Alliance Central Protocol Operations Program Office
[redacted]

December 20, 2024

[redacted]
CTEP Protocol and Information Office
Clinical Investigations Branch, CTEP, CDTD, NCI

Re: Review of Amendment #06 of Protocol #A071701

Dear Dr[redacted]

Please see the attached revised protocol and consent for Alliance A071701, "*Genomically-Guided Treatment Trial in Brain Metastases*." We would like to thank the NCI Reviewers for their review of the protocol and informed consent documents dated 07/12/2024. The Study Team's response to each review items are included in bold text, with hyperlinks to each section of the protocol and consent containing each revision.

Please let us know what further information we may provide.

Sincerely,

[redacted], MD
Executive Officer
Alliance for Clinical Trials in Oncology

I. Comments Requiring a Response – Major Issues:

#	Section	Comments
1.	13.2.2	The statistical designs for the KRAS G12C and CDK inhibitor cohorts are nearly identical with nearly identical statistical operating characteristics, except that there is no provision for early futility stopping for the latter design. The CDK inhibitor cohort should follow the same 2-stage Simon minimax design as prescribed for the KRAS G12C inhibitor cohort, which would yield .60 probability of early stopping for a true 5% OR rate, with no appreciable loss of power for a true 30% OR rate. **PI Response: We appreciate the suggestion to make the design for this arm consistent with the other arms by including an interim analysis. Thus, we have updated the design for the CDK inhibitor arm to use a two-stage Simon minimax design, parallel to what is proposed for the PI3K inhibitor arm.** **Note that the KRAS G12C inhibitor arm utilizes a two-stage Fleming phase II design with fewer patients, but it was assumed that this comment was referencing the PI3K inhibitor arm, which does use the Simon minimax design.**

II. Comments Requiring a Response – Administrative & Editorial Issues:

#	Section	Comments
2.	13.2.2	The 2-stage Fleming design given for the KRAS G12C inhibitor cohort appears to have a typographical error. The criterion for a positive cohort should be at least 3 (21%) (not 4 (29%)) responses out of 14. A design requiring observation of a 29% OR rate would have approximately 50% power to detect a true 30% OR rate. **PI Response: We sincerely thank the Reviewer for catching this error. We have updated the decision rules for this design to reflect the correct criteria for this design.**

III. Recommendations:

#	Section	Comments
3.	6.1.2 Data Management	*Please revise the following language:* **Medidata Rave** Medidata Rave is the 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. Requirements to access Rave via iMedidata: • Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems; and • Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator. Rave role requirements:

#	Section	Comments
		• Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type; • Rave Investigator role must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR); and • Rave Read Only or Rave SLA role must have at a minimum an Associate (A) registration type. Refer to [redacted] for registration types and documentation required. This study has a Delegation of Tasks Log (DTL). Therefore, those requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL. Upon initial site registration approval for the study in the Regulatory application, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata. No action will be required; each study invitation will be automatically accepted and study access in Rave will be automatically granted. 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 eLearning link in the Tasks pane located in the upper right corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the Studies pane located in the center of the iMedidata screen; 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 replace the eLearning link under the study name. ~~No action will be required by site staff (to activate their account) who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in the Regulatory application. Pending study invitations (previously sent but not accepted or declined by a site user) will be automatically accepted and study access in Rave will be automatically granted for the site user. Account activation instructions are located on the CTSU website in the *Data Management* section under the Data Management Help Topics > Rave resource materials (*Medidata Account Activation and Study Invitation*). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section or by contacting the CTSU Help Desk at [redacted] or by email at [redacted].~~ Action will be required by site staff (to activate their account) who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in the Regulatory application. Account activation instructions are located on the CTSU website in the Data Management section under the Data Management Help Topics > Rave Resources > Medidata Account Activation and Study Invitation (to activate your iMedidata account). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management Rave Resources section or by contacting the CTSU Help Desk at [redacted] or by email at [redacted].

#	Section	Comments
		<u>PI Response:</u> All text in this section has been updated to reflect current CTSU boilerplate language.

Update #04

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

PROTOCOL UPDATE TO ALLIANCE A071701

GENOMICALLY-GUIDED TREATMENT TRIAL IN BRAIN METASTASES

X	**Update:**		**Status Change:**
X	Eligibility changes		Activation
	Therapy / Dose Modifications / Study Calendar changes		Closure
X	Informed Consent changes		Suspension / temporary closure
X	Scientific / Statistical Considerations changes		Reactivation
X	Data Submission / Forms changes		
X	Editorial / Administrative changes		
X	Other: Updated CTSU language, updated expedited AE reporting table		

Reconsent is required for all patients receiving protocol-specified treatment with abemaciclib or MRTX849 (adagrasib). Please follow the policy of your IRB of record regarding notifying patients of new information contained in this update.

No recommended IRB level of review is provided by the Alliance since the CIRB is the IRB of record for this trial. The site has 30 days after the posting of this amendment to implement it at their site. Please refer to the amendment application and CIRB guidelines for further instructions.

UPDATES TO THE PROTOCOL:

Cover Page

- Telephone numbers and institution names have been removed for all Co-Chairs for consistency with the Alliance Protocol Template.
- Dr. [redacted] have replaced Dr. [redacted] as the Neuro-Onc Committee Co-Chairs. All contact information has been updated accordingly.
- Dr. [redacted] has been removed as a Breast Co-Chair.

Study Resources (Page 2)

- The telephone number and institution for [redacted] has been removed as all inquiries should be sent via email.
- Dr. [redacted] has replaced Dr. [redacted] the A071701 Pharmacy Contact. All contact information has been updated accordingly.

- All contact information for the Alliance Biorepository at Mayo Clinic has been removed and replaced with the following sentence for accuracy and consistency with the Alliance Protocol Template: "Please see contact information in the A071701 Correlative Science Manual (CSM)."
- The contact information for IROC Ohio has been updated to reflect its change of address.

Eligibility Summary (Page 4)

The following changes have been made below the **Registration Eligibility Criteria** heading for consistency with changes made in Section 3.3 to broaden eligibility criteria:

- In the 2nd criterion, "5 mm" has replaced "10 mm."
- In the 15th criterion, in the 1st sentence, the phrase "NTRK, ROS1" has been removed, and a new 2nd sentence has been added that reads: "For KRAS G12C arm, if brain metastasis tissue is not available, then presence of KRAS G12C mutation can be in the extracranial site only."
- In the 17th criterion, the phrase "CDK and PI3K arms" has replaced "CDK, PI3K, and NTRK arms."

Schema

- In the 1st and 2nd boxes for histologies, the subgroups have been removed and replaced with the phrase "All primary histologies (n=21)" to reflect that subgroups have been consolidated within treatment arms. Additionally, in the 4th box for histologies, the subgroups have been removed and replaced with the phrase "All primary histologies (n=14)" to reflect that subgroups have been consolidated within treatment arms
- In the box for the **Entrectinib** cohort, the phrase "(Closed to accrual 1/9/2024)" has been added, and all text in the box has been greyed out to reflect that accrual to this cohort has closed.
- In the box for the **MRTX849 (Adagrasib)** cohort, the phrase "**(Adagrasib)**" has been added for clarity and consistency.

Section 1.3 (Study Design)

- A new 6th paragraph has been added to provide a rationale for consolidating subgroups within treatment arms.
- In the 4th sentence of the 3rd paragraph under the **Abemaciclib** heading, the word "sex" has replaced the word "gender" to align with current federal mandates per the January 20, 2025 Executive Order.

Section 3.3 (Registration Eligibility Criteria [all patients])

- In Section 3.3.2, the phrase "5 mm" has replaced "10 mm" to allow for a broader definition of measurable CNS disease.
- In Section 3.3.5, in the 1st sentence, the phrase "NTRK, ROS1" has been removed as accrual to the NTRK, ROS1 pathway arm has closed. Additionally, a new 2nd sentence has been added that reads: "For the KRAS G12C arm, if brain metastasis tissue is not available, then presence of the KRAS G12C mutation can be in the extracranial site only."
- In Section 3.3.7, the phrase "CDK and PI3K arms" has replaced "CDK, PI3K, and NTRK arms" as accrual to the NTRK arm has closed.

Section 4.0 (Patient Registration)

All text within this section has been updated to align with the CTSU boilerplate language.

Section 4.5 (Central Biomarker Review and Laboratory Submission)

The subsection heading after the 3rd paragraph has been updated as follows to allow for use of local biomarker testing results to be submitted for eligibility review for all arms: "**For all arms ~~the Entrectinib (NTRK/ROS1) and MRTX849 (KRAS G12C) arms only~~.**"

Section 4.8 (Grouping Factors and Treatment Assignments)

In the 1st sentence, the phrase "[closed to new patient enrollment on 1/9/2024], MRTX849" has been added after the word "Entrectinib" to reflect the closure of the entrectinib cohort and the previous addition of the MRTX849 cohort.

Section 6.1.2 (Medidata Rave)

All text within this section has been updated to align with the CTSU boilerplate language.

Section 7.1 (Targeted Therapy)

- In the section entitled Abemaciclib, in the 1st bullet point below the table, the word "tablets" has replaced "capsules" for accuracy.
- In the section entitled Entrectinib, the following sentence has been added below the table to reflect cohort closure to new accrual: "**Note: Closed to accrual January 2024**."

Section 8.2.1.5 (Interstitial lung disease [ILD]/pneumonitis events)

In the heading of the 2nd table, the phrase "ALT" has been replaced with "ALT/AST" for accuracy.

Section 8.2.1.6 (Increased ALT/AST)

In the section heading, the phrase "ALT" has been replaced with "ALT/AST" for accuracy, and the 2nd paragraph has been replaced with updated language and a new table to reflect the most current guidance.

Section 9.3.1 (Expedited Reporting Requirements…)

The expedited reporting requirements table has been replaced with an updated table to reflect current NCI reporting requirements.

Section 11.2.2 (Disease Parameters for Intracranial Disease Response)

The following changes have been made to align with the changes made to broaden eligibility criteria:

- In the 1st sentence of the 1st paragraph, the phrase "5mm" has replaced "10 mm."
- The 3rd sentence of the 1st paragraph has been removed (previously, "Metastases that have received SRS should not be considered measurable").
- In the 1st sentence of the 2nd paragraph, the phrase "≥5 mm" has replaced ">=10mm."
- In the 3rd paragraph, the phrase "0.5 cm" has replaced "1cm."

Section 13.0 (Statistical Considerations)

- In Section 13.1, a new final sentence has been added which reads: "This master protocol approach will utilize basket trial design approaches to evaluate targeted therapies within the different treatment arms."
- In Section 13.2.1, in the 3rd sentence, the word "evaluated" has replaced "considered evaluable" for accuracy.

- In Section 13.2.2, the 1st paragraph, the list of cohorts following the 1st paragraph, and all text below the table have been completely revised and the 2nd paragraph has been removed to now consolidate subgroups within treatment arms and provide updated design plans.
- Section 13.2.3 and Section 13.2.4 have been removed in their entirety due to the consolidation of subgroups within treatment arms.
- All text in Section 13.3.1 has been completely revised and a new table has been added to describe the new statistical design and sample size targets.
- All text in Section 13.3.2 has been updated to reflect current accrual estimates and durations.
- In the title for Section 13.4, the word "Supplementary" has been removed.
- A new Section 13.4.1 has been added to include analysis plans for the primary endpoint. Subsequent sections have been renumbered accordingly.
- Throughout the subsections of Section 13.4, the word "arm" or the phrase "treatment arm" has replaced "cohort" for accuracy.
- In the 4th – 7th and 9th-10th paragraphs in Section 13.4.2, the phrase "based on primary histology" has replaced "among the cohorts" in the last sentence.
- In Section 13.5.1, in the 2nd sentence of the 2nd paragraph, the phrase "patients regardless of primary histology" has replaced "combining all histologic cohorts."
- In Section 13.5.2, a new 7th paragraph has been added for clarity.
- In Section 13.8, the number "501" has replaced "426" in the last sentence of the 2nd paragraph, and the domestic planned enrollment report table has been completely revised to reflect the updated sample size projections based on the consolidation of subgroups within treatment arms and the resulting design changes. Additionally, a second domestic planned enrollment report table has been added to outline the screening projections in addition to the treatment projections. Also, the word "sex" has replaced the word "gender" in four instances throughout the section to align with current federal mandates per the January 20, 2025 Executive Order.

Appendix II (Central Laboratory Biomarker Testing Procedures)

Under the **Samples Testing** heading, a new 3rd paragraph has been added for clarity that reads: "As of January 2024, the solid fusion NGS assay will not be performed, as the entrectinib arm is now closed."

UPDATES TO THE SCREENING MODEL CONSENT FORM:

No changes have been made to the Screening Model Consent Form.

UPDATES TO THE TREATMENT MODEL CONSENT FORM:

What are the study groups?

- In the 3rd paragraph of the **Group 1 – Abemaciclib** section, the number "23" has replaced "69" to reflect the change in accrual targets based on the consolidation of subgroups.
- In the 3rd paragraph of the **Group 2 – Paxalisib** section, the number "23" has replaced "69" to reflect the change in accrual targets based on the consolidation of subgroups.
- In the heading of the **Group 3** section has been revised as follows to reflect the cohort's closure to new patient enrollment: "**Group 3 – Entrectinib (the group described below closed to new patient participation in January 2024)**." Additionally, all text below the heading in this section has been highlighted in grey to designate that this group is no longer enrolling.

- In the 3rd paragraph of the **Group 4 – MRTX849** section, the number "16" has replaced "36" to reflect the change in accrual targets based on the consolidation of subgroups.
- In the box for **Group 3** in the flowchart, the phrase "(Closed as of 01/2024)" has been added, and all text in this box has been highlighted in grey to indicate that this group is no longer enrolling.

What risks can I expect from taking part in this study?

- Under the **Possible Side Effects of Abemaciclib** heading, in the **Common, Some May be Serious** table, the following changes have been made based on updated risk information:
    - Dry mouth has been removed.
    - Abdominal pain and Headache have been added.
- Under the **Possible Side Effects of Abemaciclib** heading, in the **Occasional, Some May be Serious** table, a new risk has been added that reads: "Taste changes."
- Under the **Possible Side Effects of MRTX849** heading, in the **Rare, and Serious** table, two new risks have been added that read: "Severe skin rash with blisters and peeling which can involve mouth and other parts of the body. Symptom may include generalized skin pain" and "Decreased number of platelets in the blood; this may cause bruising, difficulty with clotting of blood, or bleeding easily (thrombocytopenia)," respectively.

A replacement protocol and model consent forms have been issued.

ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

ALLIANCE A071701

GENOMICALLY-GUIDED TREATMENT TRIAL IN BRAIN METASTASES

Industry-supplied agents: Abemaciclib (Lilly) NSC #783671, Entrectinib (Genentech) NSC #801660, paxalisib (Kazia) NSC #808539, MRTX849 (Mirati) NSC # 827801; (IND #142691); IND holder: Alliance

[redacted] **Identifier: NCT03994796**

Study Chair
[redacted], MD
Massachusetts General Hospital
[redacted]
Tel: [redacted]

Study Co-Chair
[redacted]

Neurological Co-Chair
[redacted], MD

Neurological Co-Chair
[redacted]

Community Oncology Co-Chair
[redacted]

Neuro-Onc Committee Co-Chair
[redacted]

Neuro-Onc Committee Co-Chair
[redacted]

Correlative Science Co-Chair
[redacted]

Breast Co-Chair
[redacted]

Pathology Co-Chair
[redacted]

Melanoma Co-Chair
[redacted]

Thoracic Co-Chair
[redacted]

Imaging Co-Chair
[redacted]

Imaging Co-Chair
[redacted]

Radiation Oncology Co-Chair
[redacted]

ECOG-ACRIN Champion
[redacted]

Primary Statistician
Susan Geyer, PhD
[redacted]

Secondary Statistician
[redacted]

Protocol Coordinator
[redacted]

Data Manager
[redacted]

Participating Organizations: ALLIANCE / Alliance for Clinical Trials in Oncology; ECOG-ACRIN / ECOG-ACRIN Cancer Research Group; NRG / NRG Oncology; SWOG / SWOG

Study Resources:

Expedited Adverse Event Reporting
[redacted]

Medidata Rave® iMedidata portal
[redacted]

OPEN (Oncology Patient Enrollment Network)
[redacted]

Biospecimen Management System
[redacted]

Protocol Contacts:

A071701 Nursing Contact
[redacted] MSN, APN-C
[redacted]

A071701 Pharmacy Contact
[redacted], PharmD
[redacted]

Alliance Biorepository at Mayo Clinic
Please see contact information in the A071701 Correlative Science Manual (CSM).

Drug Distribution Contact
RxCrossroads by McKesson
[redacted]

IROC
University of Cincinnati
[redacted]

Protocol-related questions may be directed as follows:	
Questions	**Contact (via email)**
Questions regarding patient eligibility, treatment, and dose modification:	Study Chair, Nursing Contact, Protocol Coordinator, and (where applicable) Data Manager
Questions related to data submission, RAVE or patient follow-up:	Data Manager
Questions regarding the protocol document and model informed consent:	Protocol Coordinator
Questions related to IRB review	Alliance Regulatory Inbox [redacted]
Questions regarding CTEP-AERS reporting:	Alliance Pharmacovigilance Inbox [redacted]
Questions regarding specimens/specimen submissions:	Appropriate Alliance Biorepository
Questions regarding drug supply	RxCrossroads by McKesson [redacted]
Questions regarding drug administration	Pharmacy Contact

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

For regulatory requirements:	**For patient enrollments:**	**For data submission:**
Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal. (Sign in at [redacted] and select the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately by phone or email: [redacted] or [redacted] to receive further instruction and support. Contact the CTSU Regulatory Help Desk at [redacted] for regulatory assistance.	Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at [redacted] Contact the CTSU Help Desk with any OPEN related questions by phone or email : [redacted]	Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page located on the CTSU members' website [redacted]. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the Roster Maintenance application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the CTSU members' website.		
<u>For clinical questions (i.e., patient eligibility or treatment-related)</u> see the Protocol Contacts, Page 2.		
<u>For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission)</u> Contact the CTSU Help Desk by phone or email: CTSU General Information Line – [redacted]. All calls and correspondence will be triaged to the appropriate CTSU representative.		

Genomically-Guided Treatment Trial in Brain Metastases

Pre-Registration Eligibility Criteria

Tissue available for biomarker testing (any brain metastasis tissue and extracranial site from any prior resection or biopsy). If the patient does not have any evidence of extracranial disease, or if there is insufficient extracranial tissue for profiling, brain metastasis tissue is sufficient for eligibility.

Registration Eligibility Criteria (see Section 3.0)

-Histologically confirmed parenchymal metastatic disease to the brain from any solid tumor (see Section 3.3.1 for definitions of new or progressive brain metastases.)
-Measurable CNS disease (≥5 mm)
-Ability to obtain MRIs with contrast
-New or progressive CNS lesions after systemic therapy or prior radiotherapy
-No surgery within 2 weeks prior to or after registration.
-No chemotherapy within 14 days prior to registration.
-For melanoma, progression after immunotherapy or for BRAF positive melanoma, BRAF/MEK inhibitors
-For lung cancer, failed EGFR therapies for EGFR mutated cancer.
-For HER2-positive breast cancer, received prior HER-2 directed therapy in the metastatic setting
-For triple negative breast cancer (TNBC), at least one chemotherapy in the metastatic setting
-For ER and/or PR+ HER2- breast cancer, at least one endocrine therapy in the metastatic setting
-Patients who have received prior treatment with any of the targeted treatments on this study are not eligible for that specific treatment arm(s), but could be eligible for other arms (e.g., a patient who has had prior treatment with abemaciclib would not be eligible for the abemaciclib arm, but could be eligible for another arm).
-For patients with NTRK or ROS1 mutations, entrectinib may be used for newly diagnosed brain metastases.
-For patients with KRAS G12C mutation, MRTX849 may be used for newly diagnosed brain metastases.
-Presence of clinically actionable alteration in KRAS G12C, CDK pathway or PI3K pathway in both a brain metastasis and extracranial site per central review. For KRAS G12C arm, if brain metastasis tissue is not available, then presence of KRAS G12C mutation can be in the extracranial site only.
-Not pregnant and not nursing
- No known current diffuse leptomeningeal involvement for the CDK and PI3K arms (diffuse defined as leptomeningeal involvement throughout the CNS axis). Patients with focal leptomeningeal disease, with or without documented positive CSF cytology, are eligible.
-Age ≥ 18 years
-ECOG Performance Status 0-2
-Adequate organ function
-No uncontrolled medical comorbidities per investigator discretion. See Section 3.3.12 for more information.
-Radiation to symptomatic non-target sites within neural axis is allowed prior to registration without washout (provided there is at least one untreated measurable lesion for measurement on study and radiation is completed prior to registration).
-Concurrent systemic corticosteroids are allowed if stable dose of dexamethasone for 7 days prior to registration
-No concurrent administration of anticancer therapies (except for endocrine therapy or continuation of hormonal therapy or anti-HER2 therapy in breast cancer patients). No chemotherapy within 14 days prior to entering the study.
-Chronic concomitant treatment with strong inhibitors or strong inducers of CYP3A4 is not allowed on this study. Patients on strong CYP3A4 inhibitors or inducers must discontinue the drug for 14 days or 5 or more half-lives prior to registration on the study.
See Section 3.3.13 and Section 8.1 for more information.

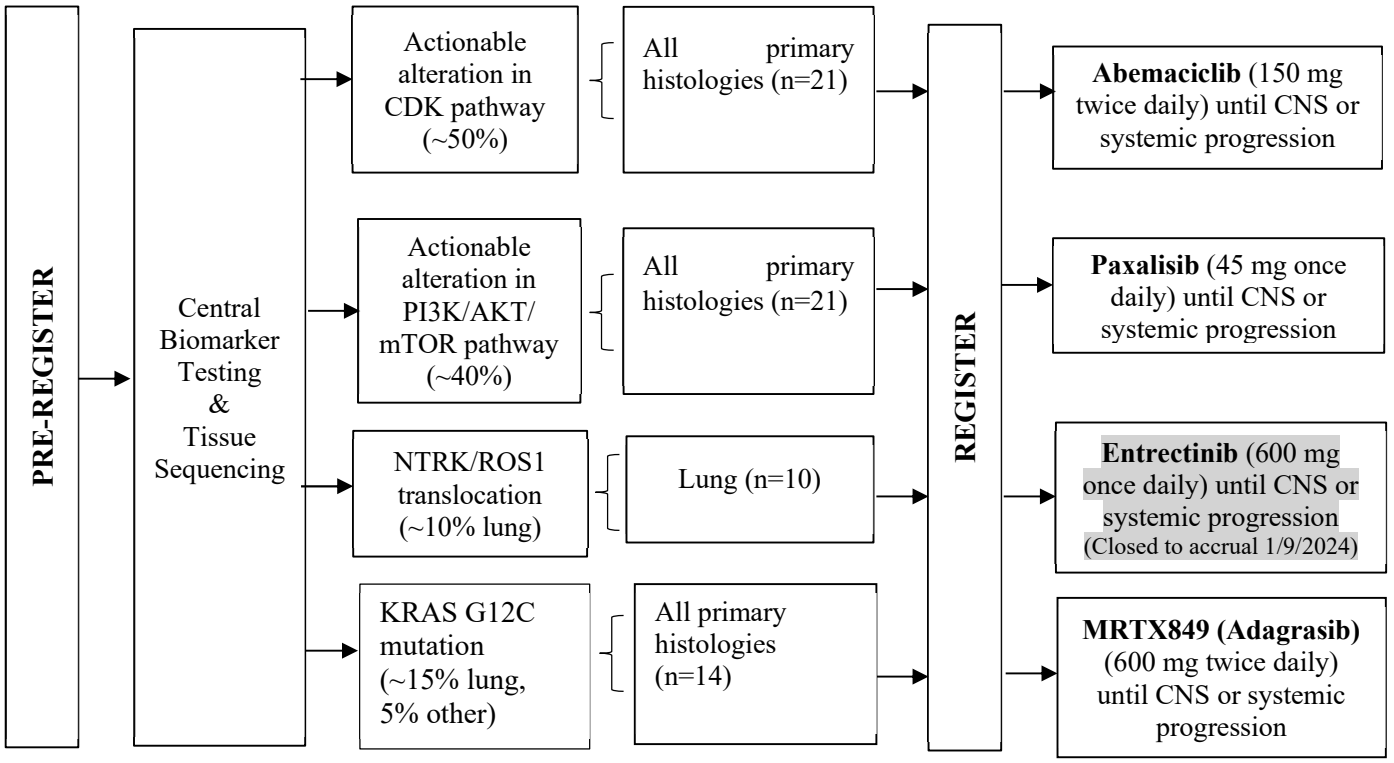
Required Initial Laboratory Values

Absolute neutrophil count (ANC): ≥ 1500/mm^3
Platelet count: ≥ 100,000/mm3
Total bilirubin: ≤ 1.5 x ULN*
AST and ALT: ≤ 2.5 x ULN**
UPC Ratio < 1 or urine protein ≤ 1 for paxalisib arm
Creatinine: ≤ 1.5 x upper limit of normal (ULN) **OR**
Calc. creatinine clearance: ≥ 45 mL/min
*except in patients with Gilbert's disease. Patients with Gilbert's syndrome with a total bilirubin ≤2.0 times ULN and direct bilirubin within normal limits are permitted.

**except for patients in the MRTX849 (KRAS G12C) arm. For this arm, patients must have creatinine clearance ≥60 mL/min or glomerular filtration rate ≥60 mL/min/1.73m^2 calculated using a validated prediction equation (e.g., Cockcroft-Gault, MDRD, or 24-hour urine CrCl).

-For paxalisib arm: UPC Ratio < 1 or urine protein ≤ 1
-For paxalisib arm: Recent acute myocardial infarction in the last 6 months or current angina pectoris are excluded. Patients with symptomatic bradycardia should have an electrocardiogram at baseline. If QT interval > 470 msec, the patient is excluded.
-For paxalisib arm: patients with uncontrolled Type I or II diabetes mellitus should be excluded. Uncontrolled diabetes is defined as HbA1c >9% in addition to fasting glucose >140 mg/dL on at least 2 occasions within 14 days prior to registration.
-For entrectinib arm: Concurrent use of H2-receptor antagonists, receptor antagonists, PPIs, and/or antacids are prohibited.
-For abemaciclib arm: Hemoglobin ≥ 8 g/dL
-For abemaciclib arm: Patients who received chemotherapy must have recovered (Common Terminology Criteria for Adverse Events [CTCAE] Grade ≤1) from the acute effects of chemotherapy except for residual alopecia or Grade 2 peripheral neuropathy prior to registration. A washout period of at least 21 days is required between last chemotherapy dose and registration (provided the patient did not receive radiotherapy). Patients who received adjuvant radiotherapy must have completed and fully recovered from the acute effects of radiotherapy. A washout period of at least 14 days is required between end of radiotherapy and registration. Breast cancer patients who have received ribociclib or palbociclib are eligible as long as there is documentation of CDK4/6 pathway alteration on a biopsy or resection at the point of progression post-ribociclib or palbociclib.
-For abemaciclib arm: A female of childbearing potential, must have a negative serum pregnancy test within 7 days of registration and agree to use a highly effective contraception method during the treatment period and for 3 weeks following the last dose of abemaciclib. Please see Section 3.6.3.
-For abemaciclib arm: Patients with active bacterial infection (requiring intravenous [IV] antibiotics at time of initiating study treatment), fungal infection, or detectable viral infection (such as known human immunodeficiency virus positivity or with known active hepatitis B or C [for example, hepatitis B surface antigen positive] are excluded. Screening is not required for enrollment.
-Patients with personal history of any of the following conditions: syncope of cardiovascular etiology, ventricular arrhythmia of pathological origin (including, but not limited to, ventricular tachycardia and ventricular fibrillation), or sudden cardiac arrest, are excluded.
-For MRTX849 arm: Hemoglobin ≥ 9 g/dL, in the absence of transfusions for at least 2 weeks.
-For MRTX849 arm: Creatinine clearance ≥60 mL/min or glomerular filtration rate ≥60 mL/min/1.73m^2 calculated using a validated prediction equation (e.g., Cockcroft-Gault, MDRD, or 24-hour urine CrCl).
-For MRTX849 arm: Recovery from the adverse effects of prior therapy to baseline or Grade 1 (any grade alopecia and Grade ≤2 peripheral neuropathy are eligible).
-For MRTX849 arm: Any of the following cardiovascular abnormalities within 6 months of study entry are excluded: symptomatic or uncontrolled atrial fibrillation, unstable angina pectoris or myocardial infarction, CHF ≥ NYHA Class 3, stroke or transient ischemic attack.
-For MRTX849 arm: Ongoing need for medication known to cause prolonged QTc interval or that are substrates of CYP3A4 with narrow therapeutic index that cannot be switched to alternative treatment prior to study entry is excluded.
-For MRTX849 arm: Prolonged QTc interval >480 milliseconds or family history or medical history of Long QT syndrome is excluded.
-For MRTX849 arm: History of intestinal disease or major gastric surgery likely to alter absorption of study treatment or inability to swallow oral medications is excluded.
-For MRTX849 arm: Known human immunodeficiency virus (HIV) infection or acute or chronic hepatitis B or C infection is excluded. Screening is not required for enrollment. Note that the following are permitted: Patients treated for hepatitis C (HCV) with no detectable viral load; Patients treated for HIV with no detectable viral load for at least 1 month prior to randomization while on a stable regimen of agents that are not strong inhibitors of CYP3A4; and patients with hepatitis B (HBV) receiving prophylaxis against reactivation of hepatitis B (either [HBsAg-positive with normal ALT and HBV DNA <2,000 IU/mL or <10,000 copies/mL] or [HBsAg-negative and anti-HBc-positive]).
-For MRTX849 arm: Women of child-bearing potential must have a negative serum or urine pregnancy test documented prior to study entry. Breast-feeding or planning to breast-feed during the study or within 6 months after the last dose of study treatment is prohibited.

