days out of 28 day cycle.

Part B (Dose-expansion scheme)

After determination of the KRT-232 (AMG 232) MTD or proven tolerability of the highest planned dose, a goal of 10 additional subjects will be treated in the Part 2 dose expansion in combination with KRd. The tentative RP2D will be determined based on the review of safety data at the MTD. The primary objective of this dose-expansion phase is to confirm the safety and tolerability of KRT-232 (AMG 232) + KRd at the MTD and tentative RP2D in a goal of 10 subjects with relapsed and/or refractory multiple myeloma.

Dose-Limiting Toxicity (DLT) Definition
A DLT is defined as any treatment emergent adverse event (TEAE) during the first treatment cycle that does not have a clear alternative cause (e.g., disease under study, concomitant therapy) based on the following criteria using NCI-CTCAE v5.0:

There should be no dose modifications of KRT-232 (AMG 232) and KRd during the DLT-evaluable period (Cycle 1). Subjects requiring dose-reductions during the DLT-evaluable period will be considered a DLT.

For hematologic events, a DLT is defined as follows:

- Grade 3 or 4 neutropenia with fever $\geq 38^0$ C lasting > 48 hours

	• Grade 4 neutropenia lasting > 7 days • Grade 3 or 4 thrombocytopenia associated with > grade 1 bleeding. Grade 4 thrombocytopenia that persists for > 14 days, despite holding treatment • Grade 4 anemia, unexplained by underlying disease • Any other grade 4 hematologic toxicity that does not resolve to subject's pre-treatment baseline level within 72 hours For non-hematologic events, a DLT is defined as follows: • Grade ≥ 3 nausea, vomiting or diarrhea lasting longer than 72 hours despite optimal medical support • Grade ≥ 3 non-hematological toxicity (excluding increased serum creatinine, or electrolyte abnormalities that are not clinically significant and require no treatment) • Any grade 3 electrolyte abnormalities that do not resolve to grade ≤2 within 72 hours • Grade 3 fatigue persisting > 7 days • Grade ≥ 3 acute kidney injury (creatinine > 3 × baseline or > 4.0 mg/dL) lasting > 72 hours • Any other grade 3 or 4 non-hematologic toxicities not predefined above will be considered a DLT. • A delay of ≥ 14 days in commencing Cycle 2 Day 1 due to lack of adequate recovery of KRT-232 (AMG 232) +KRd-related toxicities will be considered a DLT. Subjects who receive < 75% of the planned study drug doses during the first cycle of (i.e. ≤ 5/7 daily doses of KRT-232 (AMG 232) will considered nonevaluable for purposes of determining the MTD (unless due to a DLT) and will be replaced. Subjects who experience a DLT during the DLT-evaluable period will be considered evaluable for the purposes of determining the MTD as per Section 13.1.4.
Study Duration:	Subjects will receive KRT-232 (AMG 232) + KRd at a dose defined by the treatment outline above. This therapy will be continued without a cap on the number of allowed cycles, unless one of the following occurs: • Disease progression by IMWG criteria (Appendix 15.6). • Unacceptable adverse event(s) defined as: o Occurrence of an AE that is related to treatment with the study drug which, in the judgment of the investigator, compromises the subject's ability to continue study-specific procedures, or is considered to not be in the subject's best interest. o Persistent AE requiring a delay of therapy for more than 4 weeks (28 days) • Subject decides to withdraw from the study • Pregnancy o All women of child bearing potential should be instructed to contact

	the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation. o The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a subject participating in the study. • Termination of the study by sponsor • The drug manufacturer can no longer provide the study agent • Subject achieves complete remission (CR), and the subject and investigator feel that discontinuation of KRT-232 (AMG 232) + KRd is in the subject's best interests, or • Subject achieves a level of response that qualifies him or her for another therapy, such as high dose therapy with autologous stem cell transplantation, and the subject and investigator feel that discontinuation of KRT-232 (AMG 232) + KRd is in the subject's best interests At the completion or early discontinuation of treatment, subjects will be followed for an additional 30 days after the last administration of treatment or up until the initiation of the next line of treatment, whichever comes first. Subjects with adverse events until the event has resolved or the condition has stabilized.
Subject Eligibility Criteria:	**Key Inclusion Criteria:** 1. Subjects must have histologically confirmed diagnosis of multiple myeloma. 2. Subjects must have measurable disease, as defined by at least one of the following: a. Serum monoclonal protein M-protein level ≥0.5 g/dL b. Urinary M-protein excretion of ≥200 mg over a 24-hour period c. Involved free light chain level ≥10 mg/dL, along with an abnormal free light chain ratio 3. Subjects must have disease that has relapsed and/or refractory after their most recent therapy, with progressive disease (PD) being defined as an increase of 25% from the lowest response value in any one or more of the following: a. Serum M-component protein (the absolute increase must be ≥0.5 g/dL) and/or b. Urine M-component protein (the absolute increase must be ≥200 mg/24 hours) and/or c. Only in subjects without a measurable serum and urine M protein level: the difference between involved and uninvolved free light chain (FLC) levels (absolute increase) must be >10 mg/dL d. Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas e. Development of hypercalcemia (corrected serum calcium >11.5 mg/dL) that can be attributed solely to the plasma cell proliferative disorder.

	4. Subjects with one to three lines of therapy for their disease, with a line of therapy defined as one or more cycles of a planned treatment program. Using this definition, treatment with induction therapy, followed by high dose chemotherapy and autologous stem cell transplantation, and finally by maintenance therapy, would constitute one line, provided that multiple myeloma did not meet criteria for progression at any time during this period. 5. Subjects must have completed their most recent drug therapy directed at multiple myeloma in the following timeframes: a. Antitumor therapy (chemotherapy, antibody therapy, molecular targeted therapy, retinoid therapy, hormonal therapy, or investigational agent) at least 21 days prior to C1D1 KRT-232 (AMG 232) + KRd. b. Corticosteroids at least 3 weeks prior to starting KRT-232 (AMG 232) + KRd, except for a dose equivalent to dexamethasone of ≤4 mg/day c. Autologous stem cell transplantation at least 12 weeks prior to starting KRT-232 (AMG 232) + KRd d. Allogeneic stem cell transplantation at least 24 weeks prior to starting KRT-232 (AMG 232) + KRd, and these subjects must also NOT have moderate to severe active acute or chronic graft versus host disease (GVHD). 6. Subjects must be ≥ 18 years old. Because no dosing or adverse event data are currently available on the use of KRT-232 (AMG 232) in combination with KRd, subjects < 18 years of age are excluded from this study. 7. Subjects must have ECOG performance status ≤ 2 (Karnofsky ≥ 60%, see Appendix A). 8. Subjects must have normal organ and marrow function as defined below: a. Absolute neutrophil count (ANC) ≥ 1,000/mcL without growth factors within 2 week of initiation of treatment b. Platelets ≥50,000 cells/mm^3 if marrow plasmacytosis < 50% OR platelet count ≥30,000 cells/mm^3 if marrow plasmacytosis ≥ 50%. c. Hemoglobin ≥8 g/dL within 2 weeks of the initiation of treatment d. Total bilirubin < 1.5 × institutional upper limit of normal (ULN) (< 2.0 × ULN for subjects with documented Gilbert's syndrome or < 3.0 × ULN for subjects for whom the indirect bilirubin level suggests an extrahepatic source of elevation) e. AST(SGOT)/ALT(SGPT) ≤ 2.5 × ULN f. Alkaline phosphatase < 2.0 × ULN (if liver or bone disease are present, < 3.0 × ULN) g. Creatinine clearance (eGFR) ≥ 50 mL/min/1.73 m^2 9. Subjects must have adequate coagulation laboratory assessments, as follows: Prothrombin time (PT) or partial thromboplastin time (PTT) < 1.5 × upper limit of normal (ULN), OR International normalized ratio (INR) < 1.5. 10. Subjects who have received radiation therapy targeting > 10% of the bone marrow space must have completed this at least 2 weeks prior to starting therapy with KRT-232 (AMG 232) + KRd. 11. Subjects must be able and willing to provide bone marrow biopsies/aspirates and buccal swab as requested by the protocol. 12. Subjects must be willing to undergo myeloma genotyping for *TP53* mutation, insertion, or deletion at screening.

13. Subjects must have an estimated life expectancy of at least 3 months.

14. The effects of KRT-232 (AMG 232) on the developing human fetus are unknown. For this reason and because lenalidomide is known to be teratogenic, women of child-bearing potential must commit to either abstaining continuously from heterosexual sexual intercourse or agree to use 2 forms of adequate contraception or continuously abstain from the time of informed consent for the duration of study participation through 5 weeks (women) after receiving the last dose of KRT-232 (AMG 232), lenalidomide, or carfilzomib. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 3 months after completion of KRT-232 (AMG 232) administration. This includes one highly effective form of contraception (e.g. intrauterine device [IUD], hormonal [birth control pills, injections, hormonal patches, vaginal rings or implants] or partner's vasectomy) and one additional effective contraceptive method (e.g. male latex or synthetic condom, diaphragm, or cervical cap).

15. Subjects must be able to swallow medication.

16. Ability to understand and the willingness to sign a written informed consent document.

Key Exclusion Criteria:

1. Subjects with myeloma that is relapsed and/or refractory to KRd when used in combination defined as progression of disease while on therapy or within 60 days of completing therapy.

2. Subjects must show evidence of wild-type (WT) p53 status on somatic tissue specimens as assessed by DNA sequencing. Note that since patients with relapsed myeloma have a rapidly proliferating disease, patient can be enrolled and begin treatment prior to obtaining the results of this test. Patients who are discovered to have a TP53 mutation will be removed from study after cycle one and can continue on carfilzomib, lenalidomide, and dexamethasone (KRd). All enrolled patients will be followed for toxicity.

3. Subjects who have not recovered from toxicities from prior anti-tumor therapy, defined as not having resolved to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 grade 0 or 1, or to levels dictated in the eligibility criteria with the exception of alopecia (Grade 2 or 3 toxicities from prior antitumor therapy that are considered irreversible [defined as having been present and stable for > 6 months], such as grade 2 chemotherapy-induced peripheral neuropathy, may be allowed if they are not otherwise described in the exclusion criteria AND there is agreement to allow by both the investigator and sponsor).

4. Subjects who are receiving any other investigational agents.

5. Subjects who have undergone major surgery within 28 days of study day 1. Vertebroplasty and/or kyphoplasty, which must have been performed at least 1 week prior to starting KRT-232 (AMG 232) + KRd

6. Subjects with known central nervous system involvement of myeloma should be excluded from this clinical trial because of their poor prognosis and because they

	often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events. 7. Subjects with history of allergic reactions attributed to compounds of similar chemical or biologic composition to KRT-232 (AMG 232) or carfilzomib, lenalidomide, or dexamethasone. 8. Subjects' medication list such a herbal medicines (*e.g.*, St. John's wort), vitamins, and supplements will be reviewed before starting first dose of KRT-232 (AMG 232) and at each clinic visit. Any potential drug interactions will be brought and discussed with the Principle Investigator. Use of any known CYP3A4 substrates with narrow therapeutic window (such as alfentanil, astemizole, cisapride, dihydroergotamine, pimozide, quinidine, sirolimus, or terfanide) within the 14 days prior to receiving the first dose of KRT-232 (AMG 232) is not permitted. Other medications (such as fentanyl and oxycodone) may be allowed per investigator's assessment/evaluation. 9. Treatment with medications known to cause QTc interval prolongation within 7 days of study day 1 unless is not permitted unless approved by the sponsor. Use of ondansetron is permitted for treatment of nausea and vomiting. 10. Current use of warfarin, factor Xa inhibitors and direct thrombin inhibitors. Note: Low molecular weight heparin and prophylactic low dose warfarin are permitted. PT/PTT must meet the inclusion criteria. Subjects taking warfarin must have their INR followed closely. 11. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements. Subjects with myocardial infarction within 6 months of study day 1, symptomatic congestive heart failure (New York Heart Association (NYHA) Class III and higher), unstable angina, or cardiac arrhythmia requiring medication are excluded. 12. Subjects with GI tract disease causing the inability to take oral medication, malabsorption syndrome, requirement for intravenous alimentation, prior surgical procedures affecting absorption, uncontrolled inflammatory GI disease (e.g., Crohn's disease, ulcerative colitis). 13. Subjects with history of bleeding diathesis. 14. Subjects with active infection requiring IV antibiotics within 2 weeks of study enrollment (day 1) are excluded. 15. Positive Hepatitis B Surface Antigen (HepBsAg) (indicative of chronic Hepatitis B), positive Hepatitis total core antibody with negative HBsAG (suggestive of occult hepatitis B), or detectable Hepatitis C virus RNA by a polymerase-chain reaction (PCR) assay (indicative of active Hepatitis C – screening is generally done by Hepatitis C Antibody (HepCAb), followed by Hepatitis C virus RNA by PCR if HepCAb is positive). Subjects with hepatitis B virus suppressed on

	therapy, and previously treated/eradicated hepatitis C virus are eligible for study. 16. Subjects positive for human immunodeficiency virus (HIV) are NOT excluded from this study, but HIV-positive subjects must have: a. A stable regimen of highly active anti-retroviral therapy (HAART) b. No requirement for concurrent antibiotics or antifungal agents for the prevention of opportunistic infections. c. A CD4 count above 250 cells/mcL and an undetectable HIV viral load on standard PCR-based test 17. Men and women of reproductive potential who are unwilling to practice acceptable methods of effective birth control while on study through 5 weeks (women) or 3 months (men) after receiving the last dose of KRT-232 (AMG 232). Acceptable methods of effective birth control include sexual abstinence (men, women); vasectomy; or a condom with spermicide (men) in combination with barrier methods, hormonal birth control or IUD (women). 18. Pregnant women are excluded from this study because KRT-232 (AMG 232) is an agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with KRT-232 (AMG 232), breastfeeding should be discontinued if the mother is treated with KRT-232 (AMG 232). These potential risks may also apply to other agents used in this study. 19. Women who are lactating/breast feeding or who plan to breastfeed while on study through 1 week after receiving the last dose of study drug. 20. Subjects with prior treatment with an MDM2 inhibitor.
Sample Size:	The Dose Escalation phase of this study (Part 1) consists of 5 dose levels including at least 3 and up to 6 subjects for a minimum of 15 subjects if no DLT is reached, or a maximum of 30 subjects. An exploratory expansion phase with a goal enrollment of 10 subjects at the recommended phase 2 dose is also planned for a total in both phases of 25-40 subjects. During the dose-expansion phase, subjects removed from study after Cycle 1 based on the *TP53* mutation and/or deletion status will be replaced to ensure that a goal of 10 subjects with TP53 wild-type status are enrolled in the dose-expansion cohort. Based on prior phase I and II studies at MDACC targeting a similar subject population, we estimate 1.5 subjects will be accrued every month, suggesting that 16-26 months will be needed to meet the sample size. Please note this assumes no interruption in accrual. For the Dose Expansion phase (Part 2), a goal of 10 additional subjects will be enrolled. The maximum half width of the 95% confidence interval for the response rate will be 32% for 10 subjects. Including the 6 subjects enrolled at the MTD in the Part I (dose-escalation phase), the maximum half width of the 95% confidence interval for 16 subjects will be 25%.
Statistical Considerations:	The primary analysis is to assess the safety and tolerability of KRT-232 (AMG 232) + KRd in subjects with relapsed and/or refractory myeloma and to determine the MTD/tentative RP2D of KRT-232 (AMG 232) + KRd. All subjects who receive any amount of the study drug will be evaluable for toxicity. The DLT-evaluable period will be during cycle 1, although toxicity will be monitored throughout the course of treatment. The primary analysis will occur after all subjects in Part B have either discontinued the study or completed at least 6 months of treatment.

	Descriptive statistics will be provided for selected demographic, safety, PK, and PD data by dose and time as appropriate. Descriptive statistics on continuous data will include means, medians, standard deviations, and ranges, while categorical data will be summarized using frequency counts and percentages. Graphical summaries of the data may be presented. A full pharmacokinetic profile of KRT-232 (AMG 232) will be proposed in this protocol to assess exposure-response relationships with various PD endpoints (i.e., MIC-1 changes, toxicity, efficacy). KRT-232 (AMG 232) concentrations in these samples will be quantitatively measured using liquid chromatography/tandem mass spectrometric (LC/MS/MS) method that will be developed by the Analytical Pharmacology Core Laboratory at the Sidney Kimmel Comprehensive Cancer Center (SKCCC) at Johns Hopkins. For KRT-232 (AMG 232), the individual PK parameters from a single dose will be estimated for C_{max}, AUC, $T_{1/2}$, apparent Cl/F, and apparent V/F using non-compartmental or compartmental PK methods with the software WinNonlin. For serum MIC-1 levels, each individual level will be normalized to the baseline level for that subject. Advanced population PK methods may be employed to assess the link between drug exposure and biological effects and efficacy. The PK variables and changes in MIC-1 will be tabulated and descriptive statistics (e.g., geometric means and coefficients of variation) calculated for each dose level. PK parameters (i.e., $T_{1/2}$, Cl, and AUC) and MIC-1 changes will be compared across dose level using nonparametic statistical testing techniques. Exploratory correlative studies with pharmacodynamic (biological endpoints, toxicity and efficacy) will be analyzed using nonparametric statistics. Significance for comparisons will be at the $p<0.05$ level. Efficacy analysis will be performed for all subjects in the dose escalation and dose expansion part of the study. Separate efficacy analyses will be performed on the *full analysis set* which includes all subjects enrolled on study, and the *primary analysis set* which includes only subjects who were biomarker positive (*TP53* WT). Parameters assessed will include minimal residual disease (MRD) negative, stringent complete response (sCR), complete response (CR), very good partial response (VGPR), and partial response (PR), minimal response (MR), and stable disease (SD) per IMWG Uniform Response criteria. In addition, overall response rate (defined as greater than or equal to PR across all cycles of treatment), response duration, time-to-response (TTR), PFS, and OS will be assessed. Best overall response categories will be tabulated by dose cohort and overall for the IMWG categories of MRD-negative, sCR, CR, VGPR, PR, MR, SD, progressive disease, and relapse. A two-sided 95% exact binominal CI will be calculated for each category. The myeloma response rate (responses ≥PR) will also be tabulated by dose cohort and overall. Time-to-event analyses will be done using Kaplan-Meier analyses and will include time to response, duration of response, progression-free survival (PFS), and overall survival (OS), as data allow. If there is not enough data to apply the Kaplan-Meier test, the data will be summarized by descriptive statistics.

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1. OBJECTIVES

1.1. Part A: Dose-Escalation

1.1.1. Primary Objective

1) Evaluate safety and tolerability of KRT-232 (AMG 232) in combination with carfilzomib, lenalidomide, and dexamethasone (KRd).
2) Determine the Maximum Tolerated Dose (MTD) and Recommended Phase 2 Dose (RP2D) of KRT-232 (AMG 232) in combination with carfilzomib, lenalidomide, and dexamethasone (KRd)

1.1.2. Secondary Objectives

1) Evaluate PD effects of KRT-232 (AMG 232) through serum MIC-1 levels.
2) Assess KRT-232 (AMG 232) exposure-response relationships (PD, toxicity, and efficacy).

1.1.3. Exploratory Objectives

1) To observe and record anti-tumor activity of KRT-232 (AMG 232) in combination with carfilzomib, lenalidomide, and dexamethasone (KRd) in relapsed/refractory myeloma by International Myeloma Working Group (IMWG) criteria. Although the clinical benefit of KRT-232 (AMG 232) has not yet been established, the intent of offering this treatment is to provide a possible therapeutic benefit, and thus the subject will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability.
2) Evaluate RNA expression levels of relevant genes in the *TP53* pathway that may predict response to therapy using pre- and post-treatment bone marrow biopsies.

1.2. Part B: Dose-expansion

1.2.1. Primary Objectives:

1) Confirm the safety and tolerability of KRT-232 (AMG 232) in combination with carfilzomib, lenalidomide, and dexamethasone (KRd) at MTD/tentative RP2D in a goal of 10 subjects with relapsed and/or refractory myeloma

1.2.2. Secondary Objectives:

1) Evaluate the overall response rate of KRT-232 (AMG 232) in combination with carfilzomib, lenalidomide, and dexamethasone (KRd) in relapsed/refractory myeloma by International Myeloma Working Group (IMWG) criteria (Kumar et al., 2016).
2) Evaluate PD effects of KRT-232 (AMG 232) through serum MIC-1 levels.
3) Assess KRT-232 (AMG 232) exposure-response relationships (PD, toxicity, and efficacy)

1.2.3. Exploratory Objectives:

1) Evaluate RNA expression levels of relevant genes in the *TP53* pathway that may predict response to therapy using pre- and post-treatment bone marrow biopsies**.**

2. BACKGROUND

2.1. Multiple Myeloma

Multiple myeloma is currently the second most common hematologic malignancy with over 30,000 cases diagnosed annually in the United States (Dimopoulos et al., 2016). It is characterized by a malignant proliferation of plasma cells and can lead to significant morbidity and mortality due to its effect on multiple organ systems. The clinical signs and symptoms myeloma can vary, but most commonly involve bone pain due to myeloma-induced lytic bone lesions, anemia due to infiltration of plasma cell in the bone marrow, renal failure due to light chain cast nephropathy, and hypercalcemia. Despite improvements in subject outcomes with the introduction of novel agents such as bortezomib and lenalidomide over the last decade, myeloma remains incurable (Kumar et al., 2008). Eventual emergence of drug resistance continues to be a significant challenge that most subjects will encounter during their treatment course, highlighting the clear need and recognized approval path for new drugs that are active in this disease.

2.2. MDM2 regulation of *TP53*

The tumor suppressor protein 53 (p53) encoded by the TP53 gene plays a critical role in preventing cancer development in response to DNA damage and cellular stress by activating the transcription of numerous genes involved in cell cycle arrest, apoptosis, senescence, and DNA repair (Levine and Oren, 2009; Vazquez *et al.*, 2008). It has been suggested that inactivation of the p53 pathway may be required for tumor formation and survival (Vogelstein *et al.*, 2000). Approximately 50% of all human cancers have mutant p53 ($p53^{mut}$) resulting in attenuation or loss of p52 function (Rew and Sun, 2014). However, a large percentage of tumors with the wild-type p53 ($p53^{WT}$) also display a reduced p53 function, which is due to mutations or alterations in other members of the p53 pathway (Rew and Sun, 2014; Vazquez *et al.*, 2008). For example, overexpression of MDM2 by gene amplification is common in human cancers. MDM2 is a negative regulator of p53 that inhibits p53 activity by 1) directly binding to the N-terminal transcriptional activation domain of p53 and thus blocking p53 activity, 2) promoting export of p53 from the nucleus to the cytoplasm, and 3) targeting p53 for the proteasomal degradation through the MDM2 E3 ubiquitin ligase activity. Disruption of the binding of MDM2 to p53 blocks all three mechanisms and leads to reactivation of p53 in cancer cells. Therefore, neutralizing the MDM2-p53 protein-protein interaction by small molecule inhibitors may be an effective therapeutic strategy for treatment of $p53^{WT}$ tumors.

2.3. KRT-232 (AMG 232)

2.3.1. Non-Clinical Studies

Nonclinical Studies: Mechanism of Action and Activity

KRT-232 (AMG 232) is an orally (PO) bioavailable, selective small molecule inhibitor of MDM2 that blocks the protein-protein interaction between MDM2 and p53 (Investigator's Brochure, 2015; Rew and Sun, *et al*., 2014; Sun *et al.*, 2014). KRT-232 (AMG 232) neutralizes interaction between the human MDM2 and p53 with a 50% inhibition achieved at the concentration (IC_{50}) of 1.0 nM in a homogeneous time resolved fluorescence (HTRF)-based potency assay (15% human serum), and binds to human MDM2 with a dissociation constant (K_D) of 0.069 nM as measured in a Biacore direct-binding assay (Investigator's Brochure, 2015). KRT-232 (AMG 232) effectively inhibited proliferation of SJSA-1 human osteosarcoma cells *in vitro* (which displays MDM2 gene amplification and has $p53^{WT}$) at IC_{50}=9.1 nM, as assessed in a 5-ethynyl-2'-deoxyuridine (EdU) cell proliferation assay (Sun *et al.*, 2014). KRT-232 (AMG 232) demonstrated robust antitumor activity *in vivo*, resulting in dose-dependent reduction in tumor growth with half-maximal effective dose (ED_{50}) of 9.1 mg/kg in the SJSA-1 xenograft mouse model following 14-day PO once daily (QD) dosing. Complete tumor regression was observed in 10 of 12 animals at a dose of 60 mg/kg. Activation of p53 signaling was determined by induction of p21 mRNA, which is a direct transcriptional target of p53 in three $p53^{WT}$ tumor cell lines, *i.e*., SJSA-1, HCT116 (non-amplified MDM2 colorectal [CRC] cell line), and ACHN (renal carcinoma) (Canon *et al*., 2015). KRT-232 (AMG 232) increased p21 mRNA levels in these cell lines 34.9-, 9.8-, and 11.5-fold, respectively. KRT-232 (AMG 232)-mediated induction of p21 mRNA was also tested *in vivo* in the SJSA-1 xenograft murine model; animals receiving only a vehicle served as negative control/baseline. KRT-232 (AMG 232) demonstrated a robust time and concentration-dependent induction of the p21 transcript in SJSA-1 tumors, with a 30-fold increase over the control observed 4 hours after the last dose in the group treated with 50 mg/kg PO QD for 4 days (Investigator's Brochure, 2015).

Selectivity of KRT-232 (AMG 232) antitumor activity for $p53^{WT}$ cells was examined via a 5-bromo-2'-deoxyuridine (BrdU) cell proliferation assay (Sun *et al.*, 2014). Following 16 h incubation, KRT-232 (AMG 232) substantially inhibited growth of $p53^{WT}$ HCT116 (IC_{50}=10 nM) compared to no growth inhibition observed in p53-deficient ($p53^{-/-}$) cell culture.

In vivo antitumor activity of KRT-232 (AMG 232) was also assessed in xenograft mouse models of various tumor types, which have $p53^{WT}$ and non-amplified MDM2, *i.e*., A375sq2 (mutant $BRAF^{V600E}$ melanoma), HCT116 (mutant KRAS CRC), and NCI-H460 (mutant KRAS non-small cell lung cancer [NSCLC]) (Canon *et al.*, 2015). KRT-232 (AMG 232) administered PO QD to mice demonstrated a 50% tumor growth inhibition over the vehicle control at a dose of 18 mg/kg (HCT116), 31 mg/kg (A375sq2), and 78 mg/kg (NCI-H460). These data highlight variable sensitivity among different tumor types with different genetic backgrounds beyond p53 WT status. Efforts are ongoing to develop profiles that might predict which tumors will respond best to this therapeutic approach (Investigator's Brochure, 2015).

Nonclinical Pharmacology

[redacted]

[redacted]

[redacted]

[redacted]No other metabolite of KRT-232 (AMG 232) was detected in the rat or monkey plasma.