Schema



Each cycle is 28 days. Treatment is to continue until CNS or systemic progression or unacceptable adverse event. Patients will be followed for 5 years from registration or until death, whichever comes first.

Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan.

If the Group credited for enrollment is a non-Alliance Group, then other requirements from the credited Group may apply.

Table of Contents

ALLIANCE A071701 ..... **1**
Schema **6**
Table of Contents **7**
1.0 Background **10**
1.1 Trial Importance 12
1.2 Supporting Data 12
1.3 Study Design 13
2.0 Objectives **28**
2.1 Co-Primary Objectives 28
2.2 Secondary Objectives 28
2.3 Correlative Science Objective 28
3.0 Patient Selection **28**
3.1 On-Study Guidelines 29
3.2 Pre-Registration Eligibility Criterion (all patients) 29
3.3 Registration Eligibility Criteria (all patients) 29
3.4 Additional Registration Eligibility Criteria for Paxalisib Arm 32
3.5 Additional Registration Eligibility Criterion for Entrectinib Arm 32
3.6 Additional Registration Eligibility Criteria for Abemaciclib Arm 32
3.7 Additional Registration Eligibility Criterion for MRTX849 Arm 33
4.0 Patient Registration **34**
4.1 Investigator and Research Associate Registration with CTEP 34
4.2 Cancer Trials Support Unit Registration Procedures 35
4.3 Patient Pre-Registration Requirements 38
4.4 Patient Pre-Registration Procedures 38
4.5 Central Biomarker Review and Laboratory Submission 38
4.6 Patient Registration Requirements 39
4.7 Patient Registration Procedures 39
4.8 Grouping Factors and Treatment Assignments 40
5.0 Study Calendars **40**
5.1 Study Calendar – Abemaciclib 41
5.2 Study Calendar – Paxalisib 43
5.3 Study Calendar – Entrectinib 45
5.4 Study Calendar – MRTX849 47
6.0 Data and Specimen Submission **50**
6.1 Data Collection and Submission 50

6.2 Specimen Collection and Submission 52
6.3 Imaging Submission 54
7.0 Treatment Plan/Intervention 56
7.1 Targeted Therapy 57
7.2 Imaging 58
8.0 Dose and Treatment Modifications 58
8.1 Ancillary Therapy, Concomitant Medications, and Supportive Care 58
8.2 Dose Modifications 65
9.0 Adverse Events 74
9.1 Routine Adverse Event Reporting 75
9.2 CTCAE Routine Reporting Requirements 76
9.3 Expedited Adverse Event Reporting (Rave-CTEP-AERS) 77
10.0 Drug Information 82
10.1 General Considerations: 82
10.2 Paxalisib (formerly GDC-0084) 82
10.3 Entrectinib (RXDX-101, NSC #801660) 85
10.4 Abemaciclib (LY2835219, VERENZIO™, NSC#783671) 87
10.5 MRTX849 (Adagrasib, NSC# 827801) 90
11.0 Measurement of Effect 94
11.1 Extracranial response 94
11.2 Antitumor Effect – Intracranial Disease 99
12.0 End of Treatment/Intervention 103
12.1 Duration of Protocol Treatment 103
12.2 Criteria for Discontinuation of Protocol Treatment/Intervention 103
12.3 Follow-up 104
12.4 Extraordinary Medical Circumstances 104
12.5 Managing ineligible patients and registered patients who never receive protocol intervention 104
13.0 Statistical Considerations 105
13.1 Overview 105
13.2 Statistical Design and Analysis for the Primary Endpoint 105
13.3 Sample Size, Accrual Time and Study Duration 108
13.4 Analysis Plans 109
13.5 Monitoring the Study 111
13.6 Study Reporting 112
13.7 Descriptive Factors: 112
13.8 Minorities Distribution (sex, race, ethnicity) 112

14.0 Correlative And Companion Studies 113
14.1 Biobanking for Future Correlative Science Studies 113
14.2 Evaluation of Imaging Markers of Response in Brain Metastases 115
15.0 General Regulatory Considerations and Credentialing 115
15.1 Institutional Credentialing 115
15.2 IRB Terminations 116
16.0 Monitoring Plan 116
17.0 References 116
Appendix I Required Consensus MRI Acquisition Parameters 120
Appendix II Central Laboratory Biomarker Testing Procedures 126
Appendix III: Patient Medication Diaries 130
Appendix III-A: Patient medication diary – Paxalisib 131
Appendix III-B: Patient medication diary – Entrectinib 133
Appendix III-C: Patient medication diary – Abemaciclib 135
Appendix III-D: Patient medication diary – MRTX849 (Adagrasib) 137
Appendix IV: Patient Drug Information Handout and Wallet Cards 139
Appendix IV-A: Patient Drug Information Handout and Wallet Card – Paxalisib 140
Appendix IV-B: Patient Drug Information Handout and Wallet Card – Entrectinib 143
Appendix IV-C: Patient Drug Information Handout and Wallet Card – Abemaciclib 146
Appendix IV-D: Patient Drug Information Handout and Wallet Card – MRTX849 (Adagrasib) 149

1.0 BACKGROUND

Brain metastases, most commonly derived from melanoma, lung and breast cancers, are the most common brain tumor, with approximately 200,000 cases diagnosed annually in the United States.[1-3] Median survival ranges from 3 months to 27 months following spread to the central nervous system.[4] Of patients who have clinically symptomatic brain metastases, approximately half succumb to the cancer in their brain.[5] Unfortunately, treatment options are limited, and most current clinical trials in the US exclude patients with untreated brain metastases.

To date, the extent to which brain metastases, often manifesting years after the primary malignancy, share the genetic profile of the primary tumor remains unknown. This uncertainty has partially hampered the development of genomically driven clinical trials in brain metastasis patients. Given that the concept of precision medicine implies that genomic characterization of an individual patient's cancer can be used to optimize treatment decisions for that patient,[6, 7] physicians need to understand the potential therapeutic targets at each stage of disease, particularly in the setting of metastatic disease. Furthermore, patients frequently develop brain metastases even while their extracranial disease remains under control [8-10]; however, the extent of genetic heterogeneity in this setting is unknown. To determine how cancer heterogeneity might affect precision medicine approaches in patients with brain metastases, we performed whole exome sequencing on 104 patient-matched brain metastases, primary tumors and normal samples, all of which were collected in the course of clinical care[11]. In order to prioritize clinically actionable cancer-genome alterations, we used the TARGET database[12] consisting of 121 genes with specified mutation classes annotated with corresponding clinical consequences (e.g. sensitivity to a specified targeted intervention). Alterations in TARGET genes were evaluated according to defined criteria[13] for potential clinical actionability.

Across all samples, the brain metastases and primary tumors shared a common ancestor, yet continued to evolve independently. Importantly, in 53% of cases, we detected clinically actionable alterations in brain metastases that were not present in their primary tumor biopsies[11, 14]. In contrast, spatially and temporally separated brain metastasis sites were genetically homogeneous. Notably, we detected alterations associated with sensitivity to PI3K/AKT/mTOR inhibitors in 44% of brain metastases (Figure 1 below), and CDK inhibitors in 51% (Figure 1). KRAS mutations were present in 22% of brain metastases (Figure 1).

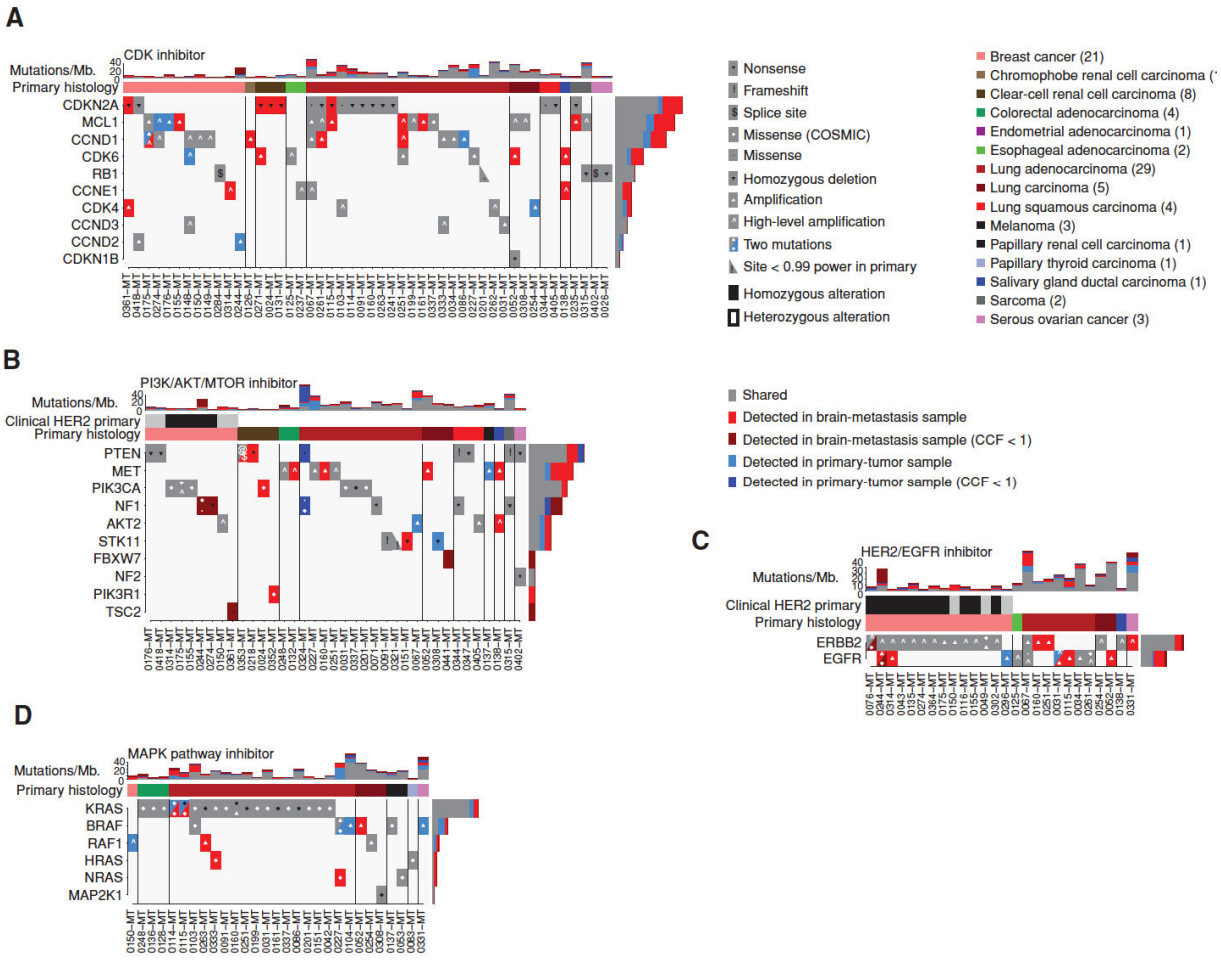


Figure 1: Landscape of genetic alterations in brain metastases and primary tumor samples (Brastianos et al. Cancer Discovery 2015)

Furthermore, studies have demonstrated a high frequency of brain metastases in cancers that harbor fusions such as ALK, ROS1 and NTRK [15, 16](e.g. 36% of ROS1 translocated lung cancer)[17]. ROS1 and NTRK fusions occur in 0.5-5% of lung, breast and colorectal cancer and melanomas[18-22].

We are proposing a prospective Phase 2 study of a CDK, PI3K, NTRK/ROS1and KRAS G12C inhibitor in patients with brain metastases harboring alterations predicting sensitivity to these inhibitors, respectively. Patients with new, recurrent or progressive brain metastases will be eligible for this trial. Tissue from brain metastases and extracranial sites (primary or extracranial metastases) will be screened for the presence of the appropriate alterations, and if present in both tumor sites (or in the intracranial site if extracranial tissue is unavailable), they will receive the appropriate inhibitors respectively. Screening will be carried out with the SNaPshot NGS assay and Solid Fusion Assay, which are fully validated clinical tests designed and developed at the MGH Center for Integrated Diagnostics. Although current systemic therapy for brain metastases is ineffective, we hypothesize that targeted therapies will demonstrate efficacy in patients harboring the appropriate mutations. This study represents a novel therapeutic approach in brain metastases, a disease with a critical need for effective therapy.

1.1 Trial Importance

CNS disease leads to devastating complications for patients, with profound consequences for quality of life, clinical trial opportunities, and duration of life [2, 4, 23-25]. The most common primary histologies that metastasize to the brain are lung, breast and melanoma. Approximately 30% of lung cancer patients will have CNS disease at time of diagnosis and an estimated 50% will eventually develop brain metastases[26]. Up to 30% of patients with advanced breast cancer and 50% of patients with advanced melanoma will develop brain metastases[27, 28].

Effective treatments for brain metastases are limited. Radiation therapy (RT) has historically been the mainstay of treatment, albeit with only a limited survival benefit and risk of cognitive impairment following therapy [29-32]. In the precision medicine era, some tyrosine kinase inhibitors (TKIs) have demonstrated good treatment efficacy for patients whose tumors harbor selected mutations or rearrangements, but this does not reflect the majority of patients [28]. Furthermore, even patients with targetable mutations in genes such as HER2 and EGFR have high rates of progression in the CNS after initial control of their systemic disease [10, 17]. Targeted or chemotherapeutic agents that cross the blood-brain barrier (BBB) are also used in these patients, but patients inevitably progress in the brain [33]. Furthermore, although immunotherapy is rapidly becoming standard of care in patients with metastatic lung cancer, melanoma and other cancers, the majority of patients treated with immunotherapy progress in the CNS [25, 34]. Novel targets are clearly needed.

The total annual cost of caring for patients with metastatic CNS disease exceeds $10 billion in the US alone, yet only about 5% of all cancer research funding is specifically devoted to the study of metastatic disease [35]. Overall, CNS metastases represent a dreaded and frequent complication for cancer patients and their families: there is an urgent need for more focused efforts to develop improved therapeutic options.

1.2 Supporting Data

Typically, patients with metastatic disease are treated systemically and the metastases are not sampled, however, patients with oligometastatic or symptomatic brain metastases (15-40% of patients) benefit from surgical excision of their metastases. We have exploited this opportunity to create an extensive clinically annotated tumor bank of matched brain metastases and primary tumors. We recently reported whole-exome sequencing of 104 patient-matched brain metastasis, primary tumor and normal tissue samples across a range of cancer types[36]. We used novel analytic tools to dissect the clonal and subclonal architecture of paired primary and metastatic tumors from next generation sequencing data and infer phylogenetic trees relating all subclones for each case (Fig. 2). In order to prioritize clinically actionable cancer-genome alterations, we annotated the phylogenetic branches with alterations that might predict sensitivity to a targeted therapeutic. In 53% of patients, clinically actionable driver mutations were found in the brain metastases that were not detected in the corresponding primary tumor. Notably, alterations in the CDK and PI3K pathways, as well as KRAS mutations, were frequent alterations in our set of brain metastases.

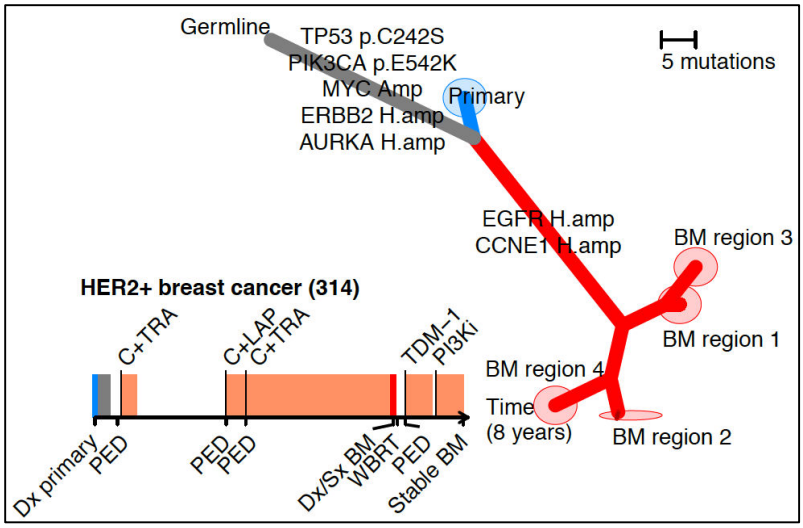


Figure 2: Phylogenetic tree for a patient with HER2-positive breast cancer that developed a brain metastasis. All regions of the brain metastases shared amplifications in *CCNE1* that were absent in the primary tumor. Branch colors indicate the types of tissue samples descended from each branch (grey: shared by all samples, blue: primary-tumor sample, red: brain metastasis). Alterations are annotated onto the phylogenetic branches on which they occurred. The timeline depicts the sequence of diagnosis, treatment, and tissue sampling, with chemotherapy treatment intervals denoted by grey rectangles, and treatment with specified targeted agents denoted by orange rectangles.

1.3 Study Design

This is a prospective Phase 2 study evaluating the efficacy of a CDK, PI3K, NTRK/ROS1 or KRAS G12C inhibitor in patients with progressive brain metastases harboring the alterations predicting sensitivity to each of these inhibitors. Patients with recurrent or progressive brain metastases will be eligible for this trial; systemic progressive disease is allowed. All tumors will be submitted to the Alliance biorepository for tracking and processing. Samples will undergo central biomarker testing. Patient's tumor samples will be tested for the presence of mutations predicting sensitivity to each inhibitor. Patients harboring these mutations and who meet eligibility will be enrolled.

The primary endpoint of response rate (RR) per RANO criteria in the central nervous system (CNS) will be evaluated separately for each inhibitor, stratified by histology cohorts within each arm. The goal will be to enroll 21 evaluable patients per histology cohort within each arm (defined by the pair of mutation and inhibitor) as shown in the schema below. CNS imaging will be obtained every 8 weeks.

Patients will be given the option of correlative participation. There will be basic science correlatives on tissue and blood and imaging correlative work on MRI. All tissue and blood samples will be routed through the Alliance biorepository for logging and sample processing. The MRI imaging will be routed from sites to the ICL, then to the radiologist for analysis.

The duration of treatment is predicted to be an average of 6 to 12 months.

Contrast-enhanced cranial magnetic resonance imaging (MRI) will be performed every 8 weeks. MRI should be performed per guidelines in Appendix I. Standard response criteria will be used (RANO criteria for brain metastases) (30). In patients who have stable disease (SD), a partial

response (PR) or a complete response (CR), the inhibitors will be continued. The inhibitors will be continued until progressive disease (PD) in the CNS or extracranial sites or study withdrawal due to toxicity or other rationale, at which time patients will be removed from the study treatment. In patients who come off study treatment for reasons other than progression, they will be followed for progression until progression is documented on imaging, or patients are initiated on a subsequent therapy. All patients who are removed from study treatment, regardless of rationale, will be followed for survival.

As of Update #04, consolidation of subgroups was made within treatment arms to be more primary histology agnostic. This is common in the context of basket trials with targeted therapies. To accommodate slower than expected accrual rates and screening patterns, subgroups for the arms with targeted therapies for CDK inhibition, PI3K inhibition, and KRAS G12C inhibition were collapsed and combined to result in a more efficient and logistically feasible design for this trial.

Paxalisib (formerly GDC-0084)

Paxalisib is a potent, oral, selective, brain-penetrant small molecule inhibitor of PI3K/mTOR specifically designed to achieve blood brain barrier penetration with substantial free brain penetration.

Preclinical data: Paxalisib was designed to efficiently cross the blood-brain barrier to achieve high drug exposure in the brain, thus maximizing its ability to target brain cancers such as brain metastases. Paxalisib has proven to be efficacious in nonclinical models of brain tumors driven by activation of the PI3K pathway, including growth inhibition of human glioma cell lines grown either *in vitro* or as subcutaneous or intracranial grafts in nude mice. Mouse xenograft models demonstrate dose-dependent tumor-growth inhibition (TGI) for paxalisib with 60% - 90% TGI observed at exposures equivalent to those achieved in the clinic. Mechanism-of-action studies indicate that phosphorylation of downstream PI3K pathway markers such as Akt and S6 are decreased in glioma lines treated with paxalisib and that drug treatment leads to G1 arrest. A correlation is seen between tissue concentrations of drug and status of pharmacodynamic markers in tumor xenografts. Results from the nonclinical pharmacology studies showed that paxalisib is a potent, selective inhibitor of class I PI3K and mTOR kinase. Paxalisib inhibited human mTOR, with a mean apparent Ki of 70 nM. Paxalisib was also potent in inhibiting growth of a panel of human glioma cell lines, with a mean 50% inhibitory concentration (IC50) on cell proliferation ranging from 0.4 to 4.5 μM. Studies of the mechanism of action in U87MG-Luc glioma cells showed that levels of pAkt and pS6 were markedly reduced following exposure to paxalisib, leading to cell cycle arrest at the G1 phase and apoptosis. *In vivo* studies in mouse xenograft models of human glioblastoma indicated that paxalisib inhibited tumor growth when administered orally. Substantial suppression of the PI3K pathway, evidenced by a marked decrease in pAkt and pS6 levels in the tumor, was also observed. Moreover, paxalisib demonstrated its pharmacologic activity without any observed cardiovascular effects. The absorption, distribution, metabolism, and excretion (ADME) of paxalisib were characterized *in vitro* and *in vivo*. Plasma clearance (CL) of paxalisib was low in mice, moderate in rats, and high in dogs and monkeys, relative to the known hepatic blood flows in these species. Plasma protein binding was low across all species tested, ranging from 56.9% to 75.5% (bound), and was 75.5 % in human plasma. Paxalisib appeared to be primarily metabolized by cytochrome P450 (CYP) 3A4, and *in vitro* CYP inhibition and induction studies suggested a low potential for CYP-related drug-drug interaction at clinically expected exposures. The toxicology program for paxalisib was designed to support once daily oral administration of paxalisib for up to 28 days to patients in clinical trials. Paxalisib was not genotoxic in a bacterial mutagenesis assay or an *in vitro* human peripheral blood chromosomal aberrations assay. No toxicologically relevant cardiovascular, neurological, or respiratory findings attributed to paxalisib were observed in the

29-day repeat-dose toxicity studies, an *in vitro* human ether-à-go-go-related gene (hERG) assay, or *in vivo* telemetry-instrumented dog safety pharmacology study.

Clinical data: A phase 1 open-label, dose-escalation study (Wen et al, J Clin Oncol 34, 2016; NCT01547546), has been completed in 47 patients with progressive or recurrent high-grade gliomas. Paxalisib was given once daily in cycles of 28 days. This first-in-human, phase 1 dose-escalation study of paxalisib at doses between 2 and 65 mg once daily demonstrated a safety profile consistent with classic PI3K/mTOR-inhibitor related adverse events (AEs) with the most frequent AEs attributed to paxalisib being fatigue, hyperglycemia, nausea, rash, hypertriglyceridemia, mucositis, hypophosphatemia, decreased appetite, and diarrhea with the most common Grade 3 AEs related to paxalisib being hyperglycemia (8.5%) and mucositis (6.4%). Dose limiting toxicities (DLTs) included 1 case of Grade 2 bradycardia and Grade 3 myocardial ischemia (15 mg), Grade 3 stomatitis (45 mg), and 2 cases of Grade 3 mucosal inflammation (65 mg).

The dose proposed for this study is based on the results of the previous phase 1 study (Wen et al, J Clin Oncol 34, 2016; NCT01547546), which defined the maximum tolerated daily dose (MTD) of paxalisib in patients with high grade gliomas (WHO Grade III–IV), who had progressed during or after treatment with at least 1 prior XRT-containing regimen for gliomas and/or were not candidates for regimens known to provide clinical benefit. The MTD was determined to be 45 mg when paxalisib was administered orally once daily (QD) in cycles of 28 days in these patients. PK analysis in the phase 1 study confirmed paxalisib was rapidly absorbed and demonstrated linear and dose-proportional increases in exposure, with a half-life supportive of both once daily and intermittent dosing. In this population of patients, the AEs and other safety findings were generally consistent with the established PI3K/mTOR inhibitor class effects and/or with the disease under study. The MTD was determined to be 45 mg in this patient population. The data therefore warrant further development of paxalisib in phase 2 studies.

Entrectinib

Entrectinib (RXDX-101) is a potent inhibitor of the receptor tyrosine kinases TRKA (encoded by the gene neurotrophic tyrosine receptor kinase [*NTRK1*), TRKB (encoded by the gene *NTRK2*), TRKC (encoded by the gene *NTRK3*) and ROS1 (encoded by the gene *ROS1*), with median inhibitory concentrations (IC50) for kinase inhibition in the low nanomolar range (1.7, 0.1, 0.1, 0.2, and 1.6 nM, respectively). Gene rearrangements in each of these genes have been observed in a variety of tumor types, including non-small cell lung cancer (NSCLC), colorectal carcinoma (CRC), salivary gland cancers, papillary thyroid cancer, melanoma, and sarcomas; overexpression of *NTRK2* have also been observed in neuroblastoma. Thus, a pan-TRK and ROS1 inhibitor such as entrectinib may have broad potential therapeutic utility (Ignyta IB, Edition 7).

Preclinical data: Extensive in vitro and in vivo pharmacology studies were performed to characterize the anti-proliferative and antitumor activity in a variety of human tumor xenograft and allograft models dependent on TRK or ROS1 oncoproteins. Entrectinib was effective in both subcutaneous and disseminated anaplastic large cell lymphoma xenograft models, at doses that were well tolerated. Of note, in an intracranial NSCLC tumor model, magnetic resonance imaging analysis demonstrated tumor shrinkage, images consistent with tumor cell necrosis, prevention of intracranial edema, and ultimately, increased survival for entrectinib treatment in a dose-dependent manner. Collectively, these findings suggest that entrectinib has the potential to treat patients with tumors that harbor *NTRK1/2/3* or *ROS1* gene rearrangements, including those patients with CNS disease.

In pharmacokinetic and toxicokinetic studies, the exposure of entrectinib (C_{max} and AUC) increased in a less than dose-proportional manner in the toxicology species (SD rats and Beagle dogs). Higher exposures were observed in females than males at all doses tested in rats and at high doses in dogs; similarly, accumulation following multiple doses was more evident in rodents and at higher doses in dogs. In a food-effect study conducted in Beagle dogs, entrectinib exposure increased 2-fold in the fed state compared to the fasted state (ratio of 2.02 for mean values based on dose normalized AUC), and inter-animal variability was greatly reduced in the presence of food. In repeat-dose toxicokinetic studies, steady state was achieved within 4 days, consistent with a terminal half-life of less than 28 hours. Entrectinib demonstrated low to moderate clearance from plasma and moderate volume of distribution across species. Entrectinib was highly protein bound (99.4% - 99.5% bound) and readily crossed the blood-brain barrier (higher concentrations were measured in the brain than in plasma of dogs and in some rats in repeat-dose toxicology studies). Incubations of entrectinib with recombinant CYP enzymes suggested that the enzymes CYP2C8, CYP2C9, CYP2C19, and CYP3A4, were capable of metabolizing entrectinib. In addition, entrectinib demonstrated potential to inhibit the metabolic activities of CYP2C9, CYP2D6, and CYP3A4 isoforms (IC_{50} values of 5.5, 5.6, and 2.8-6.3 μM, respectively) and to induce CYP3A4 (37% at 10 μM relative to positive control rifampin), suggesting the potential for drug interactions with drugs metabolized by these isoforms. Preliminary analysis of human samples suggest a dimethyl metabolite, M5, and a glucuronide are the main metabolites in humans.

Clinical data: Entrectinib was evaluated in two Phase 1 clinical studies (Study ALKA-372-001 and Study RXDX-101-01 [STARTRK-1]) designed to determine the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of entrectinib in patients with advanced or metastatic solid tumors harboring *NTRK1/2/3*, *ROS1*, or *ALK* molecular alterations. Safety, pharmacokinetics, and antitumor activity were evaluated. The following dosing regimens were tested:

- Schedule A (ALKA-372-001 study): once-daily (fasted) 4 days on, 3 days off for 3 weeks followed by 1 week rest. Doses tested ranged from 100 to 1600 mg/m^2 without dose-limiting toxicity (DLT).
- Schedule B (ALKA-372-001 study): continuous daily dosing (fed) in 4-week cycles. Doses tested ranged from 100 to 400 mg/m^2 and 600 mg fixed, without DLT.
- Schedule C (ALKA-372-001 study): once-daily (fed) 4 days on, 3 days off in 4-week cycles. Doses tested ranged from 400 to 800 mg/m^2 without DLT.
- Continuous Daily Dosing (STARTRK-1 study): once-daily (fed) in 4-week cycles. Doses tested were 100 mg/m^2, 200 mg/m^2, 400 mg/m^2, 600 mg fixed, and 800 mg fixed.

Two DLTs were observed at the fixed 800 mg/day dose: one event of Grade 3 cognitive impairment and one event of Grade 3 fatigue. Both events were reversible upon study drug interruption.

Based upon these two DLTs, 400 mg/m^2 administered once-daily on a fed regimen was selected as the BSA-based RP2D. Subsequently, additional expansion cohorts of patients were enrolled to further explore a fixed daily dosing regimen, and 600 mg/day was selected as the RP2D for future Phase 2 studies.

A total of 92 patients have been enrolled across both studies. At doses ≥ RP2D, 24 patients have been treated at 400 mg/m^2, 19 patients at 600 mg, and 12 patients at 800 mg; 9 patients have been treated > 6 months and 1 patient > 1 year.

The most common, treatment-related, adverse events (AEs) were fatigue/asthenia, dysgeusia, paresthesia, nausea, and myalgia (Table 1). Most of the AEs were Grades 1 and 2 as per NCI CTCAE v4.0; importantly, there was no evidence of cumulative toxicity. Four treatment-related serious adverse events (SAEs) were reported in the STARTRK-1 study: two SAEs occurred at 800 mg/day, the dose that exceeded the maximum tolerated dose (Grade 3 cognitive impairment and Grade 3 eosinophilic myocarditis) and two SAEs occurred at 600 mg/day (Grade 2 fatigue and fall and Grade 2 dysphagia). All resolved with study drug interruption and/or dose reduction. No treatment-related SAEs were reported in the ALKA-372-001 study.

There were no clinically significant trends in laboratory parameters across the various dosing regimens.

Table 1: Most common, treatment-related, adverse events occurring in >10% of patients (as of 15 August 2015)

Adverse Event Term	ALKA-372-001 (n=49)		STARTRK-1 (n=43)		TOTAL (n=92)	
	G1-G2	G3	G1-G2	G3	G1-G2	G3
Fatigue/Asthenia	16 (33)	1 (2)	19 (44)	3 (7)	35 (38)	4 (4)
Dysgeusia	16 (33)		20 (47)		36 (39)	
Paresthesia	20 (41)		11 (26)		31 (34)	
Nausea	17 (35)		5 (12)		22 (24)	
Myalgia	16 (33)		5 (12)		21 (23)	
Diarrhea	10 (21)		7 (16)	1 (2)	17 (18)	1 (1)
Dizziness	6 (12)		8 (19)		14 (15)	
Cognitive Disorder	3 (6)		5 (12)	2 (5)	8 (9)	2 (2)
Vomiting	9 (18)		0		9 (10)	

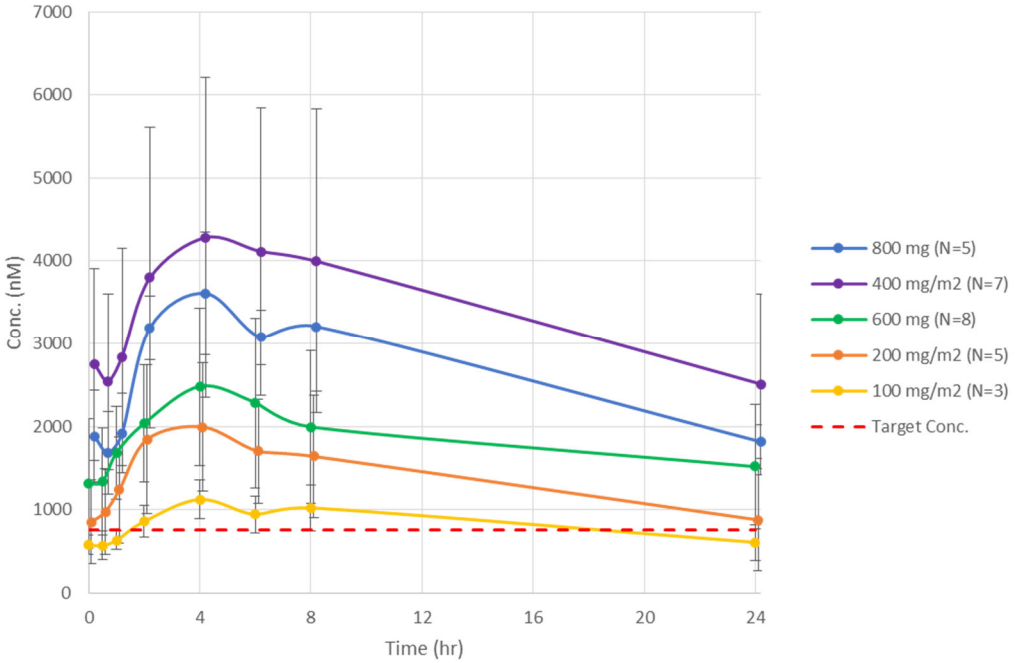
Exposures of entrectinib administered on a continuous daily dosing regimen increased in a dose-proportional manner and reached steady-state within a week of dosing. Based on accumulation, the plasma half-life was estimated to be approximately 20 to 24 hours. This estimate is consistent with that observed in healthy subjects (22 to 25 hours) following a single dose with 120-hour post-dose sampling, supporting once daily dosing of entrectinib. At both the BSA-based RP2D of 400 mg/m^2 and fixed RP2D of 600 mg, the plasma protein binding-corrected mean C_{trough} values are multiples above the concentrations required for complete tumor growth inhibition in animal models (Figure 3).

In both phase 1 studies, tumor assessments were performed at the end of Cycle 1 and every 8 weeks thereafter. Among 18 ALK-, ROS1-, or TRK-inhibitor-naïve patients (1 patient was ALK-inhibitor intolerant) with *NTRK1/2/3, ROS1,* or *ALK* gene rearrangements that were treated at or above the RP2D, a response rate of 72% (13/18: Siena et al, ECC 2015) was reported.

In August 2019, entrectinib was granted accelerated FDA approval for adults and adolescents aged 12 or older who have solid tumors that harbor an NTRK fusion mutation.

For the latest clinical data, please refer to the Investigator's Brochure.

Figure 3 Entrectinib pharmacokinetics (continuous daily dosing)



Abemaciclib

During the cell cycle, the G1 restriction point controls entry into S phase and is essential for maintaining control of cell division. The cyclin-dependent kinases (CDKs), CDK4 and CDK6, participate in a complex with D-type cyclins to initiate the transition through the G1 restriction point by phosphorylating and inactivating the retinoblastoma (Rb) tumor-suppressor protein. Alterations in this pathway occur frequently in human cancers and involve (1) loss of CDK inhibitors by mutation or epigenetic silencing, (2) mutation/overexpression of either CDK4 and CDK6 or cyclinD, or (3) inactivation of Rb. These alterations render cells less dependent on mitogenic signaling for proliferation. With the possible exception of those tumors with complete inactivation of Rb, which functions downstream of the CDK4 and CDK6–cyclinD complex, all of these cancers are potentially sensitive to pharmacologic inhibition of CDK4 and CDK6. From a therapeutic standpoint, the goal of inhibiting CDK4 and CDK6 with a small molecule inhibitor is to prevent cell cycle progression through the G1 restriction point, thus arresting tumor growth.

Abemaciclib represents a selective and potent small molecule CDK4 and CDK6 dual inhibitor with a broad antitumor activity in preclinical pharmacology models, acceptable physical and pharmacokinetic (PK) properties, and an acceptable toxicity profile in nonclinical species. Formally, abemaciclib refers to the freebase whereas LSN2813542 refers to abemaciclib mesylate; however, abemaciclib is used for uniformity throughout this Investigator's Brochure (IB), except when important for experimental clarity. This compound demonstrates significant inhibition of tumor growth as monotherapy in multiple human xenograft models including models for: breast cancer, colorectal cancer, glioblastoma multiforme, acute myeloid leukemia, melanoma, mantle cell lymphoma (MCL), and non–small-cell lung cancer (NSCLC). Although characterized by a different constellation of genomic mutations, each of these human xenografts has an intact, functional Rb protein. Xenograft growth inhibition is generally dose dependent from 25 to 100 mg/kg following daily oral administration for 21 to 28 days. Additional

nonclinical studies in xenograft models for human NSCLC and melanoma also show that abemaciclib may be used in combination with standard cytotoxic or targeted therapies to improve efficacy of these agents.

Preclinical data: In nonclinical species, abemaciclib distributes efficiently to the brain and potentially provides a unique opportunity to treat primary brain tumors as well as cancers that have metastasized to the brain. As a result of its brain exposure, treatment with abemaciclib in a rat orthotropic brain tumor model produces statistically significant and dose-dependent improvement in survival. Abemaciclib demonstrates moderate-to-high bioavailability in preclinical species. In repeat-dose toxicokinetic studies, abemaciclib showed generally dose-dependent exposure with no sex differences. Abemaciclib is highly metabolized, and hepatic elimination plays a major role in the clearance of abemaciclib and its metabolites in rats, dogs, and humans. In humans, the terminal elimination half-life (t 1/2) in plasma ranges from approximately 17 to 38 hours across the dose range tested. At a single dose of 200 mg, the mean apparent oral clearance (CL/F) is 38.3 L/hour with a high interindividual variability (105% coefficient of variation [CV]) and the apparent volume of distribution is large at 1300 L (96% CV). In the xenograft models and skin biopsies from patients, abemaciclib inhibited phosphorylated Rb (pRb) and topoisomerase II alpha (TopoIIα) at clinically relevant doses and exposures.

In preclinical species, the primary target organs for toxicity (associated with up to 3 months of continuous daily dosing) are bone marrow (resulting in pancytopenia), gastrointestinal tract, lymphoid tissues, and male reproductive tract. All of these changes demonstrated complete or partial reversibility during the recovery period. In humans, the most common (≥10%) treatment-emergent adverse events (TEAEs) possibly related to the study drug for patients who received single agent abemaciclib include diarrhea, nausea, fatigue, neutropenia, vomiting, decreased appetite, leukopenia, thrombocytopenia, anemia, abdominal pain, and blood creatinine increased. Increased rates of skeletal and cardiac variations and malformations, accompanied by decreased fetal weights, were observed in an embryo–fetal development study of abemaciclib in rats. See Investigator Brochure for more details.

Clinical data: As of 22 September 2016, 12 clinical studies were completed (7 in healthy subjects and 5 in patients) and 19 clinical studies are ongoing (3 in healthy subjects and 16 in patients). The PK profile of abemaciclib was studied using data available from a total of 222 patients enrolled in Study I3Y-MC-JPBA (JPBA). A general overview of abemaciclib PK based on several studies in healthy subjects and cancer patients (Table 6.2) is presented below. In Study JPBA, the mean concentration time profiles for abemaciclib and its metabolites at a dose of 200 mg in cancer patients are depicted in **Figure 4**:

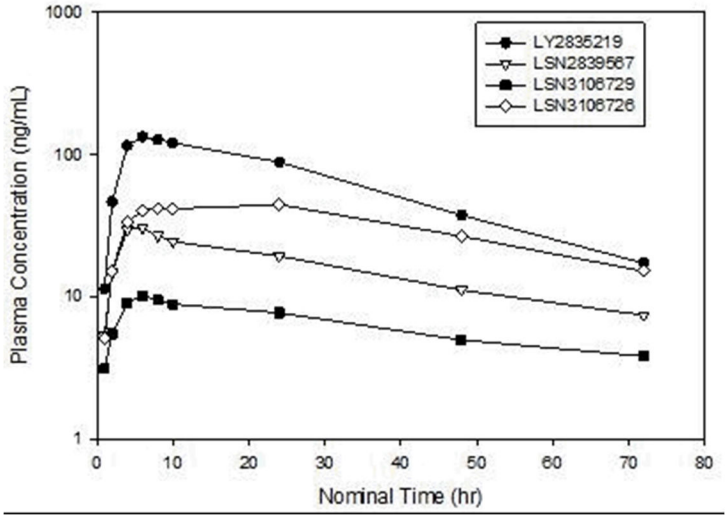


Figure 4: Abemaciclib and its metabolites' exposures after a single 200-mg dose in Study JPBA.

Safety Data:

SAEs are summarized below for events that were experienced by patients up to 22 September 2016 based on data available in LSS. Per LSS, as of 22 September 2016, 405 patients who received abemaciclib in Studies JPBA, JPBB, JPBC, JPBE, JPBH, JPBJ, JPBK, JPBN, JPBO, JPBX, JPBY, JPBZ, and JPCB experienced 724 SAEs. A total of 167 patients in 11 of these studies experienced 264 SAEs that were possibly related to the study drug. SAEs that were possibly related to study drug and were experienced by 2 or more patients who received abemaciclib monotherapy are summarized in Table 2:

Table 2: Serious Adverse Events Possibly Related to Study Drug Experienced by 2 or More Cancer Patients Treated with Abemaciclib Monotherapy

Event Preferred Term	Number of Patients
Nausea	9
Acute kidney injury	7
Dehydration	7
Vomiting	6
Pneumonia[a]	6
Thrombocytopenia[b]	6
Neutropenia[c]	6
Anaemia	5
Blood creatinine increased	4
Lung infection	4
Sepsis	4
Abdominal pain[d]	3
Confusional state	3
Decreased appetite	3
Hypokalaemia	3
Pneumonitis	3
Pyrexia	2

Encephalopathy	2
Enterocolitis infectious	2
Febrile neutropenia	2
General physical health deterioration	2
Leukopenia[e]	2
Pancreatitis	2
Pancytopenia	2
Renal failure	2

a Pneumonia = events of pneumonia, pneumocystis jirovecii pneumonia, and pneumonia fungal.
b Thrombocytopenia = events of thrombocytopenia and platelet count decreased.
c Neutropenia = events of neutropenia and neutrophil count decreased.
d Abdominal pain = events of abdominal pain and abdominal pain upper.
e Leukopenia = events of leukopenia and white blood cell decreased.

Cumulatively in healthy subjects, the most common (≥5%) AEs that were possibly related to study drug included headache (13.1%), nausea (10.0%), diarrhea (6.9%), and vomiting (5.4%). One healthy subject had an SAE of syncope possibly related to study drug. No deaths were reported in these studies. One subject in Study JPBF, who received 200-mg abemaciclib and 600-mg rifampin, discontinued due to mild (CTCAE Grade 1) vomiting.

Validated safety data for 870 patients treated with abemaciclib in Studies JPBA, JPBB, JPBC, JPBE, JPBH, JPBJ, JPBN, and JPBY are available (Lilly Investigator Brochure). Overall, the most common TEAEs (≥10%) possibly related to study drug for patients receiving abemaciclib as a single agent are diarrhea, nausea, fatigue, neutropenia, vomiting, decreased appetite, thrombocytopenia, anemia, leukopenia, abdominal pain, and blood creatinine increased. In Study JPBH, when abemaciclib was combined with endocrine therapy (anastrozole, letrozole, tamoxifen, exemestane), diarrhea has been reported in 98.5% of the metastatic breast cancer patients; and in 86.0% of the metastatic breast cancer patients when combined with targeted agents (exemestane + everolimus, or trastuzumab). As a result of the higher incidence of diarrhea, the recommended abemaciclib dose is 150 mg Q12H when combined with these agents. Furthermore, it was noted in Study JPBY (abemaciclib 150 mg Q12H in combination with anastrozole), diarrhea was reduced at 52% when patients received loperamide prophylactically. The majority of deaths reported for patients in the presented studies with available safety data were due to disease progression. Per LSS as of 22 September 2016, 167 patients in the ongoing and completed cancer patient studies experienced 264 SAEs that were reported as possibly related to study drug. SAEs that were possibly related to study drug and experienced by ≥5 patients receiving abemaciclib monotherapy included diarrhea (14 patients); nausea (9 patients); acute kidney injury and dehydration (7 patients each); anemia, pneumonia, and vomiting (6 patients each); and neutropenia and thrombocytopenia (5 patients each). SAEs that were possibly related to study drug and experienced by ≥5 patients receiving abemaciclib combinations included neutropenia (5 patients; abemaciclib with pemetrexed) and dehydration (5 patients; abemaciclib with endocrine therapy).

Efficacy Data: The results suggest that abemaciclib has clinical activity in patients with NSCLC and metastatic breast cancer. A summary of the results for patients in these populations is provided below. In Study JPBA (Phase I study of abemaciclib in patients with advanced cancer), two of 68 patients with NSCLC (2.9%) had a partial response (PR), including 1 patient who received abemaciclib 150 mg Q12H and 1 patient who received abemaciclib 200 mg Q12H. Among the remaining patients, 31 (45.6%) had stable disease (SD), 16 (23.5%) had PD, and 19

(27.9%) were not evaluable. In the metastatic breast cancer cohort, 11 of the 47 patients had a PR including 7 at the 150-mg Q12H dose and 4 at the 200-mg Q12H dose. One patient (2.1%, this patient received 150 mg Q12H) had a complete response (CR). Among the remaining patients, 11 (23.4%) had SD for ≥24 weeks, 10 (21.3%) had SD for <24 weeks, 11 (23.4%) had PD, and 3 (6.4%) were not evaluable.

MRTX849

The RAS family of proteins regulate intercellular signaling pathways responsible for growth, migration, survival and differentiation of cells. The activation of RAS proteins at the cell membrane by growth factors results in the binding of key effector molecules, formation of signaling complexes, and the initiation of a cascade of intracellular signaling pathways within the cell including the RAF and PI3 kinase pathways. KRAS is the most frequently mutated gene of the RAS family; the majority of KRAS mutations occur at residue 12. KRAS G12C mutations comprise approximately 14% of lung adenocarcinoma, 5% of colon adenocarcinoma, and smaller fractions of other types of cancer. Patients exhibiting KRAS mutations respond poorly to standard therapies and do not have effective targeted therapy options available. MRTX849 is a small molecule that elicits anti-tumor activity through selective, high affinity, covalent binding to and inhibition of the KRAS G12C mutant variant. MRTX849 effectively inhibits KRAS signaling and demonstrates cytoreductive antitumor activity in KRAS G12C-mutant models.

Preclinical data
MRTX849 inhibited viability in 17 KRAS G12C mutant cell lines in a 3D assay format (IC_{50} values from 0.2 to 1042 nM). In contrast, IC_{50} values were greater than 3000 nM in three non-G12C-mutant KRAS models evaluated. Moreover, proteomic studies demonstrated MRTX849 selectively modified KRAS G12C protein relative to all other detectable cystine-containing proteins/peptides in a KRAS G12C-mutant cell line. MRTX849 effectively modified KRAS G12C protein and inhibited KRAS-dependent signal transduction in patient- and cell line-derived human tumor xenograft models harboring KRAS G12C mutations. A dose-dependent increase in MRTX849 plasma concentration, KRAS protein modification, and KRAS-dependent signal transduction through pERK and pS6 was observed following oral administration of 10, 30 and 100 mg/kg doses of MRTX849. Consistent with these observations, MRTX849 demonstrated dose-dependent anti-tumor efficacy in KRAS G12C-mutant xenograft models, with tumor growth inhibition observed at doses as low as 3 mg/kg and maximal tumor regression observed at 100 mg/kg. MRTX849 administered at 100 mg/kg demonstrated broad cytoreductive anti-tumor efficacy in 18 out of 23 patient- and cell line-derived KRAS G12C-mutant human tumor xenograft models but did not significantly inhibit tumor growth in three non-G12C-mutant KRAS models.

In nonclinical studies, MRTX849 exhibited good oral bioavailability, extensive tissue distribution, and a projected human oral half-life consistent with once daily (QD) administration. Studies to evaluate plasma protein binding indicated reversible protein binding for MRTX849 ranging from 97-99% across species. No major differences in pharmacokinetic properties related to sex were observed. In general, oral plasma exposure increased dose-proportionately within the projected efficacious dose range with less-than-proportional increases observed at relatively higher dose levels, possibly due to saturation of absorption. MRTX849 demonstrated moderate hepatic extraction ratios across species in vitro with oxidative metabolism identified as the predominant elimination route with additional contribution from GSH-mediated clearance. In vivo, MRTX849 parent was the predominant species identified in plasma circulation or excreted in urine and bile following oral administration. MRTX849 metabolites identified in vitro and in vivo include 2 major oxidative metabolites identified at the pyrrolidine ring as well as

electrophile GSH and cysteine conjugates of both parent and oxidative metabolites. No individual metabolites comprised greater than 20% of all MRTX849-related material. Reaction phenotyping studies indicated that CYPs 3A4 and 2C8 mediate the majority of oxidative metabolism. Overall, metabolite profiles were consistent in vitro and in vivo and across all species evaluated indicating that a similar overall metabolism pattern was present in nonclinical efficacy and toxicology species compared to humans.

Reversible or time-dependent inhibition of selected CYPs suggest that MRTX849 is a moderately potent competitive inhibitor of CYP2B6, CYP2C9, and CYP3A4, as well as a time-dependent inhibitor of CYP3A4. However, MRTX849 demonstrated target potency for inhibition of KRAS G12C (cellular IC_{50} value of 0.017 uM) that was >100-fold greater compared with Ki values for inhibition of selected CYP family members. MRTX849 was determined to be a substrate of both P-gp and BCRP and is also a likely inhibitor of P-gp. Collectively, these studies indicated that MRTX849 exhibited effects on selected CYP- and efflux transporter-mediated drug clearance and has potential to effect clearance or disposition of other drugs that are metabolized by these selected CYPs or are transporter substrates, especially at higher dose levels and drug concentrations.

PK/PD studies utilizing nonclinical tumor models supported the hypothesis that AUC or average plasma concentration over a 24-hour interval was the PK parameter most closely linked to anti-tumor efficacy. Based on this observation it was hypothesized as the required plasma level required to elicit a robust tumor response based on nonclinical modeling was a free-fraction adjusted AUC_{0-24} of 0.243 µg*h/mL which translates to a human target efficacious total AUC at steady-state of 14.3 µg*h/mL. PBPK Link modeling using the target plasma exposure data derived from anti-tumor efficacy models, in vitro ADME data, and cross-species scaling projected that the oral $t_{1/2}$ in humans is estimated at approximately 15 hours and the projected efficacious human dose range is approximately 600-750 mg QD. In addition, the free-fraction adjusted AUC0-24 of 0.243 µg*h/mL, the calculated average free plasma concentration (C_{avg}) at this AUC0-24 of 0.015 µM, as well as the estimated free C_{max} concentration for this AUC based on a projected 15-hour human t1/2 of 0.025 µM were utilized for therapeutic index calculations for in vitro safety pharmacology studies and 28-Day toxicology and toxicokinetic studies conducted in rats and dogs.

A series of in vitro and in vivo safety pharmacology studies demonstrate that MRTX849 poses minimal risk for adverse effects on major physiological systems. Based on in vitro human ether-a-go-go related gene (hERG) binding, an in vitro Guinea pig Langendorff study, and ECG parameters collected in the repeat dose dog toxicology study, MRTX849 does not pose a risk for QT prolongation. In addition, there were no changes in heart rate or blood pressure in dogs treated at doses up to 25 mg/kg/day. There were no CNS related effects in the repeat dose toxicology studies, while in moribund rats treated at 300 mg/kg/day, there were observations of labored breathing suggestive of altered respiratory function due to accumulation of foamy pulmonary macrophages and the overall moribund nature of this non-tolerated dose in rats.

The nonclinical safety profile of MRTX849 was well characterized through the conduct of repeat-dose studies of up to 28-days in duration and genetic toxicology studies. In the genetic toxicology studies, MRTX849 was negative for mutagenicity and clastogenicity. In repeat dose toxicology studies, the primary target organ effects in both rats and dogs were primarily driven by possible phospholipidosis in multiple tissues. In the rat, the target tissues included lung, trachea, heart, skeletal muscle, bone marrow, spleen, pancreas and female sex organs. In the dog target tissues included bone marrow, lung, heart and spleen. The extent of vacuolization and the presence of foamy macrophages were more prominent in the rat as compared to dogs, and these

effects occurred at doses above the projected human efficacious concentrations and were reversible. Phospholipidosis is a common finding in toxicology studies conducted with cationic amphiphilic drugs like MRTX849. In both species, common target organs include the heart, spleen, lung and bone marrow. The changes in the lung appear to be associated with foamy alveolar macrophages, possibly due to phospholipidosis. Similarly, the splenic changes may also be related to scavenging of peripheral foamy inflammatory cells. This effect was not considered adverse in the dog, while in the moribund rats, it was associated with necrosis in the spleen and considered adverse. In the dog, the bone marrow changes of decreased erythropoiesis led to decreases in RBC parameters and decreased reticulocyte counts. However, in the rat 28-day study, a minor decrease in erythropoiesis was present within the bone marrow but was not reflective of a decrease in peripheral reticulocyte counts. In the heart, the microscopic findings differed between the rat and dog. In one high dose dog, the microscopic heart finding was characterized as myocardial necrosis in the papillary muscle. This type of cardiac lesion in dogs is commonly associated with exposure to positive inotropic/vasodilating drugs, and dogs appear to be overly sensitive to having this effect (Dogterom-1992). However, there were no MRTX849-induced changes in cardiovascular parameters or blood pressure changes in dogs implanted with telemetry transducers. MRTX849 was shown to inhibit the alpha-1-adrenergic receptor with a Ki value of 0.15 μM, which could lead to vasodilation which could explain the cardiac lesion in the repeat dose dog study. In the rat, the changes in the heart were limited to vacuolation due to phospholipidosis in the 300 mg/kg/day group that was terminated in extremis on Day 23. There were no vacuole changes in the heart of rats treated at the designated NOAEL in the rat of 150 mg/kg/day. The nonclinical safety findings related to MRTX849 administration represent toxicities that are considered clinically manageable, reversible, and of acceptable risk in the advanced cancer setting.

Clinical Data

As of a data cutoff date of November 27, 2020, a total of 231 patients had been enrolled into Study 849-001, including 202 patients administered MRTX849 monotherapy, and 29 patients administered MRTX849 in combination with pembrolizumab or cetuximab. Adverse events are summarized in this protocol for the 202 patients who were administered MRTX849 monotherapy. Among patients administered MRTX849 monotherapy, 197 initiated MRTX849 dosing at 600 mg twice daily. The most frequently reported treatment related adverse events in patients administered MRTX849 monotherapy are shown in Table 3, and treatment-emergent adverse events are shown in Table 4.