[redacted]

[redacted]

[redacted]

[redacted] Overall, the nonclinical PK and drug metabolism data support the clinical testing of KRT-232 (AMG 232) in human subjects.

Nonclinical Toxicology

The potential toxicity of KRT-232 (AMG 232) was evaluated in 28-day repeat-dose studies in rats and cynomolgus monkeys (Investigator's Brochure, 2015). [redacted] All observed effects in rats and monkeys were reversible.

[redacted]

KRT-232 (AMG 232) has demonstrated appropriate preclinical PK and acceptable safety profile in rats and monkeys to support clinical development. [redacted]

2.3.2. Effects in Humans

Clinical Pharmacokinetics

As of September 25, 2015, [redacted] subjects were enrolled in the ongoing FIH study of KRT-232 (AMG 232) monotherapy in subjects with solid tumors or multiple myeloma (MM) sponsored by the company. Of 39 subjects treated in the dose-finding phase with KRT-232 (AMG 232) 15-480 mg PO QD for 7 days, 35 (all solid tumors) were evaluable for PK. The plasma concentration of KRT-232 (AMG 232) [redacted]

The PK profile of the major metabolite KRT-232 (AMG 232)-acyl-glucuronide was similar to that of the parent compound; the metabolite exposure was 40% of the parent compound.

Clinical Toxicity

Among 39 subjects treated in the dose-finding phase, [redacted] Further safety/tolerability is under evaluation at the MTD in an expansion cohort (n=27).

[redacted] There were no deaths related to treatment with KRT-232 (AMG 232).

[redacted]

Overall, main AMG 233-related AEs observed in humans included thrombocytopenia, neutropenia, GI toxicity (diarrhea, nausea, and vomiting), and fatigue. Based on data from

preclinical species, additional potential toxicity risks include pancreatic toxicity, muscle tissue toxicity, and male and female reproductive system toxicity.

2.4. Other Agent(s)

In this phase 1 study, KRT-232 (AMG 232) will be dose-escalated in combination with evaluated with carfilzomib, lenalidomide, and low-dose dexamethasone (KRd).

2.4.1. Carfilzomib

Carfilzomib is a second-generation proteasome inhibitor, was initially approved by the FDA in 2012 as a single-agent for the treatment of relapsed myeloma with at least two prior lines of therapy based on the Phase 2 PX-171-003-A1 study single-arm study (Siegel et al., 2012). Overall response rate (ORR, defined as ≥ PR) of 23.7%. Most common grade 3 and 4 AEs were hematologic (24% anemia, 29% thrombocytopenia, 11% neutropenia). Most frequent grade 3 and 4 non-hematologic AEs were fatigue (7.5%), pneumonia (9.4%), and hyponatremia (8.3%). Importantly, only 12.4% of subjects experienced any treatment-emergent peripheral neuropathy (PN), and only 3 (1.1%) subjects grade 3 PN which was a significant improvement compared to its predecessor bortezomib.

2.4.2. Lenalidomide and Dexamethasone

Lenalidomide, a second-generation oral immunomodulatory (IMiD) drug, was approved by the FDA in combination with dexamethasone in relapsed myeloma in 2006 based on a phase 3 randomized study of lenalidomide and high-dose dexamethasone versus high-dose dexamethasone (Weber et al., 2007). ORR was 61.0% in the lenalidomide arm versus 19.9% in dexamethasone monotherapy group. Most common grade 3 and 4 AEs in the lenalidomide and dexamethasone arm were hematologic (41.2% neutropenia, 13% anemia, and 14.7% thrombocytopenia), while the most common grade 3 and 4 non-hematologic AEs included infection (21.4%). Moreover, venous thromboembolism (VTE) occurred in 14.7% of subjects in the lenalidomide and dexamethasone arm. A subsequent study comparing lenalidomide with high-dose (40 mg on days 1-4, 9-12, and 17-20 on 28-day cycle) versus low-dose dexamethasone (40 mg on days 1, 8, 15, and 22 on 28-day cycle) showed a significant improvement in overall survival (OS) in the low-dose dexamethasone group compared to the high-dose dexamethasone group (96% vs. 87%, $P = 0.0002$), which was mainly attributable to a decrease incidence of infections with lower doses of glucocorticoids (Rajkumar et al., 2010). Moreover, there was significant reduction in VTEs observed with lenalidomide was in combination with low-dose dexamethasone versus the high-dose dexamethasone (26% vs. 12%). Therefore, it is recommended that lenalidomide be administered in combination with low-dose dexamethasone.

2.4.3. Carfilzomib, Lenalidomide, and Dexamethasone (KRd)

The combination of carfilzomib, lenalidomide, and dexamethasone (KRd) was studied in a phase 1 trial in relapsed and refractory myeloma (Niesvizky et al., 2013), where the MTD was not reached and the maximum planned dose (Dose Level 6) of KRd (Carflzomib 27 mg/m^2,

lenalidomide 25 mg, and dexamethasone 40 mg) was recommended for further study.. Based on the encouraging results of the safety, tolerability, and efficacy of this study and a subsequent phase 2 study (Wang et al., 2013), the combination of carfilzomib, lenalidomide, and low-dose dexamethasone (KRd) was then compared to lenalidomide and low-dexamethasone (Rd) in a phase 3 registration-enabling randomized study in relapsed myeloma patients with 1-3 lines of prior therapy (ASPIRE) (Stewart, 2015). In this study, KRd was administered per the following schedule:

Cycles 1-12 (28 day cycle)
Carfilzomib 20 mg/m^2 IV on Days 1 and 2 of Cycle 1, escalating to 27 mg/m^2 IV on Days 8, 9, 15, 16 of Cycle 1 and continuing on Days 1, 2, 8, 9, 15, 16 of Cycles 2 through Cycle 12
Lenalidomide 25 mg PO on Days 1-21
Dexamethasone 40 mg PO or IV on Days 1, 8, 15, and 22
Cycles 13-18 (28-day cycle)
Carfilzomib 27 mg/m^2 IV on Days 1, 2, 15, and 16
Lenalidomide 25 mg PO on Days 1-21
Dexamethasone 40 mg PO or IV on Days 1, 8, 15, and 22
Cycles 19+ (28-day cycle)
Lenalidomide 25 mg PO on Days 1-21
Dexamethasone 40 mg PO or IV on Days 1, 8, 15, and 22

Both ORR (87.1% vs. 66.7%) and PFS (26.3 vs. 17.6 months) were superior in the KRd arm compared to the Rd arm. Most common grade 3 or 4 AEs in the KRd arm were anemia (17.9%) neutropenia (29.6%) and thrombocytopenia (16.6%). Non-hematologic grade 3 or 4 AEs occurring in ≥ 5% of subjects included fatigue (7.7%) and hypokalemia (9.4%). Based on the positive results of this study, KRd was granted FDA approval in 2015 for subjects with relapsed myeloma with 1-3 lines of therapy, and established itself as a standard-of-care in this patient population.

2.5. Rationale of KRT-232 (AMG 232) + Carfilzomib, Lenalidomide, and Dexamethasone (KRd) in Multiple Myeloma

The auto-regulatory relationship between the tumor suppressor p53 (*TP53*) and its transcriptional target murine double minute 2 (MDM2) has been well established. In unstressed cells, MDM2 maintains low levels of p53 activity by directly inhibiting its transcriptional activity, and by targeting it for proteasomal-mediated degradation through its function as an E3 ubiquitin ligase. However, in the presence of stress signals such as DNA damage, attenuation of the p53 and MDM2 interaction leads to increased apoptosis through stabilization of p53. Alterations in the MDM2-p53 axis have also been implicated in tumorigenesis, as cell survival signals such as AKT, which promotes MDM2 nuclear levels or increase MDM2 binding to p53, resulting in decreased apoptosis and cell cycle arrest.

Thus, inhibition of the MDM2-p53 interaction may be an effective therapeutic strategy in tumors that retain wild-type (WT) p53 (Shangary and Wang, 2008; Wade et al., 2013). In particular, while *TP53* mutations have been implicated in the pathogenesis of more than fifty percent of all human cancers, myeloma represents a particularly attractive target for small molecule MDM2 inhibitors given its relatively low frequency of *TP53* mutations or deletions (Lohr et al., 2014; Walker et al., 2015).

Proof-of-principle of the encouraging activity of MDM2 inhibition in myeloma preclinical models was demonstrated in our group as part the NCI-funded MD Anderson Myeloma SPORE (Gu et al., 2014). The MDM2 inhibitor KRT-232 (AMG 232) (Amgen, Inc) has also shown promise in preclinical myeloma models both *in vitro* (Figure 1) and *in vivo* (Figure 2), with anti-myeloma activity strongly correlating with *TP53* WT status. Moreover, the combination of KRT-232 (AMG 232) with other FDA-approved myeloma agents including the immunomodulatory drug (IMiD) lenalidomide (Figure 3) or second generation proteasome inhibitor carfilzomib (Figure 4) shows synergistic activity when used in combination compared to the activity of either agent when used as monotherapy. Finally, the combination of KRT-232 (AMG 232), lenalidomide, and carfilzomib demonstrates additive to synergistic activity *in vitro* in *TP53* WT myeloma cells compared to KRT-232 (AMG 232) in combination with either lenalidomide or carfilzomib (Figure 5).

Several recent landmark studies have highlighted the clinical efficacy of novel drug combinations in relapsed and/or refractory myeloma that has transformed the therapeutic landscape in this subject population. Among these include the combination of carfilzomib, lenalidomide, and dexamethasone (KRd) as demonstrated in the pivotal ASPIRE trial where KRd demonstrated a significantly longer progression free survival (PFS) compared to Rd (26.3 months versus 17.6 months, *P* 0.0001), leading to the FDA approval of KRd in myeloma subjects with 1-3 lines of prior therapy (Stewart et al., 2015). Although never compared head-to-head, KRd also compares favorably to other recently FDA-approved 3-drug combinations evaluated in the same subject population, including elotuzumab, lenalidomide, and dexamethasone (PFS 19.4 months)(Lonial et al., 2015) and ixazomib, lenalidomide, and dexamethasone (PFS 20.6 months)(Moreau et al., 2016). Therefore, based on the promising preclinical activity KRT-232 (AMG 232), lenalidomide, and carfilzomib, we herein propose a phase 1 dose-escalation and exploratory expansion study of KRT-232 (AMG 232) + KRd with the anticipation that this combination will further improve upon the clinically validated KRd backbone in *TP53* WT relapsed and/or refractory myeloma.

Figure 1. KRT-232 (AMG 232) growth inhibition *in vitro in TP53* WT (MOLP-8, MM1.S, MM1.R, IM-9, H929) and *TP53* mutant (OPM-2, RPMI-8226, KMS-12-BM) myeloma cell lines (Amgen, Inc).

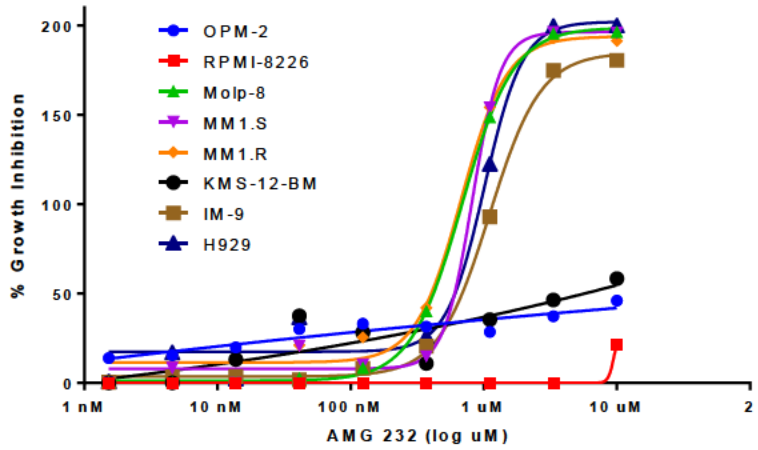


Figure 2. KRT-232 (AMG 232) growth inhibition in H929 *TP53* WT myeloma murine xenograft model (Amgen, Inc).

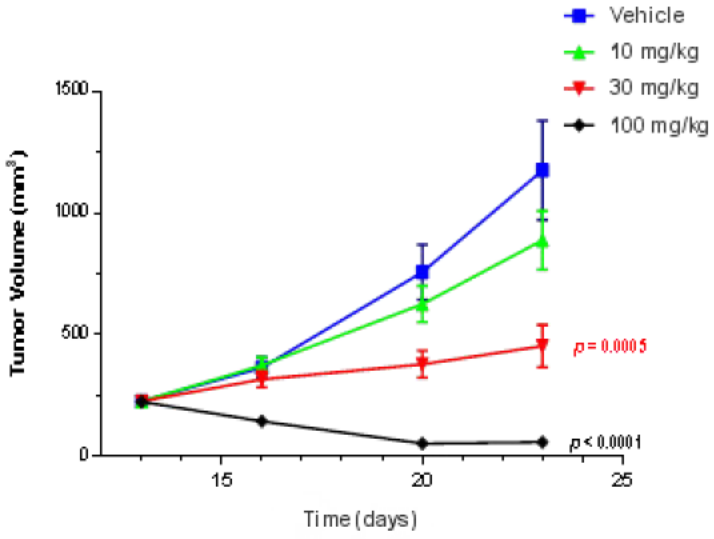


Figure 3. KRT-232 (AMG 232) + Lenalidomide in H929 *TP53* WT myeloma xenograft model. 4/10 mice in combination group exhibited complete regression of tumors (Amgen, Inc).

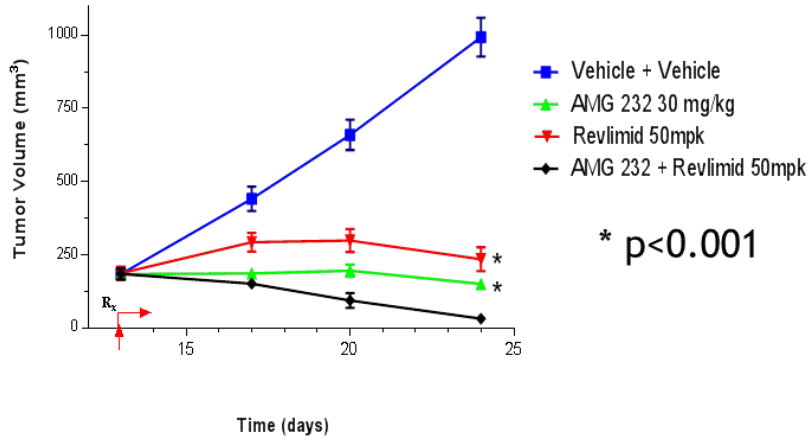


Figure 4. KRT-232 (AMG 232) + Carfilzomib in H929 *TP53* WT myeloma xenograft model. 4/10 mice in combination group exhibited complete regression of tumors (Amgen, Inc).

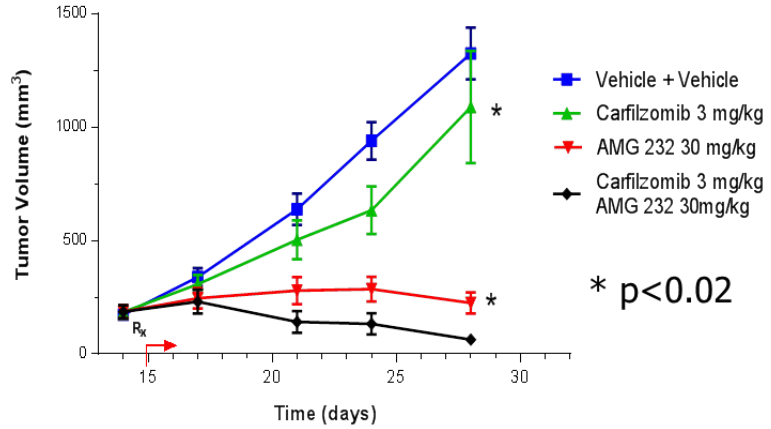
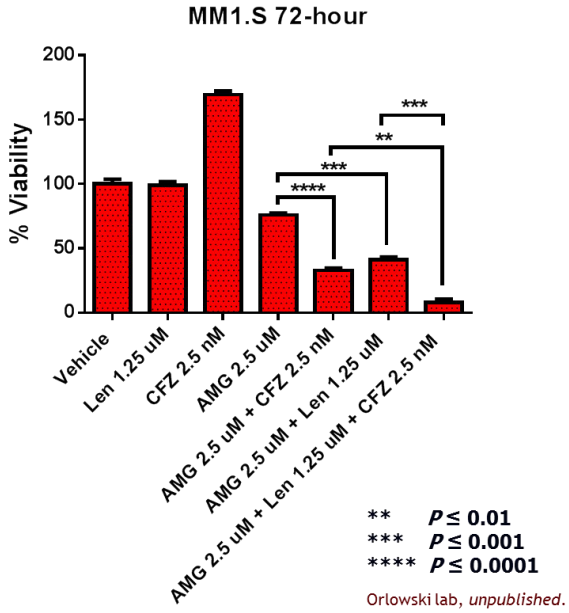


Figure 5. KRT-232 (AMG 232) + Lenalidomide + Carfilzomib in *TP53* WT MM1.S cell line.



2.6. Rationale of KRd + KRT-232 (AMG 232) Human Dosing

Dosing for the KRd backbone for the current proposed study is modeled after the Phase 3 ASPIRE study as described in Section 2.4, which was based on an earlier Phase 1 study where the MTD was not reached for KRd dosing (Niesvizky et al., 2013). Hence, KRd at these dose levels (carfilzomib 27 mg/m^2, lenalidomide 25 mg, and dexamethasone 40 mg) has an acceptable and well-studied safety profile. In practice, carfilzomib is often given at higher doses (36 mg/m^2) in combination with lenalidomide and dexamethasone, based on a phase 1/2 study of KRd in newly diagnosed multiple myeloma (Jakubowiak et al., 2012), which gives added confidence that the addition of KRT-232 (AMG 232) to the KRd backbone at its standard dosing will be feasible from a safety and tolerability standpoint.

Although the MTD of KRT-232 (AMG 232) was defined at 240 mg QD for 7 days on a 21-day cycle in the first-in-human (FIH) study of KRT-232 (AMG 232) in solid tumors (Section 2.2), the starting dose level of KRT-232 (AMG 232) for the current study will begin at 60 mg 7 days on a 28-day cycle to carefully evaluate for overlapping toxicities such as thrombocytopenia with the KRd backbone. Dose-escalation will occur using a standard 3+3 design with increasing dose levels of KRT-232 (AMG 232) at 90 mg, 120 mg, 180 mg, and 240 mg 7 days on a 28-day cycle, with the highest planned dose level 5 being comparable to the MTD in the first-in-human trial of KRT-232 (AMG 232) monotherapy. Using this standard 3+3 design, a DLT rate less than 33% would be considered acceptable.

2.7. Correlative Studies Background

2.7.1. *TP53* Genotyping

KRT-232 (AMG 232) is an inhibitor of MDM2, the E3 ubiquitin ligase of p53, and a central hypothesis of this clinical study is that the mechanism of action of KRT-232 (AMG 232) is dependent on having intact wild-type p53 to exert its anti-tumor effect. Therefore, *TP53* genotyping on plasma cells will be performed as an integral biomarker in this clinical study on pretreatment bone marrow aspirates that will be performed at screening. Subjects with *TP53* mutations will be excluded from further participation in this study.

A number of preclinical studies have suggested that wild-type *TP53* may be a biomarker for response with the use of MDM2 inhibitors, including studies performed in myeloma (Gu et al., 2014). In the clinical setting, several studies have been reported to-date evaluating the use of MDM2 inhibition in various malignancies. In a phase 1 trial of RG7112, a small molecule inhibitor MDM2, in relapsed leukemias, *TP53* mutations were identified in 19 of 96 subjects tested, and all but two subjects failed to show any clinical response, suggesting that the presence of at least one wild-type TP53 allele is necessary for response. However, wild-type *TP53* alone was not sufficient to predict response to treatment in this study (Andreeff et al., 2016).

In this study, *TP53* genotyping will be performed by a CLIA laboratory test or NCI Molecular Characterization Laboratory (MoCha)

2.7.2. Pharmacokinetic and Pharmacodynamic Studies

Macrophage inhibitor cytokine-1 (MIC-1)

MIC-1, a secreted p53 transcriptional target, will be evaluated as an integrated pharmacodynamic biomarker for p53 pathway activation in response to MDM2 inhibition in this study. In preclinical studies, increases in MIC-1 levels were observed *in vitro* and *in vivo* in response to doxorubicin treatment, and correlated with increases in other downstream markers of p53 pathway activation (Yang et al., 2003).

In a clinical study with the MDM2 inhibitor RG7112 in liposarcoma, serum MIC-1 was been assessed as a pharmacodynamic marker using an ELISA at different time points and correlated with drug exposure levels of the study drug (Ray-Coquard et al., 2012). In preliminary analyses of clinical trial data, there was an exposure-response correlation observed between changes in serum MIC-1 levels and KRT-232 (AMG 232) exposure (both maximal (C_{max}) and total exposure (AUC) (KRT-232 (AMG 232) Investigators Brochure Date: 08 Dec. 2015).

In this study, serum MIC-1 testing will be performed using an ELISA-based assay at the ETCTN central laboratory of Dr. Michelle Rudek at Johns Hopkins University. For serum MIC-1 levels, each individual level will be normalized to the baseline level for that subject collected prior to KRT-232 (AMG 232) dosing.

KRT-232 (AMG 232) pharmacokinetic profile

These studies are necessary to characterize the exposure to KRT-232 (AMG 232). KRT-232 (AMG 232) is an orally bioavailable MDM2 inhibitor. In cancer subjects, KRT-232 (AMG 232) exposure is dose proportional over the dose range proposed in this LOI (KRT-232 (AMG 232)

Investigators Brochure Date: 08 Dec. 2015). [redacted]

In this protocol, KRT-232 (AMG 232) will be combined with carfilzomib, lenalidomide, and dexamethasone. Carfilzomib is primarily inactivated by pepitdases and hydrolysis with minor contributions by CYP450 isozymes (specific isozyme not listed). Lenalidomide is not metabolized by CYP450 but is a P-glycoprotein substrate. Dexamethasone is metabolized by CYP3A4 but does not have a narrow therapeutic window. Therefore concerns of a drug-drug interaction are minimal with the combination. Other narrow therapeutic window drugs predominantly cleared by CYP2C8 and/or CYP3A4 will be excluded.

KRT-232 (AMG 232) drug-exposure measurements will be quantitatively measured using liquid chromatography/tandem mass spectrometric (LC/MS/MS) method that will be developed by the Analytical Pharmacology Core Laboratory at the Sidney Kimmel Comprehensive Cancer Center (SKCCC) at Johns Hopkins in collaboration with Dr. Michelle Rudek. For KRT-232 (AMG 232), the individual PK parameters from a single dose will be estimated for C_{max}, AUC, $T_{1/2}$, apparent Cl/F, and apparent V/F using non-compartmental or compartmental PK methods with the software WinNonlin. Advanced population PK methods may be employed to assess the link between drug exposure and biological effects and efficacy. The PK variables and changes in MIC-1 will be tabulated and descriptive statistics (e.g., geometric means and coefficients of variation) calculated for each dose level. PK parameters (i.e., $T_{1/2}$, Cl, and AUC) and MIC-1 changes will be compared across dose level using nonparametic statistical testing techniques. Exploratory correlative studies with pharmacodynamic (biological endpoints, toxicity and efficacy) will be analyzed using nonparametric statistics. Significance for comparisons will be at the $p<0.05$ level.

2.7.3. Other myeloma gene sequencing

Whole exome sequencing of frequently mutated genes in multiple myeloma will be performed on plasma cells from the screening bone marrow aspiration as an exploratory biomarker for baseline characterization of subjects (Lohr et al., 2014; Walker et al., 2015), such as *KRAS*, *BRAF*, *NRAS*, and *FGFR3* by the NCI Molecular Characterization (MoCHa) Laboratory. While no definitive relationship between these mutations and prognosis has been established in multiple myeloma, mutations in NRAS may predict sensitivity to proteasome inhibitors such as bortezomib or carfilzomib (Mulligan et al., 2014).

In this study, whole exome sequencing will be performed by the NCI Molecular Characterization Laboratory (MoCha).

2.7.4. RNA expression of *TP53*-associated genes

As an exploratory study, RNA expression levels will be assessed as pharmacodynamics biomarkers for *TP53* pathway activation and to evaluate for potential biomarkers that may predict response to therapy with KRT-232 (AMG 232) in plasma cells from screening and post-treatment bone marrow aspirations. Genes of particular interest will be those relevant genes in the *TP53* pathway including *TP53*, *PUMA*, *BAX*, *p21*, *MDM2*, *MDM4*, *CDKN2A*, *Gadd45*, and *THBS1*. In a clinical study with the MDM2 inhibitor RG7112 in relapsed leukemias, increased baseline *MDM2* expression levels assessed by qRT-PCR positively correlated with clinical responses (Andreeff et al., 2016). In addition, *PUMA*, *Gadd45*, and *THBS1* expression levels have been associated with a "p53 target signature" in myeloma datasets in which high expression of these genes corresponds to an intact functional p53 pathway (Teoh et al., 2014). RNA sequencing will be performed by the NCI Molecular Characterization (MoCha) Laboratory.

3. SUBJECT SELECTION

3.1. Inclusion Criteria

3.1.1. Subjects must have histologically confirmed diagnosis of multiple myeloma.

3.1.2. Subjects must have measurable disease, as defined by at least one of the following:

a) Serum monoclonal protein M-protein level ≥0.5 g/dL
b) Urinary M-protein excretion of ≥200 mg over a 24-hour period
c) Involved free light chain level ≥10 mg/dL, along with an abnormal free light chain ratio

3.1.3. Subjects must have disease that has relapsed and/or refractory after their most recent therapy, with progressive disease (PD) being defined as an increase of 25% from the lowest response value in any one or more of the following:

a) Serum M-component protein (the absolute increase must be ≥0.5 g/dL) and/or
b) Urine M-component protein (the absolute increase must be ≥200 mg/24 hours) and/or
c) Only in subjects without a measurable serum and urine M protein level: the difference between involved and uninvolved free light chain (FLC) levels (absolute increase) must be >10 mg/dL
d) Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue

plasmacytomas

e) Development of hypercalcemia (corrected serum calcium >11.5 mg/dL) that can be attributed solely to the plasma cell proliferative disorder.

3.1.4. Subjects with one to three lines of therapy for their disease with a line of therapy defined as one or more cycles of a planned treatment program. Using this definition, treatment with induction therapy, followed by high dose chemotherapy and autologous stem cell transplantation, and finally by maintenance therapy, would constitute one line, provided that multiple myeloma did not meet criteria for progression at any time during this period.