Table 3. Treatment-Related Adverse Events Reported in ≥ 5% of Patients Administered MRTX849 Monotherapy (N=202)

Adverse Event Preferred Term, n (%)	Any Grade (n=%)	Grade 1/2 n (%)	Grade 3/4 n (%)	Grade 5 n (%)
Any TEAE	161 (79.7)	108 (53.5)	51 (25.2)	2 (1.0)
Nausea	107 (53.0)	100 (49.5)	7 (3.5)	0
Diarrhea	94 (46.5)	88 (43.6)	6 (3.0)	0
Vomiting	72 (35.6)	68 (33.7)	4 (2.0)	0
Fatigue	55 (27.2)	46 (22.8)	9 (4.5)	0
Alanine aminotransferase increased	33 (16.3)	26 (12.9)	7 (3.5)	0
Aspartate aminotransferase increased	27 (13.4)	22 (10.9)	5 (2.5)	0
Blood creatinine increased	27 (13.4)	25 (12.4)	2 (1.0)	0
Decreased appetite	23 (11.4)	20 (9.9)	3 (1.5)	0
Electrocardiogram QT prolonged	24 (11.9)	20 (9.9)	4 (2.0)	0

Adverse Event Preferred Term, n (%)	Any Grade (n=%)	Grade 1/2 n (%)	Grade 3/4 n (%)	Grade 5 n (%)
Anaemia	20 (9.9)	19 (9.4)	1 (0.5)	0
Blood alkaline phosphatase increased	16 (7.9)	13 (6.4)	3 (1.5)	0
Dysgeusia	16 (7.9)	16 (7.9)	0	0
Lipase increased	13 (6.4)	6 (3.0)	7 (3.5)	0
Oedema peripheral	13 (6.4)	13 (6.4)	0	0

Table 4. Treatment-Emergent Adverse Events Reported in ≥ 5% of Patients Administered MRTX849 Monotherapy (N=202)

Adverse Event Preferred Term, n (%)	Any Grade (n=%)	Grade 1/2 n (%)	Grade 3/4 n (%)	Grade 5 n (%)
Any TEAE	186 (92.1)	78 (38.6)	95 (47.0)	13 (6.4)
Nausea	119 (58.9)	110 (54.5)	9 (4.5)	0
Diarrhoea	105 (52.0)	99 (49.0)	6 (3.0)	0
Vomiting	84 (41.6)	79 (39.1)	5 (2.5)	0
Fatigue	76 (37.6)	63 (31.2)	13 (6.4)	0
Anaemia	44 (21.8)	32 (15.8)	12 (5.9)	0
Blood creatinine increased	39 (19.3)	37 (18.3)	2 (1.0)	0
Alanine aminotransferase increased	38 (18.8)	29 (14.4)	9 (4.5)	0
Dyspnoea	36 (17.8)	25 (12.4)	11 (5.4)	0
Aspartate aminotransferase increased	33 (16.3)	27 (13.4)	6 (3.0)	0
Decreased appetite	31 (15.3)	27 (13.4)	4 (2.0)	0
Oedema peripheral	31 (15.3)	28 (13.9)	3 (1.5)	0
Hyponatraemia	26 (12.9)	17 (8.4)	9 (4.5)	0
Electrocardiogram QT prolonged	25 (12.4)	21 (10.4)	4 (2.0)	0
Abdominal pain	23 (11.4)	19 (9.4)	4 (2.0)	0
Blood alkaline phosphatase increased	23 (11.4)	20 (9.9)	3 (1.5)	0
Constipation	21 (10.4)	21 (10.4)	0	0
Hypoalbuminaemia	20 (9.9)	18 (8.9)	2 (1.0)	0
Hypokalaemia	20 (9.9)	17 (8.4)	3 (1.5)	0
Dizziness	18 (8.9)	18 (8.9)	0	0
Dysgeusia	18 (8.9)	18 (8.9)	0	0
Rash	18 (8.9)	17 (8.4)	1 (0.5)	0
Weight decreased	18 (8.9)	17 (8.4)	1 (0.5)	0
Hypomagnesaemia	17 (8.4)	17 (8.4)	0	0
Lipase increased	17 (8.4)	7 (3.5)	10 (5.0)	0
Lymphocyte count decreased	17 (8.4)	6 (3.0)	11 (5.4)	0
Arthralgia	16 (7.9)	16 (7.9)	0	0
Back pain	16 (7.9)	15 (7.4)	1 (0.5)	0
Dehydration	16 (7.9)	14 (6.9)	2 (1.0)	0
Headache	15 (7.4)	15 (7.4)	0	0
Pyrexia	14 (6.9)	14 (6.9)	0	0
Hypotension	13 (6.4)	9 (4.5)	4 (2.0)	0
Amylase increased	11 (5.4)	9 (4.5)	2 (1.0)	0
Blood lactate dehydrogenase increased	10 (5.0)	10 (5.0)	0	0
Dyspepsia	10 (5.0)	10 (5.0)	0	0
Lung infection	10 (5.0)	3 (1.5)	7 (3.5)	0

Adverse Event Preferred Term, n (%)	Any Grade (n=%)	Grade 1/2 n (%)	Grade 3/4 n (%)	Grade 5 n (%)
Muscular weakness	10 (5.0)	8 (4.0)	2 (1.0)	0

Treatment-emergent serious adverse events have been reported for 68 of the 202 patients administered MRTX849 monotherapy; events reported in more than 4 (2.0%) of patients include pneumonia (n=8, [4.0%]); n=6 (3.0%) patients each for hyponatraemia and lung infection; n=5 (2.5%) each for acute kidney injury, anaemia, and dyspnoea; and n=4 (2.0%) each for blood creatinine increased, hypotension, hypoxia, malignant neoplasm progression, nausea, pyrexia, and vomiting.

As of March 18, 2020, the PK profile of MRTX849 has been evaluated after administration of single and repeat oral doses in one patient each receiving 150 mg, 300 mg, and 1200 mg QD, 2 patients receiving 600 mg QD, and 19 patients receiving 600 mg BID. The BID regimen was administered at approximately 12-hour intervals. Single- and multiple-dose PK profiles are shown in Figure 1 and Figure 2. Summary of preliminary PK parameters following a single dose and multiple dose administration are shown in Table 1 and Table 2, respectively.

Among patients receiving the QD regimen, calculation of some PK parameters was hampered by vomiting post dosing in one patient each at 600 mg and 1200 mg QD, and incomplete sample collection during the 96-hour PK sampling period in the other patient at 600 mg QD. After a single dose of MRTX849 in the patients enrolled in the 150 mg, 300 mg, and 600 mg QD dosing regimens, the individual time to maximum plasma concentration (t_{max}) was between 2 to 6 hours after dosing. The individual elimination half-life ($t_{1/2}$) for 150 mg and 300 mg QD were approximately 29 and 19 hours, respectively. Drug accumulation ratio (R_{ac}) after repeated doses of 150 mg and 300 mg QD were approximately 3-fold for maximum plasma concentration (C_{max}) and 4-fold for area under the plasma concentration-time curve over the dosing interval (AUC_{τ}).

Among the 19 patients receiving the 600 mg BID regimen, all patients provided data for single-dose PK assessments (including 7 patients with data up to 96 hours post dose for the calculation of t1/2) and 17 patients provided evaluable PK data for steady-state PK assessments. The median (range) t_{max} after single and repeated doses were 6 (2 to 12) hours and 4 (0.5 to 8) hours, respectively. After a single dose, geometric mean C_{max} and AUC_{τ} were 564 ng/mL and 4.84 µg*h/mL, respectively. After repeated doses, geometric mean steady-state Cmax, minimum plasma concentration (C_{min}), and AUC_{τ} were 2890 ng/mL, 2300 ng/mL, and 31.5 µg*h/mL, respectively. Between-patient variability (geometric mean CV%) for MRTX849 exposure measures was approximately 44 to 46%. The average R_{ac} was 5.3-fold for C_{max} and 6.6-fold for AUC_{τ}. The mean $t_{1/2}$ was approximately 21 hours.

As of 27 November 2020, preliminary results from an ongoing clinical drug-drug interaction study suggest MRTX849 is a strong inhibitor of CYP3A4 and a moderate inhibitor of CYP2C9. MRTX849 increased exposure of midazolam (a CYP3A4 substrate) > 5-fold and increased exposure of warfarin (a CYP2C9 substrate) by 2-fold. MRTX849 also inhibited P-gp activity and increased the exposure of digoxin (a P-gp substrate) by 2-fold. MRTX849 did not change exposure of a BCRP substrate. For additional details on clinical drug-drug interactions please refer to the MRTX849 Investigator's Brochure.

2.0 OBJECTIVES

2.1 Co-Primary Objectives

- To determine the activity of a CDK inhibitor in patients with progressive brain metastases derived from lung cancer, breast cancer, and other cancers harboring actionable genetic alterations associated with sensitivity to CDK inhibitors as measured by response rate (RANO criteria).
- To determine the activity of a PI3K inhibitor in patients with progressive brain metastases derived from lung cancer, breast cancer, and other cancers harboring actionable genetic alterations in the PI3K pathway as measured by response rate (RANO criteria).
- To determine the activity of an NTRK/ROS1 inhibitor in patients with progressive brain metastases derived from lung cancer harboring actionable NTRK/ROS1 gene fusions as measured by response rate (RANO criteria).
- To determine the activity of a KRAS G12C inhibitor in patients with progressive brain metastases derived from lung cancer, and other cancers harboring a KRAS G12C mutation as measured by response rate (RANO criteria).

2.2 Secondary Objectives

- To evaluate the systemic response by RECIST criteria in each of the cohorts determined by treatment and primary cancer type
- To evaluate the clinical benefit rate (CR + PR + SD) by BM-RANO for CNS in each of the cohorts determined by treatment and primary cancer type
- To evaluate the clinical benefit rate (CR + PR + SD) by RECIST for extracranial disease in each of the cohorts determined by treatment and primary cancer type
- To evaluate the duration of response by BM-RANO in each of the cohorts determined by treatment and primary cancer type
- To evaluate the duration of response by RECIST in each of the cohorts determined by treatment and primary cancer type
- To evaluate the progression-free survival for intracranial disease in each of the cohorts determined by treatment and primary cancer type
- To evaluate the progression-free survival for extracranial disease in each of the cohorts determined by treatment and primary cancer type
- To evaluate the site of first progression (CNS vs non-CNS) in each of the cohorts determined by treatment and primary cancer type
- To evaluate the overall survival in each of the cohorts determined by treatment and primary cancer type
- To evaluate the toxicity profile of agents in patients with brain metastases in each of the cohorts determined by treatment and primary cancer type

2.3 Correlative Science Objective

2.3.1. To evaluate imaging markers of response in brain metastases (See Section 14.2)

3.0 PATIENT SELECTION

For questions regarding eligibility criteria, see the Study Resources page. Please note that the Study Chair cannot grant waivers to eligibility requirements.

3.1 On-Study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate.

Physicians should consider whether any of the following may render the patient inappropriate for this protocol:

- Psychiatric illness which would prevent the patient from giving informed consent.
- Medical condition such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Patients who cannot swallow oral formulations of the agent(s).
- Patients who would have completed systemic therapy (with the exception of hormonal agents) within 14 days prior to the start of study treatment.

In addition:

Women and men of reproductive potential should agree to use an appropriate method of birth control throughout their participation in this study due to the teratogenic potential of the therapy utilized in this trial. Include as applicable: Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives or double barrier method (diaphragm plus condom).

3.2 Pre-Registration Eligibility Criterion (all patients)

___ **3.2.1 Tissue available for biomarker testing (any brain metastasis tissue and extracranial site from any prior resection or biopsy).** If the patient does not have any evidence of extracranial disease, or if there is insufficient extracranial tissue for profiling, brain metastasis tissue is sufficient for eligibility.

3.3 Registration Eligibility Criteria (all patients)

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following page(s).

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

A female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

___ **3.3.1 Documentation of Disease:**

Histologic Documentation: Participants must have histologically confirmed parenchymal metastatic disease to the brain from any solid tumor. Note: this includes patients that have controlled extracranial disease with progressive intracranial metastasis, as well as patients that have progressive intracranial and extracranial disease.

New or progressive brain metastases are defined as any one of the following:

- Untreated measurable lesions in patients who have received surgery and/or SRS to one or more other lesions.
- Progressive measurable lesions after radiation, surgery, or prior systemic therapy
- Residual or progressive lesions after surgery if asymptomatic.
- Patients who have had prior WBRT and/or SRS and then whose lesions have progressed by BM-RANO criteria or there are new lesions, are eligible. Lesions treated with SRS may be eligible if there is unequivocal evidence of progression. For patients with NTRK or ROS1 mutations, entrectinib may be used for newly diagnosed brain metastases. Similarly, for patients with KRAS G12C mutations, MRTX849 may be used for newly diagnosed brain metastases.
- Patients who have not previously been treated with cranial radiation (e.g. WBRT or SRS) are eligible, but such patients must be asymptomatic or neurologically stable from their CNS metastases.

___ **3.3.2 Measurable CNS disease (≥ 5 mm) as defined in Section 11.0.**

___ **3.3.3 Ability to obtain MRIs with contrast**

___ **3.3.4 Prior Treatment**

No surgery within 2 weeks prior to or after registration.

No chemotherapy within 14 days prior to registration (**Note:** For abemaciclib arm, a 21-day chemotherapy washout is required. See Section 3.6.2).

- For melanoma, patients must have progressed after prior immune checkpoint blockade or for BRAF positive melanoma, BRAF/MEK inhibitors.
- For lung cancer, EGFR mutant patients must have failed EGFR therapies.
- For HER2-positive breast cancer patients (regardless of ER/PR status), patients must have received at least one prior HER-2 directed therapy in the metastatic setting.
- For triple negative breast cancer (TNBC), patients must have received at least one chemotherapy in the metastatic setting.
- For ER and/or PR-positive, HER2-negative breast cancer, patients must have received at least one endocrine therapy in the metastatic setting.
- Patients who have received prior treatment with any of the targeted treatments on this study are not eligible for that specific treatment arm(s), but could be eligible for other arms (e.g., a patient who has had prior treatment with abemaciclib would not be eligible for the abemaciclib arm, but could be eligible for another arm).

___ **3.3.5 Presence of clinically actionable alteration in KRAS G12C or CDK** pathway or **PI3K** pathway in both a brain metastasis and extracranial site per central review, as defined in Appendix II. For the KRAS G12C arm, if brain metastasis tissue is not available, then presence of the KRAS G12C mutation can be in the extracranial site only.

___ **3.3.6 Not pregnant and not nursing,** because this study involves investigational agents whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown. Therefore, for women of childbearing potential only, a negative pregnancy

test done ≤ 14 days prior to registration is required (**Note:** For abemaciclib arm, pregnancy test is required ≤ 7 days prior to registration. See Section 3.6.3).

___ **3.3.7 No known current diffuse leptomeningeal involvement** for the CDK and PI3K arms (diffuse defined as leptomeningeal involvement throughout the CNS axis). Patients with focal leptomeningeal disease, with or without documented positive CSF cytology, are eligible.

___ **3.3.8 Age ≥ 18 years**

___ **3.3.9 ECOG Performance Status 0-2**

___ **3.3.10 Adequate organ function**

___ **3.3.11 Required Initial Laboratory Values:**

Absolute Neutrophil Count (ANC) ≥ 1,500/mm3

Platelet Count ≥ 100,000/mm3

Total Bilirubin ≤ 1.5 x upper limit of normal (ULN)*

AST and ALT ≤ 2.5 x upper limit of normal (ULN)

Creatinine ≤ 1.5 mg/dL**

OR

Calc. Creatinine Clearance > 45 mL/min**

*except in patients with Gilbert's disease. Patients with Gilbert's syndrome with a total bilirubin ≤2.0 times ULN and direct bilirubin within normal limits are permitted.

**except for patients in the MRTX849 (KRAS G12C) arm. For this arm, patients must have creatinine clearance ≥60 mL/min or glomerular filtration rate ≥60 mL/min/1.73m^2 calculated using a validated prediction equation (e.g., Cockcroft-Gault, MDRD, or 24-hour urine CrCl).

___ **3.3.12 Comorbid conditions**

No uncontrolled medical comorbidities per investigator discretion (e.g. interstitial lung disease, severe dyspnea at rest or requiring oxygen therapy, severe renal impairment [e.g. estimated creatinine clearance <30ml/min], history of major surgical resection involving the stomach or small bowel, or preexisting Crohn's disease or ulcerative colitis or a preexisting chronic condition resulting in baseline Grade 2 or higher diarrhea)

___ **3.3.13 Concomitant medications:**

Radiation to symptomatic non-target sites within neural axis is allowed prior to registration without washout (provided there is at least one untreated target lesion for measurement on study and radiation is completed prior to registration).

Concurrent systemic corticosteroids are allowed if stable dose of dexamethasone for 7 days prior to registration. Baseline doses and changes in steroid dosing will be captured.

No concurrent administration of anticancer therapies (except for endocrine therapy or continuation of hormonal therapy or trastuzumab in breast cancer patients for the PI3K and CDK inhibitor arms). No chemotherapy, targeted therapy or immunotherapy within 14

days prior to entering the study (**Note:** For abemaciclib arm, a 21-day chemotherapy washout is required. See Section 3.6.2).

Chronic concomitant treatment with strong inhibitors of CYP3A4 is not allowed on this study. Patients on strong CYP3A4 inhibitors must discontinue the drug 14 days or 5 or more half-lives prior to registration on the study. See Section 8.1 for more information.

Chronic concomitant treatment with strong CYP3A4 inducers is not allowed. Patients must discontinue the drug 14 days or 5 or more half-lives prior to the start of study treatment. See Section 8.1 for more information.

3.4 Additional Registration Eligibility Criteria for Paxalisib Arm

___ **3.4.1 UPC Ratio < 1 or urine protein ≤ 1**

___ **3.4.2 Recent acute myocardial infarction in the last 6 months or current angina pectoris are excluded.** Patients with symptomatic bradycardia should have an electrocardiogram at baseline. If QT interval > 470 msec, the patient is excluded.

___ **3.4.3 Patients with uncontrolled Type I or II diabetes mellitus should be excluded.** Uncontrolled diabetes is defined as HbA1c >9% in addition to fasting glucose >140 mg/dL on at least 2 occasions within 14 days prior to registration.

3.5 Additional Registration Eligibility Criterion for Entrectinib Arm

___ **3.5.1 Concurrent use of H2-receptor antagonists, receptor antagonists, PPIs, and/or antacids are prohibited.**

3.6 Additional Registration Eligibility Criteria for Abemaciclib Arm

___ **3.6.1 Hemoglobin ≥ 8 g/dL**

Patients may receive erythrocyte transfusions to achieve this hemoglobin level at the discretion of the investigator. Initial treatment must not begin earlier than the day after the erythrocyte transfusion.

___ **3.6.2 Prior treatment**

Patients who received chemotherapy must have recovered (Common Terminology Criteria for Adverse Events [CTCAE] Grade ≤1) from the acute effects of chemotherapy except for residual alopecia or Grade 2 peripheral neuropathy prior to registration. A washout period of at least 21 days is required between last chemotherapy dose and registration (provided the patient did not receive radiotherapy).

Patients who received adjuvant radiotherapy must have completed and fully recovered from the acute effects of radiotherapy. A washout period of at least 14 days is required between end of radiotherapy and registration.

Breast cancer patients who have received ribociclib or palbociclib are eligible as long as there is documentation of CDK4/6 pathway alteration on a biopsy or resection at the point of progression post-ribociclib or palbociclib.

___ **3.6.3 For females of childbearing potential:**

A female of childbearing potential, must have a negative serum pregnancy test within 7 days prior to registration and agree to use a highly effective contraception method during the treatment period and for 3 weeks following the last dose of abemaciclib.

Contraceptive methods may include an intrauterine device [IUD] or barrier method. If condoms are used as a barrier method, a spermicidal agent should be added as a double barrier protection.

Cases of pregnancy that occur during maternal exposures to abemaciclib should be reported. If a patient or spouse/partner is determined to be pregnant following abemaciclib initiation, she must discontinue treatment immediately. Data on fetal outcome and breast-feeding are to be collected for regulatory reporting and drug safety evaluation.

___ **3.6.4 Patients with active bacterial infection (requiring intravenous [IV] antibiotics at time of initiating study treatment),** fungal infection, or detectable viral infection (such as known human immunodeficiency virus positivity or with known active hepatitis B or C [for example, hepatitis B surface antigen positive] are excluded. Screening is not required for enrollment.

___ **3.6.5 Patients with personal history of any of the following conditions:** syncope of cardiovascular etiology, ventricular arrhythmia of pathological origin (including, but not limited to, ventricular tachycardia and ventricular fibrillation), or sudden cardiac arrest, are excluded.

3.7 Additional Registration Eligibility Criterion for MRTX849 Arm

___ **3.7.1 Hemoglobin ≥9.0 g/dL.** Note: Transfusions will be allowed to achieve this provided the patient has not received more than 2 units of red blood cells in the prior 4 weeks.

___ **3.7.2 Any of the following cardiovascular abnormalities within 6 months of study entry are excluded:** symptomatic or uncontrolled atrial fibrillation, unstable angina pectoris or myocardial infarction, CHF ≥ NYHA Class 3, stroke or transient ischemic attack.

___ **3.7.3 Ongoing need for medication known to cause prolonged QTc interval or that are substrates of CYP3A4 with narrow therapeutic index that cannot be switched to alternative treatment prior to study entry is excluded**.

___ **3.7.4 Prolonged QTc interval >480 milliseconds or family history or medical history of Long QT syndrome is excluded.**

___ **3.7.5 Known human immunodeficiency virus (HIV) infection or acute or chronic hepatitis B or C infection is excluded. Screening is not required for enrollment. Note that the following are permitted:**

- Patients treated for hepatitis C (HCV) with no detectable viral load;
- Patients treated for HIV with no detectable viral load for at least 1 month prior to randomization while on a stable regimen of agents that are not strong inhibitors of CYP3A4; and

- Patients with hepatitis B (HBV) receiving prophylaxis against reactivation of hepatitis B (either [HBsAg-positive with normal ALT and HBV DNA <2,000 IU/mL or <10,000 copies/mL] or [HBsAg-negative and anti-HBc positive]).

___ **3.7.6 History of intestinal disease or major gastric surgery likely to alter absorption of study treatment or inability to swallow oral medications is excluded.**

___ **3.7.7 Recovery from the adverse effects of prior therapy to baseline or Grade 1 (any grade alopecia and Grade ≤2 peripheral neuropathy are eligible).**

___ **3.7.8 For females of childbearing potential**. It is not known whether MRTX849 presents a risk to the embryo or the fetus; however, based on the mechanism of action (KRAS G12C inhibition), effects on the reproductive system are not unexpected. MRTX849 is contraindicated in women who are pregnant or lactating. Women of childbearing potential and men receiving MRTX849 who are sexually active must employ an effective method of contraception throughout their period of treatment and for 6 months after their last treatment with MRTX849.

4.0 PATIENT REGISTRATION

4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations require sponsors to select qualified investigators. National Cancer Institute (NCI) policy requires all individuals contributing to NCI-sponsored trials to register with their qualifications and credentials and to renew their registration annually. To register, all individuals must obtain Cancer Therapy Evaluation Program (CTEP) credentials necessary to access secure NCI Clinical Oncology Research Enterprise (CORE) systems. Investigators and clinical site staff who are significant contributors to research must register in the Registration and Credential Repository (RCR). The RCR is a self-service online person registration application with electronic signature and document submission capability.

RCR utilizes four person registration types that are applicable to this study.

- Investigator (IVR) — MD, DO, or international equivalent;
- Non-Physician Investigator (NPIVR) — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- Associate Plus (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; and
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials.

RCR requires the following registration documents:

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

IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites in RCR to allow the following:

- Addition to a site roster;
- Selection as the treating, credit, or consenting person in OPEN;
- Ability to be named as the site-protocol Principal Investigator (PI) on the IRB approval; and
- Assignment of the Clinical Investigator (CI) task on the Delegation of Tasks Log (DTL).

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

Refer to the NCI RCR page on the CTEP website for additional information. For questions, please contact the **RCR Help Desk** by email at [redacted].

4.2 Cancer Trials Support Unit Registration Procedures

Permission to view and download this protocol and its supporting documents is restricted and is based on the person and site roster assignment housed in the Roster Maintenance application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the Cancer Trials Support Unit (CTSU) members' website.

This study is supported by the NCI CTSU.

IRB Approval

As of March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB) in order to participate in Cancer Therapy Evaluation Program (CTEP) and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases. In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating through the NCI CIRB must submit the Study Specific Worksheet (SSW) for Local Context 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 [redacted] 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 email ([redacted]) or by calling [redacted]

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following for the site to be able to have an Approved status following processing of the IRB/REB approval record:

- Have an active CTEP status;
- Have an active status at the site(s) on the IRB/REB approval (applies to US and Canadian sites only) on at least one participating organization's roster;
- If using NCI CIRB, be active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record;
- Include the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile;
- List all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Have the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional site requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO);
- An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only); and
- Compliance with all applicable protocol-specific requirements (PSRs).

4.2.1 Protocol-Specific Requirements for A071701 Site Registration

This is a study with a radiation and/or imaging (RTI) component and the enrolling site must be aligned to an RTI provider. To manage provider associations, access the Provider Association page from the Regulatory section on the CTSU members' website at [redacted]. Sites must be linked to at least one Imaging and Radiation Oncology Core (IROC) provider to participate on trials with an RTI component. Enrolling sites are responsible for ensuring that the appropriate agreements and IRB approvals are in place with their RTI provider. Only an individual with a primary role on a treating site roster can update the provider associations, though all individuals at a site may view provider associations. To find who holds primary roles at your site, view the Person Roster Browser under the RUMS section on the CTSU members' website.

4.2.2 Downloading Site Registration 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 to institutions and its associated investigators and staff on a participating roster. To view/download site registration forms:

- Log in to the CTSU members' website [redacted]);
- Click on *Protocols* in the upper left of the screen:
  - Enter the protocol number in the search field at the top of the protocol tree; or
  - Click on the By Lead Organization folder to expand, then select *Alliance*, and protocol number *A071701*.Click on *Documents, Protocol Related Documents*, and use the *Document Type* filter and select *Site Registration* to download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

4.2.3 Submitting Regulatory Requirements

Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU members' website.

To access the Regulatory Submission Portal log in 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 by phone or email: [redacted] or [redacted] to receive further instruction and support.

4.2.4 Checking Site's Registration Status

Site registration status may be verified on the CTSU members' 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.

4.2.5 Delegation of Tasks Log (DTL)

Each site must complete a protocol-specific Delegation of Tasks Log (DTL) using the DTL application which is accessible via the Delegation Log link on the CTSU members' website or directly at [redacted]. The Clinical Investigator (CI) is required to review and electronically sign the DTL prior to the site receiving an approved site registration status and enrolling patients to the study. To maintain an approved site registration status the CI must re-sign the DTL at least annually and when a new version of the DTL is released; and to activate new task assignments requiring CI sign-off. Any individual at the enrolling site on a participating roster may initiate the site DTL. Once the DTL is submitted for CI approval, only the designated DTL Administrators or the CI may update the DTL. Instructions on completing the DTL are available in the Help Topics button in the DTL application and describe DTL task assignments, CI signature, and CTEP registration requirements, as well as include a Master Task List.

4.3 Patient Pre-Registration Requirements

Patients may be pre-registered to this study on the basis of the diagnosis of recurrent or progressive brain metastases made at the original institutions.

Screening Informed Consent: the patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Current human protection committee approval of this protocol and a consent form is required prior to patient consent and registration.

Pre-registration Form: Upon completion of the screening process, the site is responsible for entering applicable data collected during Step 0 and using the "Pre-registration Form" in Medidata RAVE, irrespective of completing Step 1 of the enrollment process.

For local site HIPAA documentation, please note that the following personal health information (PHI) may be released outside of the Alliance.

- Tumor tissue for integral biomarker testing

4.4 Patient Pre-Registration Procedures

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at [redacted]) and a 'Registrar' role on either the LPO or participating organization roster. Registrars must hold a minimum of an AP registration type.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. OPEN can be accessed at [redacted] or from the OPEN tab on the CTSU members' side of the website at [redacted] To assign an IVR or NPIVR as the treating, crediting, consenting, drug shipment (IVR only), or investigator receiving a transfer in OPEN, the IVR or NPIVR must list on their Form FDA 1572 in RCR the IRB number used on the site's IRB approval.

4.5 Central Biomarker Review and Laboratory Submission

1 H&E and 15-25 unstained slides cut from the FFPE block that contains representative tumor tissue must be submitted. (See Section 6.2).

Submission of these samples for central biomarker testing is MANDATORY for all patients pre-registered to this study.

Tissue submission must be accompanied by a completed "Central Biomarker Results Form" found on the A071701 study page. Failure to submit this form with the specimens will delay turnaround time for central review and biomarker testing. The submission must also be accompanied by deidentified pathology reports for each tumor tissue. The turnaround time is approximately 21 days (15 business days). Both the extracranial tumor specimen AND the brain metastasis specimen will be centrally reviewed to confirm study eligibility and cohort assignment based on the presence of specific genetic alterations identified in the submitted tumor specimens (see Appendix II for eligible variants under this study). Sites must use this form to confirm eligibility and arm assignment.

For all arms:

If biomarker testing has already been performed by the site, the sequencing report can be sent to [redacted] to review for eligibility. If eligibility is confirmed, subjects on these

arms can be enrolled before central lab sequencing analysis. Tumor tissue is still required to be sent for central review per Section 4.5 and the Correlative Sciences Manual.

Note: To ensure that tissue samples submitted for eligibility testing are received at MGH, sites are to email [redacted] at [redacted] prior to tissue sample shipment.

4.6 Patient Registration Requirements

Informed consent: The patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Current human protection committee approval of this protocol and a consent form is required prior to patient consent and registration.

Patients with impaired decision making capacity may be enrolled on this study, where institutional policy and IRB of record allow.

4.7 Patient Registration Procedures

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 will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems;
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrars must hold the OPEN Registrar task on the DTL for the site; and
- 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, or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the Institutional Review Board (IRB) number used on the site's IRB approval on their Form Food and Drug Administration (FDA) 1572 in the Registration and Credential Repository (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 Health Insurance Portability and Accountability Act (HIPAA) authorization form (if applicable).

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

Access OPEN at [redacted] or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at

[redacted] or [redacted]. For any additional questions, contact the CTSU Help Desk at [redacted].

To receive site reimbursement for specific tests and/or bio-specimen submissions, completion dates must be entered in the OPEN Funding screen post registration. Please refer to the protocol-specific funding page on the CTSU members' website for additional information. Timely entry of completion dates is recommended as this will trigger site reimbursement.

Patient enrollment will be closely monitored to avoid exceeding the accrual goals of each study cohort. If a patient has been pre-registered, has received biomarker testing results from the central lab, and has been identified to have an eligible mutation when the accrual has goal has been met for any given cohort, the patient will be allowed to proceed to registration. Otherwise, the patient will not be allowed to register to a given cohort if the accrual goal has been met, even if a patient has previously been consented to the screening study.