3.1.5. Subjects must have completed their most recent drug therapy directed at multiple myeloma in the following timeframes:

a) Antitumor therapy (chemotherapy, antibody therapy, molecular targeted therapy, retinoid therapy, hormonal therapy, or investigational agent) at least 21 days prior to C1D1 KRT-232 (AMG 232) + KRd.
b) Corticosteroids at least 3 weeks prior to starting KRT-232 (AMG 232) + KRd, except for a dose equivalent to dexamethasone of ≤4 mg/day
c) Autologous stem cell transplantation at least 12 weeks prior to starting KRT-232 (AMG 232) + KRd
d) Allogeneic stem cell transplantation at least 24 weeks prior to starting KRT-232 (AMG 232) + KRd, and these subjects must also NOT have moderate to severe active acute or chronic graft versus host disease (GVHD).

3.1.6. Subjects must be ≥ 18 years old. Because no dosing or adverse event data are currently available on the use of KRT-232 (AMG 232) in combination with KRd, subjects < 18 years of age are excluded from this study.

3.1.7. Subjects must have ECOG performance status ≤ 2 (Karnofsky ≥ 60%, see Appendix A).

3.1.8. Subjects must have normal organ and marrow function as defined below:

a) Absolute neutrophil count (ANC) ≥ 1,000/mcL without growth factors within 2 week of initiation of treatment
b) Platelets ≥50,000 cells/mm^3 if marrow plasmacytosis < 50% OR platelet count ≥30,000 cells/mm^3 if marrow plasmacytosis ≥ 50%.
c) Hemoglobin ≥8 g/dL within 2 weeks of the initiation of treatment
d) Total bilirubin < 1.5 × institutional upper limit of normal (ULN) (< 2.0 × ULN for subjects with documented Gilbert's syndrome or < 3.0 × ULN for subjects for whom the indirect bilirubin level suggests an extrahepatic source of elevation)
e) AST(SGOT)/ALT(SGPT) ≤ 2.5 × ULN
f) Alkaline phosphatase < 2.0 × ULN (if liver or bone disease are present, < 3.0 × ULN)
g) Creatinine clearance (eGFR) ≥ 50 mL/min/1.73 m^2

3.1.9. Subjects must have adequate coagulation laboratory assessments, as follows:

Prothrombin time (PT) or partial thromboplastin time (PTT) < 1.5 × upper limit of normal (ULN), OR International normalized ratio (INR) < 1.5.

3.1.10. Subjects who have received radiation therapy targeting > 10% of the bone marrow space must have completed this at least 2 weeks prior to starting therapy with KRT-232 (AMG 232) + KRd.

3.1.11. Subjects must be able and willing to provide bone marrow biopsies/aspirates and buccal swab as requested by the protocol.

3.1.12. Subjects must be willing to undergo myeloma genotyping for *TP53* mutation, insertion, or deletion at screening.

3.1.13. Subjects must have an estimated life expectancy of at least 3 months.

3.1.14. The effects of KRT-232 (AMG 232) on the developing human fetus are unknown. For this reason and because lenalidomide is known to be teratogenic, women of child-bearing potential must commit to either abstaining continuously from heterosexual sexual intercourse or agree to use 2 forms of adequate contraception or continuously abstain from the time of informed consent for the duration of study participation through 5 weeks (women) after receiving the last dose of KRT-232 (AMG 232), lenalidomide, or carfilzomib. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 3 months after completion of KRT-232 (AMG 232) administration. This includes one highly effective form of contraception (e.g. intrauterine device [IUD], hormonal [birth control pills, injections, hormonal patches, vaginal rings or implants] or partner's vasectomy) and one additional effective contraceptive method (e.g. male latex or synthetic condom, diaphragm, or cervical cap).

3.1.15. Subjects must be able to swallow medication

3.1.16. Ability to understand and the willingness to sign a written informed consent document.

3.2. Exclusion Criteria

3.2.1. Subjects with myeloma that is relapsed and/or refractory to KRd when used in combination defined as progression of disease while on therapy or within 60 days of completing therapy.

3.2.2. Subjects must show evidence of wild-type (WT) p53 status on somatic tissue specimens as assessed by DNA sequencing. Note that since patients with relapsed myeloma have a rapidly proliferating disease, patient can be enrolled and begin treatment prior to obtaining the results of this test. Patients who are discovered to have a TP53 mutation will be removed from study after cycle one and can continue on carfilzomib, lenalidomide, and dexamethasone (KRd). All enrolled patients will be followed for toxicity.

3.2.3. Subjects who have not recovered from toxicities from prior anti-tumor therapy, defined as not having resolved to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 grade 0 or 1, or to levels dictated in the eligibility criteria with the exception of alopecia (Grade 2 or 3 toxicities from prior antitumor therapy that are considered irreversible [defined as having been present and stable for > 6 months], such as grade 2 chemotherapy-induced peripheral neuropathy, may be allowed if they are not otherwise described in the exclusion criteria AND there is agreement to allow by both the investigator and sponsor).

3.2.4. Subjects who are receiving any other investigational agents.

3.2.5. Subjects who have undergone major surgery within 28 days of study day 1. Vertebroplasty and/or kyphoplasty, which must have been performed at least 1 week prior to starting KRT-232 (AMG 232) + KRd

3.2.6. Subjects with known central nervous system involvement of myeloma should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

3.2.7. Subjects with history of allergic reactions attributed to compounds of similar chemical or biologic composition to KRT-232 (AMG 232) or carfilzomib, lenalidomide, or dexamethasone.

3.2.8. Subjects' medication list such a herbal medicines (*e.g*., St. John's wort), vitamins, and supplements will be reviewed before starting first dose of KRT-232 (AMG 232) and at each clinic visit. Any potential drug interactions will be brought and discussed with the Principle Investigator. Use of any known CYP3A4 substrates with narrow therapeutic window (such as alfentanil, astemizole, cisapride, dihydroergotamine, pimozide, quinidine, sirolimus, or terfanide) within the 14 days prior to receiving the first dose of KRT-232 (AMG 232) is not permitted. Other medications (such as fentanyl and oxycodone) may be allowed per investigator's assessment/evaluation.

3.2.9. Treatment with medications known to cause QTc interval prolongation within 7 days of study day 1 is not permitted unless approved by the sponsor. Use of ondansetron is permitted for treatment of nausea and vomiting.

3.2.10. Current use of warfarin, factor Xa inhibitors and direct thrombin inhibitors. Note: Low molecular weight heparin and prophylactic low dose warfarin are permitted. PT/PTT must meet the inclusion criteria. Subjects taking warfarin must have their INR followed closely.

3.2.11. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.12. Subjects with myocardial infarction within 6 months of study day 1, symptomatic congestive heart failure (New York Heart Association (NYHA) Class III and higher), unstable angina, or cardiac arrhythmia requiring medication are excluded.

3.2.13. Subjects with GI tract disease causing the inability to take oral medication, malabsorption syndrome, requirement for intravenous alimentation, prior surgical procedures affecting absorption, uncontrolled inflammatory GI disease (*e.g.*, Crohn's disease, ulcerative colitis).

3.2.14. Subjects with history of bleeding diathesis.

3.2.15. Subjects with active infection requiring IV antibiotics within 2 weeks of study enrollment (day 1) are excluded.

3.2.16. Positive Hepatitis B Surface Antigen (HepBsAg) (indicative of chronic Hepatitis B), positive Hepatitis total core antibody with negative HBsAG (suggestive of occult hepatitis B), or detectable Hepatitis C virus RNA by a polymerase-chain reaction (PCR) assay (indicative of active Hepatitis C – screening is generally done by Hepatitis C Antibody (HepCAb), followed by Hepatitis C virus RNA by PCR if HepCAb is positive). Subjects with hepatitis B virus suppressed on therapy, and previously treated/eradicated hepatitis C virus are eligible for study.

3.2.17. HIV-positive subjects positive for human immunodeficiency virus (HIV) are NOT excluded from this study, but HIV-positive subjects must have:

a) A stable regimen of highly active anti-retroviral therapy (HAART)
b) No requirement for concurrent antibiotics or antifungal agents for the prevention of opportunistic infections.
c) CD4 count above 250 cells/mcL and an undetectable HIV viral load on standard PCR-based test

3.2.18. Pregnant women are excluded from this study because KRT-232 (AMG 232) is an agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with KRT-232 (AMG 232), breastfeeding should be discontinued if the mother is treated with KRT-232 (AMG 232). These potential risks may also apply to other agents used in this study.

3.2.19. Women who are lactating/breast feeding or who plan to breastfeed while on study through 1 week after receiving the last dose of study drug.

3.2.20. Subjects with prior treatment with an MDM2 inhibitor.

3.3. Inclusion of Women and Minorities

NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf.

4. REGISTRATION PROCEDURES

4.1. Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five person registration types.
• IVR: MD, DO, or international equivalent,
• NPIVR: advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD),
• AP: clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System (RUMS), OPEN, Rave, acting as a primary site contact, or with consenting privileges, ~~(e.g., Roster Update Management System [RUMS], OPEN, Rave,),~~

• Associate (A): other clinical site staff involved in the conduct of NCI-sponsored trials, and
• Associate Basic (AB): individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✔	✔			
Financial Disclosure Form	✔	✔	✔		
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔		
GCP training	✔	✔	✔		
Agent Shipment Form (if applicable)	✔				
CV (optional)	✔	✔	✔		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

• Addition to a site roster,
• Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN,
• Act as the site-protocol Principal Investigator (PI) on the IRB approval, and
• Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators act as the Site-Protocol PI, (Investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the Clinical Investigator (CI) on the DTL must be rostered at the enrolling site with a participating organization.

Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the RCR Help Desk by email at RCRHelpDesk@nih.gov.

4.2. Site Registration

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval

Sites participating with the NCI Central Institutional Review Board (NCI CIRB) must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by emailing the email address above or calling 1-888-651-CTSU (2878).

In addition, the Site-Protocol PI (i.e., the investigator on the IRB/REB approval) must meet the following five criteria to complete processing of the IRB/REB approval record:
• Holds an Active CTEP status,
• Rostered at the site on the IRB/REB approval (applies to US and Canadian sites only) and on at least one participating roster,
• If using NCI CIRB, rostered on the NCI CIRB Signatory record,
• Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile, and
• Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional requirements to obtain an approved site registration status include:
• An active Federalwide Assurance (FWA) number,
• An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO), and
• Compliance with all protocol-specific requirements (PSRs).

4.2.1. Downloading Regulatory Documents

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a Participating Organization (PO) on the protocol. One way to search for a protocol is listed below.

• Log on to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password,
• Click on Protocols in the upper left of your screen
o Enter the protocol number in the search field at the top of the protocol tree, or
o Click on the By Lead Organization folder to expand, then select LAO-TX035, and protocol number 10076,
• Click on Documents, select Site Registration, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load automatically to the CTSU.)

Protocol Specific Requirements For 10076 Site Registration

• Specimen Tracking System Training Requirement:
o All data entry users (Clinical Research Associate role) at each participating site will need to complete the Theradex-led training.
o Theradex will provide a certificate of completion, which will need to be submitted to the CTSU through the Regulatory Submission Portal.
o The training is a one-time only requirement per individual. If an individual has previously completed the training for another ETCTN study, the training does not need to be completed again nor does the certificate of completion need to be resubmitted to the CTSU. However, new versions of the Specimen Tracking System may require new training.
o This training will need to be completed before the first patient enrollment at a given site.

o Please contact STS Support at Theradex for the training (STS.Support@theradex.com, Theradex phone: 609-799-7580).

4.2.2. Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal on the CTSU website.
To access the Regulatory Submission Portal, log on to the CTSU members' website, go to the Regulatory section, and select Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Checking Site Registration Status

Site's registration status may be verified on the CTSU website.

- Click on *Regulatory* at the top of the screen,
- Click on *Site Registration*, and
- Enter the site's 5-character CTEP Institution Code and click on Go.
    - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

4.3. Subject Registration

4.3.1. OPEN / IWRS

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN or IWRS will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account.
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or PO roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type.
- If a DTL is required for the study, the registrar must hold the OPEN Registrar task on the DTL for the site.
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes, and
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. IWRS system also sends an email confirmation of the registration. You may print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

Patient enrollment for this study will be facilitated using the Slot Reservation System in conjunction with the registration system in OPEN. Prior to discussing protocol entry with the patient, all site staff must use the CTSU OPEN Slot Reservation System or the IWRS Slot Reservation System to ensure that a slot on the protocol is available to the patient. Once a slot reservation confirmation is obtained, site staff may then proceed to CTSU OPEN Step 1 to enroll the patient to this study.

This Study will use the ETCTN Specimen Tracking System (STS).

- All biospecimens collected for this trial must be submitted using the ETCTN Specimen Tracking System (STS) unless otherwise noted.
- The system is accessed through Rave user roles: "Rave CRA" and "Rave CRA

(Labadmin)" for data entry at the treating institutions and "Biorepository" for users receiving the specimens for processing and storage at reference labs and the NCI Early-Phase and Experimental Clinical Trials Biospecimen Bank (EET Biobank, formerly known as the ETCTN Biorepository).

- Please refer to the Medidata Account Activation and Study Invitation Acceptance link on the CTSU website in the Data Management section under the Rave Home tab and then under Rave Resource Materials.
- **Important: Failure to complete required fields in STS may result in a delay in sample processing.** Any case reimbursements associated with sample submissions will not be credited if samples requiring STS submission are not logged into STS.

Detailed instructions on use of the STS can be found in Section **Error! Reference source not f ound.**.

4.3.2. Subject Enrollment Instructions

- Sites must reserve a slot in Theradex IWRS. Each site is allowed 1 slot reservations at a time with a 5 day guaranteed hold for each slot.

- Next, fax the following redacted documents for review:
  1. Latest clinic note
  2. Pathology report showing histologically confirmed diagnosis of multiple myeloma
  3. Documentation of measurable disease (defined by at least one of the following):
     a. Serum monoclonal protein M-protein level ≥0.5 g/dL
     b. Urinary M-protein excretion of ≥200 mg over a 24-hour period
     c. Involved free light chain level ≥10 mg/dL, along with an abnormal free light chain ratio

- Fax to: Astrid Murga/Hans Lee, MD at 713-794-5656. Include your contact information in the fax cover sheet.

- Each reservation will need to be authorized and approved by an MD Anderson designee prior to registering the patient in OPEN. Once the slot is approved in IWRS, you may proceed with registering your patient in OPEN.

There is a two-step process to enrollment in CTSU OPEN. The subject cannot be fully registered in CTSU OPEN without knowledge of the TP53 mutation status which is part of the ***eligibility*** criteria 3.2.2. However, a patient may begin Cycle 1 of therapy provided they meet all other eligibility criteria aside from criteria 3.2.2.

The two-step enrollment process is as follows:

(1) Register in CTSU OPEN **Step 1 once slot is approved through Theradex IWRS** to obtain patient's unique study ID
(2) Subject may begin Cycle 1 therapy after eligibility is established even if TP53 mutation

status is not yet known as per ***eligibility*** criteria 3.2.2

(3) Study site receives *TP53* results during Cycle 1 therapy (or before) with 2 possibilities below:

a) If non-wild-type (WT) *TP53* results, the patient is withdrawn from protocol for not meeting eligibility criteria prior to cycle 2 therapy. The site will need to complete step 2 of OPEN to indicate the patient has failed eligibility.

b) If wild-type (WT) *TP53* results meeting eligibility criteria, the patient can continue on protocol. The site will complete step 2 of OPEN to indicate that patient has met eligibility prior to commencing cycle 2 therapy.

4.3.3. OPEN/IWRS Questions?

Further instructional information on OPEN is provided on the OPEN tab of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

Theradex has developed a Slot Reservations and Cohort Management User Guide, which is available on the Theradex website: http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11 This link to the Theradex website is also on the CTSU website OPEN tab. For questions about the use of IWRS for slot reservations, contact the Theradex Helpdesk at 609-619-7802 or Theradex main number 855-828-6113; CTMSSupport@theradex.com.

4.4. General Guidelines

Following registration, subjects should begin protocol treatment within 14 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a subject does not receive protocol therapy following registration, the subject's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

5. TREATMENT PLAN

5.1. KRT-232 (AMG 232) + Carfilzomib, Lenalidomide, and Dexamethasone (KRd)

This will be a two-part Phase 1 dose-escalation and exploratory dose-expansion study of KRT-232 (AMG 232) in combination with carfilzomib, lenalidomide, and dexamethasone (KRd) in relapsed and/or refractory *TP53* WT myeloma subjects with 1-3 lines of prior therapy. Part A will consist of a dose-escalation phase of KRT-232 (AMG 232) to assess its safety and tolerability and identify an MTD/tentative RP2D in combination with KRd. KRT-232 (AMG 232) dose will be assigned according to the dose level stated in Section 5.4. Please refer to Section 5.4 to KRT-232 (AMG 232) dose escalation After the MTD has been established, Part B of the study will involve an exploratory-dose expansion study of a goal of 10 additional subjects with relapsed and/or refractory myeloma who will be enrolled at the tentative RP2D.

Due to the timely need to initiate treatment in relapsed myeloma, *TP53* mutation status at screening is NOT required prior to KRT-232 (AMG 232) dosing. However, subjects found to have *TP53* mutation and/or deletion from screening bone marrow biopsy will be removed from study after C1 and continue on standard-of-care KRd alone. Toxicity monitoring of such subjects removed from active therapy with KRT-232 (AMG 232) will continue as described in the Treatment Plan. During the dose-expansion phase, subjects removed from study after Cycle 1 based on the *TP53* mutation and/or deletion status will be replaced to ensure that a goal of 10 subjects with TP53 wild-type status are enrolled in the dose-expansion cohort.

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the subject's malignancy.

5.2. KRT-232 (AMG 232) Administration

KRT-232 (AMG 232) will be administered QD for 7 days every 28 days (i.e., 7 consecutive days of dosing followed by 21 consecutive days off treatment).

For QD dosing, subjects should self-administer KRT-232 (AMG 232) with or without food**.**with a full glass of water. KRT-232 (AMG 232) should not be crushed, chewed, or dissolved in water. Subjects should not be re-dosed with KRT-232 (AMG 232) after vomited doses.

The subject will be requested to maintain a medication diary of each dose of medication. The medication diary will be returned to clinic staff at the end of each course (APPENDIX E).

5.3. Carfilzomib, Lenalidomide, and Dexamethasone Administration

Regimen Description					
Agent	**Premedications; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Carfilzomib	**IV Hydration:** 250 mL to 500 mL normal saline (250 mL/hr) prior to each dose for Cycle 1 (optional for subsequent cycles). **Dexamethasone:** 4 mg PO or IV administered 30 minutes to 4 hours prior to Days 1-2, Days 8-9, and Days 15-16 dose	20 mg/m2 on Cycle 1, Day 1 and Cycle 1, Day 2 in 50 mL D5W[b] 27 mg/m2 starting on Cycle 1, Day 8 and all subsequent doses in 50 mL D5W[b]	IV over 10-30 minutes (allowable window of +10 minutes)	**Cycles 1-12:** Days 1-2, 8-9, 15-16 for Cycles 1-12. **Cycles 13-18**: Days 1-2, 15-16.	28 days (4 weeks)

	Ondansetron (optional) 8 mg IV or PO 30 minutes prior to each dose				
Lenalidomide	Can be taken with or without food. capsules should be swallowed whole with water and capsules should not be opened, broken, or chewed.	25 mg	Oral	Days 1-21	
Dexamethasone	None	40 mg	Oral or IV	Days 1, 8, 15, and 22	
[a]Premedication with dexamethasone 4 mg is required before each carfilzomib dose during Cycle 1 and is optional for subsequent cycles. During Cycle 1 and if pretreatment dexamethasone is necessary beyond Cycle 1, the treatment dose of dexamethasone 40 mg IV or PO will be given 30 minutes to 4 hours prior to each carfilzomib dose on Days 1, 8, and 15 which will serve as both the pretreatment and treatment dose of dexamethasone. [b]Calculate carfilzomib dose using the patient's actual body surface area at baseline. In patients with a body surface area greater than 2.2 m^2, calculate the dose based upon a body surface area of 2.2 m^2.					

Doses of lenalidomide or oral dexamethasone that are skipped or vomited will not be made up.

5.4. KRT-232 (AMG 232) + Carfilzomib, Lenalidomide, and Dexamethasone Treatment Plan

Dose Regimen

KRT-232 (AMG 232) + carfilzomib, lenalidomide, and dexamethasone will be administered per the following schedule:

Cycles 1-12 (28 day cycle)

- KRT-232 (AMG 232) once daily by mouth 7 out of 28 days
- Carfilzomib 20 mg/m^2 IV on Days 1 and 2 of Cycle 1, escalating to 27 mg/m^2 IV on Days 8, 9, 15, 16 of Cycle 1 and continuing on Days 1, 2, 8, 9, 15, 16 of Cycles 2 through Cycle 12
- Lenalidomide 25 mg PO on Days 1-21
- Dexamethasone 40 mg PO or IV on Days 1, 8, 15, and 22

Cycles 13-18 (28 days each)

- KRT-232 (AMG 232) once daily by mouth 7 out of 28 days
- Carfilzomib 27 mg/m^2 IV on Days 1, 2, 15, and 16
- Lenalidomide 25 mg PO on Days 1-21
- Dexamethasone 40 mg PO or IV on Days 1, 8, 15, and 22

Cycles 19+ (28 days each)

- KRT-232 (AMG 232) once daily by mouth 7 out of 28 days
- Lenalidomide 25 mg PO on Days 1-21
- Dexamethasone 40 mg PO or IV on Days 1, 8, 15, and 22

Part A (Dose-escalation scheme)
The MTD is defined as the highest dose at which six subjects have been treated and less than two subjects experienced DLT within the first cycle of treatment in Phase I of the trial. To determine the MTD, escalation for KRT-232 (AMG 232) will be conducted following the "3+3" design with de-escalation. A cohort of three subjects will be treated at the starting dose level and observed until the end of the first cycle (subjects non-evaluable for DLT will be replaced). The dose level will be escalated with each new cohort until at least one out of three subjects of a cohort experiences DLT. If one subject experiences a DLT, then three additional subjects will be treated at the same dose level; if none of the three additional subjects experiences a DLT, then the dose escalation will be continued by treating the next cohort of three subjects at the next higher dose level. If at least two out of up to six subjects at a dose level experience a DLT, the MTD will be considered to have been exceeded, and up to 3 more subjects will be treated at the next lower dose if there are less than 6 subjects already treated at that dose. The dose steps for escalation are displayed below:

Dose Escalation Schedule	
Dose Level	Dose of KRT-232 (AMG 232)*
- 1	30 mg/day PO x 7 days out of 28 day cycle
+ 1	60 mg/day PO x 7 days out of 28 day cycle
+ 2	90 mg/day PO x 7 days out of 28 day cycle
+ 3	120 mg/day PO x 7 days out of 28 day cycle
+ 4	180 mg/day PO x 7 days out of 28 day cycle
+ 5	240 mg/day PO x 7 days out of 28 day cycle

If dose-de-escalation is needed for Dose level 1, Dose level -1 is defined as 30 mg/day x 7 days out of 28 day cycle.

There should be no dose modifications of KRT-232 (AMG 232) and KRd during the DLT-evaluable period (Cycle 1). Subjects requiring dose-reductions during the DLT-evaluable period will be considered a DLT.

Part B (Dose-expansion scheme)
After determination of the KRT-232 (AMG 232) MTD or proven tolerability of the highest planned dose, and a goal of 10 additional subjects will be treated in the Part 2 dose expansion in combination with KRd. The primary objective of this dose-expansion phase is to confirm the safety and tolerability of KRT-232 (AMG 232) + KRd at the MTD and tentative RP2D in a goal

of 10 subjects with relapsed and/or refractory multiple myeloma. The tentative RP2D will be determined based on the review of safety data at the MTD.

During the dose-expansion phase, subjects removed from study after Cycle 1 based on the *TP53* mutation and/or deletion status will be replaced to ensure that a goal of 10 subjects with TP53 wild-type status are enrolled in the dose-expansion cohort.

The subject will be requested to maintain a medication diary of each dose of medication. The medication diary will be returned to clinic staff at the end of each course.

KRT-232 (AMG 232)

The following medications and/or therapies should not be administered within the timeframes specified prior to enrollment and during the study (unless otherwise specified below):

- Antitumor therapy (chemotherapy, antibody therapy, molecular targeted therapy, retinoid therapy, hormonal therapy, or investigational agent) within 21 days of study day 1; concurrent use of hormone deprivation therapy for hormone-refractory prostate cancer or breast cancer and continuation of previous hormone therapy in breast cancer subjects are permitted.
- Treatment with immune modulators including, but not limited to, corticosteroids, cyclosporine and tacrolimus within 3 weeks prior to enrollment, except for a corticosteroid dose equivalent to dexamethasone of ≤4 mg/day
- Therapeutic or palliative radiation therapy within 4 weeks of KRT-232 (AMG 232) day 1.
- All herbal medicines (*e.g.*, St. John's wort), vitamins, and supplements consumed by the subject within the 30 days prior to receiving the first dose of KRT-232 (AMG 232), and continuing use, if applicable, will be reviewed by the Principal Investigator and the sponsor.
- Use of any known CYP3A4 substrates with narrow therapeutic window (such as alfentanil, astemizole, cisapride, dihydroergotamine, pimozide, quinidine, sirolimus, or terfanide) within the 14 days prior to receiving the first dose of KRT-232 (AMG 232). Other medications (such as fentanyl and oxycodone) may be allowed per investigator's assessment/evaluation.
- Use of any known CYP2C8 substrates with a narrow therapeutic window within the 14 days prior to receiving the first dose of KRT-232 (AMG 232)
- Treatment with medications known to cause QTc interval prolongation within 7 days of study day 1 unless approved by the sponsor. Use of ondansetron is permitted for treatment of nausea and vomiting. Systemic anticoagulation therapy, with warfarin, direct thrombin inhibitors, indirect thrombin inhibitors and direct factor Xa inhibitors, within 14 days or 5 half-lives (whichever is longer) of day 1. Low molecular weight heparin and prophylactic low-dose warfarin are permitted.
- Autologous stem cell transplantation at least 12 weeks prior to starting KRT-232 (AMG 232) + KRd
- Allogeneic stem cell transplantation at least 24 weeks prior to starting KRT-232 (AMG 232) + KRd, and these subjects must also NOT have moderate to severe active acute or

chronic graft versus host disease (GVHD).

5.5. Prophylactic and Supportive Medications

At least 24 hours prior to Cycle 1 Day 1, the following treatments should be started:

- Valacyclovir 500 mg PO daily (or equivalent antiviral), continuing for the duration of treatment (additional prophylaxis is at the Investigator's discretion) for varicella zoster prevention while on carfilzomib-based therapy
- Pantoprazole 40mg PO daily, or other oral proton-pump inhibitor to prevent peptic disease for the duration of treatment with dexamethasone
- Aspirin (enteric-coated) PO daily at the standard prophylactic dose continuing for the duration of treatment with lenalidomide and dexamethasone. Other antiplatelet or anticoagulation medications may be used in cases of intolerance to aspirin at the Investigator's discretion.