4.8 Grouping Factors and Treatment Assignments

Grouping factors will include the treating targeted agent (Abemaciclib, Paxalisib, Entrectinib [closed to new patient enrollment on 1/9/2024], MRTX849) and the primary cancer type (lung, breast, other). See Section 13.0 (Statistical Considerations).

5.0 STUDY CALENDARS

Pre-Study Testing Intervals

The pre-study testing intervals are guidelines only. Laboratory and clinical parameters during treatment are to be followed using individual institutional guidelines and the best clinical judgment of the responsible physician. It is expected that patients on this study will be cared for by physicians experienced in the treatment and supportive care of patients on this trial.

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

To be completed ≤ 28 DAYS before registration: All laboratory studies, history and physical.

To be completed ≤ 42 DAYS before registration: Any baseline exams used for screening unless otherwise specified below, or any X-ray, scan of any type or ultrasound of uninvolved organs which is not utilized for tumor measurement.

5.1 Study Calendar – Abemaciclib

	Prior to Registration*	Every cycle from the start of treatment	Every 2 cycles from the start of treatment	Post treatment follow-up**
Tests & Observations				
History and physical, weight, PS	X	X		X
Height	X			
Pulse, Blood Pressure	X	X		
ECG	X (1)	X (1)		X (1)
Adverse Event Assessment	X (2)	X (2)		X (2)
Patient Medication Diary	X (3)	X (3)		X (3)
Laboratory Studies				
Complete Blood Count, Differential, Platelets	X	A		X
Serum Creatinine	X	X		X
Glucose	X	X		
Albumin	X			X
AST, ALT, Alk. Phos., Bili	X	A		X
Serum HCG	X (4)			
Staging				
Central biomarker testing for eligibility	X (5)			
Contrast-enhanced cranial MRI	B		B	B
CT Chest, Abdomen, Pelvis (bone imaging only required if indicative of bony metastases at baseline or if signs or symptoms suggestive of bony metastases develop, and if bone metastases are the only site of evaluable extracranial disease)	X (6)		C,D (6)	C,D (6)
Correlative studies: For patients who consent to participate				
Tissue and Blood samples	At baseline, every 2 cycles, and at progression. See Section 6.2. If the patient does not have any evidence of extracranial disease or if there is insufficient extracranial tissue for testing, brain metastasis tissue is sufficient for eligibility.			

* Labs completed prior to registration may be used for day 1 of cycle 1 tests if obtained ≤ 14 days prior to treatment. For subsequent cycles, labs, scans, tests and observations may be obtained ≤ 3 days prior to day of treatment.

** Physical examination and staging scans are required ≤ 6 weeks from date of last treatment, then every 8-10 weeks for the first 2 years from registration, then every 3 months (+/- 2 weeks) for years 3-4 from registration, then every 6 months thereafter until intracranial and/or extracranial disease progression (or until 5 years following registration if disease progression does not occur). This can be a virtual visit (and not face-to-face) as long as the patient is not having toxicities from the drugs

or symptoms from tumor. Thereafter, survival information is required every 6 months until 5 years following registration. See also Section 12.0.

1 As clinically indicated
2 Solicited AEs are to be collected starting at baseline. Routine AEs are to be collected starting after registration through the last study visit. See Section 9.2 for AEs collected within 30 days of last treatment date, and Section 9.3 for expedited reporting of SAEs.
3 The diary must begin the day the patient starts taking the medication and must be completed per protocol and returned to the treating institution OR compliance must be documented in the medical record by any member of the care team.
4 For women of childbearing potential (see Section 3.3). Must be done ≤ 7 days prior to registration.
5 See Section 6.2 for central biomarker submission.
6 Baseline scans (within 14 days prior to registration) should include a CT Chest, Abdomen, Pelvis and brain MRI. Supporting documentation is to be submitted, per Section 6.1.1. If the baseline scans were a CT or MRI and bone scan, follow-up bone scans are required only for patients with bone metastases as the only site of evaluable disease, and are optional for other patients. Response assessment should include assessment of all sites of disease and use the same imaging method as was used at baseline.

A. Every two weeks for the first two cycles, then every cycle thereafter
B. Within 14 days prior to registration, every 2 months for the first 2 years of treatment, then every 3 months for years 3-4, then every 4 months thereafter until progression or until 5 years following registration. See Appendix I for MRI acquisition parameters.
C. Every 2 cycles (beginning prior to Cycle 1) until evidence of CNS or systemic progression or relapse. Scans may be done up to 7 days prior to beginning a cycle. Confirmatory scans should also be obtained at least 4 weeks following documentation of objective response (see Section 11.0).
D. Bone imaging (after baseline) is required only if indicative of bony metastases at baseline or if signs or symptoms suggestive of bony metastases develop, and if bone metastases are the only site of evaluable disease. Bone imaging should follow the same schedule as CT scans if indicated.

5.2 Study Calendar – Paxalisib

	Prior to Registration*	Every cycle from the start of treatment	Every 2 cycles from the start of treatment	Post treatment follow-up**
Tests & Observations				
History and physical, weight, PS	X	X		X
Height	X			
Pulse, Blood Pressure	X	X		
ECG	X		A	X
Adverse Event Assessment	X (1)	X (1)		X (1)
Patient Medication Diary	X (2)	X (2)		X (2)
Laboratory Studies				
Complete Blood Count, Differential, Platelets	X	X		X
Serum Creatinine	X	X		X
Glucose	X	X		
Albumin	X			X
AST, ALT, Alk. Phos., Bili	X	X		X
Triglycerides, cholesterol	X(3)		X(3)	
Serum or Urine HCG	X (4)			
UPC ratio/urine protein	X (5)			
Staging				
Central biomarker testing for eligibility	X (6)			
Contrast-enhanced cranial MRI	B		B	B
CT Chest, Abdomen, Pelvis (bone imaging only required if indicative of bony metastases at baseline or if signs or symptoms suggestive of bony metastases develop, and if bone metastases are the only site of evaluable extracranial disease)	X (7)		C,D(7)	C,D(7)
Correlative studies: For patients who consent to participate				
Tissue and Blood samples	At baseline, then blood samples every 2 cycles. See Section 6.2. If the patient does not have any evidence of extracranial disease or if there is insufficient extracranial tissue for testing, brain metastasis tissue is sufficient for eligibility.			

* Labs completed prior to registration may be used for day 1 of cycle 1 tests if obtained ≤ 14 days prior to treatment. For subsequent cycles, labs, scans, tests and observations may be obtained ≤ 3 days prior to day of treatment.

** Physical examination and staging scans are required ≤ 6 weeks from date of last treatment, then every 8-10 weeks for the first 2 years from registration, then every 3 months (+/- 2 weeks) for years 3-4 from registration, then every 6 months thereafter until intracranial and/or extracranial disease progression (or until 5 years following registration if disease progression does not occur). This can be a virtual visit (and not face-to-face) as long as the patient is not having toxicities from the drugs

or symptoms from tumor. Thereafter, survival information is required every 6 months until 5 years following registration. See also Section 12.0.

1 Solicited AEs are to be collected starting at baseline. Routine AEs are to be collected starting after registration through the last study visit. See Section 9.2 for AEs collected within 30 days of last treatment date, and Section 9.3 for expedited reporting of SAEs.
2 The diary must begin the day the patient starts taking the medication and must be completed per protocol and returned to the treating institution OR compliance must be documented in the medical record by any member of the care team.
3 Triglycerides and cholesterol should be checked prior to cycle 1 and then every 4 cycles.
4 For women of childbearing potential (see Section 3.3). Must be done ≤ 14 days prior to registration.
5 All patients receiving paxalisib will have a urinalysis or urine protein performed ≤ 72 hours prior to the first cycle. If urine protein is ≥ 2+, 24-hour urine collection or UPC ratio will be required. Patients discovered to have ≥ 2+ proteinuria on dipstick urinalysis should undergo a 24-hour urine collection and must demonstrate ≤ 1.0 g of protein in 24 hours OR Urine protein/creatinine ratio ≤ 1.0
6 See Section 6.2 for central biomarker submission.
7 Baseline scans (within 14 days prior to registration) should include a CT Chest, Abdomen, Pelvis and brain MRI. Supporting documentation is to be submitted, per Section 6.1.1. If the baseline scans were a CT or MRI and bone scan, follow-up bone scans are required only for patients with bone metastases as the only site of evaluable disease, and are optional for other patients. Response assessment should include assessment of all sites of disease and use the same imaging method as was used at baseline.

A. ECG is required every 2 cycles from the start of treatment. A second ECG may be done 2 hours after the first dose of paxalisib, if clinically indicated.
B. Within 14 days prior to registration, every 2 months for the first 2 years of treatment, then every 3 months for years 3-4, then every 4 months thereafter until progression or until 5 years following registration. See Appendix I for MRI acquisition parameters.
C. Every 2 cycles (beginning prior to Cycle 1) until evidence of CNS or systemic progression or relapse. Scans may be done up to 7 days prior to beginning a cycle. Confirmatory scans should also be obtained at least 4 weeks following documentation of objective response (see Section 11.0).
D. Bone imaging (after baseline) is required only if indicative of bony metastases at baseline or if signs or symptoms suggestive of bony metastases develop, and if bone metastases are the only site of evaluable disease. Bone imaging should follow the same schedule as CT scans if indicated.

5.3 Study Calendar – Entrectinib

	Prior to Registration*	Every cycle from the start of treatment	Every 2 cycles from the start of treatment	Post treatment follow-up**
Tests & Observations				
History and physical, weight, PS	X	X		X
Height	X			
Pulse, Blood Pressure	X	X		
ECG	X	A		X
Adverse Event Assessment	X (1)	X (1)		X (1)
Patient Medication Diary	X (2)	X (2)		X (2)
Laboratory Studies				
Complete Blood Count, Differential, Platelets	X	B		X
Comprehensive Metabolic Panel	X	B		X
Albumin	X			X
Serum or Urine HCG	X (3)			
Staging				
Central biomarker testing for eligibility	X (4)			
Contrast-enhanced cranial MRI	C		C	C
CT Chest, Abdomen, Pelvis (bone imaging only required if indicative of bony metastases at baseline or if signs or symptoms suggestive of bony metastases develop, and if bone metastases are the only site of evaluable extracranial disease)	X (5)		D,E (5)	D,E(5)
Correlative studies: For patients who consent to participate				
Tissue and Blood samples	At baseline, then blood samples every 2 cycles. See Section 6.2. If the patient does not have any evidence of extracranial disease or if there is insufficient extracranial tissue for testing, brain metastasis tissue is sufficient for eligibility.			

* Labs completed prior to registration may be used for day 1 of cycle 1 tests if obtained ≤ 14 days prior to treatment. For subsequent cycles, labs, scans, tests and observations may be obtained ≤ 3 days prior to day of treatment.

** Physical examination and staging scans are required ≤ 6 weeks from date of last treatment, then every 8-10 weeks for the first 2 years from registration, then every 3 months (+/- 2 weeks) for years 3-4 from registration, then every 6 months thereafter until intracranial and/or extracranial disease progression (or until 5 years following registration if disease progression does not occur). This can be a virtual visit (and not face-to-face) as long as the patient is not having toxicities from the drugs or symptoms from tumor. Thereafter, survival information is required every 6 months until 5 years following registration. See also Section 12.0.

1 Solicited AEs are to be collected starting at baseline. Routine AEs are to be collected starting after registration through the last study visit. See Section 9.2 for AEs collected within 30 days of last treatment date, and Section 9.3 for expedited reporting of SAEs.
2 The diary must begin the day the patient starts taking the medication and must be completed per protocol and returned to the treating institution OR compliance must be documented in the medical record by any member of the care team.
3 For women of childbearing potential (see Section 3.3). Must be done ≤ 14 days prior to registration.
4 See Section 6.2 for central biomarker submission.
5 Baseline scans (within 14 days prior to registration) should include a CT Chest, Abdomen, Pelvis and brain MRI. Supporting documentation is to be submitted, per Section 6.1.1. If the baseline scans were a CT or MRI and bone scan, follow-up bone scans are required only for patients with bone metastases as the only site of evaluable disease, and are optional for other patients. Response assessment should include assessment of all sites of disease and use the same imaging method as was used at baseline.

A. Day 1 of cycles 2-4
B. Day 1 and Day 15 of cycle 1, then on Day 1 of subsequent cycles
C. Within 14 days prior to registration, every 2 months for the first 2 years of treatment, then every 3 months for years 3-4, then every 4 months thereafter until progression or until 5 years following registration. See Appendix I for MRI acquisition parameters.
D. Every 2 cycles (beginning prior to Cycle 1) until evidence of CNS or systemic progression or relapse. Scans may be done up to 7 days prior to beginning a cycle. Confirmatory scans should also be obtained at least 4 weeks following documentation of objective response (see Section 11.0).
E. Bone imaging (after baseline) is required only if indicative of bony metastases at baseline or if signs or symptoms suggestive of bony metastases develop, and if bone metastases are the only site of evaluable disease. Bone imaging should follow the same schedule as CT scans if indicated.

5.4 Study Calendar – MRTX849

	Prior to Registration*	Every cycle from the start of treatment	Every 2 cycles from the start of treatment	Post treatment follow-up**
Tests & Observations				
History and physical, weight, PS	X	X		X
Height	X			
Pulse, Blood Pressure	X	X		
Single 12-lead ECG	X (1)	A (1)	A (1)	X (1)
Adverse Event Assessment	X (2)	X (2)		X (2)
Patient Medication Diary	X (3)	X (3)		
Laboratory Studies				
CBC, Differential, Platelets	X	B		X
Comprehensive Metabolic Panel	X	B		X
Albumin, TSH, urinalysis	X			X
Serum or Urine HCG	X (4)			
Sparse blood PK sampling, triplicate ECG		C, D	C, D	
ECHO or MUGA (preferred)	E	E		
Staging				
Central biomarker testing for eligibility	X (5)			
Contrast-enhanced cranial MRI	F		F	F
CSF Cytology			G	
CT Chest, Abdomen, Pelvis (bone imaging only required if indicative of bony metastases at baseline or if signs or symptoms suggestive of bony metastases develop, and if bone metastases are the only site of evaluable extracranial disease)	X (6)		G, H (6)	G, H (6)
Correlative studies: For patients who consent to participate				
Tissue and Blood samples	At baseline, every 2 cycles, and at progression. See Section 6.2. If the patient does not have any evidence of extracranial disease or if there is insufficient extracranial tissue for testing, brain metastasis tissue is sufficient for eligibility.			
CSF sample for PK (I)	See Section 6.2.1			

* Labs completed prior to registration may be used for day 1 of cycle 1 tests if obtained ≤ 14 days prior to treatment. For subsequent cycles, labs, scans, tests and observations may be obtained ≤ 3 days prior to day of treatment.

** Physical examination and staging scans are required ≤ 6 weeks from date of last treatment, then every 8-10 weeks for the first 2 years from registration, then every 3 months (+/- 2 weeks) for years 3-4 from registration, then every 6 months thereafter until intracranial and/or extracranial disease progression (or until 5 years following registration if disease progression does not occur).

ECG, ECHO/MUGA, and lab assessments are required only at the last treatment visit prior to follow-up. This can be a virtual visit (and not face-to-face) as long as the patient is not having toxicities from the drugs or symptoms from tumor. Thereafter, survival information is required every 6 months until 5 years following registration. See also Section 12.0.

1 Single 12-lead ECGs are to be performed in the semi-recumbent position. Assessments will include an evaluation of heart rate, PR, QRS, RR, QT, and QTc intervals.
2 Solicited AEs are to be collected starting at baseline. Routine AEs are to be collected starting after registration through the last study visit. See Section 9.2 for AEs collected within 30 days of last treatment date, and Section 9.3 for expedited reporting of SAEs.
3 The diary must begin the day the patient starts taking the medication and must be completed per protocol and returned to the treating institution OR compliance must be documented in the medical record by any member of the care team.
4 For women of childbearing potential (see Section 3.3). Must be done ≤ 14 days prior to registration.
5 See Section 6.2 for central biomarker submission.
6 Baseline scans (within 14 days prior to registration) should include a CT Chest, Abdomen, Pelvis and brain MRI. Supporting documentation is to be submitted, per Section 6.1.1. If the baseline scans were a CT or MRI and bone scan, follow-up bone scans are required only for patients with bone metastases as the only site of evaluable disease, and are optional for other patients. Response assessment should include assessment of all sites of disease and use the same imaging method as was used at baseline.

A. Single 12-lead ECG: to be performed as clinically indicated.
B. Day 1 and Day 15 of Cycle 1-3, then on Day 1 of subsequent cycles
C. Pharmacokinetic (PK) Sampling: Predose and peak blood samples for MRTX849 PK will be collected on Cycle 1 Day 1 and Cycle 1 Day 15 and predose samples only will be collected on Day 1 of Cycles 3, 5, and 7, corresponding to disease assessment time points. Predose samples should be collected up to 60 minutes prior to dosing in clinic. Peak samples should be collected approximately 4 to 6 hours after dosing unless logistically infeasible. In addition to the scheduled samples, an unscheduled predose PK blood sample should be collected as soon as possible after an SAE, immediately prior to treatment interruption or dose reduction for a treatment-related non-serious AE, and at a clinic visit at least one week following a dose reduction of MRTX849.
D. Triplicate ECGs: To be performed predose and at peak on Cycle 1 Day 1 and Cycle 1 Day 15, and to be performed predose only on Day 1 of Cycles 3, 5, and 7. To be performed after the patient has rested in the supine position for at least 5 minutes. All ECGs will be obtained prior to and as close as possible to PK sample collection. Three individual ECG tracings should be obtained as closely as possible in succession, between approximately 1 and 2 minutes apart. The full set of triplicates should be completed in approximately 4 minutes or less.
E. ECHO or MUGA (preferred): To be performed at baseline (within the 45 days prior), and then as clinically indicated. The same modality should be used throughout a patient's participation when possible.
F. Within 14 days prior to registration, every 2 months for the first 2 years of treatment, then every 3 months for years 3-4, then every 4 months thereafter until progression or until 5 years following registration. See Appendix I for MRI acquisition parameters.
G. Every 2 cycles (beginning prior to Cycle 1) until evidence of CNS or systemic progression or relapse. Scans may be done up to 7 days prior to beginning a cycle. Confirmatory scans should also be obtained at least 4 weeks following documentation of objective response (see Section 11.0). ONLY for patients with Leptomeningeal disease CSF cytology must be performed within +/-7 days of MRI imaging.

H. Bone imaging (after baseline) is required only if indicative of bony metastases at baseline or if signs or symptoms suggestive of bony metastases develop, and if bone metastases are the only site of evaluable disease. Bone imaging should follow the same schedule as CT scans if indicated.
I. Optional CSF collection for MRTX849 PK on C1D15: Refer to the A071701 Correlative Science Manual for details on collection, processing and shipment of the samples.

6.0 DATA AND SPECIMEN SUBMISSION

6.1 Data Collection and Submission

6.1.1 Data submission schedule

A Data Submission Schedule (DSS) is available on the Alliance study webpage, within the Case Report Forms section. The Data Submission Schedule is also available on the CTSU site within the study-specific Case Report Forms folder.

6.1.2 Medidata Rave

Medidata Rave is the 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.

Requirements to access Rave via iMedidata:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only or Rave SLA role must have at a minimum an Associate (A) registration type.

Refer to [redacted] for registration types and documentation required.

This study has a Delegation of Tasks Log (DTL). Therefore, those requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in the Regulatory application, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata. No action will be required; each study invitation will be automatically accepted and study access in Rave will be automatically granted. 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 eLearning link in the Tasks pane located in the upper right corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the Studies pane located in the center of the iMedidata screen; 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 replace the eLearning link under the study name.

Action will be required by site staff (to activate their account) who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in the Regulatory application. Account activation instructions are located on the CTSU website in the Data Management section under the Data Management Help Topics > Rave Resources > Medidata Account Activation and Study Invitation (to activate your

iMedidata account). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management Rave Resources section or by contacting the CTSU Help Desk at [redacted] or by email at [redacted]

6.1.3 Supporting Documentation to be Submitted to the Alliance

This study requires supporting documentation for diagnosis, response and progression. Supporting documentation will include local radiology reports, radiologic images (to be submitted to IROC Ohio per Section 6.3), and other documents as listed below. Supporting documentation must be de-identified and submitted via Rave at the following time points:

Baseline: Radiologic images (submit to IROC Ohio), imaging report, pathology report, central biomarker form

During treatment and follow-up: Radiologic images (submit to IROC Ohio), all imaging reports

Response: Radiologic images (submit to IROC Ohio), imaging report

Progression: Radiologic images (submit to IROC Ohio), imaging report, pathology report (if applicable)

6.1.4 ICAREdata® Project

Selected sites will be participating in the ICAREdata® project. - The Integrating Clinical Trials and Real-world Endpoints data (ICAREdata) initiative is a program led by the Alliance Data Innovation Lab which is a component of the Alliance for Clinical Trials in Oncology.

The ICAREdata® project aims to expand the ability to achieve clinical research goals by providing new ways to collect data required for clinical trials. Today, virtually all clinical trials data are collected using special forms and computer applications, such as a software known as Medidata Rave. Instead of using these "add on" data collection systems, the ICAREdata project will gather study data directly from the Electronic Health Record (EHR). As with all research data collections, data collected by the ICAREdata project are stored in a secured repository.

Select institutions will be invited to participate and will receive training on the specific ICAREdata® requirements. As with all clinical trials data management, the nature of data collected using the ICAREdata methods will be specific to a particular research protocol, and might include demographic information, diagnosis, laboratory values, physician assessments, and other results, such as adverse event reports. The Data Innovation Lab will manage data collection, working with the IT department at these sites to configure the EHR to deliver mCODE (minimal common oncology data elements) data and other required outcome data in the form of structured ICAREdata questions. Clinicians will provide the study required data by answering standardized questions or data fields as part of their encounter visit with the subjects. The IT departments will also work to implement the data transfer capability from the site EHR to the Alliance Data Innovation Lab via a secure/tested extraction method.

Investigators and research staff at limited select sites that utilize the EHR research adverse events data collection tool will be asked to complete a brief voluntary survey. The research staff and investigator's email addresses at these predetermined sites will be submitted at the time of Adverse Events data collection tool training. The survey will take approximately 5 minutes to complete. It will solicit feedback on the investigators and study staff experiences including overall staff acceptance, usability, preferences for using the tool

to document any adverse events. The plan survey administration timeline is at baseline and then a select period thereafter. Ultimately, the survey will be used to gather general feedback of the usability of the tool across multiple site level stakeholders.

Data will be encrypted at-rest and in-transit using a secure interface with an established authorization protocol handled by the ICAREdata infrastructure. Alliance Data Lab staff will issue a client ID and credentials to participating ICAREdata sites that will be used to authenticate those sites for access to the ICAREdata infrastructure service/extraction method to submit data. The clinical site will be responsible for securely storing these credentials (e.g., installed on a server that an IT administrator manages) such that those staff responsible for submitting data will have the proper access. Data will be stored and maintained in HIPAA compliant data repositories (such as AWS) and access controlled by an identity server with strict management to ensure confidentiality, integrity, and availability of PHI. Strict access controls will be maintained. Only authorized Alliance Data Lab personnel will have access to the data and scope of access will be further controlled based on role and level of need to know.

Participating institutions may email the Alliance Data Innovation Lab at [redacted] with any questions.

6.1.5 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, DQP Form Status and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, forms with current status, and timeliness reports. Site staff should review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff who are rostered to a site and have access to the CTSU website. Staff who have Rave study access can access the Rave study data via direct links available in the DQP modules.

CTSU Delinquency Notification emails are sent to primary contacts at sites twice a month. These notifications serve as alerts that queries and/or delinquent forms require site review, providing a summary count of queries and delinquent forms for each Rave study that a site is participating in. Additional site staff can subscribe and unsubscribe to these notifications using the CTSU Report and Information Subscription Portal on the CTSU members' website.

To learn more about DQP use and access, click on the Help Topics button displayed on the Rave Home, DQP Queries, DQP Delinquent Forms, DQP Form Status, and DQP Reports modules.

6.2 Specimen Collection and Submission

Correlative Science Manual (CSM): The Alliance A071701 Correlative Science Manual (CSM) contains instructions for specimen collection, processing, and shipping. The manual can be found on the study-specific webpage on the Alliance, BioMS, and CTSU websites. Questions regarding the CSM should be directed to the contact(s) specified in the manual.

For all patients registered to Alliance A071701: Biomarker testing will be conducted using the FFPE tissue from the diagnostic biopsies or surgery specimens. If the patient does not have any evidence of extracranial disease or if there is insufficient extracranial tissue for testing, brain metastasis tissue is sufficient for eligibility. The submission of these samples for review is required for all patients registered to this study, including those who are found to be ineligible and those who do not receive protocol therapy. Please also include a copy of the patient's pathology report, de-identified. Testing will not be initiated until all specimens are received.

Dr. [redacted] laboratory at Massachusetts General Hospital will perform integral molecular testing on the tumor sections. Results will be returned to the site within 21 days of complete specimen receipt at Massachusetts General Hospital.

For patients registered to A071701 biobanking: All participating institutions must ask patients for their consent to participate in biobanking for future research, although patient participation is optional. Biomarker studies will be performed. For patients who consent to participate biospecimens will be collected at the following time points:

	≤ 120 days after pre-registration	**≤ 90 days after registration**	**Every 2 cycles during tx**	**Progression**
Mandatory for all patients pre-registered to A071701				
A representative H&E slide and 15-25 unstained slides[1] per block	X			
For patients consented to biobanking				
One paraffin block from ***any primary tumor, recurrent or metastatic tumors*** (or 15 slides)		X		X
Whole Blood (EDTA/lavender top, provided in study kits)		1 x 10 mL		
Whole blood for ctDNA plasma (STRECK tubes, provided in study kits)		2 x 10 mL	2 x 10 mL	2 x 10 mL

[1]Tumor tissue cut from 1) a single paraffin block containing the brain metastasis and 2) a single paraffin block containing tumor from any extracranial site with at least 1 cm^2 of representative and viable tumor tissue (if unable to provide 15-25 slides, submit however many possible so as not to deplete the block).
Effective Update #01: For patients who consent to biobanking on the screening model consent form, leftover tissue will be sent to the biobank for future research, regardless of whether or not an actionable mutation was identified on the screening tissue sample. This will not be applicable for patients consented prior to the release of Update #01.

6.2.1 For patients in the MRTX849 arm

Blood collection is required for all patients on MRTX849 arm, while CSF collection is for patients who consented.

One CSF sample should be collected at C1D15 from each patient who consent. Collection of CSF must occur after a minimum of 7 days of uninterrupted dosing of MRTX849 (i.e., at steady-state) and within ±1 hour of the C1D15 blood PK sample collection. Both CSF PK and post-dose PK blood samples at C1D15 must be collected approximately 4-6 hours after an MRTX849 dose (i.e. at peak).

	C1D1	C1D15	C3D1	C5D1	C7D1
Mandatory for all patients consented to the MRTX849 arm of A071701					
Whole Blood in EDTA Tubes for MRTX PK analysis (kits provided)	1 x 4 ml, pre-dose and peak*	1 x 4 ml, pre-dose and peak*	1 x 4 ml, pre-dose only	1 x 4 ml, pre-dose only	1 x 4 ml, pre-dose only
Optional for patients consented to the MRTX849 arm of A071701					
CSF in Diamond Midi Centrifuge Tubes for MRTX PK [1] (kits provided)		1x 5 ml, at peak[1] only			

* Blood and CSF for the peak dose should be collected 4-6 hours after dose of MRTX849.

[1] CSF should be collected only from patients received 7 consecutive days of MRTX849, and within one hour of the whole blood collection for pharmacokinetics of C1D15.

6.3 Imaging Submission

The following are acceptable imaging submission methods:

6.3.1 Digital Image Submission Using TRIAD

Transfer of Images and Data (TRIAD) is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit images. TRIAD anonymizes and validates the images as they are transferred.

6.3.1.1 TRIAD Access Requirements

TRIAD Access Requirements:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems;
- Registration type of: Associate (A), Associate Plus (AP), Non-Physician Investigator (NPIVR), or Investigator (IVR). Refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in RCR; and
- TRIAD Site User role on an NCTN, ETCTN, or other relevant roster.

All individuals on the Imaging and Radiation Oncology Core provider roster have access to TRIAD and may submit images for credentialing purposes, or for enrollments to which the provider is linked in OPEN.

6.3.1.2 TRIAD Installation

To submit images, the individual holding the TRIAD Site User role will need to install the TRIAD application on their workstation. TRIAD installation documentation is available at [redacted]

This process can be done in parallel to obtaining your CTEP-IAM account and RCR registration.

For questions, contact TRIAD Technical Support staff via email [redacted] or [redacted]

6.3.1.3 Procedures for Data Submission via TRIAD

The standard TRIAD-based data transfer approach will be provided separately through IROC efforts via the specific trial e-mail, [redacted], per the request of participating sites before their first imaging data submission.