5.6. Definition of Dose-Limiting Toxicity

A DLT is defined as any treatment emergent adverse event (TEAE) during the first treatment cycle that does not have a clear alternative cause (e.g., disease under study, concomitant therapy) based on the following criteria using NCI-CTCAE v5.0:

- Hematological toxicity
  - Grade 3 or 4 neutropenia with fever $\geq 38^0$ C lasting > 48 hours
  - Grade 4 neutropenia lasting > 7 days
  - Grade 3 or 4 thrombocytopenia associated with > grade 1 bleeding. Grade 4 thrombocytopenia that persists for > 14 days, despite holding treatment
  - Grade 4 anemia, unexplained by underlying disease
  - Any other grade 4 hematologic toxicity that does not resolve to subject's pre-treatment baseline level within 72 hours

- Non-hematological toxicity
  - Grade ≥ 3 nausea, vomiting or diarrhea lasting longer than 72 hours despite optimal medical support
  - Grade ≥ 3 non-hematological toxicity (excluding increased serum creatinine, or electrolyte abnormalities that are not clinically significant and require no treatment)
  - Any grade 3 electrolyte abnormalities that do not resolve to grade ≤ 2 within 72 hours
  - Grade 3 fatigue persisting > 7 days
  - Grade ≥ 3 acute kidney injury (creatinine > 3 × baseline or > 4.0 mg/dL) lasting > 72 hours
  - Any other grade 3 or 4 non-hematologic toxicities not predefined above will be considered a DLT.
  - A delay of ≥ 14 days in commencing Cycle 2 Day 1 due to lack of adequate

recovery of KRT-232 (AMG 232) +KRd-related toxicities will be considered a DLT.

Subjects who receive < 75% of the planned study drug doses during the first cycle of (i.e. ≤ 5/7 daily doses of KRT-232 (AMG 232) will considered nonevaluable for purposes of determining the MTD (unless due to a DLT) and will be replaced. Subjects who experience a DLT during the DLT-evaluable period will be considered evaluable for the purposes of determining the MTD as per Section 13.1.4

Management and dose modifications associated with the above adverse events are outlined in Section 6.

Dose escalation will proceed within each cohort according to the following scheme. Dose-limiting toxicity (DLT) is defined above.

Number of Subjects with DLT at a Given Dose Level	**Escalation Decision Rule**
0 out of 3	Enter 3 subjects at the next dose level.
≥ 2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional subjects will be entered at the next lowest dose level if only 3 subjects were treated previously at that dose.
1 out of 3	Enter at least 3 more subjects at this dose level. If 0 of these 3 subjects experience DLT, proceed to the next dose level. If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional subjects will be entered at the next lowest dose level if only 3 subjects were treated previously at that dose.
≤ 1 out of 6 at highest dose level below the maximally administered dose	This is generally the recommended phase 2 dose. At least 6 subjects must be entered at the recommended phase 2 dose.

5.7. Dose Expansion Cohorts:

Once the RP2D is reached, a goal of 10 additional subjects will be treated at this dose. For the expansion cohort, subjects will continue to be monitored for occurrence of DLT. If 2 of the first 5 subjects or if ≥ 4 of 10 subjects experience DLT, the Principal Investigator will discuss with all study investigators and with CTEP whether further addition of subjects is needed to re-assess the RP2D. When the first 5 additional patients are enrolled in the expansion phase, with a total of 11 patients including the 6 patients who had been already treated at the RP2D, the probabilities of observing 3 or more patients with DLT are 22.1%, 68.7% and 96.7% if the true toxicity rate are 15%, 30%, and 50%. When all 10 additional patients are enrolled in the expansion phase, with a

total of 16 patients including the 6 patients who had been already treated at the RP2D, the probabilities of observing 5 or more patients with DLT are 7.9%, 55%, and 96.2% if the true toxicity rate are 15%, 30%, and 50%. Monitoring of all safety and toxicity data is done by the Principal Investigator and the Corresponding Organization on a real-time basis as data are entered into Medidata Rave using the Web Reporting Module. All participating sites are expected to notify the Principal Investigator when a DLT has occurred.

5.8. General Concomitant Medication and Supportive Care Guidelines

5.8.1. Concomitant Medications

Because there is a potential for interaction of KRT-232 (AMG 232) with other concomitantly administered drugs, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the subject is taking any agent known to affect or with the potential for drug interactions. The principal investigator should be notified if the subject is taking CYP3A4 substrates with narrow therapeutic window (such as alfentanil, astemizole, cisapride, dihydroergotamine, pimozide, quinidine, sirolimus, or terfanide) or any known CYP2C8 substrates with a narrow therapeutic window while receiving AMG232.

A patient drug information leaflet and wallet card for the potential drug-interactions will be provided to each subject as referenced in Appendix B.

As noted in section 3.2.9, for treating emesis, other medications (such as fentanyl and oxycodone) may be allowed per investigator's assessment/evaluation. The study team should check a frequently-updated medical reference for a list of drugs to avoid or minimize use of.

5.8.2. Hydration

Adequate hydration is required prior to dosing of carfilzomib in Cycle 1, especially in patients at high risk of tumor lysis syndrome or renal toxicity. The recommended hydration includes both oral fluids (30 mL per kg at least 48 hours before Cycle 1, Day 1) and intravenous fluids (250 mL to 500 mL of appropriate intravenous fluid prior to each dose in Cycle 1). If needed, give an additional 250 mL to 500 mL of intravenous fluids following carfilzomib administration. Continue oral and/or intravenous hydration, as needed, in subsequent cycles. Monitor patients for evidence of volume overload and adjust hydration to individual patient needs, especially in patients with or at risk for cardiac failure.

5.8.3. Infusion Reactions

Infusion reactions, including life-threatening reactions, have occurred in patients receiving carfilzomib. Symptoms include fever, chills, arthralgia, myalgia, facial flushing, facial edema, vomiting, weakness, shortness of breath, hypotension, syncope, chest tightness, or angina. These reactions can occur immediately following or up to 24 hours after administration of carfilzomib. Dexamethasone will be administered will be required as a premedication during Cycle 1 prior to carfilzomib infusion to reduce the incidence and severity of infusion reactions (See Section 5.7). Subjects will be informed about risk and of symptoms and to contact a physician immediately if symptoms of an infusion reaction occur.

5.8.4. Blood Pressure Monitoring

Hypertension, including hypertensive crisis and hypertensive emergency, has been observed with carfilzomib. Some of these events have been fatal. Monitor blood pressure regularly in all patients. If hypertension cannot be adequately controlled, withhold carfilzomib and evaluate. Consider whether to restart carfilzomib based on a benefit/risk assessment.

5.9. Treatment Duration

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression by IMWG criteria (Appendix 15.6).
- Unacceptable adverse event(s) defined as:
    - Occurrence of an AE that is related to treatment with the study drug which, in the judgment of the investigator, compromises the subject's ability to continue study-specific procedures, or is considered to not be in the subject's best interest.
    - Persistent AE requiring a delay of therapy for more than 4 weeks (28 days)
- Subject decides to withdraw from the study
- Pregnancy
    - All women of child bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.
    - The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a subject participating in the study.
- Termination of the study by sponsor
- The drug manufacturer can no longer provide the study agent
- Subject achieves complete remission (CR), and the subject and investigator feel that discontinuation of KRT-232 (AMG 232) + KRd is in the subject’s best interests, or
- Subject achieves a level of response that qualifies him or her for another therapy, such as high dose therapy with autologous stem cell transplantation, and the subject and investigator feel that discontinuation of KRT-232 (AMG 232) + KRd is in the subject’s

best interests

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the Case Report Form (CRF).

5.10. Duration of Follow Up

Subjects will be followed for 30 days after removal from study or until death, whichever occurs first. Subjects removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

6. DOSING DELAYS/DOSE MODIFICATIONS

This section provides guidelines for dose modification guidelines and holding parameters for KRT-232 (AMG 232), carfilzomib, lenalidomide, and dexamethasone to manage possible toxicity. There should be no dose modifications of KRT-232 (AMG 232) and KRd during the DLT-evaluable period (Cycle 1). Subjects requiring dose-reductions during the DLT-evaluable period (Cycle 1) will be considered a DLT.

Guidelines on dose-reductions for carfilzomib were based on the Carfilzomib Prescribing Information 2016 (Amgen Inc, 2016).

Guidelines on dose-reduction for lenalidomide were based on the Lenalidomide Prescribing Information 2015 (Celgene Inc, 2015).

6.1. Criteria for Beginning or Delaying a Subsequent Treatment Cycle

The criteria for toxicity recovery before the subject can begin the next cycle of treatment are as follows:

- ANC $\geq 1000/mm^3$.
- Platelet count $\geq 50{,}000/mm^3$
- All non-hematologic toxicity considered to be related to treatment with study therapy must have resolved to $\leq$ Grade 2, to the subject's baseline values, or to a severity level considered stable and tolerable by the investigator/subject (eg, Grade 2 chronic kidney disease due to underlying MM).

If the subject does not meet the above-cited criteria for retreatment, initiation of the next cycle of KRT-232 (AMG 232) + KRd should be delayed for 1 week. After 1 week, the subject should be re-evaluated to determine whether the criteria for retreatment have been met. If the subject continues not to meet the previously cited criteria, delay KRT-232 (AMG 232) + KRd and continue to re-evaluate.

The maximum delay before treatment regimen of KRT-232 (AMG 232) + KRd should be discontinued will be 4 weeks (28 days) or at the discretion of the Principal Investigator, with the exception of C2D1 for which a delay ≥or, with in initiating C2D1 will be considered a DLT and subject will be removed from study (Section 5.6).

6.2. Dose Reductions

KRT-232 (AMG 232)

Dose Level	KRT-232 (AMG 232) Dose
- 1	30 mg/day PO x 7 days out of 28 day cycle
+ 1	60 mg/day PO x 7 days out of 28 day cycle
+ 2	90 mg/day PO x 7 days out of 28 day cycle
+ 3	120 mg/day PO x 7 days out of 28 day cycle
+ 4	180 mg/day PO x 7 days out of 28 day cycle
+5	240 mg/day PO x 7 days out of 28 day cycle

Carfilzomib

Dose Level	Carfilzomib Dose
- 2	15 mg/m^2
- 1	20 mg/m^2
+1	27 mg/m^2

Lenalidomide

Dose Level	Lenalidomide Dose
- 3	5 mg
- 2	10 mg
- 1	15 mg
+1	25 mg

Dexamethasone

Dose Level	Dexamethasone Dose
- 2	12 mg
- 1	20 mg
+ 1	40 mg

6.3. Non-Hematologic Toxicity Dose Delay/Dose Modification Guidelines.

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	

[redacted]	**Management/Next Dose for KRT-232 (AMG 232)**
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	
[redacted]	

[redacted]	**Management/Next Dose for KRT-232 (AMG 232)**
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	
[redacted]	

[redacted]	**Management/Next Dose for KRT-232 (AMG 232)**
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	
[redacted]	

[redacted]	**Management/Next Dose for KRT-232 (AMG 232)**
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	

Acute Renal Injury	**Management/Next Dose for Carfilzomib**
≤ Grade 1	No change in dose.
≥ Grade 2 or Creatinine clearance < 15 mL/min, or creatinine clearance decreases to less than or equal to 50% of baseline, or need for dialysis	Withhold dose and continue monitoring renal function (serum creatinine or creatinine clearance) If attributable to carfilzomib, resume when renal function has recovered to within 25% of baseline; start at 1 dose level reduction If not attributable to carfilzomib, dosing may be resumed at the discretion of the physician For subjects on dialysis receiving carfilzomib, the dose is to be administered after the dialysis procedure
*Subjects requiring a delay of > 4 weeks should go off protocol therapy. **Subjects requiring > two dose reductions should go off protocol therapy.	

Hepatic Impairment Grade 3 or 4 elevation of transaminases, bilirubin or other liver abnormalities	25% dose reduction in case of baseline or treatment emergent mild or moderate hepatic impairment. -Withhold carfilzomib until resolved or returned to baseline. -After resolution, consider if restarting carfilzomib appropriate; may be reinitiated at a reduced dose with frequent monitoring of liver function. -If tolerated, the reduced dose may be escalated to previous dose at the discretion of the physician. -Monitor liver enzymes regularly, regardless of baseline values, and modify dose based on toxicity.
Posterior Reversible Encephalopathy Syndrome (PRES)	-If PRES is suspected, hold carfilzomib. Consider evaluation with MRI for onset of symptoms suggest PRES. -If PRES is confirmed, permanently discontinue carfilzomib. -If PRES is excluded, may resume carfilzomib at same dose if clinically appropriate. -If PRES recurs, permanently discontinue carfilzomib
Thrombotic Microangiopathy (TMA)	-If TMA is suspected, hold carfilzomib and manage as per standard of care. -If TMS is confirmed and related to carfilzomib, permanently discontinue carfilzomib. -If TMA is excluded, may restart carfilzomib.

- For other ≥ 3 non-hematologic toxicity assessed as KRT-232 (AMG 232)-related, KRT-232 (AMG 232) will be held until toxicity resolves to ≤ Grade 1 or baseline. KRT-232 (AMG 232) will be restarted at 1 dose decrement.

- For other ≥ 3 non-hematologic toxicity assessed as carfilzomib-related, carfilzomib will be held until toxicity resolves to ≤ Grade 1 or baseline. Consider restarting carfilzomib at 1 dose decrement at physician's discretion.

- For other ≥ 3 non-hematologic toxicity assessed as lenalidomide-related, lenalidomide will be held until toxicity resolves to ≤ Grade 2 or baseline. Consider restarting lenalidomide at 1 dose decrement at physician's discretion.

6.4. Hematologic Toxicity Dose Delay/Dose Modification Guidelines.

Neutropenia	**Management/Next Dose for KRT-232 (AMG 232)**	**Management/Next Dose for Carfilzomib**
≤ Grade 2	No change in dose.	No change in dose.
Grade 3	Hold treatment. Add colony stimulating factor.[a] Check weekly CBC. Resume at same dose level when until ≤ Grade 2. For subsequent grade 3 or 4 neutropenia, restart at 1 dose decrement.	No change in dose.
Grade 4	[redacted]	Hold treatment. Add colony stimulating factor. Check weekly CBC. Resume at same dose level when ≤ Grade 3. For subsequent grade 4 neutropenia, restart at 1 dose decrement.
[*]Subjects requiring a delay of > 4 weeks should go off protocol therapy. [**]Subjects requiring > two dose reductions should go off protocol therapy.		
[a]Colony stimulating factors such as filgrastim or sargramostim as examples.		

Neutropenia	**Management/Next Dose for Lenalidomide**
≤ Grade 2	No change in dose
Grade 3 or 4	Hold treatment. Add colony stimulating factor.[a] Check weekly CBC. Resume at same dose level when ≤ Grade 2.

Neutropenia	**Management/Next Dose for Lenalidomide**
	For subsequent grade 3 or 4 neutropenia, restart at 1 dose decrement.
*Subjects requiring a delay of > 4 weeks should go off protocol therapy. **Subjects requiring > two dose reductions should go off protocol therapy.	
[a]Colony stimulating factors such as filgrastim or sargramostim as examples.	

[redacted]	**Management/Next Dose for KRT-232 (AMG 232)**
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	

Thrombocytopenia	**Management/Next Dose for Carfilzomib**
≥ 10,000 cells/mm^3	No change in dose
< 10,000 cells/mm^3 or bleeding	Hold treatment. Check weekly CBC Resume at same dose level when ≥ 10,000 cells/mm^3 For subsequent thrombocytopenia < 10,000 cells/mm^3, restart at 1 dose decrement.
*Subjects requiring a delay of > 4 weeks should go off protocol therapy. **Subjects requiring > two dose reductions should go off protocol therapy.	

Thrombocytopenia	**Management/Next Dose for Lenalidomide**
≥ 30,000 cells/mm^3	No change in dose
< 30,000 cells/mm^3	Hold until treatment. Check weekly CBC. Hold prophylactic anticoagulation. Restart at 1 dose decrement ≥ 30,000 cells/mm^3
*Subjects requiring a delay of > 4 weeks should go off protocol therapy. **Subjects requiring > two dose reductions should go off protocol therapy.	

6.5. Dexamethasone Toxicity Dose Delay/Dose Modification Guidelines.

Body System	**Symptom**	**Recommended Action**
Gastrointestinal	Dyspepsia, gastric or duodenal ulcer, gastritis Grade 1–2 (requiring medical management)	Treat with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, decrease dexamethasone dose by 1 dose level.
Gastrointestinal	> Grade 3 (requiring hospitalization or surgery)	Hold dexamethasone until symptoms adequately controlled. Restart dexamethasone at 1 dose decrement along with concurrent therapy with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures,

		discontinue dexamethasone permanently.
Gastrointestinal	Acute pancreatitis	Discontinue dexamethasone permanently.
Cardiovascular	Edema > Grade 3 (limiting function and unresponsive to therapy or anasarca)	Diuretics as needed, and restart dexamethasone at 1 dose decrement; if edema persists despite above measures, decrease dose another level. Discontinue dexamethasone permanently if symptoms persist despite second reduction.
Neurology	Confusion or mood alteration > Grade 2 (interfering with function +/– interfering with activities of daily living)	Hold dexamethasone until symptoms resolve. Restart dexamethasone at 1 dose decrement. If symptoms persist despite above measures, reduce by another dose decrement.
Musculoskeletal	Muscle weakness > Grade 2 (symptomatic and interfering with function +/– interfering with activities of daily living)	Decrease dexamethasone by 1 dose level. If weakness persists, decrease dose by 1 more dose level. Discontinue dexamethasone permanently if symptoms persist.
Metabolic	Hyperglycemia ≥ Grade 3	Treatment with insulin or other hypoglycemic agents as needed. If uncontrolled despite above measures, decrease dose by 1 dose level until levels are satisfactory.
All Other	Other nonhematologic toxicity ≥ Grade 3 felt related to dexamethasone	Hold dexamethasone dose. Resume at 1 dose decrement when toxicity has resolved to Grade 2 or less or to baseline. If toxicity recurs, discontinue dexamethasone permanently.

6.6. Hepatotoxicity Stopping and Rechallenge Rules

Subjects with abnormal hepatic laboratory values (*e.g.*, ALP, AST, ALT, total bilirubin, or INR) or signs/symptoms of hepatitis may meet the criteria for withholding of investigational product. Withholding is either permanent or conditional depending upon the clinical circumstances discussed below (as specified in the Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009).

Criteria for Permanent Withholding of KRT-232 (AMG 232) Due to Potential Hepatotoxicity

KRT-232 (AMG 232) should be permanently withheld and the subject should be followed according to the recommendations in APPENDIX C if ALL of the criteria below are met:

- Increased AST or ALT from the relevant baseline value as specified below:
    - Baseline AST/ALT level is < 1 × ULN and AST/ALT is elevated > 3 × ULN
      AND
    - Total bilirubin level is > 2 × ULN or INR is > 1.5
      AND
    - No other cause for the combination of the above laboratory abnormalities is immediately apparent; important alternative causes for elevated AST/ALT and/or elevated total bilirubin values include, but are not limited to:
        - Hepatobiliary tract disease
        - Viral hepatitis (*e.g.*, hepatitis A/B/C/D/E, Epstein-Barr virus (EBV),

cytomegalovirus (CMV), herpes simplex virus (HSV), varicella, toxoplasmosis, and parvovirus)
- Right sided heart failure, hypotension or any cause of hypoxia to the liver causing ischemia
- Exposure to hepatotoxic agents/drugs including herbal and dietary supplements, plants, and mushrooms,
- Heritable disorders causing impaired glucuronidation (*e.g.*, Gilbert's syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (*e.g.*, indinavir and atazanavir)
- Alpha-one antitrypsin deficiency
- Alcoholic hepatitis
- Autoimmune hepatitis
- Wilson's disease and hemochromatosis
- Nonalcoholic steatohepatitis (NASH) or other "fatty liver disease"
- Non-hepatic causes (*e.g.*, rhabdomyolysis and hemolysis).

Criteria for Conditional Withholding of KRT-232 (AMG 232) due to Potential Hepatotoxicity

For subjects who do not meet the criteria for permanent withholding of KRT-232 (AMG 232) outlined above and with no underlying liver disease and eligibility criteria requiring normal transaminases and total bilirubin level at baseline or subjects with underlying liver disease and baseline abnormal transaminases, the following rules are recommended for conditional withholding of KRT-232 (AMG 232) [redacted]

- Elevation of either AST/ALT according to the following schedule:
    - AST/ALT baseline value is any AND AST/ALT is elevated to any of the following values:
        - >8 × ULN at any time
        - >5 × ULN but <8 × ULN for ≥ 2 weeks
        - >5 × ULN but < 8 × ULN and unable to adhere to enhanced monitoring schedule > 3 × ULN with clinical signs or symptoms that are consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, jaundice, rash, or eosinophilia (> 5%).

          OR
        - Total bilirubin is > 3 × ULN at any time

          OR
        - Alkaline phosphatase is > 8 × ULN at any time

KRT-232 (AMG 232) should be withheld pending investigation into alternative causes of drug-induced liver injury. If KRT-232 (AMG 232) is withheld, the subject should be followed according to recommendations for possible drug-induced liver injury in APPENDIX C. Rechallenge may be considered if an alternative cause for impaired liver tests (*i.e.*, ALT, AST, alkaline phosphatase) and/or elevated total bilirubin level is discovered and the laboratory abnormalities resolve to normal or baseline.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 6.1) and the characteristics of an observed AE (Section 6.2 and 6.3) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) **in addition** to routine reporting.

7.1. Comprehensive Adverse Events and Potential Risks List (CAEPR)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset of AEs, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with ***bold*** and ***italicized*** text. The SPEER is a list of events that are protocol-specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm for further clarification.

NOTE: The highest grade currently reported is noted in parentheses next to the AE in the SPEER. Report **ONLY** AEs higher than this grade expeditiously. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

CAEPRs for CTEP IND Agent

7.1.1. CAEPR for KRT-232 (AMG 232)

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
KRT-232 (AMG 232, NSC 789723)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 379 patients.* Below is the CAEPR for KRT-232 (AMG 232).

> **NOTE:** Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.4, December 8, 2023[1]

Adverse Events with Possible Relationship to KRT-232 (AMG 232) (CTCAE 5.0 Term) [n= 379]	Specific Protocol Exceptions to Expedited Reporting (SPEER)
[redacted]	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

Adverse events reported on KRT-232 (AMG 232) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that KRT-232 (AMG 232) caused the adverse event:

[redacted]

[redacted]

Note: KRT-232 (AMG 232) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.1.2. Adverse Event List(s) for *[Other Investigational Agent(s)]*

7.1.3. CAEPR for Lenalidomide

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
Lenalidomide (CC-5013, NSC 703813)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 4081 patients.* Below is the CAEPR for Lenalidomide (CC-5013).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.8, June 27, 2019[1]

Adverse Events with Possible Relationship to Lenalidomide (CC-5013) (CTCAE 5.0 Term) [n= 4081]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 3)***
	Blood and lymphatic system disorders - Other (pancytopenia)		
	Febrile neutropenia		
	Hemolysis		
CARDIAC DISORDERS			
		Atrial fibrillation	
		Heart failure	
		Myocardial infarction[2]	
EAR AND LABYRINTH DISORDERS			
	Vertigo		
ENDOCRINE DISORDERS			
		Hyperthyroidism	
	Hypothyroidism		***Hypothyroidism (Gr 3)***
EYE DISORDERS			
	Blurred vision		
	Cataract		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
Constipation			***Constipation (Gr 3)***
Diarrhea			***Diarrhea (Gr 3)***
	Dry mouth		
	Dyspepsia		
	Nausea		***Nausea (Gr 3)***
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		***Chills (Gr 2)***
	Edema limbs		***Edema limbs (Gr 3)***
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 3)***
	Generalized edema		
	Non-cardiac chest pain		
	Pain		
HEPATOBILIARY DISORDERS			
		Hepatic failure	
		Hepatobiliary disorders - Other (cholestasis)	
IMMUNE SYSTEM DISORDERS			
		Allergic reaction	
		Anaphylaxis	
		Immune system disorders - Other (angioedema)	

Adverse Events with Possible Relationship to Lenalidomide (CC-5013) (CTCAE 5.0 Term) [n= 4081]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Immune system disorders - Other (graft vs. host disease)[3]	
INFECTIONS AND INFESTATIONS			
	Infection[4]		***Infection[4] (Gr 3)***
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Bruising		
	Fall		
INVESTIGATIONS			
	Alanine aminotransferase increased		
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased		
	Blood bilirubin increased		
	GGT increased		
	Investigations - Other (C-Reactive protein increased)		
		Lipase increased	
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 4)***
Neutrophil count decreased			***Neutrophil count decreased (Gr 4)***
Platelet count decreased			***Platelet count decreased (Gr 4)***
	Weight loss		***Weight loss (Gr 2)***
	White blood cell decreased		***White blood cell decreased (Gr 4)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 3)***
	Dehydration		
	Hyperglycemia		
	Hyperuricemia		
	Hypocalcemia		
	Hypokalemia Hypomagnesemia		
	Hyponatremia		
	Hypophosphatemia		
	Iron overload		
		Tumor lysis syndrome	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Back pain		
	Bone pain		
	Generalized muscle weakness		
	Muscle cramp		***Muscle cramp (Gr 2)***
	Myalgia		***Myalgia (Gr 2)***
	Pain in extremity		
		Rhabdomyolysis[5]	
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
		Leukemia secondary to oncology chemotherapy[6]	

Adverse Events with Possible Relationship to Lenalidomide (CC-5013) (CTCAE 5.0 Term) [n= 4081]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Myelodysplastic syndrome[6]	
		Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (tumor flare)[7]	
		Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (second primary malignancies)	
		Treatment related secondary malignancy[6]	
NERVOUS SYSTEM DISORDERS			
	Dizziness		
	Depressed level of consciousness		
	Dysesthesia		
	Dysgeusia		
	Headache		
	Paresthesia		
	Peripheral motor neuropathy		
	Peripheral sensory neuropathy		
		Stroke[2]	
	Syncope		
	Tremor		
PSYCHIATRIC DISORDERS			
	Depression		
	Insomnia		***Insomnia (Gr 2)***
	Psychiatric disorders - Other (mood altered)		
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 3)***
	Epistaxis		
		Pneumonitis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Dry skin		
		Erythema multiforme	
	Hyperhidrosis		***Hyperhidrosis (Gr 2)***
	Pruritus		***Pruritus (Gr 2)***
	Rash maculo-papular		***Rash maculo-papular (Gr 3)***
		Skin and subcutaneous tissue disorders - Other (drug reaction with eosinophilia and systemic symptoms [DRESS])	
	Skin and subcutaneous tissue disorders - Other (pyoderma gangrenosum)		
		Stevens-Johnson syndrome	
		Toxic epidermal necrolysis	

Adverse Events with Possible Relationship to Lenalidomide (CC-5013) (CTCAE 5.0 Term) [n= 4081]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
SURGICAL AND MEDICAL PROCEDURES			
		Surgical and medical procedures - Other (impaired stem cell mobilization)[8]	
VASCULAR DISORDERS			
	Hematoma		
	Hypertension		
	Hypotension Peripheral ischemia		
	Thromboembolic event[9]		***Thromboembolic event[9] (Gr 3)***
	Vasculitis		

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Myocardial infarction and cerebrovascular accident (stroke) have been observed in multiple myeloma patients treated with lenalidomde and dexamethasone.

[3]Graft vs. host disease has been observed in subjects who have received lenalidomide in the setting of allo-transplantation.

[4]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

[5]The rare adverse event of rhabdomyolysis has been observed with lenalidomide. The reports of rhabdomyolysis were confounded by concurrent use of statins and dexamethasone, concurrent viral and bacterial infections, trauma, and serotonin syndrome. Statins, infections, trauma, and serotonin syndrome are known risk factors for rhabdomyolysis.

[6]There has been an increased frequency of secondary malignancies (SPM) including ALL, AML, and MDS, and certain other types of cancers of the skin and other organs in multiple myeloma (MM) patients being treated with melphalan, prednisone, and lenalidomide post bone marrow transplant. The use of lenalidomide in cancers other than MM, shows that invasive SPMs occurred in a small number of patients. Patients treated with lenalidomide should be closely followed for the occurance of SPMs.

[7]Serious tumor flare reactions have been observed in patients with chronic lymphocytic leukemia (CLL) and lymphoma.

[8]A decrease in the number of stem cells (CD34+ cells) collected from patients treated with >4 cycles of lenalidomide has been reported.

[9]Significantly increased risk of deep vein thrombosis (DVT), pulmonary embolism (PE), and arterial thrombosis has been observed in patients with multiple myeloma receiving lenalidomide with dexamethasone.

[10]Gastrointestinal hemorrhage includes: Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

[11]Gastrointestinal obstruction includes: Colonic obstruction, Duodenal obstruction, Esophageal obstruction, Ileal obstruction, Jejunal obstruction, Obstruction gastric, Rectal obstruction, and Small intestinal obstruction under the GASTROINTESTINAL DISORDERS SOC.

[12]Osteonecrosis of the jaw has been seen with increased frequency when lenalidomide is used in combination with bevacizumab, docetaxel (Taxotere®), prednisone, and zolendronic acid (Zometa®).

NOTE: While not observed in human subjects, lenalidomide, a thalidomide analogue, caused limb abnormalities in a developmental monkey study similar to birth defects caused by thalidomide in humans. If lenalidomide is used during pregnancy, it may cause birth defects or embryo-fetal death. Pregnancy must be excluded before start of treatment. Prevent pregnancy during treatment by the use of two reliable methods of contraception.

NOTE: In a trial of first line treatment of patients with chronic lymphocytic leukemia (CLL), single agent lenalidomide (CC-5013) increased the risk of death as compared to control arm (chlorambucil).

NOTE: In two randomized trials of patients with multiple myeloma (MM), the addition of MK-3475 (pembrolizumab) to a thalidomide analog plus dexamethasone, resulted in increased mortality. Treatment of patients with MM with a PD-1 or PD-L1 blocking antibody, such as MK-3475 (pembrolizumab), in combination with a thalidomide analog, such as lenalidomide, is not recommended outside of controlled clinical trials.

NOTE: In a clinical trial in patients with Mantle cell lymphoma (MCL), there was an increase in early deaths (within 20 weeks); 12.9% in the lenalidomide (CC-5013) arm vs. 7.1% in the control arm.

Adverse events reported on lenalidomide (CC-5013) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that lenalidomide (CC-5013) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (monocytosis); Disseminated intravascular coagulation; Eosinophilia
CARDIAC DISORDERS - Atrial flutter; Atrioventricular block first degree; Cardiac arrest; Cardiac disorders - Other (cardiovascular edema); Cardiac disorders - Other (ECG abnormalities); Chest pain - cardiac; Left ventricular systolic dysfunction; Palpitations; Pericarditis; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia; Ventricular tachycardia
EAR AND LABYRINTH DISORDERS - Tinnitus
ENDOCRINE DISORDERS - Cushingoid
EYE DISORDERS - Dry eye; Flashing lights; Retinopathy
GASTROINTESTINAL DISORDERS - Abdominal distension; Anal mucositis; Ascites; Colonic perforation; Dysphagia; Flatulence; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (Crohn's disease aggravated); Gastrointestinal disorders - Other (diverticulitis); Gastrointestinal disorders - Other (pale feces); Gastrointestinal hemorrhage[10]; Gastrointestinal obstruction[11]; Ileus; Mucositis oral; Pancreatitis; Rectal mucositis; Small intestinal mucositis
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Malaise; Multi-organ failure
HEPATOBILIARY DISORDERS - Cholecystitis
INFECTIONS AND INFESTATIONS - Conjunctivitis; Infections and infestations - Other (opportunistic infection associated with >=Grade 2 Lymphopenia); Myelitis
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fracture; Hip fracture; Vascular access complication
INVESTIGATIONS - Activated partial thromboplastin time prolonged; Cholesterol high; Creatinine increased; Electrocardiogram QT corrected interval prolonged; INR increased; Investigations - Other (hemochromatosis)
METABOLISM AND NUTRITION DISORDERS - Acidosis; Hypercalcemia; Hyperkalemia; Hypoglycemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Chest wall pain; Joint effusion; Muscle weakness lower limb; Neck pain; Osteonecrosis of jaw[12]
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain

NERVOUS SYSTEM DISORDERS - Ataxia; Cognitive disturbance; Dysphasia; Edema cerebral; Encephalopathy; Intracranial hemorrhage; Ischemia cerebrovascular; Leukoencephalopathy; Memory impairment; Nervous system disorders - Other (hyporeflexia); Spinal cord compression; Seizure; Somnolence; Transient ischemic attacks
PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Psychosis
RENAL AND URINARY DISORDERS - Urinary frequency; Urinary incontinence; Urinary tract pain
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Reproductive system and breast disorders - Other (hypogonadism); Vaginal hemorrhage
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Allergic rhinitis; Atelectasis; Bronchopulmonary hemorrhage; Hypoxia; Laryngeal mucositis; Pharyngeal mucositis; Pleural effusion; Pulmonary hypertension; Respiratory failure; Tracheal mucositis; Voice alteration
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Nail loss; Photosensitivity; Rash acneiform; Skin and subcutaneous tissue disorders - Other (Sweet's Syndrome); Urticaria
VASCULAR DISORDERS - Hot flashes; Phlebitis; Vascular disorders - Other (hemorrhage NOS)

Note: Lenalidomide (CC-5013) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Adverse Event List(s) for other Commercial Agent(s)

In the Phase 3 randomized ASPIRE (Stewart et al., 2015) trial of carfilzomib, lenalidomide, and dexamethasone (KRd) vs. lenalidomide and dexamethasone (Rd), the following adverse reactions occurred in ≥ 10% of subjects in the KRd arm during cycles 1-12.

	KRd Arm (N = 392) n (%)	
Adverse Reactions by Body System	**Any Grade**	**≥ Grade 3**
Blood and Lymphatic System Disorders		
Anemia	138 (35)	53 (14)
Neutropenia	124 (32)	104 (27)
Thrombocytopenia	100 (26)	58 (15)
Gastrointestinal Disorders		
Diarrhea	115 (29)	7 (2)
Constipation	68 (17)	0
Nausea	60 (15)	1 (0)
General Disorders and Administration Site Conditions		
Fatigue	109 (28)	21 (5)
Pyrexia	93 (24)	5 (1)
Edema peripheral	63 (16)	2 (1)
Asthenia	53 (14)	11 (3)
Infections and Infestations		
Upper respiratory tract infection	85 (22)	7 (2)
Nasopharyngitis	63 (16)	0
Bronchitis	54 (14)	5 (1)

Pneumonia[a]	54 (14)	35 (9)
Metabolism and Nutrition Disorders		
Hypokalemia	78 (20)	22 (6)
Hypocalcemia	55 (14)	10 (3)
Hyperglycemia	43 (11)	18 (5)
Musculoskeletal and Connective Tissue Disorders		
Muscle spasms	88 (22)	3 (1)
Nervous System Disorders		
Peripheral neuropathies[b]	43 (11)	7 (2)
Psychiatric Disorders		
Insomnia	63 (16)	6 (2)
Respiratory, Thoracic, and Mediastinal Disorders		
Cough[c]	91 (23)	2 (1)
Dyspnea[d]	70 (18)	9 (2)
Skin and Subcutaneous Tissue Disorders		
Rash	45 (12)	5 (1)
Vascular Disorders		
Embolic and thrombotic events venous[e]	49 (13)	16 (4)
Hypertension[f]	41 (11)	12 (3)

KRd = Carfilzomib, lenalidomide, and dexamethasone; Rd = lenalidomide and dexamethasone

[a]Pneumonia includes pneumonia and bronchopneumonia.

[b]Peripheral neuropathies includes peripheral neuropathy, peripheral sensory neuropathy, and peripheral motor neuropathy.

[c]Cough includes cough and productive cough.

[d]Dyspnea includes dyspnea and dyspnea exertional.

[e]Embolic and thrombotic events, venous include deep vein thrombosis, pulmonary embolism, thrombophlebitis superficial, thrombophlebitis, venous thrombosis limb, post thrombotic syndrome, venous thrombosis.

[f]Hypertension includes hypertension, hypertensive crisis.

- For complete information on potential adverse events for carfilzomib, please refer to Carfilzomib Prescribing Information 2016 (Amgen Inc, 2016).

- For complete information on potential adverse events for lenalidomide, please refer to Lenalidomide Prescribing Information 2015 (Celgene Inc, 2015).

7.2. Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access

to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 7.1.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.
  - Other AEs for the protocol that do not require expedited reporting are outlined in section 7.3.4.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3. Expedited Adverse Event Reporting

Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP Web site (https://eapps-ctep.nci.nih.gov/ctepaers). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP Web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm). These requirements are briefly outlined in the tables below (Section 6.3.3).

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

Distribution of Adverse Event Reports

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Principal Investigator and Adverse Event Coordinator(s) (if applicable) of the Corresponding Organization or Lead Organization, the local treating physician, and the Reporter and Submitter. CTEP-AERS provides a copy feature for other e-mail recipients.

Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific subject ID assigned during trial registration on all reports.

Note: A death on study requires <u>both</u> routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "Disease Progression"** in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **<u>MUST</u>** immediately report to the sponsor (NCI) **<u>ANY</u>** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **<u>ANY</u>** of the following outcomes:
Death
A life-threatening adverse event
An adverse event that results in in subject hospitalization or prolongation of existing hospitalization for ≥ 24 hours
A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
A congenital anomaly/birth defect.
Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the subject or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

<u>ALL</u> <u>SERIOUS</u> adverse events that meet the above criteria MUST be immediately reported to the NCI via electronic submission within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.
<u>Expedited AE reporting timelines are defined as:</u>
"24-Hour; 5 Calendar Days" - The AE must initially be submitted electronically within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
"10 Calendar Days" - A complete expedited report on the AE must be submitted electronically within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:
All Grade 3, 4, and Grade 5 AEs
Expedited 10 calendar day reports for:
Grade 2 AEs resulting in hospitalization or prolongation of hospitalization
[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.
Effective Date: May 5, 2011

Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions

Not Applicable.

7.4. Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported expeditiously through CTEP-AERS must <u>also</u> be reported in routine study data submissions.**

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. AEs are reported in a routine manner at scheduled times during the trial using Medidata Rave. For this trial the Adverse Event CRF is used for routine AE reporting in Rave.

7.5. Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported expeditiously via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

7.6. Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine AE reporting unless otherwise specified.

7.7. Pregnancy, Contraception, and Risk of Embryo-Fetal Toxicity

Lenalidomide, a thalidomide analogue, caused limb abnormalities in a developmental monkey study. Thalidomide is a known human teratogen that causes severe life-threatening human birth defects. If lenalidomide is used during pregnancy, it may cause birth defects or embryo-fetal death. Carfilzomib can cause fetal harm based on findings from animal studies and the drug's mechanism of action. There are no adequate and well-controlled studies in pregnant women using carfilzomib. It is not known what effects KRT-232 (AMG 232) has on human pregnancy or development of the embryo or fetus. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner.

Nonsterilized female patients of reproductive potential must agree to one of the following through defined periods during and after study treatment as specified below. Non-reproductive potential is defined as female subjects who are permanently sterile or are post-menopausal (no menses in 12 consecutive months without an alternative medical cause).

- Agree to practice 2 effective methods of contraception from the time of signing of the informed consent form through 5 weeks after the last dose of study drug. This includes one highly effective form of contraception and one additional effective contraceptive method (see examples below).

  Highly effective methods:
  - Intra-uterine devices (IUD)
  - Hormonal (birth control pills/oral contraceptives, injectable contraceptives, contraceptive patches, or contraceptive implants)

  Other effective methods (barrier methods):
  - Latex or non latex condom with or without a spermicidal agent
  - Diaphragm with spermicide; Cervical cap with a spermicide; Sponge with a spermicide OR

- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception.)

Male patients, even if surgically sterilized (ie, status postvasectomy) must agree to one of the following defined periods during and after study treatment as specified below.

- Agree to practice effective barrier contraception during the entire study treatment period and through 90 days after the last dose of study drug, OR

- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods for the female partner] and withdrawal are not acceptable methods of contraception.)

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 7.1.

8.1. CTEP IND Agent(s)

Investigator Brochure Availability
The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. Questions about IB access may be directed to the PMB IB coordinator via email.

KRT-232 (AMG 232) (NSC 789723)

Chemical Name: 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl) acetic acid

International Non-Proprietary Name (INN): Navtemadlin

Classification: MDM2 inhibitor

Molecular Formula: $C_{28}H_{35}Cl_2NO_5S$ **M.W.:** 568.55

Mode of Action: AMG 232 (KRT 232) is a small molecule, cytotoxic chemotherapeutic agent that binds to murine double minute chromosome 2 (MDM2) and inhibits the MDM2/tumor protein 53 protein-protein interaction.

Description: Is a slightly hygroscopic, anhydrous, and crystalline white to off-white powder.

How Supplied: Kartos Therapeutics supplies, and the Pharmaceutical Management Branch distributes AMG 232 (KRT 232) as an immediate release tablet formulated as either an uncoated tablet with a low drug load (LDL tablet) or a film-coated tablet with a high drug load (HDL tablet).

The current supply is uncoated tablet with a low drug load (LDL tablet):
- 15 mg tablet: white to off-white round
- 60 mg tablet: white to off-white oval

Future supply is film-coated tablet with a high drug load or HDL tablet. The HDL tablet drug label has a blue bar to differentiate from the LDL tablet bottle:

- 15 mg tablet: green round
- 30 mg tablet: light orange round
- 60 mg tablet: blue oval
- 120 mg tablet: purple oval

AMG 232 (KRT 232) supply is packaged as 30 tablets per high-density polyethylene bottle and closed with aluminum foil lined heat induction seals and polypropylene child-resistance closures. Inactive ingredients of the tablets are lactose monohydrate, microcrystalline cellulose, hydroxylpropyl cellulose, croscarmellose sodium, and magnesium stearate.

Preparation: AMG 232 (KRT 232) uncoated tablets (LDL tablet) can be dispensed in the original container or in pharmacy dispensing bottles. **The film-coated tablets (HDL tablet) must be dispensed in the original bottle.** There are no data to support the re-packaging of HDL tablets in containers other than the original bottle.

Storage: Store intact bottles according to the drug label.

Uncoated tablet (LDL tablet):

- AMG 232 (KRT 232) 15 mg Tablets: below 25^0C (77^0F), protect from light.
- AMG 232 (KRT-232) 60 mg Tablets: 15^0C – 30^0C (59^0F - 86^0F), protect from light

Film-coated tablet (HDL tablet): 15^0C – 30^0C (59^0F - 86^0F), protect from light.

If a storage temperature excursion is identified, promptly return AMG 232 (KRT 232) to the proper storage temperature and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability: Shelf-life stability studies of AMG 232 (KRT 232) tablets are ongoing.

Route(s) **of Administration:** Oral.

Method of Administration: AMG 232 (KRT 232), uncoated (LDL) or coated (HDL) tablet, can be taken with a glass of water with or without food.

Potential Drug Interactions:
AMG 232 (KRT 232) is metabolized by three uridine diphosphoglucuronosyl transferases (UGT1A1, UGT1A3, and UGT1A4) to an acyl glucuronide (M1). In vitro, M1 is not impacted by UGT1A1 polymorphic genotypes UGT1A1*1/*1, UGT1A1*1/*28 or UGT1A1*28/*28.

AMG 232 (KRT 232) is not metabolized by CYP450 isozymes. *In-vitro* study suggests that AMG 232 is a substrate for P-glycoprotein, a competitive moderate inhibitor of CYP2C8, and a time-dependent moderate inhibitor of CYP3A4. M1 is a weak inhibitor of CYP2B6. KRT-232

has the potential to cause a minor drug-drug interaction (DDI) with drugs cleared predominantly by CYP3A4 (inhibition and induction). There is no identified DDI potential for other CYP enzymes. Use caution in patients taking CYP3A4 substrates with narrow therapeutic ranges.

Since AMG 232 (KRT 232) absorption was not impacted in the presence of high pH as demonstrated in a PK simulation, KRT-232 is not likely to be affected by proton pump inhibitor-mediated increase in gastric pH.

In pooled human liver microsomes, AMG 232 (KRT 232) and M1 are moderate inhibitors of UGT1A1. In human hepatocytes, UGT1A1/3/4 enzymatic activities were increased by AMG 232(KRT 232) at concentration > 5 μm and the mRNA transcripts were minimally increased by AMG 232 (KRT 232) at concentration ≥10 μm. Since the exposure of AMG 232 is expected to be low (unbound C_{max} = 0.161 μm at 480 mg), an increase in metabolism and CL via auto-induction are not expected.

AMG 232 (KRT 232) is not a BCRP substrate. Although AMG 232 (KRT 232) is an inhibitor of OAT3 (moderate to potent), OATP1B1 (moderate to potent), OATP1B3 (moderate to potent), OAT1 (moderate), BCRP (very weak), OCT2 (very weak), and P-glycoprotein (moderate), the ratios of unbound C_{max} to the in vitro IC_{50} is low (<0.03) at the proposed doses; thus, the potential for AMG 232 (KRT 232) to cause transporter-mediated DDIs due to inhibition of the transporter is low.

Patient Care Implications
Advise women study participants of reproductive potential to use effective contraception while receiving AMG 232 (KRT 232) and 1 month + 1 week (or 5 weeks) after the last dose of AMG 232 (KRT 232). Men study participants must continue to use contraception for 3 months and 1 week (or 13 weeks) after the last dose of AMG 232 (KRT 232). Refer to the protocol document for specific guidance.

Availability

KRT-232 (AMG 232) is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

KRT-232 (AMG 232) is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 12.3).

Agent Ordering and Agent Accountability

NCI-supplied agents may be requested by the responsible investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the subject is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of

Investigator), Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

No starter supplies. Sites may order agent supplies when subject enrollment is confirmed. Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://ctepcore.nci.nih.gov/OAOP
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- IB Coordinator: IBCoordinator@mail.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

8.2. Other Investigational Agent(s)

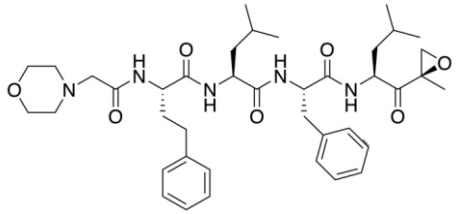
N/A

8.3. Commercial Agent(s)

8.3.1. Carfilzomib

Product description: Carfilzomib is an antineoplastic agent available for intravenous use only. Carfilzomib is a sterile, white to off-white lyophilized powder and is available as a single-dose 30 mg or 60 mg vial. Each 30 mg vial contains 30 mg of carfilzomib, 1500 mg sulfobutylether

beta-cyclodextrin, and 28.9 mg anhydrous citric acid and sodium hydroxide for pH adjustment (target pH 3.5). Each 60 mg vial contains 60 mg of carfilzomib, 3000 mg sulfobutylether beta-cyclodextrin, 57.7 mg citric acid, and sodium hydroxide for pH adjustment (target pH 3.5). Carfilzomib is a modified tetrapeptidyl epoxide, isolated as the crystalline free base.
The chemical name for carfilzomib is (2S)-N-((S)-1-((S)-4-methyl-1-((R)-2-methyloxiran- 2-yl)-1-oxopentan-2-ylcarbamoyl)-2-phenylethyl)-2-((S)-2-(2-morpholinoacetamido)-4-phenylbutanamido)-4-methylpentanamide. Carfilzomib has the following structure:



Carfilzomib is a crystalline substance with a molecular weight of 719.9. The molecular formula is $C_{40}H_{57}N_5O_7$. Carfilzomib is practically insoluble in water and very slightly soluble in acidic conditions.

Solution preparation (how the dose is to be prepared): Please refer to please refer to the FDA approved package insert for additional information.

Route of administration: Carfilzomib is infused over 10 or 30 minutes. Do not administer as a bolus. Flush the intravenous administration line with normal saline or 5% dextrose injection, USP immediately before and after carfilzomib administration. Do not mix carfilzomib with or administer as an infusion with other medicinal products.

Administration Precautions:

- Dose Calculation - Calculate the carfilzomi dose [see Dosage and Administration (2.2)] using the subject's actual body surface area at baseline. In subjects with a body surface area greater than 2.2 m^2, calculate the dose based upon a capped body surface area of 2.2 m^2.
- Hydration - Adequate hydration is required prior to dosing in Cycle 1, especially in subjects at high risk of tumor lysis syndrome or renal toxicity. The recommended hydration includes both oral fluids (30 mL per kg at least 48 hours before Cycle 1, Day 1) and intravenous fluids (250 mL to 500 mL of appropriate intravenous fluid prior to each dose in Cycle 1). If needed, give an additional 250 mL to 500 mL of intravenous fluids following carfilzomib administration. Continue oral and/or intravenous hydration, as needed, in subsequent cycles. Monitor subjects for evidence of volume overload and adjust hydration to individual subject needs, especially in subjects with or at risk for cardiac failure.
- Electrolyte Monitoring - Monitor serum potassium levels regularly during treatment with carfilzomib.
- Premedications - Premedicate with the recommended dose of dexamethasone for monotherapy or the recommended dexamethasone dose if on combination therapy. Administer dexamethasone orally or intravenously at least 30 minutes but no more

than 4 hours prior to all doses of Carfilzomib during Cycle 1 to reduce the incidence and severity of infusion reactions. Reinstate dexamethasone premedication if these symptoms occur during subsequent cycles.

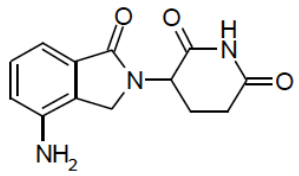
- Thromboprophylaxis - Thromboprophylaxis is recommended for subjects being treated with the combination of carfilzomib with dexamethasone or with lenalidomide plus dexamethasone. The thromboprophylaxis regimen should be based on an assessment of the subject's underlying risks.
- Infection Prophylaxis - Consider antiviral prophylaxis for subjects being treated with carfilzomib to decrease the risk of herpes zoster reactivation.

Agent Ordering: Carfilzomib is commercially available.

Please refer to the FDA approved package insert for additional information.

8.3.2. Lenalidomide

Product description: Lenalidomide, a thalidomide analogue, is an immunomodulatory agent with antiangiogenic and antineoplastic properties. The chemical name is 3- (4-amino-1-oxo 1,3-dihydro-2*H*-isoindol-2-yl) piperidine-2,6-dione and it has the following chemical structure:



3-(4-amino-1-oxo 1,3-dihydro-2*H*-isoindol-2-yl) piperidine-2,6-dione

The empirical formula for lenalidomide is C13H13N3O3, and the gram molecular weight is 259.3. Lenalidomide is an off-white to pale-yellow solid powder. It is soluble in organic solvent/water mixtures, and buffered aqueous solvents. Lenalidomide is more soluble in organic solvents and low pH solutions. Solubility was significantly lower in less acidic buffers, ranging from about 0.4 to 0.5 mg/ml. Lenalidomide has an asymmetric carbon atom and can exist as the optically active forms S(-) and R(+), and is produced as a racemic mixture with a net optical rotation of zero.

Solution preparation: Lenalidomide is available in 2.5 mg, 5 mg, 10 mg, 15 mg, 20 mg and 25 mg capsules for oral administration. Each capsule contains lenalidomide as the active ingredient and the following inactive ingredients: lactose anhydrous, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. The 5 mg and 25 mg capsule shell contains gelatin, titanium dioxide and black ink. The 2.5 mg and 10 mg capsule shell contains gelatin, FD&C blue #2, yellow iron oxide, titanium dioxide and black ink. The 15 mg capsule shell contains gelatin, FD&C blue #2, titanium dioxide and black ink. The 20 mg capsule shell contains gelatin, FD&C blue #2, yellow iron oxide, titanium dioxide and black ink.

Route of administration: Lenalidomide should be taken orally at about the same time each day, either with or without food. REVLIMID capsules should be swallowed whole with water. The capsules should not be opened, broken, or chewed.

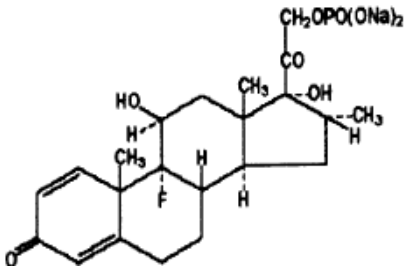
Agent Ordering: Lenalidomide is commercially available.

Please refer to the FDA approved package insert for additional information.
Dexamethasone

In this study, dexamethasone may be administered intravenously or by mouth.

8.3.3. Dexamethasone sodium phosphate (intravenous)

Product Description: Dexamethasone sodium phosphate, a synthetic adrenocortical steroid, is a white or slightly yellow, crystalline powder . It is freely soluble in water and is exceedingly hygroscopic. The molecular weight is 516.41 . It is designated chemically as 9-fluoro-110,17-dihydroxy-16amethyl-21-(phosphonooxy) pregna-l,4-diene-3,20-dione disodium salt. The empirical formula is C22H28FNa2O8P.



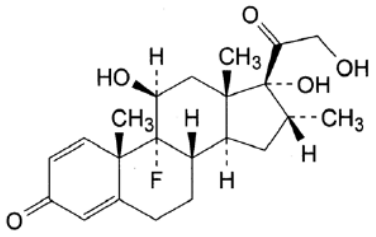
Solution Preparation: Please refer to the FDA approved package insert for information on solution preparation.

Route of Administration: In this study, dexamethasone sodium phosphate formulation will be administered intravenously.

Agent Ordering: Dexamethasone sodium phosphate is commercially available.

Please refer to the FDA approved package insert for additional information.