6.3.2 Web Transfer ([redacted])

Any PCs with internet access and web browser (e.g., Internet Explorer, Mozilla Firefox) can be used to web transfer DICOM images and other required files to the Imaging Core Lab. The standard Web Transfer information will be provided separately through the specific trial e-mail, per the request by participating sites before their first data submission.

6.3.3 FTP Transfer

Any FTP software can be used to initiate access to the secure FTP Server of the Imaging Core Laboratory. The standard FTP access information will be provided separately through the specific trial e-mail, per the request by participating sites before their first data submission.

6.3.4 Mail/CD Shipment

Only if electronic data transfer approaches cannot be achieved, the de-identified images in digital DICOM format can be burned to a CD and mailed to the Imaging Core Lab. Submit only one patient's images per CD, with the patient's Alliance ID number, study type, date of scans, and name of submitting institution.

Submit these data to:

[redacted]
Attn: Alliance Trial A071701
The Ohio State University
[redacted]
Tel: [redacted]
Fax: [redacted]

Once the imaging data submission is done, send an e-mail to the Imaging Core Lab at the specific trial email [redacted] to inform that the study has been submitted from the institution. Please include the basic information of submitted data sets as follows:

1) Alliance patient ID number
2) Scan time point (i.e., baseline)
3) Date of scans
4) Institution name

IROC Ohio will acknowledge receipt of the imaging data via email confirmation to the institution within 1 business day of receipt, and will notify the institution and Alliance imaging committee of the quality check report within 3 business days.

7.0 TREATMENT PLAN/INTERVENTION

Protocol treatment is to begin ≤ 10 days of registration.

For questions regarding treatment, please see the study contacts page.

It is acceptable for individual chemotherapy doses to be delivered ≤ a 24-hour (business day) window before and after the protocol-defined date for Day 1 of a new cycle. For example, if the treatment due date is a Friday, the window for treatment includes the preceding Thursday through the following Monday. In addition, patients are permitted to have a new cycle of chemotherapy delayed up to 7 days for major life events (e.g., serious illness in a family member, major holiday, vacation that cannot be rescheduled) without this being considered a protocol violation. Documentation to justify this delay should be provided.

For all arms, each cycle will consist of 28 days. Treatment will continue until disease progression or unacceptable adverse event.

In patients harboring alterations predicting sensitivity to CDK inhibitors, a CDK inhibitor (abemaciclib) will be administered. In patients harboring alterations predicting sensitivity to PI3K inhibitors, a PI3K inhibitor (paxalisib) will be administered. In patients harboring NTRK or ROS1 fusions, an NTRK/ROS1 inhibitor (entrectinib) will be administered. In patients harboring a KRAS G12C mutation, a KRAS G12C inhibitor (MRTX849) will be administered. Dose modifications will be reductions in total dose administered per day based on CTCAE graded toxicity. There will not be re-escalation of dose once reductions are made.

Table 1. Dose table

Target Cancer Genes	Agent	Dose	Route	Day	ReRx
CDK4, CDK6, CDKN2A, CCND1, CCND2, CCND3, CCNE1	Abemaciclib	150mg	Oral	Twice daily	Days 1-28
AKT1, PI3K, PTEN	Paxalisib	45mg	Oral	Once daily	Days 1-28
NTRK1, NTRK2, NTRK3, ROS1	Entrectinib	600mg	Oral	Once Daily	Days 1-28
KRAS G12C	MRTX849	600mg	Oral	Twice daily	Days 1-28

7.1 Targeted Therapy

Abemaciclib

Agent	Dose	Route	Frequency
Abemaciclib	150 mg	Oral	Twice daily

- Patients should be instructed to take the abemaciclib tablets at approximately the same time each day.
- If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose
- Any doses that are missed (not taken within 2 hours of the intended time) should be skipped and should not be replaced or made up on a subsequent day.

Entrectinib

Agent	Dose	Route	Frequency
Entrectinib	600 mg	Oral	Once daily

Note: Closed to accrual January 2024.

- Entrectinib should be administered approximately at the same time each day.
- For patients experiencing fatigue, nausea, or other mild tolerability issues, an evening time administration is recommended.
- On Day 1 clinic visit days, entrectinib should be taken at the clinic after all the pre-dose assessments have been conducted, at the direction of the study research nurse/treating physician.
- On Day 15 and other visits (e.g., scans), entrectinib should be taken at home prior to coming to the clinic, according to the patient's daily routine.
- It is anticipated that individual patients may occasionally forget to take a dose. In those cases, missed doses should be replaced only if the patient remembers within a 2-hour window. After that, patients should just take the next dose the following day, without compensating for the missed dose.
- If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose

Paxalisib

Agent	Dose	Route	Frequency
Paxalisib	45 mg	Oral	Once daily

- Paxalisib should be administered approximately at the same time each day.
- Paxalisib should be administered on empty stomach (1 hour before or 2 hours after food).

MRTX849

Agent	Dose	Route	Frequency
MRTX849	600 mg	Oral	Twice daily

- MRTX849 tablets may be taken with or without food.
- Drug product should be taken with at least 240 mL (8 ounces) of water.
- Patients should swallow the MRTX849 drug product whole and not chew them.
- If vomiting occurs after dosing, MRTX849 doses should not be replaced.
- Twice daily dosing should be at 12-hour intervals to the extent possible.
- If a dose is inadvertently missed, the dose should be skipped if > 4 hours has elapsed since the expected dosing time. Dosing may resume at the next appointed time.
- On the days of PK sampling, the first doses of the day should be taken in the clinic and administration time recorded.

7.2 Imaging

Acquisition of MR imaging in a uniform manner for all patients across the study and for an individual patient on serial imaging is critical information for this trial. We have defined the standard imaging parameters that are required for imaging on 1.5 T and 3 T MRI scanners and sites should follow these parameters for all patients (see Appendix I for standard acquisition parameters).

MRIs will be done every 2 months for the first 2 years of treatment and then every 3 months for years 3-4, then every 4 months thereafter until progression or until 5 years following registration.

8.0 Dose and Treatment Modifications

8.1 Ancillary Therapy, Concomitant Medications, and Supportive Care

8.1.1 Patients should not receive any other treatment which would be considered treatment for the primary neoplasm or impact the primary endpoint with the exception of endocrine therapy or anti-HER2 therapy as listed in Section 3.3. This includes any surgical

intervention, radiotherapy, cryotherapy, ablation, etc., performed on the primary neoplasm.

8.1.2 Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records. For the MRTX849 arm, the use of bisphosphonates or RANKL inhibitors regardless of indication is allowed provided patients have been on stable oral doses for at least 2 weeks prior to study entry or stable with 2 parenteral injections prior to study entry; this stable dose should be maintained during the treatment period. Patients requiring initiation of bisphosphonates or a RANKL inhibitor during the course of the study should be evaluated to rule out disease progression.

8.1.3 Treatment with hormones or other chemotherapeutic agents may not be administered except for steroids given for adrenal failure; endocrine and anti-HER2 therapy as listed in Section 3.3, hormones administered for non-disease-related conditions (e.g., insulin for diabetes); and intermittent use of dexamethasone as an antiemetic or for cerebral edema.

8.1.4 Antiemetics may be used at the discretion of the attending physician, with the exception of steroids above. Specific guidance on antiemetics in the MRTX849 arm is listed in Section 8.1.16.

8.1.5 Patients with severe diarrhea should be assessed for intravenous hydration and correction of electrolyte imbalances.

Diarrhea management with abemaciclib: In the event of diarrhea, supportive measures should be initiated as early as possible. These include the following:

- At the first sign of loose stools, the patient should initiate anti-diarrheal therapy (for example, loperamide) and notify the investigator/site for further instructions and appropriate follow-up.
- Patients should also be encouraged to drink fluids (for example, 8 to 10 glasses of clear liquids per day).
- Site personnel should assess response within 24 hours.
- If diarrhea does not resolve with anti-diarrheal therapy within 24 hours to either baseline or Grade 1, abemaciclib should be suspended until diarrhea is resolved to baseline or Grade 1.
- When abemaciclib recommences dosing should be adjusted as outlined in Section 8.2.1.1.
- In severe cases of diarrhea, the measuring of neutrophil counts and body temperature and proactive management of diarrhea with antidiarrheal agents should be considered. If diarrhea is severe (requiring IV rehydration) and/or associated with fever or severe neutropenia, broad-spectrum antibiotics such as fluoroquinolones must be prescribed. Patients with severe diarrhea or any grade of diarrhea associated with severe nausea or vomiting should be carefully monitored and given intravenous fluid (IV hydration) and electrolyte replacement.

8.1.6 Irradiate a symptomatic lesion, or one that may produce disability (e.g., unstable femur, symptomatic CNS lesion) prior to study initiation, provided other measurable CNS

disease is present. Patients who require radiation therapy to a target lesion during protocol treatment will be removed from protocol therapy due to disease progression

8.1.7 Alliance Policy Concerning the Use of Growth Factors

The following guidelines are applicable unless otherwise specified in the protocol.

Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 33: 3199-3212, 2015 and American Society of Clinical Oncology – American Society of Hematology Clinical Practice Guideline Update on the Use of Epoetin and Darbepoetin in Adult Patients with Cancer. J Clin Oncol 28:4996-5010, 2010.

Epoetin (EPO): Use of epoetin in this protocol is permitted at the discretion of the treating physician.

Filgrastim (G-CSF) tbo-filgrastim, and sargramostim (GM-CSF)

White Blood Cell Growth Factors (Includes: filgrastim (G-CSF), pegfilgrastim) and other FDA approved white blood cell growth factor biologics)

1. White blood cell growth factor treatment for patients on protocols that do not specify their use is discouraged.
2. White blood cell growth factor may not be used:
    a. To avoid dose reductions, delays or to allow for dose escalations specified in the protocol.
    b. For the treatment of febrile neutropenia the use of CSFs should not be routinely instituted as an adjunct to appropriate antibiotic therapy. However, the use of CSFs may be indicated in patients who have prognostic factors that are predictive of clinical deterioration such as pneumonia, hypotension, multi-organ dysfunction (sepsis syndrome) or fungal infection, as per the ASCO guidelines. Investigators should therefore use their own discretion in using the CSFs in this setting. The use of CSF (filgrastim/pegfilgrastim) must be documented and reported. (e.g. on CRFs per protocol requirements)
    c. If white blood cell growth factors are used, they must be obtained from commercial sources. Selection of white blood cell growth factor products should be per institutional guidelines.

8.1.8 Hypersensitivity/infusion reactions

Treat hypersensitivity and infusion reactions to drug[s] as per institutional standards.

8.1.9 CYP3A4 Inhibitors

Chronic concomitant treatment with strong inhibitors of CYP3A4 is not allowed during this trial. The following drugs are EXAMPLES of strong inhibitors of CYP3A4 and are not allowed during treatment.

- Indinavir
- Clarithromycin
- Ketoconazole

Because lists of these agents are constantly changing, please consult and review any drugs for their potential to inhibit CYP3A4. Examples of resources that may be utilized include the product information for the individual concomitant drug in question, medical reference texts such as the Physicians' Desk Reference, the FDA website, or your local institution's pharmacist.

8.1.10 CYP3A4 Inducers

Chronic concomitant treatment with strong inducers of CYP3A4 is not allowed during this trial. The following drugs are EXAMPLES of strong inducers of CYP3A4 and are not allowed during treatment.

- Rifampin
- Carbamazepine

Because lists of these agents are constantly changing, please consult and review any drugs for their potential to induce CYP3A4. Examples of resources that may be utilized include the product information for the individual concomitant drug in question, medical reference texts such as the Physicians' Desk Reference, the FDA website, or your local institution's pharmacist.

8.1.11 Hyperglycemia and metabolic effects with Paxalisib

It is known that PI3K-mTOR pathway inhibitors can affect glucose and/or insulin metabolism, leading to hyperglycemia. Cases of hyperglycemia, including Grade 3 in severity, have been observed in the paxalisib single-agent study GO28070. Glucose levels at baseline and during study should be carefully monitored, and appropriate dose delays/dose modifications for managing hyperglycemia should be implemented per protocol guidelines. Glucose will be monitored every cycle. Patients should be instructed to report symptoms associated with hyperglycemia such as thirst, frequent urination, and blurred vision. Use of oral anti-hyperglycemic agents, such as metformin, for patients experiencing Grade ≥ 2 hyperglycemia may be implemented. For Grade 3 or greater hyperglycemia, consider increasing dose of anti-hyperglycemic agents, such as metformin, and initiating insulin. Anti-hyperglycemic agents should be used to control severe hyperglycemia per institutional standard of care. Recommended management of hyperglycemia:

- For Grade 2 or greater hyperglycemia, consider initiating oral glucose lowering medication such as metformin
- For Grade 3 or greater hyperglycemia, hydration status should be clinically assessed. If clinical assessment is consistent with dehydration, fluids should be given as clinically appropriate. If patient is asymptomatic, consider increasing oral glucose lowering medication. If patient is symptomatic, rapid/short acting insulin should be initiated according to institution sliding scale coverage as per institutional guidelines, and consider increasing oral glucose lowering medication. For persistent Grade 3 or greater hyperglycemia, hold paxalisib until glucose is < Grade 3, then restart at one dose level reduced and consult with endocrinologist.

Other metabolic effects known to be associated with mTOR inhibitors include hyperlipidemia. Cases of low-grade hypercholesterolemia and hypertriglyceridemia have been observed in the paxalisib single-agent study GO28070. Cholesterol and triglyceride levels should be monitored per protocol guidelines. Use of lipid-lowering therapy for patients experiencing Grade ≥ 2 elevations may be initiated per institutional standard of care guidelines.

8.1.12 Potential lung inflammation/pneumonitis with paxalisib

Lung inflammation was not observed in any of the rat studies and was not observed in the 29-day dog study. Evidence of lung inflammation was observed in the 8-day dog pilot study. However, this finding was observed only at doses exceeding the MTD in this species. Interstitial lung inflammation/non-infectious pneumonitis has been observed in cancer patients receiving other PI3K and mTOR inhibitors. Patients should be monitored carefully for changes in pulmonary status (including physical examinations, pulse oximetry, and periodic CT scans) during treatment with paxalisib. Patients experiencing symptomatic or asymptomatic pneumonitis should be treated per standard of care and protocol guidelines adapted from recommendations by (White, Camus et al. 2010) for the management of pneumonitis in cancer patients receiving everolimus. Use of corticosteroids should be considered for symptomatic cases of non-infectious pneumonitis. Appropriate dosing adjustment should be performed per protocol guidelines.

8.1.13 Rash with paxalisib

Treatment-related rash has been commonly reported in cancer patients receiving other PI3K and mTOR inhibitors in clinical studies. This rash is commonly manifested as maculo-papular with or without pruritus. Rash and other dermatologic events should be closely monitored and patients should apply Sun Protection Factor 50+ sunscreen if exposed to direct sunlight for longer than 15 minutes after the appearance of any rash. For severe rash, dosing of paxalisib should be interrupted and patients should be treated with supportive therapy per standard of care. Use of topical antihistamine, as well as topical or systemic corticosteroids, may be considered.

8.1.14 Cardiac symptoms on paxalisib

Patients should be instructed to contact their treating physician if they experience dizziness, light-headedness, fainting, sensations of heart palpitations, or slow or irregular pulse. Electrocardiograms will be closely monitored. Cardiac enzymes may be measured if deemed necessary.

8.1.15 Radiotherapy with abemaciclib

Limited data are available with abemaciclib and radiotherapy or alternate dosing schedules (e.g. induction phase). Thus, caution should be exercised with coadministering abemaciclib with radiotherapy.

8.1.16 Nausea, Vomiting and Diarrhea with MRTX849

Nausea and vomiting have been reported in patients taking MRTX849 and have generally been limited to Grade 1 and 2, often occurred shortly after dosing, and decreased with continued dosing over a few days. Patients should be advised of the possibility of developing nausea and vomiting. When possible, patients should have anti-emetics available to self-administer soon after onset. Patients assessed as having greater potential to develop nausea may be treated prophylactically and dividing a dose over a few minutes may be considered. Recurrent episodes may be treated with anti-emetics such as prochlorperazine, and where an anticipatory component may exist, lorazepam.

Because ondansetron has recently been assessed to pose a known risk for QT prolongation, it should be avoided, particularly at high parenteral doses. If effective alternative anti-emetics are not available, oral administration of ondansetron at doses up to 4 mg every 6 hours, with a maximum total daily dose of 16 mg, is permitted in patients without underlying bradycardia, CHF, or congenital long QT syndrome provided that an ECG is

obtained at the beginning of each cycle, and that potassium and magnesium levels are obtained at the beginning of each cycle and supplemented if below the reference range.

Diarrhea has been reported with MRTX849 and has generally been limited to Grade 1 and 2 and often reported as a few loose stools that improve with continued dosing. Patients should be advised of the possibility of developing diarrhea and to take loperamide or a similar medication as needed if diarrhea develops.

Due to the observation of creatinine increases with MRTX849, fluid status should be evaluated in patients who develop vomiting or diarrhea, and oral and/or intravenous hydration should be considered if clinically warranted. In addition, more frequent electrolyte monitoring that includes potassium and magnesium should be considered. Patients developing electrolyte abnormalities should receive electrolyte supplementation in order to mitigate the risk for QT prolongation. If warranted, treatment should be interrupted but may be restarted once nausea or diarrhea is controlled and electrolytes supplemented.

8.1.17 QT Prolongation with MRTX849

A positive relationship between MRTX849 concentrations and QTc change was observed in patients; therefore use of medications known to prolong QTc and pose risk of Torsades de Pointes are to be avoided. For guidance on the management of specific MRTX849 treatment-related QTc prolongation AEs, refer to Section 8.2. Routine patient care should include the following:

- Assessments of electrolytes where warranted, including in patients with vomiting, diarrhea, or past instances of hypokalemia or hypomagnesemia
- Proactive intravenous and/or oral supplementation of electrolytes where warranted:
    - Potassium (K+) for serum values below 3.5 mEq/L
    - Magnesium (Mg++) for serum values below 1.5 mEq/L supplementation (including intravenous route if diarrhea from oral administration is a concern)
- Inclusion of arrythmia in the differential diagnosis of adverse events (e.g., palpitations, syncope, pre-syncope, or unexplained dyspnea) and where warranted, unscheduled ECGs with timely entry of all unscheduled ECG results into the study database.

8.1.18 Substrates of CYP3A4 with MRTX849

MRTX849 is a strong inhibitor of CYP3A4. Thus, co-administration of MRTX849 with drugs that are primarily metabolized by CYP3A4 with a narrow therapeutic index should be avoided. Caution is recommended when MRTX849 is administered with moderate/sensitive CYP3A substrates without a narrow therapeutic index, and the dose of moderate/sensitive CYP3A substrates may need to be reduced.

Co-administration of MRTX849 with strong CYP3A and/or P-gp inducers should be avoided.

8.1.19 Substrates of CYP2B6 and CYP2C9 with MRTX849

MRTX849 is a moderate inhibitor of CYP2C9 and CYP2B6. Patients are advised to avoid co-administration of MRTX849 with substrates of CYP2C9 or CYP2D6 with a

narrow therapeutic index. If alternative treatments cannot be used, consider a dose reduction of the concomitant CYP2C9 or CYP2D6 substrate drug. Caution is recommended when MRTX849 is administered with moderate/sensitive CYP2C9 or CYP2D6 substrates without a narrow therapeutic index, and the dose of moderate/sensitive CYP2C9 or CYP2D6 substrates may need to be reduced.

8.1.20 Gastric Acid Reducing Medications with MRTX849

Because MRTX849 solubility is maximal at low pH, drugs that reduce gastric acid secretion may decrease MRTX849 exposure which may reduce MRTX849 efficacy. Proton pump inhibitors (PPIs) should be avoided. As an alternative to PPIs, preference should be given first to antacids administered more than 2 hours before and more than 2 hours after dosing with MRTX849, and second to an H2 antagonist with dosing separated by more than 2 hours from of MRTX849 dosing (e.g., MRTX849 at 8AM and 8PM, and a short-acting H2 blocker at 10AM and 10PM).

8.1.21 P-glycoprotein (P-gp) Substrates with MRTX849

MRTX849 is a weak inhibitor of P gp. No dosage adjustments for P-gp substrates are warranted during co-administration with MRTX849. No dose adjustment of MRTX849 is needed when MRTX849 is co-administered with CYP3A and/or P-gp inhibitors.

Co-administration of MRTX849 with strong CYP3A and/or P-gp inducers should be avoided.

8.1.22 Herbal Medications/Preparations with MRTX849

Herbal medications and preparations should be avoided throughout the study. Herbal medications include, but are not limited to: St. John's wort, green tea, milk thistle, turmeric/curcumin, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe (yohimbine), saw palmetto, ginseng, quercetin and Schisandra extract.

8.1.23 Hormonal Contraceptives and Thrombotic Events with MRTX849

In female patients using hormonal contraceptives, the potential exists for MRTX849 to inhibit hepatic CYP3A4 and increase exposure to hormonal contraceptive levels, with the associated risk of venous thromboembolism (e.g., deep vein thrombosis or pulmonary embolism). Precautions should be taken in patients with recent, clinically significant thrombotic events, and all patients using hormonal contraceptives should be closely monitored for emerging signs of thrombotic events. Treatment with MRTX849 should be interrupted in patients with signs or symptoms of thrombosis and permanently discontinued in patients who develop clinically significant thromboembolic complications. If in the judgment of the Investigator resumption of treatment with MRTX849 is in the best interest of the patient, concomitant treatment with hormonal contraceptives should be discontinued.

8.1.24 Strong Inhibitors of BCRP with MRTX849

MRTX849 is a substrate of BCRP. The effect of strong inhibitors of BCRP (e.g. curcumin, cyclosporin, and eltrombopag) on MRTX849 has not been evaluated. Strong inhibitors of BCRP should be avoided.

8.2 Dose Modifications

8.2.1 Abemaciclib Dose Modifications

- If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. Reductions or increases apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.
- Abemaciclib will not be re-escalated once reduced.
- If dose reductions beyond dose level -2 is required or abemaciclib is held for 28 days, abemaciclib will be discontinued.
- If more than one of these toxicities apply, use the most stringent criteria (i.e., the greatest dose reduction.)
- If the patient experiences a significant adverse event requiring a dose reduction at the start of the next cycle, then the dose will remain lowered.
- Descriptors below utilize CTCAE version 5.0. Expedited reporting via CTEP-AERS may be required for some adverse events (See Section 9.0).

8.2.1.1 Abemaciclib Dose Levels

Dose Level	Drug Name	Dose
0*	Abemaciclib	150 mg PO twice daily
-1	Abemaciclib	100 mg PO twice daily
-2	Abemaciclib	50 mg PO twice daily

*Dose level 0 refers to the starting dose.

8.2.1.2 Hematologic Adverse Event

- **Grade 3 hematologic toxicity:** Dose interruption until recovery to grade ≤2. Re-initiate abemaciclib at the same dose. If toxicity recurs at grade 3: temporary dose interruption until recovery to grade ≤2 and reduce abemaciclib to the next lower dose level.
- **Grade 4 hematologic toxicity:** Dose interruption until recovery to grade ≤2. Re-initiate abemaciclib at the next lower dose level.
- **Regardless of severity:** if patient requires administration of blood cell growth factors, dose must be suspended for at least 48 hours after the last dose of blood cell growth factors was administered and until toxicity resolves to at least Grade 2. The dose must be reduced at the next lower dose level unless already performed for incidence of toxicity that leads to the use of growth factor

8.2.1.3 Non-hematologic adverse event (for diarrhea, see Section 8.2.1.5)

- **Grade 3 or 4 non-hematologic toxicity:** Dose interruption until recovery to grade ≤1. Reduce abemaciclib to the next lower dose level.
- **Persistent or recurrent Grade 2 toxicity that does not resolve with maximal supportive measures:** Suspend dose until toxicity resolves to baseline or Grade 1. Resume at next lower dose.

8.2.1.4 Diarrhea

- **Persistent or recurrent Grade 2 diarrhea that does not resolve with maximal supportive measures within 24 hours to baseline or Grade 1:** Dose interruption until recovery to grade ≤1. Reduce abemaciclib to the next lower dose level.
- **Grade 3 or 4 diarrhea or requires hospitalization:** Dose interruption until recovery to grade ≤1. Reduce abemaciclib to the next lower dose level

8.2.1.5 Interstitial lung disease (ILD)/pneuominitis events

Interstitial lung disease (ILD) / pneumonitis has been identified as an adverse drug reaction for abemaciclib. Adverse events reported included events such as interstitial lung disease, pneumonitis, obliterative bronchiolitis, organizing pneumonia, pulmonary fibrosis. The majority of events were Grade 1 or Grade 2 with serious cases and fatal events reported.

Monitor for clinical symptoms or radiological changes indicative of ILD/pneumonitis and please ask patients to report any new or worsening pulmonary symptoms. Symptoms may include hypoxia, cough, dyspnea, or interstitial infliltrates on radiologic exams; these symptoms should be investigated and treated as per local clinical practice and/or guidelines (including corticosteroids as appropriate). Infectious, neoplastic, and other causes for such symptoms should be excluded by means of appropriate investigations. Investigations may include imaging such as high resolution computer tomography (HRCT), broncheoalveolar lavage (BAL), and biopsy as clinically indicated (see also table below: *refer to dose adjustment table for interstitial lung disease/pneumonitis*).

Dose Modification and Management — Interstitial Lung Disease/Pneumonitis

CTCAE Grade	Abemaciclib Dose Modifications
Grade 1 or 2	No dose modification is required.
Persistent or recurrent Grade 2 toxicity that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Suspend dose until toxicity resolves to baseline or Grade 1. Resume at next lower dose.
Grade 3 or 4	Discontinue abemaciclib.

Dose Modification and Management — Nonhematologic Toxicities Excluding Diarrhea, ALT/AST Increased, and ILD/Pneumonitis

CTCAE Grade	Abemaciclib Dose Modifications
Grade 1 or 2	No dose modification is required.
Persistent or recurrent Grade 2 toxicity that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Suspend dose until toxicity resolves to baseline or Grade 1. Resume at next lower dose.
Grade 3 or 4	

8.2.1.6 Increased ALT/AST

- **Persistent or recurrent Grade 2 or Grade 3 (>5.0-20.0 x ULN) that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1:** Suspend dose until recovery to grade ≤1. Resume abemaciclib at the next lower dose level.
- **Grade 3 (>5.0 x ULN) with total bilirubin >2 x ULN, in the absence of cholestasis:** Discontinue abemaciclib.
- **Grade 4 (> 20 x ULN):** Discontinue abemaciclib

To ensure patient safety the investigator should collect specific recommended clinical information and follow-up laboratory tests as shown below.

Liver testing including ALT, AST, alkaline phosphatase (ALP), total bilirubin (TBL), direct bilirubin (D. Bil), gamma-glutamyltransferase (GGT), and creatine kinase (CK), should be repeated within 2 to 4 days to confirm the abnormality and to determine if it is increasing or decreasing, if one or more of these conditions occur:

If a participant with baseline results of...	**develops the following elevations:**
ALT or AST <1.5×ULN	ALT or AST ≥5×ULN or ALT or AST ≥3×ULN concurrent with TBL ≥2×ULN
ALT or AST ≥1.5×ULN	ALT or AST ≥3× baseline or ALT or AST ≥2× baseline concurrent with TBL ≥2×ULN

Hepatic Monitoring Tests for a Hepatic Treatment Emergent Abnormality

Hepatic Hematology	**Haptoglobin**
Hemoglobin	
Hematocrit	**Hepatic Coagulation**
RBC	Prothrombin Time
WBC	Prothrombin Time, INR
Neutrophils, segmented and bands	
Lymphocytes	**Hepatic Serologies[a]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-nuclear antibody**
AST	**Anti-actin antibody**
GGT	**Anti-smooth muscle antibody**
CPK	

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalized ratio; RBC = red blood cells; WBC = white blood cells.

[a] Reflex/confirmation dependent on regulatory requirements and/or testing availability.

8.2.1.6 Other toxicities

- Consider performing an analysis of serum potassium, calcium, phosphorus, and magnesium for all adverse reactions that are potentially associated/aggravated with electrolyte imbalance (e.g. diarrhea, nausea/vomiting, non-QT related cardiovascular events). If electrolyte values are below the lower limit of normal, interrupt abemaciclib administration, correct electrolytes with supplements as soon as possible, and repeat electrolyte testing until documented normalization of the electrolytes.

8.2.2 Entrectinib Dose Modifications

- If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. Reductions or increases apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.
- Entrectinib will not be re-escalated once reduced.
- If dose reductions beyond dose level -2 is required or entrectinib is held for 28 days, entrectinib will be discontinued.
- If more than one of these toxicities apply, use the most stringent criteria (i.e., the greatest dose reduction.)

- If the patient experiences a significant adverse event requiring a dose reduction at the start of the next cycle, then the dose will remain lowered.
- Descriptors below utilize CTCAE version 5.0. Expedited reporting via CTEP-AERS may be required for some adverse events (See Section 9.0).