8.3.4. Dexamethasone (oral)
Product Description: Dexamethasone, a synthetic adrenocortical steroid, is a white to practically white, odorless, crystalline powder. It is stable in air. It is practically insoluble in water. The molecular formula is C22H29FO5. The molecular weight is 392.47. It is designated chemically as 9-fluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene,3,20-dione and the structural formula is:



Solution Preparation: Dexamethasone tablets are available for oral administration containing either 0.5 mg, 0.75 mg, 1 mg, 1.5 mg, 2 mg, 4 mg or 6 mg of Dexamethasone USP. Each tablet contains the following inactive ingredients: lactose monohydrate, magnesium stearate, starch, sugar, D&C Yellow #10 (0.5 mg and 4 mg), FD&C Blue #1 (0.75 mg and 1.5 mg), FD&C Green #3 (4 mg and 6 mg), FD&C Red #3 (1.5 mg), FD&C Red #40 (1.5 mg), FD&C Yellow #6 (0.5 mg and 4 mg) and Yellow Iron Oxide (1 mg).

Route of administration: Dexamethasone will be administered by mouth.

Agent Ordering: Dexamethasone is commercially available.

Please refer to the FDA approved package insert for additional information.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1. Integral Laboratory or Imaging Studies

9.1.1. *TP53* DNA Sequencing

Background: In the two largest sequencing studies to-date in myeloma, *TP53* mutations occur in only 3-8% of myeloma subjects (Lohr et al., 2014; Walker et al., 2015). A number of preclinical studies have suggested that wild-type *TP53* may be a biomarker for response with the use of MDM2 inhibitors, including studies performed in myeloma (Gu et al., 2014). In the clinical setting, several studies have been reported to-date evaluating the use of MDM2 inhibition in various malignancies. In a phase 1 trial of RG7112, a small molecule inhibitor MDM2, in relapsed leukemias, *TP53* mutations were identified in 19 of 96 subjects tested, and all but two subjects failed to show any clinical response, suggesting that the presence of at least one wild-type *TP53* allele is necessary for response. However, wild-type *TP53* alone was not sufficient to predict response to treatment in this study (Andreeff et al., 2016).

Method: The test will be performed by the NCI Molecular Characterization Laboratory (MoCha) or by an outside CLIA-certified laboratory. The MoCha laboratory will use human reference genome GRCh37 (hg19) as a reference sequence to determine mutational status of the *TP53* gene in the patient's tumor samples.

A minimum of 5% plasma cells on either the bone marrow biopsy or bone marrow aspirate is required to ensure sufficient plasma cells were present in the bone marrow to prevent from reporting false negative results on *TP53* mutational status.

If testing is performed by a CLIA-certified laboratory outside of MoCHa, the coordinating molecular pathologist listed on the protocol face page will be responsible for confirming and signing a clinical report on *TP53*-wild type status for purposes of trial eligibility and treatment assignment. A copy of a CLIA laboratory or the MoCHA laboratory report (Appendix 15.4) must be captured in the patient's trial record.

Analysis: Due to the timely need to initiate treatment in relapsed myeloma, *TP53* mutation status at screening is NOT required prior to KRT-232 (AMG 232) dosing. However, subjects found to have *TP53* mutation and/or deletion from screening bone marrow biopsy as assessed by a CLIA-certified laboratory or the NCI Molecular Characterization Laboratory (MoCha) will be removed from study after C1 and continue on standard-of-care KRd alone.

9.1.1.1. Specimen Tracking System Instructions

Bone marrow aspirate specimens (Section 9.1.1.2. and Section 9.4.1.1.), blood specimens (Section 9.5), and nucleic acids (Section 9.1.1.3. and Section 9.4.1.2.) for biobanking for this trial must be submitted using the ETCTN Rave Specimen Tracking System (STS) unless otherwise noted. The system is accessed through special Rave user roles: "CRA Specimen Tracking" for data entry at the treating institutions and "Biorepository" for users receiving the specimens for processing and storage at reference labs and the Biorepository. Please refer to the Medidata Account Activation and Study Invitation Acceptance link on the CTSU website under the Rave/DQP tab.

Important: Failure to complete required fields in STS may result in a delay in sample processing. Any case reimbursements associated with sample submissions will not be credited if samples requiring STS submission are not logged into STS.

Additionally, please note that the STS software creates pop-up windows when reports are generated, so you will need to enable pop-ups within your web browser while using the software.

For questions regarding the Specimen Tracking System, please contact the Theradex Help Desk at CTMSSupport@theradex.com.

A shipping manifest **must** be included with all sample submissions.

Specimen Labeling

Blood Specimen Labels

Include the following on blood specimens for optional blood samples for biobanking as per Section 9.5:
Patient Study ID
Specimen ID (automatically generated by Rave)
Time point

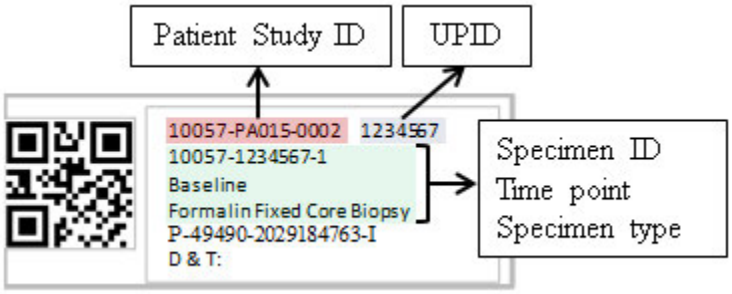
Specimen type (*e.g.*, blood, serum)
Collection date

Tissue Specimen Labels
Include the following on all tissue specimens or containers (*e.g.*, bone marrow aspirate tube):
Patient Study ID
Specimen ID (automatically generated by Rave)
Time point
Specimen type (*e.g.*, bone marrow aspirate, buccal mucosal swab)
Collection date

Nucleic Acid Specimen Labels
Include the following on nucleic acids (*e.g.*, DNA, RNA, cDNA):
Patient Study ID
Specimen ID (automatically generated by Rave)
Time point
Specimen category (e.g. bone marrow)
Specimen type (*e.g.*, DNA, RNA, cDNA)
Collection date

Example of Specimen Label

The following image is an example of a tissue specimen label printed on a standard Avery label that is 1" high and 2.625" wide.



The QR code in the above example is for the Specimen ID shown on the second line.
NOTE: The QR code label is currently under development at Theradex as of 31-Aug-2018; therefore, labels generated by the STS for this study may not include a QR code.

The second line item from the end includes four data points joined together:
Tissue only: Primary (P), Metastatic (M), Normal (N) tissue indicated at the beginning of the specimen ID; this field is blank if not relevant (e.g., for blood)
Block ID or blank if not relevant
SPID (Surgical Pathology ID) or blank if none

The last alpha-numeric code is protocol specific and is only included if the protocol requires an additional special code classification

The last line on the example label is for the handwritten date and optional time.

9.1.1.2. Collection of Specimen (s)

Bone marrow biopsy and aspiration will be performed at screening and at the end of study at the local study site. An optional bone marrow biopsy and aspiration will be performed pre-Cycle 2, Day 1. Immediately after marrow is aspirated, place 3-5 mL of bone marrow aspirate into sterile EDTA (lavender top tube). Mix well by inversion. Bone marrow aspirate specimen should be labeled as per the Specimen Tracking Instructions (Section 9.1.1.1.)

A bilateral bone marrow biopsy and aspiration will be performed *at screening* to ensure a high quality specimen for integral biomarker testing. Standard-of-care testing (e.g. flow cytometry, FISH) should be performed on the bone marrow aspirate from one side, and the bone marrow aspirate for integral biomarker testing should taken from "first pull" on the contralateral side.

9.1.1.3. Handling and Processing of Specimens(s)

After bone marrow aspirate collection, specimen will be processed at the MD Anderson Tissue Qualification Laboratory (TQL) where it will be logged into the PowerPath database. Subsequently, the MD Anderson Molecular Diagnostics Laboratory (MDL) will perform CD138 bead enrichment from the bone marrow sample, followed by DNA and RNA extraction in a CLIA-certified environment. The MD Anderson TQL and MDL will serve as a central site for myeloma tissue processing for the study.

For study sites outside of MD Anderson, bone marrow aspirates should be kept at room temperature until same-day overnight shipping at ambient temperature to the MD Anderson TQL where it will logged prior to further processing.

The bone marrow aspirate tube and 3-5 unstained slides should shipped to the following address:

MD Anderson Department of Pathology
Tissue Qualification Laboratory
Unit 0085
1515 Holcombe Blvd
Room G1.3598,
Houston, Texas 77030

An email should be sent to the MD Anderson TQL at path-tql@mdanderson.org prior to sending the specimen alerting the laboratory that the specimen is being shipped.

9.1.1.4. Shipping of Specimen(s)

After tissue processing by the MD Anderson MDL, DNA for *TP53*-wild type status determination will be shipped according the CLIA laboratory test manufacturer's instructions (if this method is used), or follow the laboratory manual for shipping specimens from the MD

Anderson TQL to the NCI MoCha laboratory. Nucleic acids shipped to the MoCha laboratory should be labeled as per the Specimen Tracking Instructions (Section 9.1.1.1.).

9.1.1.5. Site(s) Performing Correlative Study.
NCI Molecular Characterization Laboratory (MoCha) or any CLIA laboratory test.

9.2. Investigational Device Information

N/A

9.3. Integrated Correlative Studies

9.3.1. KRT-232 (AMG 232) Pharmacokinetic Profile

Background: This assay will be utilized to determine KRT-232 (AMG 232) concentrations and ultimately the drug exposure. There was an exposure-response correlation observed between changes in serum MIC-1 levels and KRT-232 (AMG 232) exposure (both maximal (C_{max}) and total exposure (AUC) (Amgen Inc., 2015).

Method: KRT-232 (AMG 232) blood levels will be measured by LC-MS/MS. The bioanalytical method for determining KRT-232 (AMG 232) in human plasma will be developed and validated utilizing liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) techniques. The analytical method will be validated as recommended by the FDA Guidance for Industry: Bioanalytical Method Validation, May 2001 (REF: Guidance for Industry: Bioanalytical Method Validation. U.S. Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Veterinary Medicine (CVM). Draft Guidance, September 2013. U.S. Food and Drug Administration).

Analysis: The PK profile of KRT-232 (AMG 232) will be compared. The plasma concentration-time data will be will be analyzed by standard noncompartmental analysis as implemented in the program Phoenix WinNonlin (Pharsight, A CertaraTM Company, Cary, NC). Pharmacokinetic parameters such as C_{max}, T_{max}, AUC, Cl/F, Vd/F and$T_{1/2}$ will be calculated and reported. Additional compartmental and/or pharmacometric analyses may be explored to elucidate inter- and intra-subject variability.

9.3.1.1. Collection of Specimen(s)
Blood samples (~6 mL) will be taken into K3EDTA tubes at designated time points, and immediately placed on ice. C1D1: pre KRT-232 (AMG 232), 1, 3, 5, 8, and 24 hours post (24 hr post is C1D2).

9.3.1.2. Handling of Specimens(s)
At each time point, ~6 mL of peripheral blood will be collected in a purple-top EDTA vacutainer (Becton Dickinson Catalog # 367863 or 367899, Franklin Lakes, NJ).

Obtain venous blood by standard phlebotomy technique from a peripheral access point. NOTE: Suggest using a minimum 18G needle to avoid sample hemolysis.

Fill-up the tubes as much as possible until blood flow stops.
GENTLY invert each tube several times (8-10 times) immediately after collection to avoid sample hemolysis.
Place samples immediately **on ice** after collection; samples must be processed **within 30 minutes**.

9.3.1.3. Processing instructions:

1) Invert sample 8-10 times immediately before processing.
2) Centrifuge at 2500-3000 rpm for 10 minutes in swinging bucket (SW) or 15 minutes in a fixed angel (FA) rotor at 4ºC in a refrigerated centrifuge. Make sure that the centrifuge reaches speed and is maintained throughout the entire spin.
3) Carefully remove tube from centrifuge.
4) Using a pipette, transfer equal aliquots of plasma into 2-3 labeled 2 mL cryovials, not exceeding 1.5 mL per cryovial.
5) Label samples as KRT-232 (AMG 232) PK, including study number (NCI10076), unique subject ID (assigned by OPEN), initials, date of collection, draw time, and time point.
6) Store plasma samples at -70ºC or below until shipment or transfer to Johns Hopkins.

9.3.1.4. Shipping of Specimen(s)

Specimens should be stored through the duration of KRT-232 (AMG 232) correlative studies (through C1D2) and shipped as a batch by participant (more than one participant/shipment is acceptable if the site has >1 participant on-study). A participant's samples should be shipped to the APC lab within 1 month of the last sample's collection date. (i.e., if C1D1 sample is collected on 1/1/2017, all of that participant's samples should be at the APC lab by 2/1/2017). The APC lab may contact the study team to request shipment off-schedule. The MIC-1 and KRT-232 (AMG 232) pharmacokinetic specimens can be shipped in the same shipment.

Please ship 1-2 aliquots to the APC laboratory. Once receipt is confirmed, the back-up aliquot may be shipped. The back-up can be shipped later

Preparing the shipment
*Samples should be stored in cardboard boxes (5 1/8" x 5 1/8" x 2", LxWxH).
*Please organize the samples by Subject and Time point in the box.
*Do not store in plastic bags (they break on dry-ice and labels will detach).
*A copy of each of the pharmacokinetic sample collection forms for the respective subjects or a sample list should be included with each shipment. To prevent problems with illegible writing on tubes, consider numbering them (in addition to sample label) and numbering samples on the sample sheet.
*Note the study number, PI, and the drugs used/to be measured.
*A name, phone number and email address should be included with samples so that receipt can be acknowledged.
*Please notify the lab by e-mail onc-pharmacology@lists.johnshopkins.edu (preferable) or telephone (410-502-7192 or 410-955-1129) or fax (410-502-0895) at least 24 hours prior to shipment.

Shipping
*All samples should be shipped via overnight express courier in insulated containers with enough dry ice to maintain the samples in a frozen state.
*Overnight shipments should occur on Monday through Wednesday (Tuesday is the preferred day) except when the following day is a holiday.

Analytical Pharmacology Core Laboratory*
Attn: NCI10076 KRT-232 (AMG 232) Study Samples
1650 Orleans St. CRB1 Rm 184
Baltimore, MD 21231-1000
Phone: 410-502-7192 or 410-955-1129
Fax: 410-502-0895

Site(s) Performing Correlative Study
ETCTN Central Laboratory: Dr. Michelle Rudek, The Analytical Pharmacology Core Laboratory at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins (SKCCC)

9.3.2. MIC-1

Background: MIC-1, a secreted protein that is strongly induced by activated p53, can be detected in the peripheral blood following MDM2 inhibition (64). Therefore, MIC-1 could have utility as a pharmacodynamic biomarker for KRT-232 (AMG 232). MIC-1 level can be determined by a sensitive ELISA test and if correlated with dose or other pharmacodynamic effects can serve as a serum biomarker for p53 activation. We anticipate that most subjects treated with KRT-232 (AMG 232) will have an induction in MIC-1 and the level MIC-1 induction will be correlated with the dose of KRT-232 (AMG 232) and the combination with KRd.. A commercially available ELISA kit (e.g., Biovendor, LLC, Asheville, NC) will be utilized to measure serum MIC-1 levels. This is for an integrated assay aimed at assessing drug response in subjects on the clinical trial and will be utilized to determine serum MIC-1 concentrations and ultimately the drug response.

Method: A commercially available ELISA kit (e.g., Biovendor, LLC, Asheville, NC) will be utilized to measure serum MIC-1 levels.

Analysis: For serum MIC-1 levels, each individual level will be normalized to the baseline level for that subject. In preliminary analyses of clinical trial data, there was an exposure-response correlation observed between changes in serum MIC-1 levels and KRT-232 (AMG 232) exposure (both maximal (Cmax) and total exposure (AUC).

9.3.2.1. Collection of Specimen(s)

Blood samples (~6 mL) will collected be in red-topped vacutainer tube at designated time points. Serum samples from the peripheral blood will be collected for MIC-1 assay at screening, C1D1 (pre-KRT-232 (AMG 232)), and C1D2 (~24 hour post KRT-232 (AMG 232)).

9.3.2.2. Handling of Specimens(s)

At each time point, ~6 mL of peripheral blood will be collected in a red-topped vacutainer (Becton Dickinson Catalog #367815, Franklin Lakes, NJ).

- Obtain venous blood by standard phlebotomy technique from a peripheral access point. NOTE: Suggest using a minimum 18G needle to avoid sample hemolysis.
- Fill-up the tubes as much as possible until blood flow stops.
- GENTLY invert each tube several times (8-10 times) immediately after collection to avoid sample hemolysis.
- Transport the tube(s) as soon as possible to the laboratory. Allow the blood to clot in an upright position for at least 30 minutes but not longer than 1 hour before centrifugation.

9.3.2.3. Processing instructions:

1) Centrifuge at 2200-2500 rpm for 15 minutes in swinging bucket (SW) or 15 minutes in a fixed angel (FA) rotor. Make sure that the centrifuge reaches speed and is maintained throughout the entire spin.
2) Carefully remove tube from centrifuge.
3) Using a pipette, transfer equal aliquots of plasma into ~4-6 labeled 2 mL cryovials, with a minimum volume of 0.5 mL per cryovial.
4) Label samples as **MIC-1**, including study number (NCI10076), unique subject ID (assigned by the consortium), initials, date of collection, draw time, and time point.
5) Store serum samples at -70^{o}C or below until shipment or transfer to Johns Hopkins.

9.3.2.4. Shipping of Specimen(s)

Serum samples will be shipped frozen according to Section 9.3.1.4.

9.3.2.5. Site(s) Performing Correlative Study

ETCTN Central Laboratory: Dr. Michelle Rudek, The Analytical Pharmacology Core Laboratory at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins (SKCCC)

9.4. Exploratory/Ancillary Correlative Studies

9.4.1. DNA and RNA sequencing of exploratory biomarkers

9.4.1.1. Collection of Specimen(s)

Bone marrow biopsy and aspiration will be performed at screening and at the end of study at the local study site. An optional bone marrow biopsy and aspiration will be performed pre-Cycle 2, Day 1. Immediately after marrow is aspirated, place 3-5 mL of bone marrow aspirate into sterile EDTA (lavender top) tube. Mix well by inversion. Bone marrow aspirate specimen should be labeled as per the Specimen Tracking Instructions (Section 9.1.1.1.). Buccal mucosa collection will also be performed at screening which will serve as a germline control for whole exome sequencing. See Appendix G for details regarding details of performing buccal swabs for the collection of buccal mucosa.

9.4.1.2. Handling and Processing of Specimens(s)

After bone marrow aspirate collection, specimen will be processed at the MD Anderson Tissue Qualification Laboratory (TQL) where it will be logged into the PowerPath database. Subsequently, the MD Anderson Molecular Diagnostics Laboratory (MDL) will perform CD138 bead enrichment from the bone marrow sample, followed by DNA and RNA extraction in a CLIA-certified environment. The MD Anderson MDL will also perform DNA extraction from the buccal mucosal swab which will serve as a germline control. The MD Anderson TQL and MDL will serve as a central site for myeloma tissue processing for the study.

For study sites outside of MD Anderson, bone marrow aspirates should be kept at room temperature until same-day overnight shipping at ambient temperature to the MD Anderson TQL where it will logged prior to further processing. Buccal swab should be sent in the same specimen container as the bone marrow aspirate to the MD Anderson TQL.

The bone marrow aspirate tube, 3-5 unstained slides, and buccal swab should shipped to the following address:

MD Anderson Department of Pathology
Tissue Qualification Laboratory
Unit 0085
1515 Holcombe Blvd
Room G1.3598,
Houston, Texas 77030

An email should be sent to the MD Anderson TQL at path-tql@mdanderson.org prior to sending the specimen alerting the laboratory that the specimen is being shipped.

9.4.1.3. Shipping of Specimen(s)

After tissue processing by the MD Anderson MDL, DNA and cDNA will be shipped according to the laboratory manual for shipping specimens from the MD Anderson TQL to the NCI MoCha laboratory. Nucleic acids shipped to the MoCha laboratory should be labeled as per the Specimen Tracking Instructions (Section 9.1.1.1.).

9.4.1.4. Site(s) Performing Correlative Study

The NCI Molecular Characterization (MoCha) Laboratory.

9.5. Optional biobanking of blood and marrow samples

Optional biobanking will be available for blood and left-over bone marrow aspirate samples collected during the study for future analyses. These samples may be used for further exploratory studies, which include genomic sequencing, based on emerging scientific knowledge to better understand the target disease, the effects of study treatment, and potential mediators of primary and acquired resistance to therapy. Consent will be obtained per the ICF from subjects who wish to participate in optional sample biobanking.

For optional serum banking, approximately 10 mL of blood will be collected in a heparin (green top) tube to bank viably frozen peripheral blood mononuclear cells, and approximately 7 mL of blood will be collected in a red top tube for serum banking. Blood specimens should be labeled as per the Specimen Tracking Instructions (Section 9.1.1.1.) Collection of optional blood sample for biobanking will occur at screening outlined in the Study Calendar (Section 10.).

For study sites outside of MD Anderson, blood samples for biobanking should be kept at room temperature until same-day overnight shipping at ambient temperature to MD Anderson in same shipping container as bone marrow aspirate tubes and unstained slides as described in Section 9.1.1.2.

9.6. Other studies: Minimal Residual Disease Testing

Minimal residual disease (MRD) testing will be assessed as per standard of care per the updated 2016 IMWG response guidelines (Appendix F). In this study, MRD will be assessed using the CLIA-certified clonoSEQ® (Adaptive Biotechnologies) VDJ NGS assay.

In subjects achieving a biochemical complete response (CR) defined as a negative SPEP, UPEP, serum IFE, and urine IFE, a bone marrow biopsy and aspiration will be performed to confirm CR and to assess for MRD using the clonoSEQ® assay. In subjects achieving MRD negativity, a bone marrow biopsy and aspirate may subsequently be performed every 12 months (+/- 30 days) to evaluate for sustained MRD per IMWG response criteria (see Appendix F).

Sample Collection:
Immediately after marrow is aspirated, place 2 mL of bone marrow aspirate into sterile EDTA (lavender top) tube. Mix well by inversion.

Handling of Specimens(s)
Specimens should be stored at ambient room temperature until same day overnight shipping.

Shipping of Specimen(s).

Bone marrow aspirate specimen for in EDTA tube should be shipped at ambient temperature overnight to the following address:

MD Anderson Department of Pathology
Tissue Qualification Laboratory
Unit 0085
1515 Holcombe Blvd
Room G1.3598,
Houston, Texas 77030

Archived DNA from the subject's myeloma cells that was banked from the pretreatment screening bone marrow aspiration as per Section 9.1.1.2. will also be sent concurrently to

Adaptive Biotechnologies and will be used to identify the dominant clonotype(s) and "tracking" sequence for MRD detection using the clonoSEQ® assay.

clonoSEQ® ID gDNA and tracking specimens (bone marrow aspirate samples stored in EDTA tube at -80 degrees Celsius until ready for shipment) will be shipped in batch. Coordinating site (MDACC) will email ISTSampleMgmt@adaptivebiotech.com the sample type, number of total samples, how many samples for clonality/ID vs tracking/MRD and the contact name, shipping address and phone number to receive a shipper with FedEx return shipping label.

When coordinating site (MDACC) is ready to ship samples, the shipping manifest will be completed and a hard copy to include in the shipper with the samples. Shipping Shipping manifest and FedEx tracking number will be emailed to ISTSampleMgmt@adaptivebiotech.com. Samples should be shipped no later than a Wednesday. For shipping near a holiday, please contact ISTSampleMgmt@adaptivebiotech.com.

9.7. Summary of Bone Marrow Biopsy and Aspirate Studies

Study	Baseline	Post Cycle 1	Complete remission	End of Study
DNA and RNA sequencing for integral, integrative, and exploratory studies.	X	X		X
Pathology review/immuno-Histochemistry*	X	X	X	X
Flow Cytometry*	X	X	X	X
FISH/Cytogenetics*	X			X
ClonoSEQ® VDJ NGS for MRD testing	X		X	X
Biobanking	X	X	X	X

*Testing will be performed at local study site as per standard of care

10. STUDY CALENDAR

10.1. Part A: Dose Escalation

Cycle (a)	Pre-Cycle	Cycle 1			Cycle 2	Cycle 3-12	Cycle 13-18	Cycle 18+	Post-Cycle
Visit Number	1	2	3	4	5	TBD	TBD	TBD	TBD
Visit Description	Screening	Exam and 1st dose	Exam	Exam	Exam	Exam	Exam	Exam	EOT (b)
Cycle Day(s)	-28 to 0	1	8	15	1	1	1	1	ND
Visit Window (days)			+/-2	+/-2	+/-4	+/-4	+/-4	+/-4	+/-5
KRT-232 (AMG 232)		A			A	A	A	A	
Carfilzomib		B1			B1	B1	B2		
Lenalidomide		C			C	C	C	C	
Dexamethasone		D			D	D	D	D	
Informed Consent	X								
Demographics	X								
Medical History (c)	X								
Adverse events	X	X	X	X	X	X	X	X	X
Prior/concomitant medications	X	X	X	X	X	X	X	X	X
ECOG performance status	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X
Height	X	X							
Physical Exam, including weight (c)	X	X	X	X	X	X	X	X	X
CBC with diff, platelets	X	X (d)	X	X	X (e)	X (e)	X (e)	X	X
Serum chemistries (f)	X	X (d)	X	X	X (g)	X (g)	X (g)	X	X
aPTT, PT, and INR	X								
Hepatitis panel (h)	X								
Urine or serum β-HCG (i)	X	X	X	X	X	X	X	X	X
Myeloma laboratory assessment (j)	X	X			X	X	X	X	X
Bone marrow aspiration and biopsy (k)	X				X (l)				X (l)
TP53 status (NGS)	X								
Blood sample for drug exposure measurement (m)		X				[a]			
MIC-1 serum sample (n)	X	X							
Bucccal mucosal swab	X								
Blood sample for banking (o)	X								
Myeloma bony survey (p)	X								
Echocardiogram	X								
Dispense KRT-232 (AMG 232)		X			X	X	X	X	X
Pill diaries dispensed/reviewed		X	X	X	X	X	X	X	X

A: KRT-232 (AMG 232), dose as assigned, Day 1 through D7
B1: Carfilzomib 20 mg/m^2 IV on Days 1 and 2 of Cycle 1, escalating to 27 mg/m^2 IV on Days 8, 9, 15, 16 of Cycle 1 and continuing on Days 1, 2, 8, 9, 15, 16 of Cycles 2 through Cycle 12
B2: Carfilzomib 27 mg/m^2 IV on Days 1, 2, 15, and 16
C: Lenalidomide 25 mg PO on Days 1-21
D: Dexamethasone 40 mg PO or IV on Days 1, 8, 15, and 22

a. Each cycle will last 28 days. Cohort safety assessment for DLTs will be performed after Day 28 of Cycle 1.
b. End-of-Treatment Visit will occur 30 (± 5) days after the last administration of KRT-232 (AMG 232). If the subject begins another form of anticancer therapy before the end of the 30 (± 5)-day period, every effort will be made to complete all the End-of-Treatment assessments prior to commencing the new therapy. If there is an abnormality in need of monitoring beyond the End-of-Treatment Visit, subjects will be followed until resolution or confirmed stability of the abnormality.
c. A complete history & physical examination should be performed at screening. Thereafter, only a symptom-directed physical exam is required.
d. CBC and serum chemistries for Cycle 1/Day 1 pre-dose can be collected within 48 hours before the first dose.
e. CBC are collected pretreatment (within 48 hours) on Days 8 and 15 during Cycles 2-12 and Day 15 during Cycles 13-18.
f. Serum chemistries: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, magnesium.
g. Basic Metabolic Panel (bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, sodium) are collected pretreatment (within 48 hours) on Days 8 and 15 during Cycles 2-12 and Day 15 during Cycles 13-18.
h. Hepatitis panel will include HAV Ab, qualitative HBsAb, HBsAg, HBcAb, and HCV Ab
i. Two negative pregnancy tests must be obtained prior to initiating therapy in female subjects of childbearing potential during the screening period. The first test should be performed within 10-14 days and the second test within 24 hours prior to initiating therapy and then weekly during the first month, then monthly thereafter in women with regular menstrual cycles or every 2 weeks in women with irregular menstrual cycles as per the lenalidomide Risk Evaluation and Mitigation Strategy (REMS) program.
j. Myeloma laboratory assessment includes serum free light-chain assay, serum protein electrophoresis (and immunofixation if needed to confirm CR if no M-protein detected on electrophoresis), serum quantitative immunoglobulins (IgG, IgA, IgM), 24-hour urine protein electrophoresis (and immunofixation if needed to confirm CR if no M-protein detected on electrophoresis), and β2-microglobulin. Initial pretreatment assessment can be collected within 1 week of first dose.
k. Initial pretreatment/screening bone assessment requires bilateral biopsy and aspirates. Can occur within 4 weeks of first dose date. Bone marrow analysis should include morphologic review, quantification of percentage of plasma cells, flow cytometry, and myeloma fluorescence *in situ* hybridization (FISH) panel (performed locally) as per standard of care.
l. Optional bone marrow biopsy and aspiration for Cycle 2/Day 1 may be performed anytime from Cycle 1/Day 24 to Cycle 2/Day 5. Mandatory bone marrow biopsy and aspiration at EOT would be performed within 30 days following the last study treatment, preferably prior to initiating new therapy. In patients achieving a biochemical CR (negative SPEP/UPEP and urine/serum IFE), an additional bone marrow should be performed to confirm a CR with MRD testing using the clonoSEQ® NGS assay (Adaptive Biotechnologies) with minimum sensitivity to 10^{-5} nucleated cells. In patients achieving MRD negativity, a bone marrow biopsy and aspirate may subsequently be performed every 12 months (+/- 30 days) to evaluate for sustained MRD.
m. Blood samples for drug exposure measurement will be collected Cycle 1/Day 1 pre-dose and post-dose at 1 hr, 3 hr, 5 hr, 8 hr, and 24 hr (C1D2).

n. Blood samples for MIC-1 testing will be collected at screening, Cycle 1/Day 1 pre-dose, and post-dose at 24 hr (C1D2)
o. Blood samples for optional biobanking will be collected at screening. Approximately 10 mL of blood will be collected in a heparin (green top) tube and approximately 7 mL of blood will be collected in a red top tube.
p. One additional bony survey may be performed solely to confirm a CR, if this is indicated by serum and urine immunofixation assays.

ECOG = Eastern Cooperative Oncology Group; EOT = End of Treatment; MIC-1 = macrophage inhibitory cytokine-1; TBD = to be determined.

10.2. Part B: Dose Expansion

Cycle (a)	Pre-Cycle	Cycle 1			Cycle 2	Cycle 3-12	Cycle 13-18	Cycle 18+	Post-Cycle
Visit Number	1	2	3	4	5	TBD	TBD	TBD	TBD
Visit Description	Screening	Exam and 1st dose	Exam	Exam	Exam	Exam	Exam	Exam	EOT (b)
Cycle Day(s)	-28 to 0	1	8	15	1	1	1	1	ND
Visit Window (days)			+/-2	+/-2	+/-4	+/-4	+/-4	+/-4	+/-5
KRT-232 (AMG 232)		A			A	A	A	A	
Carfilzomib		B1			B1	B1	B2		
Lenalidomide		C			C	C	C	C	
Dexamethasone		D			D	D	D	D	
Informed Consent	X								
Demographics	X								
Medical History (c)	X								
Adverse events	X	X	X	X	X	X	X	X	X
Prior/concomitant medications	X	X	X	X	X	X	X	X	X
ECOG performance status	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X
Height	X	X							
Physical Exam, including weight (c)	X	X	X	X	X	X	X	X	X
CBC with diff, platelets	X	X (d)	X	X	X (e)	X (e)	X (e)	X	X
Serum chemistries (f)	X	X (d)	X	X	X (g)	X (g)	X (g)	X	X
aPTT, PT, and INR	X								
Hepatitis panel (h)	X								
Urine or serum β-HCG (i)	X	X	X	X	X	X	X	X	X
Myeloma laboratory assessment (j)	X	X			X	X	X	X	X
Bone marrow aspiration and biopsy (k)	X				X (l)				X (l)
TP53 status (NGS)	X								
Blood sample for drug exposure measurement (m)		X				[a]			
MIC-1 serum sample (n)	X	X							
Buccal mucosal swab	X								
Blood sample for banking (o)	X								
Myeloma bony survey (p)	X								
Echocardiogram	X								
Dispense KRT-232 (AMG 232)		X			X	X	X	X	X
Pill diaries dispensed/reviewed		X	X	X	X	X	X	X	X

A: KRT-232 (AMG 232), dose as assigned, Day 1 through D7
B1: Carfilzomib 20 mg/m^2 IV on Days 1 and 2 of Cycle 1, escalating to 27 mg/m^2 IV on Days 8, 9, 15, 16 of Cycle 1 and continuing on Days 1, 2, 8, 9, 15, 16 of Cycles 2 through

Cycle 12
B2: Carfilzomib 27 mg/m^2 IV on Days 1, 2, 15, and 16
C: Lenalidomide 25 mg PO on Days 1-21
D: Dexamethasone 40 mg PO or IV on Days 1, 8, 15, and 22

a. Each cycle will last 28 days. Cohort safety assessment for DLTs will be performed after Day 28 of Cycle 1.
b. End-of-Treatment Visit will occur 30 (± 5) days after the last administration of KRT-232 (AMG 232). If the subject begins another form of anticancer therapy before the end of the 30 (± 5)-day period, every effort will be made to complete all the End-of-Treatment assessments prior to commencing the new therapy. If there is an abnormality in need of monitoring beyond the End-of-Treatment Visit, subjects will be followed until resolution or confirmed stability of the abnormality.
c. A complete history & physical examination should be performed at screening. Thereafter, only a symptom-directed physical exam is required.
d. CBC and serum chemistries for Cycle 1/Day 1 pre-dose can be collected within 48 hours before the first dose.
e. CBC are collected pretreatment (within 48 hours) on Days 8 and 15 during Cycles 2-12 and Day 15 during Cycles 13-18.
f. Serum chemistries: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, magnesium.
g. Basic Metabolic Panel (bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, sodium) are collected pretreatment (within 48 hours) on Days 8 and 15 during Cycles 2-12 and Day 15 during Cycles 13-18.
h. Hepatitis panel will include HAV Ab, qualitative HBsAb, HBsAg, HBcAb, and HCV Ab
i. Two negative pregnancy tests must be obtained prior to initiating therapy in female subjects of childbearing potential during the screening period. The first test should be performed within 10-14 days and the second test within 24 hours prior to initiating therapy and then weekly during the first month, then monthly thereafter in women with regular menstrual cycles or every 2 weeks in women with irregular menstrual cycles as per the lenalidomide Risk Evaluation and Mitigation Strategy (REMS) program.
j. Myeloma laboratory assessment includes serum free light-chain assay, serum protein electrophoresis (and immunofixation if needed to confirm CR if no M-protein detected on electrophoresis), serum quantitative immunoglobulins (IgG, IgA, IgM), 24-hour urine protein electrophoresis (and immunofixation if needed to confirm CR if no M-protein detected on electrophoresis), and β2-microglobulin. Initial pretreatment assessment can be collected within 1 week of first dose.
k. Initial pretreatment/screening bone assessment requires bilateral biopsy and aspirates. Can occur within 4 weeks of first dose date. Bone marrow analysis should include morphologic review, quantification of percentage of plasma cells, flow cytometry, and myeloma fluorescence *in situ* hybridization (FISH) panel (performed locally) as per standard of care.
l. Optional bone marrow biopsy and aspiration for Cycle 2/Day 1 may be performed anytime from Cycle 1/Day 24 to Cycle 2/Day 5. Mandatory bone marrow biopsy and aspiration at EOT would be performed within 30 days following the last study treatment, preferably prior to initiating new therapy. In patients achieving a biochemical CR (negative SPEP/UPEP and urine/serum IFE), an additional bone marrow should be performed to confirm a CR with MRD testing using the clonoSEQ® NGS assay (Adaptive Biotechnologies) with minimum sensitivity to 10^{-5} nucleated cells. In patients achieving MRD negativity, a bone marrow biopsy and aspirate may subsequently be performed every 12 months (+/- 30 days) to evaluate for sustained MRD.
m. Blood samples for drug exposure measurement will be collected Cycle 1/Day 1 pre-dose and post-dose at 1 hr, 3 hr, 5 hr, 8 hr, and 24 hr (C1D2).
n. Blood samples for MIC-1 testing will be collected at screening, Cycle 1/Day 1 pre-dose, and post-dose at 24 hr (C1D2)

o. Blood samples for optional biobanking will be collected at screening. Approximately 10 mL of blood will be collected in a heparin (green top) tube and approximately 7 mL of blood will be collected in a red top tube.
p. One additional bony survey may be performed solely to confirm a CR, if this is indicated by serum and urine immunofixation assays.

ECOG = Eastern Cooperative Oncology Group; EOT = End of Treatment; MIC-1 = macrophage inhibitory cytokine-1; TBD = to be determined.

11. MEASUREMENT OF EFFECT

11.1. Multiple Myeloma Response Assessment

Although the clinical benefit of KRT-232 (AMG 232) has not yet been established, the intent of offering this treatment is to provide a possible therapeutic benefit in combination with KRd, and thus the subject will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability. Subjects with measurable disease will be assessed by standard criteria. Responses levels, including MRD-negative, sCR, CR, VGPR, PR, MR, SD, and progressive disease will be determined by the IMWG Uniform Response Criteria as per Appendix F (Kumar et al., 2016). For the purposes of this study, subjects should be re-evaluated for response every 4 weeks. In addition to a baseline myeloma laboratory testing, confirmatory myeloma laboratory assessment will also be obtained within 4 weeks following initial documentation of an objective response.

11.2. Other Response Parameters

N/A

12. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1. Study Oversight

This protocol is monitored at several levels, as described in this section. The Protocol Principal Investigator is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, subject-specific clinical and laboratory data, and routine and serious adverse events; reporting of expedited adverse events; and accumulation of reported adverse events from other trials testing the same drug(s). The Protocol Principal Investigator and statistician have access to the data at all times through the CTMS web-based reporting portal.

For the Phase 1 portion of this study, all decisions regarding dose escalation/expansion/de-escalation require sign-off by the Protocol Principal Investigator through the CTMS/IWRS. In addition, for the Phase 1 portion, the Protocol Principal Investigator will have at least monthly,

or more frequently, conference calls with the Study Investigators and the CTEP Medical Officer(s) to review accrual, progress, and adverse events and unanticipated problems.

All Study Investigators at participating sites who register/enroll subjects on a given protocol are responsible for timely submission of data via Medidata Rave and timely reporting of adverse events for that particular study. This includes timely review of data collected on the electronic CRFs submitted via Medidata Rave.

All studies are also reviewed in accordance with the enrolling institution's data safety monitoring plan.

12.2. Data Reporting

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments. To access Rave via iMedidata:
• Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account, and
• Assigned one of the following Rave roles on the relevant Lead Protocol Organization (LPO) or Participating Organization roster at the enrolling site: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator. Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.
o To hold Rave CRA or Rave CRA (Lab Admin) role, site staff must hold a minimum of an AP registration type,
o To hold Rave Investigator role, the individual must be registered as an NPIVR or IVR, and
o To hold Rave Read Only role, site staff must hold an Associates (A) registration type.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site staff must log in to the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM username and password, and click on the accept link in the upper right-corner of the iMedidata page. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the Rave EDC link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a Rave EDC link will display under the study name.

Site staff that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Rave section under the Rave resource materials (Medidata Account Activation and

Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

Method

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. On-site audits will be conducted three times annually (one annual site visit and two data audits). For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 799-7580 or by email at CTMSSupport@theradex.com for additional support with Rave and completion of CRFs.

Responsibility for Data Submission

For ETCTN trials, it is the responsibility of the PI(s) at the site to ensure that all investigators at the ETCTN Sites understand the procedures for data submission for each ETCTN protocol and that protocol specified data are submitted accurately and in a timely manner to the CTMS via the electronic data capture system, Medidata Rave.

Data are to be submitted via Medidata Rave to CTMS on a real-time basis, but no less than once every 2 weeks. The timeliness of data submissions and timeliness in resolving data queries will be tracked by CTMS. Metrics for timeliness will be followed and assessed on a quarterly basis. For the purpose of Institutional Performance Monitoring, data will be considered delinquent if it is greater than 4 weeks past due.

Data from Medidata Rave and CTEP-AERS is reviewed by the CTMS on an ongoing basis as data is received. Queries will be issued by CTMS directly within Rave. The queries will appear on the Task Summary Tab within Rave for the CRA at the ETCTN to resolve. Monthly web-based reports are posted for review by the Drug Monitors in the IDB, CTEP. Onsite audits will be conducted by the CTMS to ensure compliance with regulatory requirements, GCP, and NCI policies and procedures with the overarching goal of ensuring the integrity of data generated from NCI-sponsored clinical trials, as described in the ETCTN Program Guidelines, which may be found on the CTEP (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm) and CTSU websites.

An End of Study CRF is to be completed by the PI, and is to include a summary of study endpoints not otherwise captured in the database, such as (for phase 1 trials), the recommended phase 2 dose (RP2D), and a description of any dose-limiting toxicities (DLTs). CTMS will utilize a core set of eCRFs that are Cancer Data Standards Registry and Repository (caDSR) compliant (http://cbiit.nci.nih.gov/ncip/biomedical-informatics-resources/interoperability-and-semantics/metadata-and-models). Customized eCRFs will be included when appropriate to meet

unique study requirements. The PI is encouraged to review the eCRFs, working closely with CTMS to ensure prospectively that all required items are appropriately captured in the eCRFs prior to study activation. CTMS will prepare the eCRFs with built-in edit checks to the extent possible to promote data integrity.

CDUS data submissions for ETCTN trials activated after March 1, 2014, will be carried out by the CTMS contractor, Theradex. CDUS submissions are performed by Theradex on a monthly basis. The trial's lead institution is responsible for timely submission to CTMS via Rave, as above.

The study data manager listed on the protocol face page is responsible for logging the TP53-wild type status confirmation report regardless of test result into the routine reporting system used by Theradex Oncology. This confirmed eligibility report must be sent by email to the submitting physicians/Principal Investigators/Clinical Trials Operations Offices per normal routine and kept on file by the coordinating site per normal routine for audit.

Further information on data submission procedures can be found in the ETCTN Program Guidelines (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm).

Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, and DQP Delinquent Forms modules.'

Note: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization (LPO) for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendaring functionality.

12.3. CTEP Multicenter Guidelines

N/A

12.4. Collaborative Agreements Language

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a subject or subject's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and

unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

12.5. Genomic Data Sharing Plan

N/A

13. STATISTICAL CONSIDERATIONS

13.1. Analysis Sets

13.1.1. Enrolled Analysis Set

The enrolled analysis set will include all subjects who signed an ICF and were enrolled in either the Dose Escalation part or Dose Expansion part of the study.

13.1.2. Full Analysis Set

The full analysis set will include all subjects enrolled in the Dose Escalation part or the Dose Expansion part who received any amount of KRT-232 (AMG 232) and who had at least 1 post-baseline disease assessment.

13.1.3. Primary Analysis Set

The primary analysis set will include all subjects in the full analysis set who were biomarker positive.

13.1.4. Dose-Limiting Toxicity Evaluable Set

The DLT-evaluable set will include all subjects enrolled in the Dose Escalation part who had a DLT within the first 4 weeks (28 days) on study, or without DLT but received at least 75% of scheduled KRT-232 (AMG 232) doses during the first 3 weeks (21 days). Subjects who complete C1 but are removed from study due to a *TP53* mutation and/or deletion are still eligible to be included in the DLT-evaluable set.

13.1.5. Safety Analysis Set

The safety analysis set will include all subjects enrolled who received any amount of KRT-232 (AMG 232). Subjects will be summarized according to treatment actually received.

Three groups of subjects will be identified within the safety analysis set: (1) subjects in the Dose Escalation part, (2) subjects in the Dose Expansion part, and (3) all subjects in the study.

13.1.6. Pharmacokinetic Analysis Set

The PK analysis set will include all subjects in the enrolled analysis set who received any amount of KRT-232 (AMG 232) and had measurable plasma concentrations of KRT-232 (AMG 232).

13.1.7. Pharmacodynamic/Biomarker Analysis Set

The biomarker analysis set will include all subjects in the enrolled analysis set who received any amount of KRT-232 (AMG 232) and who had the baseline assessment and where applicable, at least 1 post-baseline assessment for biomarkers.

13.2. Study Design/Endpoints

The primary endpoint is to assess the safety and tolerability of KRT-232 (AMG 232) + KRd in subjects with relapsed and/or refractory myeloma and to determine the MTD/tentative RP2D of KRT-232 (AMG 232) + KRd.

All subjects who receive any amount of the study drug will be evaluable for toxicity. The DLT-evaluable period will be during cycle 1, although toxicity will be monitored throughout the course of treatment. The primary analysis will occur after all subjects in Part B have either discontinued the study or completed at least 6 months of treatment.

13.2.1. Safety Analyses

Safety parameters will include SAEs, TEAEs, physical examination findings (including ECOG performance status), vital sign measurements, and standard clinical laboratory parameters (serum chemistry, hematology, urinalysis). Adverse events will be graded according to the NCI-CTCAE v5.0. In the Dose Escalation part, the incidence of DLTs will also be evaluated.

Safety analyses in general will be descriptive and will be presented in tabular format with the appropriate summary statistics. In the Dose Escalation part, the number of DLTs identified among the DLT-evaluable subjects in the DLT-evaluable set will be listed and summarized for each dose of KRT-232 (AMG 232).

13.2.2. Adverse Event Analyses

A TEAE is defined as an adverse event that emerges during the treatment period (from first dose date till 30 (± 5) days after the last dosing date), having been absent at pre-treatment; or reemerges during treatment, having been present at baseline but stopped prior to treatment; or worsens in severity after starting treatment relative to the pre-treatment state, when the adverse event is continuous. The number and percentage of subjects reporting TEAEs will be tabulated by the worst NCI- CTCAE grade, system organ class (SOC), and preferred term.

Similarly, the number and percentage of subjects reporting treatment-emergent SAEs will be tabulated, as well as TEAEs/SAEs considered related to KRT-232 (AMG 232) + KRd.

A by-subject adverse event (including TEAE) data listing will be provided including, but not limited to, verbatim term, preferred term, SOC, NCI-CTCAE grade, and relationship to study drug.

Deaths, other SAEs, and other significant adverse events, including those leading to permanent discontinuation from KRT-232 (AMG 232) + KRd, will be listed.

13.2.3. Clinical Laboratory Evaluation Analyses

Descriptive statistics will be provided for selected clinical laboratory test results (hematology and blood chemistry) and changes from baseline by scheduled time of evaluation, including the End-of-Treatment Visit, maximum post-treatment value, and minimum post-treatment value.

Abnormal laboratory results will be graded according to NCI-CTCAE, v5.0, if applicable. A shift table, presenting the 2-way frequency tabulation for baseline and the worst post-treatment value according to the NCI-CTCAE grade, will be provided for selected clinical laboratory tests. Abnormal clinical laboratory test results that are deemed of clinical significance or of grade 3 or 4 will be listed.

13.2.4. Vital Signs Analyses

Descriptive statistics will be provided for the vital signs measurements and changes from baseline by scheduled time of evaluation, including the End-of-Treatment Visit and the maximum and minimum post-treatment values.

13.3. Sample Size/Accrual Rate

The Dose Escalation phase of this study (Part 1) consists of 5 dose levels including at least 3 and up to 6 subjects for a minimum of 15 subjects if no DLT is reached, or a maximum of 30 subjects. An exploratory expansion phase including a goal of 10 subjects at the recommended phase 2 dose is also planned for a total in both phases of 25-40 subjects. During the dose-expansion phase, subjects removed from study after Cycle 1 based on the *TP53* mutation and/or deletion status will be replaced to ensure that a goal of 10 subjects with TP53 wild-type status are enrolled in the dose-expansion cohort. Based on prior phase I and II studies at MDACC targeting a similar subject population, we estimate 1.5 subjects will be accrued every month, suggesting that 16-26 months will be needed to meet the sample size. Please note this assumes no interruption in accrual.

For the Dose Expansion phase (Part 2), the goal is to enroll 10 additional subjects. However, additional subjects may be enrolled if for example, two or more subjects are undergoing screening at the same time when only one study slot is remaining, and both subjects are deemed eligible for study participation. The maximum half width of the 95% confidence interval for the response rate will be 32% for 10 subjects. Including the 6 subjects enrolled at the MTD in the Part I (dose-escalation phase), the maximum half width of the 95% confidence interval for 16 subjects will be 25%.

Estimated monthly accrual is 2.5 subjects/month.

PLANNED ENROLLMENT REPORT

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	1			1
Asian	1	1			2
Native Hawaiian or Other Pacific Islander	1	0			1
Black or African American	3	3			6
White	12	12			24
More Than One Race			3	3	6

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
Total	17	17	3	3	40

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13.4. Stratification Factors

N/A

13.5. Analysis of Secondary Endpoints

PK and PD analysis
Descriptive statistics will be provided for selected PK, and PD data by dose and time as appropriate. Descriptive statistics on continuous data will include means, medians, standard deviations, and ranges, while categorical data will be summarized using frequency counts and percentages. Graphical summaries of the data may be presented.

A full pharmacokinetic profile of KRT-232 (AMG 232) will be proposed in this protocol to assess exposure-response relationships with various PD endpoints (i.e., MIC-1 changes, toxicity, efficacy). KRT-232 (AMG 232) concentrations in these samples will be quantitatively measured using liquid chromatography/tandem mass spectrometric (LC/MS/MS) method that will be developed by the Analytical Pharmacology Core Laboratory at the Sidney Kimmel Comprehensive Cancer Center (SKCCC) at Johns Hopkins. For KRT-232 (AMG 232), the individual PK parameters from a single dose will be estimated for C_{max}, AUC, $T_{1/2}$, apparent Cl/F, and apparent V/F using non-compartmental or compartmental PK methods with the software WinNonlin. For serum MIC-1 levels, each individual level will be normalized to the baseline level for that subject. Advanced population PK methods may be employed to assess the link between drug exposure and biological effects and efficacy. The PK variables and changes in MIC-1 will be tabulated and descriptive statistics (e.g., geometric means and coefficients of variation) calculated for each dose level. PK parameters (i.e., $T_{1/2}$, Cl, and AUC) and MIC-1 changes will be compared across dose level using nonparametric statistical testing techniques. Exploratory correlative studies with pharmacodynamic (biological endpoints, toxicity and efficacy) will be analyzed using nonparametric statistics. Significance for comparisons will be at the $p<0.05$ level.

13.6. Efficacy Analysis

Efficacy analysis will be performed for all subjects in the dose escalation and dose expansion part of the study. Separate efficacy analyses will be performed on the *full analysis set* which includes all subjects enrolled on study, and the *primary analysis set* which includes only subjects who were biomarker positive (*TP53* WT). Parameters assessed will include minimal residual

disease (MRD) negative, stringent complete response (sCR), complete response (CR), very good partial response (VGPR), and partial response (PR), minimal response (MR) and stable disease (SD) per IMWG Uniform Response criteria. In addition, overall response rate (defined as greater than or equal to PR across all cycles of treatment), response duration, time-to-response (TTR), PFS, and OS will be assessed.

Best overall response categories will be tabulated by dose cohort and overall for the IMWG categories of MRD-negative, sCR, CR, VGPR, PR, MR, SD, progressive disease. A two-sided 95% exact binominal CI will be calculated for each category. The myeloma response rate (responses ≥PR) will also be tabulated by dose cohort and overall. Time-to-event analyses will be done using Kaplan-Meier analyses and will include time to response, duration of response, progression-free survival (PFS), and overall survival (OS), as data allow. If there is not enough data to apply the Kaplan-Meier test, the data will be summarized by descriptive statistics.

Time to response (for responders only) will be calculated as the time from the date of first study treatment dosing to the first date of documented response (PR or better) based on IMWG uniform response criteria. Time to response will be summarized by descriptive statistics by dose cohorts.

Duration of response (for responders only) is defined as the time from the earliest date of documented response (PR or better, based on IMWG uniform response criteria) to the earliest date when disease progression was confirmed. Subjects who are non-responders will be excluded from this analysis. Detailed censoring rules for duration of response will be specified in the SAP.

PFS will be calculated as the time from the time of enrollment until documented disease progression, as determined by the Investigator using IMWG uniform response criteria, or death from any cause, whichever occurs first. Kaplan-Meier methods will be used to estimate PFS over time and the median duration of PFS. Subjects with no PFS event will be censored at the date of their last myeloma disease assessment.

OS is defined as the time from the initial administration of KRT-232 (AMG 232) + KRd to death form
any cause. Kaplan-Meier methods will be used to estimate the OS function. Subjects who do not die will be censored at the date that the subject was last known to be alive.

13.7. Analysis of Exploratory Endpoint

Exploratory analyses of RNA expression levels of relevant genes in the *TP53* pathway that may predict response to therapy will be performed on pre- and post-treatment bone marrow biopsies. An optional post-treatment bone marrow biopsy will be pre Cycle 2 Day 1. An estimated 75% of subjects are expected to consent to this optional post-treatment bone marrow biopsy; thus we expect 19-30 of the planned 25-40 subjects to provide an additional biopsy. These exploratory analyses will potentially guide future studies with larger cohorts of patients.

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15. APPENDICES

15.1. APPENDIX A: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

15.2. APPENDIX B: PATIENT DRUG INTERACTIONS HANDOUT AND WALLET CARD

Information for Patients, Their Caregivers and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

Patient Name:	**Diagnosis:**	**Trial #:**	
Study Doctor:	**Study Doctor Phone #:**	**Study Drug(s):**	**AMG 232 (KRT 232)**

Please show this paper to all your healthcare providers (doctors, physician assistants, nurse practitioners, pharmacists), and tell them you are taking part in a clinical trial sponsored by the National Cancer Institute.