8.2.2.1 Entrectinib Dose Levels

Dose Level	Drug Name	Dose
0*	Entrectinib	600mg po qday
-1	Entrectinib	400 mg po qday
-2	Entrectinib	200 mg po qday

Toxicity*	Grade 1	Grade 2	Grade 3	Grade 4
Non-hematologic	Continue at same dose level	Continue at same dose level For prolonged or intolerable CNS toxicity, withhold dose until toxicity is ≤ G1 or has returned to baseline, then reduce by 1 dose level and resume treatment	Withhold dose until toxicity is ≤ G1 or has returned to baseline, then reduce by 1 dose level and resume treatment	Withhold dose until toxicity is ≤ G1 or has returned to baseline, then reduce by 1 dose level and resume treatment; or discontinue treatment as per the Investigator's discretion
Hematologic	Continue at same dose level	Continue at same dose level	Withhold dose until toxicity is ≤ G2, or has returned to baseline, then resume treatment at the same dose level or reduce by 1 dose level as per the Investigator's discretion Grade 3 lymphopenia without other dose-limiting events (e.g., opportunistic infection) may continue study treatment without interruption	Withhold dose until toxicity is ≤ G2, or has returned to baseline, then reduce the dose by 1 dose level and resume treatment Grade 4 lymphopenia without other dose-limiting events (e.g., opportunistic infection) may continue study treatment without interruption
Prolonged QTc	Continue at same dose level	Interrupt entrectinib until recovery to baseline Assess and correct electrolytes and concomitant medications Continue at same dose level	Interrupt entrectinib until recovery to baseline Assess and correct electrolytes and concomitant medications. Reduce dose by 1 dose level and resume treatment. If an alternative cause for QTc prolongation is found and corrected, resume at same dose level	Discontinue treatment permanently

Toxicity*	Grade 1	Grade 2	Grade 3	Grade 4
Pneumonitis (in absence of disease progression, pulmonary embolism, positive cultures or radiation effect)	Withhold dose until toxicity is Grade 0, then resume treatment at same dose Discontinue treatment permanently if pneumonitis recurs	Withhold dose until toxicity is Grade 0, then resume treatment at same dose Discontinue treatment permanently if pneumonitis recurs	Discontinue treatment permanently	Discontinue treatment permanently

*dose modifications to be based on worst toxicity grade as per NCI CTCAE v5.0

8.2.3 Paxalisib Dose Modifications

- If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. Reductions or increases apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.
- Paxalisib will not be re-escalated once reduced.
- If dose reductions beyond dose level -2 is required or paxalisib is held for 28 days, paxalisib will be discontinued.
- If more than one of these toxicities apply, use the most stringent criteria (i.e., the greatest dose reduction.)
- If the patient experiences a significant adverse event requiring a dose reduction at the start of the next cycle, then the dose will remain lowered.
- Descriptors below utilize CTCAE version 5.0. Expedited reporting via CTEP-AERS may be required for some adverse events (See Section 9.0).

8.2.3.1 Paxalisib Dose Levels

Dose Level	Drug Name	Dose
0*	Paxalisib	45 mg
-1	Paxalisib	30 mg
-2	Paxalisib	15 mg

*Dose level 0 refers to the starting dose.

8.2.3.2. Hematologic Adverse Event

- **Grade 3 hematologic toxicity:** Dose interruption until recovery to grade ≤2. Re-initiate paxalisib at the same dose. If toxicity recurs at grade 3: temporary dose interruption until recovery to grade ≤2 and reduce paxalisib to the next lower dose level.
- **Grade 4 hematologic toxicity:** Dose interruption until recovery to grade ≤2. Re-initiate paxalisib at the next lower dose level.

8.2.3.3. Non-hematologic Adverse Event

- **Grade 3 or 4 non-hematologic toxicity:** Dose interruption until recovery to grade ≤1. Reduce paxalisib to the next lower dose level.

8.2.3.4. Other toxicities

- Consider performing an analysis of serum potassium, calcium, phosphorus, and magnesium for all adverse reactions that are potentially associated/aggravated with electrolyte imbalance (e.g. diarrhea, nausea/vomiting, non-QT related cardiovascular events). If electrolyte values are below the lower limit of normal, interrupt paxalisib administration, correct electrolytes with supplements as soon as possible, and repeat electrolyte testing until documented normalization of the electrolytes.

8.2.4 MRTX849 Dose Modifications

- Provided below are guidelines for the management of adverse events that are considered to be causally related to MRTX849 (MRTX849 treatment-related AEs) and recommended dose modifications.
- If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. Reductions apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.
- MRTX849 will not be re-escalated once reduced.
- If dose reductions beyond dose level -3 is required or MRTX849 is held for 28 days, MRTX849 will be discontinued.
- If more than one of these toxicities apply, use the most stringent criteria (i.e., the greatest dose reduction.)
- If the patient experiences a significant adverse event requiring a dose reduction at the start of the next cycle, then the dose will remain lowered.
- Descriptors below utilize CTCAE version 5.0. Expedited reporting via CTEP-AERS may be required for some adverse events (See Section 9.0).

8.2.4.1 MRTX849 Dose Reduction Steps in Response to Treatment-Related Adverse Events

Dose Level	Drug Name	Dose
0*	MRTX849	600 mg PO BID
-1	MRTX849	400 mg PO BID
-2	MRTX849	600 mg PO QD
-3	MRTX849	400 mg PO QD

*Dose level 0 refers to the starting dose.

8.2.4.2. Hematologic Treatment-Related Adverse Event

- **Grade 3 or 4 hematologic toxicity:** Dose interruption until recovery to grade ≤1 or return to baseline level. MRTX849 may be resumed at the same dose, with the following exceptions below. One dose level reduction should be implemented in the following cases:
  - Grade 4 neutropenia persisting for ≥ 8 days;
  - Grade 3 thrombocytopenia with clinically significant bleeding;
  - Grade 4 thrombocytopenia;

- Grade 4 anemia;
- Grade 3 or 4 febrile neutropenia

8.2.4.3. Non-hematologic Treatment-Related Adverse Event

- **Grade 3 or 4 non-hematologic toxicity:** Dose interruption until recovery to grade ≤1 or return to baseline value (See table below). If the toxicity is adequately managed by routine supportive care (such as anti-emetics, anti-diarrheals, or electrolyte supplementation as the table below), treatment may be resumed at the same dose; if not, treatment may be resumed at a reduced dose level. Recurrence of the toxicity may be managed similarly.

MRTX849 Dose Modifications – Non-Hematologic Treatment-Related Toxicities		
Toxicity	**Treatment Delay**	**Dose Modification**
Gastrointestinal Toxicity		
Grade 3 nausea, vomiting or vomiting that is managed with supportive care and persists for ≤72 hours	Hold until ≤Grade 1 or return to baseline	Patient may resume at the same dose level
Grade 3 Nausea >72 hours, despite therapy Grade 3/4 Vomiting >24 hours despite therapy (or >72 hours while optimizing therapy) Grade 3 Diarrhea >48 hours, despite therapy.	Hold until ≤ Grade 1 or return to baseline	Decrease one dose level
Grade 4 Diarrhea, despite therapy	Discontinue	
Asymptomatic Grade 3 Amylase or Lipase Elevation >8 days	Hold until ≤ Grade 1 or return to baseline	Patient may resume at the same dose level
Symptomatic Grade 3/4 Amylase or Lipase Elevation	Hold until ≤ Grade 1 or return to baseline	Decrease one dose level
Grade 3/4 Pancreatitis	Discontinue	
Other Grade 3 AEs	Hold until ≤ Grade 1 or return to baseline	Patient may resume at the same dose level or one dose level lower
Other Grade 4 AEs	Discontinue	
Laboratory Investigation-Based Toxicities		
Grade 3 or 4 electrolyte abnormality that is not clinically significant and resolves spontaneously or with conventional medical treatment within 48 hours	Hold until ≤Grade 1 or return to baseline	Patient may resume at the same dose level or 1 dose level lower

Grade 3 or 4 creatinine increase	Hold until ≤Grade 1 or return to baseline	If resolution to Grade 1 or baseline occurs within 22 days, may resume at the same dose level or decrease by 1 dose level. If no resolution to Grade 1 or baseline within 22 days, discontinue MRTX849
Hepatic Toxicities		
Grade 2 increase in hepatic transaminases (AST or ALT)	Not required	Decrease by 1 dose level
Grade 3 increased hepatic transaminases (AST or ALT)	Hold until ≤Grade 1 or return to baseline	Decrease by 1 dose level
Grade 4 increased hepatic transaminases (AST or ALT)	Discontinue	
Grade 3 or 4 increased bilirubin (without increases in transaminases or alkaline phosphatase)	Hold until ≤Grade 1 or return to baseline	If resolution to Grade 1 or baseline occurs within 22 days, decrease by 1 dose level. If no resolution to Grade 1 or baseline within 22 days, discontinue MRTX849
If patient develops values for LFTs meeting Hy's Law (concurrent increase in AST and/or ALT ≥ 3 × ULN, bilirubin ≥ 2 × ULN but without concurrent increases in alkaline phosphatase [i.e., alkaline phosphatase < 2 × ULN] and that is not attributable to liver metastases or biliary obstruction)	MRTX849 should be permanently discontinued	MRTX849 should be permanently discontinued and steroids administered; these cases should be reported as SAEs.
Other Grade 3/4 Hepatic AEs	Hold until ≤Grade 1 or return to baseline	Patient may resume at the same dose level or 1 dose level lower
Cardiac Toxicities		
QTcF Prolongation* > 500 msec and increase > 60 msec on at least 2 ECGs ≤ 22 days	Hold until ≤ Grade 1 or return to baseline (<15 msec above baseline)	Decrease by one or two dose levels
QTcF Prolongation* > 500 msec and increase > 60 msec on at least 2 ECGs > 22 days	Discontinue	

Decrease in LVEF ≥ 20% from baseline and below LLN* Symptomatic left ventricular systolic dysfunction*	Discontinue	
Other Grade 3/4 AEs	Hold until ≤Grade 1 or return to baseline	Decrease by 1 dose level
*Cardiology consultation should be obtained for cases of QTcF prolongation or LVEF decreases falling into the categories indicated. Additional assessments of LVEF may be performed as clinically indicated at the Investigator's discretion if there are signs or symptoms of cardiotoxicity. In addition, more frequent monitoring of electrolytes that include potassium and magnesium should be considered for patients with vomiting, diarrhea, or past instances of hypokalemia or hypomagnesemia that could recur, and oral and/or intravenous supplementation should be considered for levels below the lower limit of normal. Arrythmia should be included in the differential diagnosis of relevant adverse events (e.g., palpitations, syncope, pre-syncope, or unexplained dyspnea), and unscheduled ECGs should be performed for patients with such events or electrolyte abnormalities as clinically indicated.		
Pneumonitis		
Grade 2	Hold until ≤ Grade 1 or return to baseline	Decrease by 1 dose level For Grade 2 recurrent pneumonitis, discontinue study treatment
Grade 3 or 4	Discontinue	
Other Treatment-Related Toxicities		
Grade 3 or 4 fatigue that persists ≤ 8 days	Hold until ≤Grade 1 or return to baseline	Patient may resume at the same dose level or 1 dose level lower
Grade 3 AEs	Hold until ≤ Grade 1 or return to baseline	Decrease 1 or more dose levels lower
Grade 4 AEs	Hold until ≤ Grade 1 or return to baseline	For AEs that are not life-threateningand that can be managed, treatment may resume at a lower dose level Otherwise, discontinue study treatment

9.0 ADVERSE EVENTS

The prompt reporting of adverse events is the responsibility of each investigator engaged in clinical research, as required by Federal Regulations. Adverse events must be described and graded using the terminology and grading categories defined in the NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. Expedited adverse event reports will also be reported using

CTCAE version 5.0 criteria. The CTCAE is available at [redacted]. Attribution to protocol treatment for each adverse event must be determined by the investigator and reported on the required forms. Please refer the NCI Guidelines: Adverse Event Reporting Requirements for further details on AE reporting procedures.

9.1 Routine Adverse Event Reporting

Adverse event data collection and reporting, which are required as part of every clinical trial are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times according to the study calendar in Section 5.0.

9.1.1 Rave CTEP-AERS integration

The Rave Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) integration enables evaluation of post-baseline Adverse Events (AE) entered in Rave to determine whether they require expedited reporting and facilitates entry in CTEP-AERS for those AEs requiring expedited reporting. Sites must initiate all AEs for this study in Medidata Rave.

All AEs that occur after baseline are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment or reporting period, and used to collect AEs that start during the period or persist from the previous reporting period. The CRA will enter AEs that occur prior to the start of treatment on a baseline form that is not included in the Rave-CTEP-AERS integration. AEs that occur prior to enrollment must begin and end on the baseline Adverse Events form and should not be included on the standard Adverse Events form that is available at treatment unless there has been an increase in grade.

Prior to sending AEs through the rules evaluation process, site staff should verify the following on the Adverse Event form in Rave:

The reporting period (course/cycle) is correct; and

AEs are recorded and complete (no missing fields) and the form is query free.

The CRA reports AEs in Rave at the time the Investigator learns of the event. If the CRA modifies an AE, it must be re-submitted for rules evaluation.

Upon completion of AE entry in Medidata Rave, the CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form. Both NCI and protocol-specific reporting rules evaluate the AEs submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Medidata Rave for AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form.

In the rare occurrence that Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at [redacted] Once Internet connectivity is restored, the 24-hour notification that was phoned in must be entered immediately into CTEP-AERS using the direct link from Medidata Rave.

Additional information about the CTEP-AERS integration is available on the CTSU website:

- Study specific documents: Protocols > Documents> Education and Promotion; and

- Expedited Safety Reporting Rules Evaluation user guide: Resources > CTSU Operations Information> User Guides & Help Topics.

NCI requirements for SAE reporting are available on the CTEP website:

NCI Guidelines for Investigators: Adverse Event Reporting Requirements is available at [redacted]

9.1.2 Solicited Adverse Events:

The following adverse events are considered "expected" and their presence/absence should be solicited, and severity graded, at baseline and for each cycle of treatment by CTCAE.

CTCAE v5.0 Term	CTCAE v5.0 System Organ Class (SOC)
Neutrophil count decreased	Investigations
Platelet count decreased	Investigations
Rash maculo-papular	Skin and subcutaneous tissue disorders
Hyperglycemia	Metabolism and nutrition disorders
Electrocardiogram QT corrected interval prolonged (for Entrectinib arm only or as clinically indicated)	Investigations
Alanine aminotransferase increased	Investigations
Aspartate aminotransferase increased	Investigations
Blood bilirubin increased	Investigations

Number of stools per day should also be collected for all patients at baseline.

9.2 CTCAE Routine Reporting Requirements

In addition to the solicited adverse events listed in Section 9.1, the following table outlines the combinations of time points, grades and attributions of AEs that require routine reporting to the Alliance Statistics and Data Center. Questions about routine reporting should be directed to the Data Manager.

Combinations of CTCAE Grade & Attribution Required for Routine AE Data Submission on Case Report Forms (CRFs)

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated			a	a	a
Unlikely			a	a	a
Possible	a[1]	a	a, b	a, b	a, b
Probable	a[1]	a	a, b	a, b	a, b
Definite	a[1]	a	a, b	a, b	a, b

a) Adverse Events: Other CRF - Applies to AEs occurring between registration and within 30 days of the patient's last treatment date, or as part of the Clinical Follow-Up Phase.

b) Adverse Events: Late CRF - Applies to grades 3, 4, or 5 AEs occurring greater than 30 days after the patient's last treatment date.

[1]For entrectinib arm only

9.3 Expedited Adverse Event Reporting (Rave-CTEP-AERS)

Investigators are required by Federal Regulations to report serious adverse events as defined in the table below. Alliance investigators are required to notify the Study Chair, and their Institutional Review Board if a patient has a reportable serious adverse event. The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website at: [redacted] All appropriate treatment areas should have access to a copy of the CTCAE. All reactions determined to be "reportable" in an expedited manner must first be reported in Rave on the "Adverse Events" form and sent for rule evaluation at the time of the event. Adverse event data should not be entered in CTEP-AERS prior to entry in Rave for rules evaluation. Additional information about Rave-CTEP-AERS is available on the [redacted] website under the "Resources" tab for each protocol.

For further information on the NCI requirements for SAE reporting, please refer to the 'NCI Guidelines for Investigators: Adverse Event Reporting Requirements' document published by the NCI.

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

9.3.1 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]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** SAEs, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64).

An AE is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening AE
3) An AE that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) 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 patient 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).

ALL SAEs that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Grade 1-2 Timeframes	Grade 3-5 Timeframes
24-Hour notification, 10 Calendar Days	24-Hour notification, 5 Calendar Days

NOTE: Protocol-specific exceptions to expedited reporting of SAEs are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timeframes are defined as:

- "24-Hour notification, 5 Calendar Days" - The SAE must initially be reported via CTEP-AERS within 24 hours of learning of the SAE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "24-Hour notification, 10 Calendar Days" - The SAE must initially be reported via CTEP-AERS within 24 hours of learning of the SAE, followed by a complete expedited report within 10 calendar days of the initial 24-hour report.

[1]SAEs 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 notifications are required for all SAEs followed by a complete report

- Within 5 calendar days for Grade 3-5 SAEs
- Within 10 calendar days for Grade 1-2 SAEs

[2]For studies using nuclear medicine or molecular imaging IND agents (NM, SPECT, or PET), the SAE 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: August 30, 2024

9.3.2 Expedited AE reporting timelines defined

"24 hours; 5 calendar days" – The investigator must initially report the AE via CTEP-AERS ≤ 24 hours of learning of the event followed by a complete CTEP-AERS report ≤ 5 calendar days of the initial 24-hour report.

"10 calendar days" - A complete CTEP-AERS report on the AE must be submitted ≤ 10 calendar days of the investigator learning of the event.

Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions (see below).

Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS.

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

9.3.3 Additional Instructions or Exclusions to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent Under a CTEP IND or non-CTEP IND

All adverse events reported via CTEP-AERS (i.e., serious adverse events) should also be forwarded to your local IRB.

≤ Grade 4 hematosuppression (including anemia, thrombocytopenia, lymphopenia and leukopenia) and hospitalization resulting from such do not require CTEP-AERS, but should be submitted as part of study results. All other grade 3, 4, or 5 adverse events that precipitate hospitalization or prolong an existing hospitalization must be reported via CTEP-AERS.

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.

Any death occurring within 30 days of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours.

Any death occurring greater than 30 days after the last dose of the investigational agent/intervention requires expedited reporting within 24 hours only if it is possibly, probably, or definitely related to the investigational agent/intervention.

Pregnancy loss is defined in CTCAE v5.0 as "Death in utero." Any Pregnancy loss should be reported expeditiously, as Grade 4 "Pregnancy loss" under the Pregnancy, puerperium and perinatal conditions SOC. A Pregnancy loss should NOT be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEP-AERS recognizes this event as a patient death.

A neonatal death should be reported expeditiously as Grade 4, "Death neonatal" under the General disorders and administration SOC.

All new malignancies must be reported via CTEP-AERS whether or not they are thought to be related to either previous or current treatment. All new malignancies should be

reported, i.e. solid tumors (including non-melanoma skin malignancies), hematologic malignancies, myelodysplastic syndrome/acute myelogenous leukemia, and in situ tumors.

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 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.

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 reporting unless otherwise specified.

Whenever possible, the CTEP-AERS reports for new malignancies should include tumor pathology, history or prior tumors, prior treatment/current treatment including duration, any associated risk factors or evidence regarding how long the new malignancy may have been present, when and how the new malignancy was detected, molecular characterization or cytogenetics of the original tumor (if available) and of any new tumor, and new malignancy treatment and outcome, if available.

Treatment expected adverse events include those listed in Section 10.0 and in the package insert.

CTEP-AERS reports should be submitted electronically.

When submitting CTEP-AERS reports for “Pregnancy”, “Pregnancy loss”, or “Neonatal loss”, the Pregnancy Information Form should be completed and submitted, along with any additional medical information (form is available on the CTEP website at [redacted]). The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the “Description of Event” section of the CTEP-AERS report.

For patients receiving entrectinib:

Adverse Event Special Interest (AESIs) are a subset of Events to Monitor (EtMs) of scientific and medical concern specific to the product, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is required. Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial Sponsor to other parties (e.g., Regulatory Authorities) may also be warranted.

The Entrectinib Adverse Events of Special interest for this study include:

AE Term	CTCAE v5.0 term	CTCAE v5.0 System Organ Class (SOC)
Grade ≥ 2 Congestive Heart Failure	Heart failure	Cardiac disorders
Grade ≥ 2 QT Prolongation	Electrocardiogram QT corrected interval prolonged	Investigations
Grade ≥ 3 Cognitive Disturbance	Cognitive disturbance	Nervous system disorders
Any grade syncope	Syncope	Nervous system disorders
Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law: -Treatment-emergent ALT or AST > 3 x ULN in combination with total bilirubin > 2 x ULN -Treatment-emergent ALT or AST > 3 x ULN in combination with clinical jaundice	Hepatic failure	Hepatobiliary disorders
Any grade 2 AEs that are considered possibly, probably, or definitely related to entrectinib		

The Adverse Events of Special Interest listed above should be reported via CTEP-AERS (24 hour; 5 calendar days) and the Adverse Events form in Medidata Rave®.

In addition to all protocol defined adverse events and AESIs from the study, the following Special Situation Reports should be reported, even in the absence of an AE.

- Data related to the product usage during pregnancy or breastfeeding
- Data related to overdose, abuse, misuse or medication error (including potentially exposed or intercepted medication errors)

Special Situation Reports that are deemed serious by the investigator should be reported via CTEP-AERS (24 hour; 5 calendar days) as "Injury, poisoning and procedural complications – Other, specify" under the "Injury, poisoning and procedural complications" SOC. All Special Situation Reports, regardless of seriousness, should also be reported via the Special Situations – Entrectinib Arm Only form in Medidata Rave®.

10.0 DRUG INFORMATION

10.1 General Considerations:

Abemaciclib, paxalisib, entrectinib, and MRTX849 will be provided free of charge for all cohorts and distributed by RxCrossroads by McKesson.

Sites should submit initial and resupply requests using drug order forms for A071701 posted on the CTSU/Alliance websites.

Investigators ordering and/or dispensing supplied agents at any time for study treatment must be currently registered with PMB, DCTD, NCI. A registered investigator must co-sign for other non-registered personnel prescribing the supplied agents.

Questions related to study drug supply should be directed to RxCrossroads by McKesson.

RxCrossroads by McKesson Specialty
[redacted]
Phone: [redacted]
Fax: [redacted]
Email: [redacted]

Patients' returns, expired, and unused study drugs should be destroyed on site per institutional policies with documentation on the drug accountability record form.

Institutional pharmacists should refer to the CTMB Guidelines Section 5.3 and the PMB website training videos.

Drug may be destroyed within 90 days after the last patient is treated at the institution.

All study agents are to be administered at the registering institution.

If the Group credited for enrollment is a non-Alliance Group, then other requirements from the credited Group may apply.

Ninety days after the last patient is treated at the institution, any expired or remaining supplies should be destroyed according to institutional procedure.

Product complaints: A product complaint is any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness or performance of a product after it has been released and distributed to the commercial market or clinical trial. Please email any complaints related to the study agents to [redacted]

10.2 Paxalisib (formerly GDC-0084)

Procurement

Paxalisib is patient specific and may NOT be dispensed to another patient.

Patient-specific supply may be confirmed by checking to see if a patient ID number is included on the drug invoice.

Paxalisib will be provided by Kazia Therapeutics and distributed by RxCrossroads by McKesson. Use the Alliance A071701 Drug Order Request Form on the A071701 study page on the Alliance and CTSU websites.

Study drug cannot be shipped post-distribution.

Formulation

Chemical name: 5-(6,6-dimethyl-4-morpholino-8,9-dihydro-6H-[1,4]oxazino[3,4-e]purin-2-yl)pyrimidin-2-amine

Molecular formula: $C_{18}H_{22}N_8O_2$

Molecular weight: 382.42 g/mol

Solubility: pH dependent solubility; 0.49 mg/mL in 0.1 N HCl, 0.03 mg/mL in fed-state simulated intestinal fluid (pH 5.0) and 0.01 mg/mL at fasted-state simulated intestinal fluid (pH 6.8) at 37 °C, 0.002 mg/mL in deionized water at pH 7.0 at room temperature

Mode of action: Paxalisib is a potent, oral, selective, brain-penetrant small molecule inhibitor of class I phosphoinositide 3 kinase (PI3K) and mammalian target of rapamycin (mTOR) kinase which has been specifically developed for the treatment of brain cancer.

Description: Paxalisib API is a free base, appearing as a white to yellow solid.

How supplied: Paxalisib is provided as GMP manufactured 15 mg capsules, size 0 and opaque white. Excipients used in the 15 mg capsule formulation are microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, and colloidal silicon dioxide.

Capsules will be provided in 60 cc white HDPE bottles (35 capsules per bottle).

Storage and Stability

Storage: Paxalisib capsules should be stored at 15 – 30 °C (59 – 86 °F). Temperature excursions during storage should be reported to [redacted]

Stability: solid-state stability studies showed that paxalisib is very stable against heat and light. In solution, paxalisib is stable under heat conditions and slightly sensitive to oxidative conditions.

Shelf life surveillance of paxalisib in the bottle is ongoing.

Administration

Paxalisib should be administered orally once daily as a single dose, one hour before or two hours after food consumption on treatment days. Capsules should be swallowed whole and never opened. Patients should record the time and date of each dose taken in a medication diary. If the patient vomits or misses a dose of paxalisib, instruct the patient to take the next dose at its scheduled time.

Drug Accountability

Manual or electronic NCI Investigational Agent Accountability Record Form for Oral Agents should be used to document receipt, dispensing, patients' returns and disposal of study drugs.

Investigator Brochure Availability

The investigator brochure for paxalisib may be obtained by contacting the Alliance Central Protocol Operations Program office at [redacted]

Drug Interactions

In vitro data suggest that paxalisib is metabolized by CYP3A4 and induces the expression of CYP3A4; however, the potential for in vivo CYP3A4 induction is low at clinically relevant concentrations of paxalisib.

Concomitant use of strong CYP3A4 inhibitors (including but not limited to: atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandamycin, voriconazole, and grapefruit juice) or strong CYP3A4 inducers (including but not limited to: rifampin, carbamazepine, rifapentine, phenytoin, phenobarbital, and St. John's wort or hyperforin) should be avoided. Enzyme inducing anti-epileptic drugs should also be avoided. If use of such drugs is necessary, the risks and benefits should be discussed with the Medical Monitor prior to its concomitant use with paxalisib.

Pharmacokinetics

Paxalisib is rapidly absorbed with a median T_{max} of approximately 2 hours following a single dose. Paxalisib has a mean half-life of approximately 18.7 hours, which is supportive of once daily dosing. Clinical trial data showed linear and dose proportional increase in C_{max} and AUC0-24 following single and multiple doses.

Adverse Events

Common known potential toxicities, >10%:

Fatigue, diarrhea, nausea, loss of appetite, vomiting, ulcers inside the mouth, rash, abnormal cholesterol blood test

Occasional known potential toxicities, <10%:

Inflammation inside the mouth, high blood sugar levels, tremor, dry or itchy skin

Rare known potential toxicities, <3%:

Heart attack, dizziness or lightheadedness, slow heart rate

Nursing Guidelines.

1. Paxalisib is given once daily either one hour before or two hours after food. Instruct patients to swallow capsules whole and to never open. Remind patient of need to record date and time in a medication diary.

2. There are many drug to drug interactions with this agent. Assess patient's concomitant medications including OTC and herbal supplements. Instruct patients not to start any new medications without first discussing with the study team.

3. Gastrointestinal side effects are common, including diarrhea, nausea, and vomiting. Treat symptomatically and monitor for effectiveness.

4. Patients may experience mouth sores. Treat symptomatically and monitor for effectiveness.

5. Patients may experience high blood glucose levels. Monitor patients with known diabetes or those at high risk closely.

6. Patients may experience pruritus and dry skin. Encourage frequent moisturizing of the skin with topical emollients.

7. Rarely cardiac events can occur, including bradycardia and MI. Instruct patient to report any chest pain, SOB, or dizziness to the study team.

10.3 Entrectinib (RXDX-101, NSC #801660)

Entrectinib has been approved by U.S. Food and Drug Administration in August 2019 for adults and pediatric patients 12 years of age and older with solid tumors that have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have progressed following treatment or have no satisfactory standard therapy.

Procurement

Entrectinib will be provided by Genentech Inc. and distributed by RxCrossroads by McKesson. Use the Alliance A071701 Drug Order Request Form on the A071701 study page on the Alliance and CTSU websites.