These are the things that your healthcare providers need to know:

AMG 232 (KRT 232) interacts with certain specific liver enzymes and certain transport proteins that help move drugs in and out of cells.

	Explanation
CYP Isoenzymes	The enzymes in question are CYP3A4 and CYP2C8. AMG 232 (KRT 232) is a moderate inhibitor of CYP3A4 and CYP2C8 and also induces CYP3A4 and may effect other drugs that are metabolized by these enzymes. KRT-232 has the potential to cause a minor drug-drug interaction (DDI) with drugs cleared predominantly by CYP3A4 (inhibition and induction). Use caution in patients taking CYP3A4 substrates with narrow therapeutic ranges.
Glucuronidation	AMG 232 (KRT 232) is metabolized by UGT1A1, UGT1A3, and UGT1A4 and is a moderate inhibitor of UGT1A1. AMG 232 (KRT 232) may be affected by other drugs that inhibit or induce these enzymes and may affect other drugs that are metabolized by UGT1A1.
Transport Proteins	The protein in question is P-gp. AMG 232 (KRT 232) is a substrate of P-gp and may be affected by other drugs that inhibit or induce this transport protein.

These are the things that you need to know:

The study drug AMG 232 (KRT 232), may interact with other drugs which can cause side effects. For this reason, it is very important to tell your doctors about all your medicines, including: (a) medicines you are taking before this clinical trial, (b) medicines you start or stop taking during this clinical trial, (c) medicines you buy without a prescription (over-the-counter remedy), (d) herbals

or supplements (e.g. St. John's Wort). It is helpful to bring your medication bottles or an updated medication list with you.

Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered substrates of CYP3A4 and CYP2C8 or inhibitors or inducers of transport protein P-gp.

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.

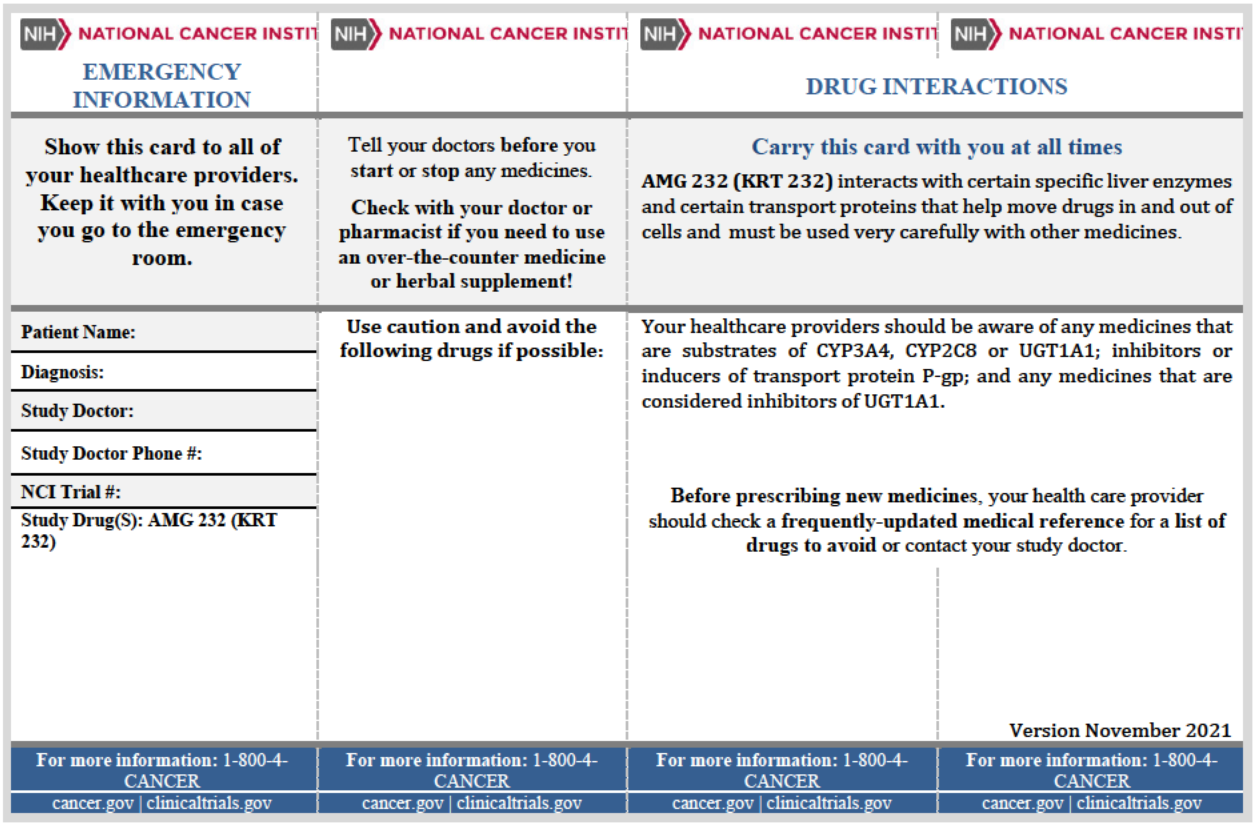
- Make sure your doctor knows to avoid certain prescription medicines.
    - Avoid any medicines considered substrates of CYP3A4 and CYP2C8.
    - Avoid any medicines considered inhibitors or inducers of P-gp.
    - Avoid any medications considered inhibitors or substrates of UGT1A1.

- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine.

Version: November 2021

(Next page: Patient Drug Interaction Wallet Card)

15.3. PATIENT DRUG INTERACTION WALLET CARD



NIH NATIONAL CANCER INSTITUTE

EMERGENCY INFORMATION

Show this card to all of your healthcare providers. Keep it with you in case you go to the emergency room.

Patient Name:

Diagnosis:

Study Doctor:

Study Doctor Phone #:

NCI Trial #:

Study Drug(S): AMG 232 (KRT 232)

For more information: 1-800-4-CANCER
cancer.gov | clinicaltrials.gov

NIH NATIONAL CANCER INSTITUTE

Tell your doctors **before** you start or stop any medicines.

Check with your doctor or pharmacist if you need to use an over-the-counter medicine or herbal supplement!

Use caution and avoid the following drugs if possible:

For more information: 1-800-4-CANCER
cancer.gov | clinicaltrials.gov

NIH NATIONAL CANCER INSTITUTE

DRUG INTERACTIONS

Carry this card with you at all times

AMG 232 (KRT 232) interacts with certain specific liver enzymes and certain transport proteins that help move drugs in and out of cells and must be used very carefully with other medicines.

Your healthcare providers should be aware of any medicines that are substrates of CYP3A4, CYP2C8 or UGT1A1; inhibitors or inducers of transport protein P-gp; and any medicines that are considered inhibitors of UGT1A1.

Before prescribing new medicines, your health care provider should check a **frequently-updated medical reference** for a **list of drugs to avoid** or contact your study doctor.

For more information: 1-800-4-CANCER
cancer.gov | clinicaltrials.gov

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For more information: 1-800-4-CANCER
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15.4. APPENDIX C: Drug-Induced Liver Injury (DILI) Reporting & Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of drug-induced liver injury (DILI), cases of concurrent AST or ALT and TBL and/or INR elevation according to the criteria specified in Section 6.1 require the following:

The event is to be reported to CTEP as a serious adverse event within 24 hours of discovery or notification of the event (*i.e.*, before additional etiologic investigations have been concluded)
The appropriate CRF (*e.g.*, Adverse Event CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to CTEP.
Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Section 7.

Additional Clinical Assessments and Observation

All subjects in whom investigational product(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in Section 6.1 or who experience AST or ALT elevations ≥ 3 × ULN are to undergo a period of "close observation" until abnormalities return to normal or to the subject's baseline levels. Assessments that are to be performed during this period include:

Repeat AST, ALT, ALP, bilirubin (total and direct), and INR within 24 hours
In cases of TBL > 2 × ULN or INR > 1.5, retesting of liver tests, BIL (total and direct), and INR is to be performed every 24 hours until laboratory abnormalities improve.

Testing frequency of the above laboratory tests may decrease if the abnormalities stabilize or the investigational product(s) or protocol-required therapies has/have been discontinued AND the subject is asymptomatic.

Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL:
Obtain complete blood count (CBC) with differential to assess for eosinophilia
Obtain serum total immunoglobulin IgG, Anti-nuclear antibody (ANA), Anti Smooth Muscle Antibody, and Liver Kidney Microsomal antibody 1 (LKM1) to assess for autoimmune hepatitis
Obtain serum acetaminophen (paracetamol) levels
Obtain a more detailed history of:
Prior and/or concurrent diseases or illness
Exposure to environmental and/or industrial chemical agents
Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting and fever
Prior and/or concurrent use of alcohol, recreational drugs and special diets
Concomitant use of medications (including non-prescription medicines and herbal and dietary supplements), plants, and mushrooms
Obtain viral serologies

Obtain CPK, haptoglobin, LDH, and peripheral blood smear
Perform appropriate liver imaging if clinically indicated
Obtain appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
Obtain hepatology consult (liver biopsy may be considered in consultation with an hepatologist)
Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal. The "close observation period" is to continue for a minimum of 4 weeks after discontinuation of all investigational product(s) and protocol-required therapies.

The potential DILI event and additional information such as medical history, concomitant medications and laboratory results must be captured in corresponding CRFs.

15.5. APPENDIX D: CASE REPORT FORM FOR TP53 NGS ASSAY

Clinical Study: _____
Report Date: _____

TUMOR SPECIMEN REPORT

The OCAv3 next-generation sequencing (NGS) assay as employed for KRT-232 (AMG 232) TP53 detection is intended to provide information about mutation or lack of mutation within the TP53 DNA of the patient's tumor. Mutations determined by comparison to the Human Reference Genome hg19 are categorized as single nucleotide variants (SNVs) or insertions/deletions (indels). **NOTE: This report does not indicate potential treatment assignment.**

Patient Initials (First, Last):	**Patient Identifier:**	**MoCha Sample ID:**	**Gender:**
Referring Physician:		**Fax:**	**Tel:**
Biopsy Site:	**Date Collected:**	**Primary Diagnosis:**	**Tumor Content (%)[1]:**

Mutation(s) Detected: None identified *(Delete this text if variants are reported)*

Chromosome:Position	**Nucleotide Change**	**Protein Change**	**VAF[2]**	**Mutation Type[3]**

[1]Tumor content was provided by site/address. Reported assay characteristics cannot be guaranteed for specimens that present a tumor content below 20%.

[2]Analytical sensitivity is ≥5%

[3] Single nucleotide variant (SNV) or insertion/deletion (INDEL)

Comments:

SIGNATURE APPROVAL:

The signature below attests that the signee has reviewed the data and results reported and concurs with the stated conclusions.

DISCLAIMER: This assay is considered a Laboratory Developed Test (LDT). Its performance characteristics have been determined through extensive testing although it has not been cleared by the US Food and Drug Administration and such approval is not required for clinical implementation. Furthermore, any Comments included in this report are strictly interpretive and the opinion of the reviewer. This laboratory is certified under the Clinical Laboratory Improvement Amendments (CLIA) for the performance of high-complexity molecular testing for clinical purposes.

Sequencing Assay Information

Methodology, Scope, and Application: *The sequencing test utilizes the Thermo Fisher Scientific Oncomine® Comprehensive Assay v3.0 (OCAv3), a next-generation sequencing (NGS) assay that utilizes a multiplex polymerase chain reaction (PCR) with DNA extracted from formalin-fixed tissue for sequencing on the Ion S5 XL platform and analyzed by Torrent Suite Software v5.2 and Torrent Variant Caller v5.2. The OCv3 NGS Assay can reliably identify the presence or absence of mutations and polymorphisms within the TP53 gene, with results compared to the TP53 sequence (NM_000546) in Human Reference Genome hg19. The OCAV3 NGS Assay is a laboratory developed test designed to find gene mutations within tumors (somatic mutations). It was not designed to find hereditary mutations. Only DNA is analyzed in this application; RNA analysis is not performed.*

Analytical Sensitivity and Specificity: *The OCAV3 NGS Assay has been determined to be suitably analytically sensitive and specific for the various types of abnormalities within its reportable range, demonstrating 97.18% sensitivity compared with orthogonal assay results and 100% specificity for the mutation types reported. 99.99% or greater reproducibility has been demonstrated. All quality measures for this assay were within defined assay parameters.*

15.6. APPENDIX E: MEDICATION DIARY

DOSING DIARY: KRT-232 (AMG 232) + Carfilzomib, Lenalidomide, and Dexamethasone

Subject Identification Number _____ **Subject Initials _____**

Investigator _____ **Cycle _____**

Subject Completion Instructions

This is a "diary" that you will use to keep track of when you take your oral study medications including KRT-232 (AMG 232), lenalidomide, and dexamethasone.

Please avoid food for 2 hours before and 2 hours after KRT-232 (AMG 232) study drug administration. KRT-232 (AMG 232) should be taken with a full glass (240 mL) of water. Lenalidomide and dexamethasone study drugs may be taken with or without food.

It is important that you fill out this diary every day once you take your study medications. Record the date and if tablet(s) was taken for that day. If Yes, record the time tablet(s) was taken in the next column.
You must bring this diary and all unused medication to the clinic at each visit. Therefore, it is important that you keep them in a safe place where they will not be lost.
If you have any questions about your treatment, or in case of overdose, contact your study doctor at the number below:

_____ _____
Investigator Phone Number

Your assigned daily dose of KRT-232 (AMG 232) on Days 1 through Day 7 is _____ mg.
____ 15 mg tablet ____ 60 mg tablet

What if I miss a dose of KRT-232 (AMG 232)?
If you forget a dose of KRT-232 (AMG 232) and it has been less than 12 hours since your regular time, take it as soon as you remember. Otherwise, skip the missed dose. Do not take a double dose (two doses at the same time) to make up for a forgotten dose. If you vomit after taking a dose, do not repeat the dose, and you should resume dosing at the time of your next scheduled dose.

Your assigned daily dose of Lenalidomide on Days 1 through Day 21 is _____ mg.
____ 5 mg capsule ____ 10 mg capsule ____ 15 mg capsule ____ 25 mg capsule

What if I miss a dose of lenalidomide?
f you forget a dose of lenalidomide and it has been less than 12 hours since your regular time, take it as soon as you remember. Otherwise, skip the missed dose. Do not take a double dose (two doses at the same time) to make up for a forgotten dose. If you vomit after taking a dose, do not repeat the dose, and you should resume dosing at the time of your next scheduled dose.

Your assigned daily dose of oral Dexamethasone on Days 1, 8, and 15 is _____ mg. If you are receiving dexamethasone intravenously on these days with carfilzomib, you will be instructed to not take oral dexamethasone doses on these days.
____ 4 mg tablet

Your assigned daily dose of oral Dexamethasone on Day 22 is _____ mg.
____ 4 mg tablet

What if I miss a dose of dexamethasone?
If you forget a dose of dexamethasone, take it as soon as you remember it as long as your next scheduled dose is at least 72 hours away. Otherwise, skip the missed dose. Do not take a double dose (two doses at the same time) to make up for a forgotten dose. If you vomit after taking a dose, do not repeat the dose, and you should resume dosing at the time of your next scheduled dose.

Please take the specified number of tablets or capsules recorded below each study drug.

KRT-232 (AMG 232) Dosing Schedule

Day	Date *(dd/mmm/yyyy)*	Was dose taken? *If Yes, record time taken.*	Time of Dose	Number of Tablets Taken *Record the **number** of tablets taken next to each strength.*
1	__ __/__ __ __/__ __ __ __	☐ Yes ☐ No	___:___ ☐ AM ☐ PM	____ 15 mg ____ 60 mg ____
2	__ __/__ __ __/__ __ __ __	☐ Yes ☐ No	___:___ ☐ AM ☐ PM	____ 15 mg ____ 60 mg ____
3	__ __/__ __ __/__ __ __ __	☐ Yes ☐ No	___:___ ☐ AM ☐ PM	____ 15 mg ____ 60 mg ____
4	__ __/__ __ __/__ __ __ __	☐ Yes ☐ No	___:___ ☐ AM ☐ PM	____ 15 mg ____ 60 mg ____
5	__ __/__ __ __/__ __ __ __	☐ Yes ☐ No	___:___ ☐ AM ☐ PM	____ 15 mg ____ 60 mg ____
6	__ __/__ __ __/__ __ __ __	☐ Yes ☐ No	___:___ ☐ AM ☐ PM	____ 15 mg ____ 60 mg ____
7	__ __/__ __ __/__ __ __ __	☐ Yes ☐ No	___:___ ☐ AM ☐ PM	____ 15 mg ____ 60 mg ____

Lenalidomide Dosing Schedule

Day	Date *(dd/mmm/yyyy)*	Was dose taken? *If Yes, record time taken.*	Time of Dose	Number of Capsules Taken *Record the **number** of capsules taken next to each strength.*
1	__ __/__ __ __/__ __ __ __	☐ Yes ☐ No	___:___ ☐ AM ☐ PM	____ 5 mg ____ 10 mg ____ 15 mg ____ 25 mg
2	__ __/__ __ __/__ __ __ __	☐ Yes ☐ No	___:___ ☐ AM ☐ PM	____ 5 mg ____ 10 mg ____ 15 mg ____ 25 mg
3	__ __/__ __ __/__ __ __ __	☐ Yes ☐ No	___:___ ☐ AM ☐ PM	____ 5 mg ____ 10 mg ____ 15 mg ____ 25 mg
4	__ __/__ __ __/__ __ __ __	☐ Yes ☐ No	___:___ ☐ AM ☐ PM	____ 5 mg ____ 10 mg ____ 15 mg ____ 25 mg
5	__ __/__ __ __/__ __ __ __	☐ Yes ☐ No	___:___ ☐ AM ☐ PM	____ 5 mg ____ 10 mg ____ 15 mg ____ 25 mg
6	__ __/__ __ __/__ __ __ __	☐ Yes ☐ No	___:___ ☐ AM ☐ PM	____ 5 mg ____ 10 mg ____ 15 mg ____ 25 mg
7	__ __/__ __ __/__ __ __ __	☐ Yes ☐ No	___:___ ☐ AM ☐ PM	____ 5 mg ____ 10 mg ____ 15 mg ____ 25 mg
8	__ __/__ __ __/__ __ __ __	☐ Yes ☐ No	___:___ ☐ AM ☐ PM	____ 5 mg ____ 10 mg ____ 15 mg ____ 25 mg
9	__ __/__ __ __/__ __ __ __	☐ Yes ☐ No	___:___ ☐ AM ☐ PM	____ 5 mg ____ 10 mg ____ 15 mg ____ 25 mg
10	__ __/__ __ __/__ __ __ __	☐ Yes ☐ No	___:___ ☐ AM ☐ PM	____ 5 mg ____ 10 mg ____ 15 mg ____ 25 mg
11	__ __/__ __ __/__ __ __ __	☐ Yes ☐ No	___:___ ☐ AM ☐ PM	____ 5 mg ____ 10 mg ____ 15 mg ____ 25 mg
12	__ __/__ __ __/__ __ __ __	☐ Yes ☐ No	___:___ ☐ AM ☐ PM	____ 5 mg ____ 10 mg ____ 15 mg ____ 25 mg
13	__ __/__ __ __/__ __ __ __	☐ Yes ☐ No	___:___ ☐ AM ☐ PM	____ 5 mg ____ 10 mg ____ 15 mg ____ 25 mg
14	__ __/__ __ __/__ __ __ __	☐ Yes ☐ No	___:___ ☐ AM ☐ PM	____ 5 mg ____ 10 mg ____ 15 mg ____ 25 mg
15	__ __/__ __ __/__ __ __ __	☐ Yes ☐ No	___:___ ☐ AM ☐ PM	____ 5 mg ____ 10 mg ____ 15 mg ____ 25 mg
16	__ __/__ __ __/__ __ __ __	☐ Yes ☐ No	___:___ ☐ AM ☐ PM	____ 5 mg ____ 10 mg ____ 15 mg ____ 25 mg

17	__ __/__ __ __/__ __ __ __	☐ Yes ☐ No	___:___ ☐ AM ☐ PM	____ 5 mg ____ 10 mg ____ 15 mg ____ 25 mg
18	__ __/__ __ __/__ __ __ __	☐ Yes ☐ No	___:___ ☐ AM ☐ PM	____ 5 mg ____ 10 mg ____ 15 mg ____ 25 mg
19	__ __/__ __ __/__ __ __ __	☐ Yes ☐ No	___:___ ☐ AM ☐ PM	____ 5 mg ____ 10 mg ____ 15 mg ____ 25 mg
20	__ __/__ __ __/__ __ __ __	☐ Yes ☐ No	___:___ ☐ AM ☐ PM	____ 5 mg ____ 10 mg ____ 15 mg ____ 25 mg
21	__ __/__ __ __/__ __ __ __	☐ Yes ☐ No	___:___ ☐ AM ☐ PM	____ 5 mg ____ 10 mg ____ 15 mg ____ 25 mg

Dexamethasone Dosing Schedule

Day	**Date** *(dd/mmm/yyyy)*	**Was dose taken?** *If Yes, record time taken.*	**Time of Dose**	**Number of Tablets Taken** *Record the **number** of tablets taken next to each strength.*
1*	__ __/__ __ __/__ __ __ __	☐ Yes ☐ No	___:___ ☐ AM ☐ PM	____ 4 mg
8*	__ __/__ __ __/__ __ __ __	☐ Yes ☐ No	___:___ ☐ AM ☐ PM	____ 4 mg
15*	__ __/__ __ __/__ __ __ __	☐ Yes ☐ No	___:___ ☐ AM ☐ PM	____ 4 mg
22	__ __/__ __ __/__ __ __ __	☐ Yes ☐ No	___:___ ☐ AM ☐ PM	____ 4 mg

***If you are receiving dexamethasone intravenously on these days with carfilzomib, you will be instructed to not take oral dexamethasone doses on these days.**

15.7. APPENDIX F: IMWG Response Criteria (Kumar et al., 2016)

IMWG MRD criteria (requires a complete response as defined below)	
Sustained MRD-negative	MRD negativity in the marrow (NGF or NGS, or both) and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (eg, MRD-negative at 5 years)
Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by next generation flow (NGF) on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
Sequencing MRD-negative	Absence of clonal plasma cells by next generation sequencing (NGS) on bone marrow aspirate in which presence of a clone is defined as less than two identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the LymphoSIGHT platform (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
Imaging plus MRD-negative	MRD negativity as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT or decrease to less mediastinal blood pool SUV or decrease to less than that of surrounding normal tissue
Standard IMWG response criteria	
Stringent complete response	Complete response as defined below plus normal FLC ratio and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells)
Complete response	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow aspirates
Very good partial response	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M-protein plus urine M-protein level <100 mg per 24 h
Partial response	≥50% reduction of serum M-protein plus reduction in 24 h urinary M-protein by ≥90% or to <200 mg per 24 h; If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria; If serum and urine M-protein are unmeasurable, and serum-free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma-cell percentage was ≥30%. In addition to these criteria, if present at baseline, a ≥50% reduction in the size (SPD) of soft tissue plasmacytomas is also required
Minimal response	≥25% but ≤49% reduction of serum M-protein and reduction in 24-h urine M-protein by 50–89%. In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size (SPD) of soft tissue plasmacytomas is also required
Stable disease	Not meeting criteria for complete response, very good partial response, partial response, minimal response, or progressive disease
Progressive disease	Any one or more of the following criteria: Increase of 25% from lowest confirmed response value in one or more of the following criteria: Serum M-protein (absolute increase must be ≥0.5 g/dL); Serum M-protein increase ≥1 g/dL, if the lowest M component was ≥5 g/dL; Urine M-protein (absolute increase must be ≥200 mg/24 h); In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL); In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be ≥10%); Appearance of a new lesion(s), ≥50% increase from nadir in SPD of >1 lesion, or ≥50%

	increase in the longest diameter of a previous lesion >1 cm in short axis; ≥50% increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease
Clinical relapse	Clinical relapse requires one or more of the following criteria: Direct indicators of increasing disease and/or end organ dysfunction (CRAB features) related to the underlying clonal plasma-cell proliferative disorder. It is not used in calculation of time to progression or progression-free survival but is listed as something that can be reported optionally or for use in clinical practice; Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression); Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and ≥1 cm) increase as measured serially by the SPD§§ of the measurable lesion; Hypercalcemia (>11 mg/dL); Decrease in hemoglobin of ≥2 g/dL not related to therapy or other non-myeloma-related conditions; Rise in serum creatinine by 2 mg/dL or more from the start of the therapy and attributable to myeloma; Hyperviscosity related to serum paraprotein
Relapse from complete response (to be used only if the end point is disease-free survival)	Any one or more of the following criteria: Reappearance of serum or urine M-protein by immunofixation or electrophoresis; Development of ≥5% plasma cells in the bone marrow; Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcemia see above)
Relapse from MRD negative (to be used only if the end point is disease-free survival)	Any one or more of the following criteria: Loss of MRD negative state (evidence of clonal plasma cells on NGF or NGS, or positive imaging study for recurrence of myeloma); Reappearance of serum or urine M-protein by immunofixation or electrophoresis; Development of ≥5% clonal plasma cells in the bone marrow; Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcemia)

15.8. APPENDIX G: COLLECTION OF BUCCAL SWAB AT SCREENING

Materials:

IsoHelix SK-1S DNA Swab: 1 buccal swab with one 5ml tube and cap

Patient Preparation

Patient should not eat, drink, smoke, chew gum or brush teeth for 1 hour prior to buccal collection.

Specimen Labeling and Identification

- Specimen should be labeled as per the Specimen Tracking Instructions (Section 9.1.1.1.)

Collection of Buccal cells:

Note: The collector should wear gloves to prevent any DNA contamination.

1) Check the seal of the buccal swab to make sure it has not been broken.
2) Check the expiration date (if on the swab) to ensure it's not expired.
3) Thoroughly rinse out the patient's mouth twice with water.
4) Open pouch from end opposite swab, and use care not to touch swab.
5) Collect tissue by **rubbing** the swab firmly on the inside of both cheeks, **approximately 30 seconds on each side**, making certain to move the brush over the entire cheek.
6) Place head of swab into collection tube and snap off handle, leaving swab in tube.
7) Carefully place the cap on the tube.
8) Be sure to double check the patient identifiers.

Specimen Shipping and Delivery

Non-MDACC study sites will ship buccal swabs in the same specimen container as the bone marrow aspirate to the MD Anderson TQL.

DNA will be extracted by the MD Anderson Molecular Diagnostics Laboratory (MDL) and shipped to the NCI MoCha laboratory for DNA sequencing.

Please refer to Section 9.1.1.2 and 9.1.1.3 in the protocol for additional details.

Unacceptable Specimens:

1. Unlabeled or mislabeled specimens.
2. Any buccal swab that has been subjected to possible DNA contamination
3. Any buccal swab that has been subjected to UV light.