Formulation

Chemical name: N-[5-[(3,5-difluorophenyl)methyl]-1H-indazol-3-yl]-4-(4-methylpiperazin-1-yl)-2-(oxan-4-ylamino)benzamide

Molecular formula: $C_{31}H_{34}F_2N_6O_2$

Molecular weight: 560.65g/mol

Mode of action: a potent and selective inhibitor of the receptor tyrosine kinases TRKA (encoded by the gene neurotrophic tyrosine kinase [NTRK]1, TRKB (encoded by the gene NTRK2), TRKC (encoded by the gene NTRK3), and ROS1 (encoded by the gene ROS1), with median inhibitory concentrations (IC50) for kinase inhibition in the low nanomolar range (1.7, 0.1, 0.2, and 1.6 nM, respectively).

Upon administration, entrectinib binds to and inhibits TRKA, TRKB, TRKC, and ROS1. Inhibition of these kinases may result in a disruption of TRKA-, TRKB-, TRKC-, and ROS1-mediated signaling. This leads to an induction of apoptosis and an inhibition of tumor cell proliferation in tumor cells that express these kinases. TRKA, TRKB, TRKC, and ROS1 are overexpressed in a variety of cancer cell types.

Description: a white to tan, pink, orange or brownish crystalline powder.

How supplied: an oral capsule dosage form at strength of 200 mg.

The 200 mg strength is provided in white size #00 hard gelatin capsules, containing the following compendial excipients: betaine hydrochloride (acidulant), isomalt, pre-gelatinized starch, colloidal silicon dioxide, and magnesium stearate.

Each bottle contains 30 capsules.

Storage and Stability

Storage: controlled room temperature at 15– 30 °C (59 – 86 °F). Temperature excursions during storage should be reported to [redacted]

Entrectinib must be stored in the original packaging at controlled room temperature. Sites should dispense in the original bottle.

Stability: Shelf life surveillance of entrectinib in the bottle is ongoing.

Administration

Entrectinib should be administered orally once daily within 30 minutes following a meal on a continuous daily dosing regimen. Capsules should be swallowed whole and not opened. Patients should record the time and date that they take each dose in a medication diary. If the patient

vomits or misses a dose of entrectinib, instruct the patient to take the next dose at its scheduled time.

Drug accountability

Manual or electronic NCI Investigational Agent Accountability Record Form for Oral Agents should be used to document receipt, dispensing, patients' returns and disposal of study drugs.

Investigator Brochure Availability

The investigator brochure for entrectinib may be obtained by contacting the Alliance Central Protocol Operations Program office at [redacted]

Drug interactions

Entrectinib is mainly eliminated through hepatic clearance and CYP3A plays a significant role in the biotransformation of entrectinib. Co-administration of strong or moderate CYP3A inhibitors and inducers should be avoided.

No dose adjustments are required when entrectinib is co-administered with PPIs or other drugs that raise gastric pH (e.g. H2 receptor antagonists or antacids).

Pharmacokinetics

Following a single dose of entrectinib in healthy volunteers, entrectinib was readily absorbed and generally detectable in circulation at 0.5 hours post dose with median T_{max} at 3.5 to 4 hours in the fasted state. T_{max} appeared to occur later under a fed state, with median T_{max} occurring at 5 – 7 hours, Mean calculated half-life of entrectinib was greater than 20 hours, which supports once daily dosing. Exposures of entrectinib appear to increase linearly across the study's dose range (400, 600, or 800 mg dose).

Adverse Events

Common known potential toxicities, >10%

Fatigue; tingling, tickling, prickling or burning sensation of skin; diarrhea; nausea; loss of taste or bad taste in mouth; vomiting; anemia which may require blood transfusion; low levels of white blood cells or neutrophils; dizziness; constipation; confusion; increased creatinine; difficulty swallowing; abdominal pain; difficulty sleeping; blurred vision; hypotension; headache; pain in arms or legs, neck, or back; pain in muscles or joints; edema; neuropathy; difficulty with coordination, balance or walking; shortness of breath; cough; abnormal liver tests; decreased appetite; fever; lung infection; urinary tract infection; rash-anywhere including face, arms, and legs.

Occasional, <10%

Difficulty with understanding, memory and attention; ;; fatigue or drowsiness; pain, numbness, dryness, tingling or burning feeling in mouth or throat; indigestion; dry or itchy skin; low levels of electrolytes; abnormal blood pancreas test; general sensitivity to light or eyes sensitive to light; skin pain; fractures.

Rare known potential toxicities, <3%:

Allergic reaction involving the heart muscle; weakness of heart muscle causing decreased pumping of blood; irregular rate or rhythm of heartbeat; tumor lysis syndrome; prolonged QT interval.

Risk of sun exposure: Some drugs have a potential to be photo-reactive. This means that your body could experience side effects (such as a sunburn) through sunlight exposure after taking a drug. Entrectinib has a potential to be photo-reactive. You should be careful with sun exposure

by using daily sunscreen, lip balm, and wearing protective clothing, sunglasses, and a hat when going outdoors.

Nursing Guidelines

1. Entrectinib must be given within 30 minutes following a meal. Capsules should be swallowed whole and not opened. Remind patients to record daily dose in medication diary per study.

2. Assess patient's concomitant medications, including OTC and supplements. There are many drug to drug interactions.

3. Patients should not be on H2 blockers, PPIs or antacids while on study agent. If these are clinically required, only H2 blockers or antacids should be used. PPIs should be avoided. These should only be used 12 hours prior or after a dose of entrectinib.

4. Gastrointestinal side effects can be seen, including diarrhea, nausea, constipation and vomiting. Treat symptomatically and assess for response.

5. Patients may experience anemia that may require transfusions. Monitor CBCs and instruct patients to report any increase in fatigue to study team.

6. Patients may experience CNS side effects including difficulty in understanding, memory or attention issues, coordination, balance and walking. It is important to assess patient neuro status and instruct patients to report any changes from baseline.

7. Monitor renal function, as creatinine increases are seen.

8. Monitor LFTs, as liver function can be affected.

9. Instruct patients to report any SOB, dyspnea on exertion, edema, or palpitations to study team. Arrhythmias and LVEF dysfunction have been seen.

10.4 Abemaciclib (LY2835219, VERENZIO™, NSC#783671)

Abemaciclib has been approved by U.S. Food and Drug Administration (FDA) in September 2017 for the following indications:

- In combination with fulvestrant for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer with disease progression following endocrine therapy
- As monotherapy for the treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting

In February, 2018, U.S. FDA has approved abemaciclib in combination with an aromatase inhibitor (AI) as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced or metastatic breast cancer.

Procurement

Abemaciclib will be provided by Eli Lilly and company and distributed by RxCrossroads by McKesson. Use the Alliance A071701 Drug Order Request Form on the A071701 study page on the Alliance and CTSU websites.

Formulation

Chemical name: 2-Pyrimidinamine,N-[5-[(4-ethyl-1-piperazinyl)methyl]-2-pyridinyl]-5-fluoro-4-[4¬ fluoro-2-methyl-1-(1-methylethyl)-1H-benzimidazol-6-yl]-N-(5-((4-ethylpiperazin-1-yl)methyl)pyridine-2-yl)-5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1Hbenzo[d]imidazole-6-yl)pyrimidin-2-amine

Molecular formula: $C_{27}H_{32}F_2N_8$

Molecular weight: 506.59 g/mol

Solubility: 0.001 mg/mL in water, 22.313 mg/mL in ethanol

Mode of action:

Abemaciclib is a selective and potent inhibitor of cyclin-dependent kinases 4 and 6 (CDK4 and CDK 6).

These kinases are activated upon binding to D-cyclins, which initiates the transition through the G1 restriction point by phosphorylating and inactivating the retinoblastoma (Rb) tumor-suppressor protein. The inhibition of CDK4 and CDK6 is to prevent cell cycle progression through the G1 restriction point, thus arresting tumor growth.

Abemaciclib demonstrates significant inhibition of tumor growth as monotherapy in multiple human xenograft models including models for: breast cancer, colorectal cancer, glioblastoma multiforme, acute myeloid leukemia, melanoma, mantle cell lymphoma (MCL), and non-small-cell lung cancer (NSCLC). In nonclinical species, abemaciclib distributes efficiently to the brain and potentially provides a unique opportunity to treat primary brain tumors as well as cancers that have metastasized to the brain.

Description: practically white to yellow solid

How supplied:

Abemaciclib is supplied as 50 mg in tablet formulation.

Tablet product:

A modified oval, immediate release, aqueous film-coated abemaciclib tablets in 50 mg strength with the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, silicon dioxide, sodium stearyl fumarate, color mixture beige (50 mg tablets).

Each bottle contains 60 tablets.

Storage and Stability

Storage: store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

Stability: stable at room temperature

Administration

Abemaciclib should be administered orally twice daily with or without food at approximately the same times every day. If the patient vomits or misses a dose of abemaciclib, instruct the patient to take the next dose at its scheduled time.

Patients should swallow whole tablets and not chew, crush, or split tablets before swallowing.

Drug accountability

Manual or electronic NCI Investigational Agent Accountability Record Form for Oral agents should be used to document receipt, dispensing, patient's returns, and disposal of study drugs.

Investigator Brochure Availability

The investigator brochure for abemaciclib may be obtained by contacting the Alliance Central Protocol Operations Program office at [redacted]

Drug interactions

Abemaciclib is predominantly cleared by oxidative metabolism via CYP3A. Clinical drug interaction studies with a CYP3A4 inhibitor and CYP3A inducer significantly altered the PK of abemaciclib and its circulating major metabolites.

CYP3A inducers: Avoid concomitant use of CYP3A inducers and consider alternative agents.

CYP3A4 inhibitors: Strong CYP3A4 inhibitors increased the exposure of abemaciclib plus its active metabolites to a clinically meaningful extent and may lead to increased toxicity. Co-administration of abemaciclib with strong CYP3A inducers decreased the plasma concentrations of abemaciclib plus its active metabolites and may lead to reduced activity. Avoid concomitant use of strong CYP3A inhibitors (for example, voriconazole) and use caution with coadministered moderate (for example, ciprofloxacin) or weak (for example, ranitidine) CYP3A inhibitors. If coadministration with a strong CYP3A inhibitor is unavoidable, reduce the abemaciclib dose to 100 mg twice daily or, in the case of ketoconazole, reduce the abemaciclib dose to 50 mg twice daily. In patients who have had a dose reduction to 100 mg twice daily due to adverse reactions, further reduce the abemaciclib dose to 50 mg twice daily. Avoid grapefruit or grapefruit juice. If a CYP3A inhibitor is discontinued, increase the abemaciclib dose (after 3-5 half-lives of the inhibitor) to the dose that was used before starting the inhibitor.

Pharmacokinetics

The pharmacokinetics of abemaciclib were characterized in patients with solid tumors, including metastatic breast cancer, and in healthy subjects. Following single and repeated twice daily dosing of 50 mg to 200 mg of abemaciclib, the increase in plasma exposure (AUC) and Cmax was approximately dose proportional. Steady state was achieved within 5 days following repeated twice daily dosing, and the estimated geometric mean accumulation ratio was 2.3 (50% CV) and 3.2 (59% CV) based on C_{max} and AUC, respectively.

Absorption: In the dose range of 50 to 275 mg, abemaciclib absorption is slow, with a T_{max} ranging from 4 to 6 hours, and AUC and C_{max} generally increased in a dose-proportional manner after a single dose and also with multiple twice daily doses. The mean absolute bioavailability of abemaciclib after a single oral dose of 200 mg is 45%.

Effect of food: In a study of the effect of a high-fat meal using the proposed commercial formulation, abemaciclib exposure increased by 27% based on AUC and by 35% based on C_{max}. A high-fat meal did not change the interindividual variability in PK. Although the change in AUC and C_{max} in the food effect study was statistically significant, it was small relative to the variability in exposure in the cancer patient population, and therefore not considered to be clinically relevant. Based on available data, abemaciclib can be taken without regard to meals.

Distribution: In vitro, abemaciclib was bound to human plasma proteins, serum albumin, and alpha-1-acid glycoprotein in a concentration independent manner from 152 ng/mL to 5066 ng/mL.

Metabolism: Hepatic metabolism is the main route of clearance for abemaciclib. Abemaciclib is metabolized to several metabolites primarily by cytochrome P450 (CYP) 3A4, with formation of N-desethylabemaciclib (M2) representing the major metabolism pathway. Additional metabolites include hydroxyabemaciclib (M20), hydroxy-N-desethylabemaciclib (M18), and an oxidative metabolite (M1).

Elimination: The geometric mean apparent oral clearance (CL/F) of abemaciclib was 38.3 L/h (105% CV), and the mean plasma elimination half-life T1/2 for abemaciclib in patients at a dose of 200 mg was 21 (12 – 63) hours. The mean T1/2 ranged from 17 to 38 hours with no consistent trends related to dose, suggesting no dose dependent change in CL.

Excretion: After a single 150 mg oral dose of radiolabeled abemaciclib in healthy subjects, approximately 81% of the dose was recovered in feces and approximately 3.4% recovered in urine. The majority of the dose eliminated in feces was metabolites indicating that abemaciclib is highly metabolized.

Adverse Events

Common known potential toxicities, >10%

Fatigue, diarrhea, nausea, loss of appetite, neutropenia, leukopenia, vomiting, anemia that may require blood transfusion, thrombocytopenia, inflammation or ulcers inside the mouth, alopecia

Occasional known potential toxicities, < 10%

Increased creatinine: Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular transporters without affecting glomerular function (as measured by iohexol clearance). In clinical studies, increases in serum creatinine occurred within the first month of abemaciclib dosing, remained elevated but stable through the treatment period, were reversible upon treatment discontinuation, and were not accompanied by changes in markers of renal function, such as blood urea nitrogen (BUN), cystatin C, or calculated glomerular filtration rate based on cystatin C.

Nursing Guidelines

1. Abemaciclib can be taken with or without regard to food. Patients should be instructed to take at the same time each day. Do not crush, chew, or split tabs; they should be taken whole. Patients should be instructed not to take pills that are not intact.

2. Do not make up missed or vomited doses. Instruct patient to take the next dose at its scheduled time.

3. Assess patient's concomitant medications, including OTC. Patients who are taking strong CYP3A inhibitors will need to reduce their dose of abemaciclib according to protocol instructions.

4. Gastrointestinal side effects, including diarrhea, nausea, abdominal pain, and vomiting are common. Treat symptomatically and monitor for effectiveness.

5. Monitor CBC w/diff as cytopenias are commonly seen. Instruct patients to report any signs or symptoms of infection, and/or excessive bruising/bleeding to the study team.

6. Increased incidences of VTEs have been seen in patients receiving abemaciclib. Instruct patients to report any swelling of extremities, and /or SOB, DOE or chest pain to the study team immediately and/or seek out emergency medical care.

7. Headache has been seen. Treat symptomatically and monitor for effectiveness.

10.5 MRTX849 (Adagrasib, NSC# 827801)

Procurement

MRTX849 (Adagrasib) will be provided by Mirati Therapeutics and distributed by RxCrossroads by McKesson. Use the Alliance A071701 Drug Order Request Form on the A071701 study page on the Alliance and CTSU websites. MRTX849 is patient specific and may NOT be dispensed to another patient.

Formulation and Packaging

Mode of action: MRTX849 is a potent, oral, selective, covalent small molecule inhibitor of the KRAS G12C mutant variant.

The MRTX849 tablet formulation is available as immediate release, white to off-white, film-coated tablets in 200 mg unit dose strength. Excipients in the tablet formulation include microcrystalline cellulose, mannitol, crospovidone, colloidal silicon dioxide, and magnesium stearate. The film coat consists of hypromellose, titanium dioxide, polydextrose, talc, maltodextrin, and medium chain triglycerides (vegetable).

MRTX849 tablets are packaged in 132-count or 180-count, HDPE, white bottles with child resistant closures and heat induction seals.

Each bottle is minimally labeled with contents, product lot number, manufacturing date, required storage conditions, Sponsor identification, and regional specific cautionary statement "New Drug – Limited by Federal Law to Investigational Use Only."

Storage and Stability

Tablets of MRTX849 should be stored at the clinic and by the patient at room temperature (range is 2-25°C, 36-77°F) according to instructions on the label. Transient temperature excursions up to 30 minutes at 40°C/75%RH during storage and shipping are acceptable. The storage area should be secure with limited access.

Stability: Shelf life surveillance of MRTX849 in the bottle is ongoing.

Administration

MRTX849 should be administered orally twice daily (approximately every 12 hours).

MRTX849 drug product may be taken with or without food. MRTX849 should be taken with at least 240 mL (8 ounces) of water. MRTX849 pills should be swallowed whole, not chewed. If vomiting occurs, doses should not be replaced. If a dose is inadvertently missed, the dose should be skipped if > 4 hours has elapsed since the expected dosing time. Dosing may resume at the next appointed time. Patients should record the time and date of each dose taken in a medication diary.

Drug Accountability

Manual or electronic NCI Investigational Agent Accountability Record Form for Oral Agents should be used to document receipt, dispensing, patients' returns and disposal of study drugs.

Investigator Brochure Availability

The investigator brochure for MRTX849 may be obtained by contacting the Alliance Central Protocol Operations Program office at [redacted]

Drug Interactions

Gastric Acid Reducing Medications: Because MRTX849 solubility is maximal at low pH, drugs that reduce gastric acid secretion should be carefully managed or avoided where possible. When a gastric acid reducing medication is required, preference should be given first to antacids administered more than 2 hours before and more than 2 hours after dosing with MRTX849, and second to an H2 antagonist administered 2 hours after dosing of MRTX849 (such that the H2 antagonist drug level nadirs near the time of the next dose of MRTX849). Proton pump inhibitors should be avoided when possible given the risk of MRTX849 underexposure.

Anti-emetics: For patients on MRTX849, prophylactic anti-emetics may be used. It is recommended that patients use drugs that do not cause QT prolongation. Note that some anti-

emetics have a known risk for Torsade de Pointes including ondansetron, and alternatives should be used. If effective alternative anti-emetics are not available, oral administration of ondansetron at doses up to 4 mg every 6 hours, with a maximum total daily dose of 16 mg, is permitted in patients without underlying bradycardia, CHF, or congenital Long QT Syndrome It is recommended that an ECG is obtained at the beginning of each cycle, and that potassium and magnesium levels are obtained at the beginning of each cycle and supplemented if below the reference range. Use of intravenous administration of ondansetron is to be avoided.

Strong Inhibitors of CYP3A4/P-gp and Inducers of CYP3A4: MRTX849 is a substrate of CYP3A4 and P-gp. Co-administration of MRTX849 with strong CYP3A4/P-gp inhibitors may significantly increase the exposure to the study treatment, which may increase the risk of adverse reactions. Co-administration of MRTX849 with strong CYP3A4 inducers may significantly decrease the exposure to the study treatment, which may decrease the efficacy of the study treatment. Discontinue use of strong inhibitors or inducers of CYP3A4 a minimum of 5 times their half -life prior to study treatment. Use of strong inhibitors of CYP3A4/P-gp and inducers of CYP3A4 during study treatment is to be avoided. Consider using alternative medications that are not strong inhibitors or inducers of CYP3A4.

Substrates of Cytochrome P450:

MRTX849 is a strong inhibitor of CYP3A4. Patients are advised to avoid co administration of MRTX849 with drugs with a narrow therapeutic index that are highly dependent on CYP3A for clearance. Caution is recommended when MRTX849 is administered with moderate/sensitive CYP3A substrates without a narrow therapeutic index, and the dose of moderate/sensitive CYP3A substrates may need to be reduced.

MRTX849 is a moderate inhibitor of CYP2C9 and CYP2D6. Patients are advised to avoid co-administration of MRTX849 with substrates of CYP2C9 or CYP2D6 with a narrow therapeutic index. If alternative treatments cannot be used, consider a dose reduction of the concomitant CYP2C9 or CYP2D6 substrate drug. Caution is recommended when MRTX849 is administered with moderate/sensitive CYP2C9 or CYP2D6 substrates without a narrow therapeutic index, and the dose of moderate/sensitive CYP2C9 or CYP2D6 substrates may need to be reduced.

MRTX849 (adagrasib) is a weak inhibitor of CYP2B6. No dose adjustments for CYP2B6 substrates are needed during co-administration with MRTX849 (adagrasib).

BCRP: MRTX849 is a substrate of BCRP. The effect of strong inhibitors of BCRP (e.g. curcumin, cyclosporin, and eltrombopag) on MRTX849 has not been evaluated. Strong inhibitors of BCRP should be avoided.

P-gp Transporters: MRTX849 is a weak inhibitor of P gp. No dosage adjustments for P-gp substrates are warranted during co-administration with MRTX849.

No dose adjustment of MRTX849 is needed when MRTX849 is co-administered with CYP3A and/or P-gp inhibitors. Co-administration of MRTX849 with strong CYP3A and/or P-gp inducers should be avoided.

Pharmacokinetics

Single-Dose PK: MRTX849 exhibits the following single-dose PK characteristics following a single 600 mg oral dose administration of MRTX849 capsules under fasting conditions:

Median tmax was 4.17 hours, indicating that MRTX849 is steadily absorbed following oral administration.

The between-patient variability for Cmax, and AUC∞ was relatively high as the geometric CV% ranged from 95% to 142%.

Geometric mean CL/F and Vz/F was 16.0 L/h and 527 L, respectively.

Arithmetic mean t1/2 was 23.0 h.

Multiple-Dose PK: MRTX849 exhibits the following multiple-dose PK characteristics following administration of MRTX849 600 mg BID (capsules) under fasting conditions:

Median tmax values on C1D1 and C1D8 were 6.03 and 2.96 hours, respectively. The shorter tmax on C1D8 could be due to the relatively flat concentration-time profile and low geometric mean peak-to-trough concentration ratio (PTR) of 1.07 on C1D8.

Between-patient variability (geometric mean CV%) for MRTX849 exposure measures (Cmax and AUCτ) reduced from C1D1 (approximately 76 to 95%) to C1D8 (approximately 37 to 44%).

Steady state appeared to have been reached by C1D8. The geometric mean Cmin on Cycle 1 Day 8 was 2693 ng/mL.

Multiple dosing of 600 mg BID resulted in approximately 5- to 6-fold accumulation (Rac) and a low PTR of 1.07 at steady state. Additionally, steady-state concentrations exceeded the target efficacious average concentration derived from the least sensitive preclinical xenograft model.

Multiple dosing of 150 and 300 mg QD resulted in less drug accumulation (approximately 3- to 4-fold) and a higher peak-to-trough concentration ratio (approximately 3) in individual patients compared to the 600 mg BID regimen. Additionally, concentrations at C1D8 were all substantially below the target efficacious average concentration derived from the least sensitive preclinical xenograft model.

Adverse Events

Common (>10%) reported treatment-related adverse events: nausea, diarrhea, vomiting, fatigue, increased liver enzymes (ALT and AST), increased serum creatinine, decreased appetite, QT prolongation.

Occasional (<10%) reported treatment-related adverse events: anemia, change in taste, alkaline phosphatase increased, peripheral edema, increased lipase.

Nursing Guidelines.

1. MRTX849 is given twice daily with or without food. MRTX849 is taken with 240 mL of water. Instruct patients to swallow tablets whole. If a dose is inadvertently missed, the dose should be skipped if > 4 hours has elapsed since the expected dosing time. Dosing may resume at the next appointed time. If vomiting occurs, doses should not be replaced. Twice daily dosing should be at 12-hour intervals to the extent possible. Remind patient of need to record date and time in a medication diary.

2. On the days of PK sampling, the first doses of the day should be taken in the clinic and administration time recorded from the night before, and the morning dose.

2. There are many potential drug-drug interactions with this agent. Assess patient's concomitant medications including OTC and herbal supplements. Instruct patients not to start any new medications without first discussing with the study team.

3. Gastrointestinal side effects are common, including nausea, vomiting and diarrhea. Patients should have anti-emetics and anti-diarrhea medications available to self-administer soon after onset. Treat symptomatically and monitor for effectiveness. Patients assessed as having greater potential to develop nausea may be treated prophylactically. Refer to the protocol for specific guidance on the management of gastrointestinal side effects.

11.0 MEASUREMENT OF EFFECT

11.1 Extracranial response

For the purposes of this study, participants should be re-evaluated for extracranial response every 8 weeks for the first 2 years from registration, then every 3 months for years 3-4 from registration, then every 6 months thereafter. In addition to a baseline scan, confirmatory scans should also be obtained 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 Definitions

Evaluable for Target Disease Response. Only those participants who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for target disease response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Participants who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.1.2 Disease Parameters for Extracranial Disease Response

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray or ≥10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all considered non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same participant, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow up.

11.1.3 Methods for Evaluation of Disease for Extracranial Response

All measurements should be taken and recorded in metric notation using a ruler, calipers, or a digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 14 days before registration.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm in diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray. Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung; however, CT is preferable.

Conventional CT and MRI. This guideline has defined measurability of lesions on CT scan based on the assumption that CT thickness is 5mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size of a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

FDG-PET. While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm: Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

PET-CT. At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later data and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure from CT, MRI may be used instead of CT in selected instances.

Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases.

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

11.1.4 Response Criteria in Extracranial Disease

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Evaluation of Non-target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

Evaluation of New Lesions

The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Participants with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks Confirmation**

CR	Non-CR/Non-PD	No	PR	≥4 wks Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** Only for non-randomized trials with response as primary endpoint.

*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

For Participants with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	**New Lesions**	**Overall Response**
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date

that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started, or death due to any cause. Participants without events reported are censored at the last disease evaluation).

Duration of overall complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

Progression-Free Survival

Overall Survival: Overall Survival (OS) is defined as the time from registration to death due to any cause, or censored at date last known alive.

Progression-Free Survival: Progression-Free Survival (PFS) is defined as the time from registration to the earlier of progression or death due to any cause. Participants alive without disease progression are censored at date of last disease evaluation.

Time to Progression: Time to Progression (TTP) is defined as the time from registration to progression, or censored at date of last disease evaluation for those without progression reported.

11.2 Antitumor Effect – Intracranial Disease

For the purposes of this study, participants should be re-evaluated for intracranial response every 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained at 8 weeks following initial documentation of objective response. Response and progression will be evaluated in this study using the BM-RANO Response Criteria, as specified below[37, 38].

11.2.1 Definitions

Evaluable for objective response. Only those participants who have measurable CNS disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for target disease response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable non-measurable evaluable disease. Participants who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.2.2 Disease Parameters for Intracranial Disease Response

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥5 mm with MRI. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

For multifocal intracranial disease, no more than 5 target measurable lesions (each ≥5 mm in diameter) should be selected for measurement. Target lesions should be selected on the

basis of their size (lesions with longest diameter), be representative of other lesions and lend themselves to reproducible repeated measurements.

Non-measurable disease. Masses with margins not clearly defined, lesions with maximal diameter < 0.5 cm.

Target lesions. All measurable lesions up to a maximum of 5 lesions in total, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), and in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameter for all target lesions will be calculated and reported as the baseline sum diameters.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow up.

11.2.3 Methods for Evaluation of Disease

All measurements should be taken and recorded in metric notation using a ruler, calipers, or a digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 14 days before registration.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Conventional CT and MRI. This guideline has defined measurability of lesions on CT scan based on the assumption that CT thickness is 5mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size of a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

11.2.4 Response Criteria in Intracranial Disease

Evaluation of Intracranial Lesions

Complete Response (CR): Requires all of the following:

- complete disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks
- no new lesions
- stable or decreasing corticosteroids (the steroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan)
- stable or improved clinically

Participants with non-measurable disease cannot have a complete response. The best possible response is stable disease.

Partial Response (PR): All of the following criteria must be met:

- Greater than or equal to 30% decrease in the sum longest diameter of CNS target lesions compared to baseline sum of target lesions sustained for at least 4 weeks. In the absence of a confirming scan 4 weeks later, this scan will be considered only stable disease.
- no progression of non-measurable disease.
- no new lesions
- stable or reduced corticosteroid dose (the steroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan)
- stable or improved clinically

Progressive Disease (PD): At least one of the following must be true:

- At least 20% increase in the sum of longest diameter of target lesions using the same techniques as baseline, taking as reference the smallest sum on study (this includes baseline if that is the smallest sum)
- clear worsening of any non-measurable disease*
- appearance of any new enhancing lesion/site
- clear clinical worsening (unless clearly unrelated to this cancer, e.g. seizures, medication side effects, complications of therapy, cerebrovascular events, infection)
- failure to return for evaluation due to death or deteriorating condition
- Progression of non-measurable CNS lesions is defined as follows:

  a lesion initially at baseline </=5mm in diameter that increases to >/= 10mm in diameter, or
  a lesion initially at baseline 6-9 mm in diameter that increases by at least 5 mm in diameter.

Stable Disease (SD): All of the following criteria must be met:

- Does not qualify for CR, PR or progression
- All measurable and non-measurable sites must be assessed using the same techniques as baseline
- Stable clinically

A summary of the response criteria is in the table below:

	Complete Response	Partial Response	Stable Disease	Progressive Disease
T1-Gd+	None	≥ 30% decrease in sum of longest diameters	<30% decrease-<25% increase	≥20% increase in the sum of the longest diameters of

		of target lesions		target lesions*
New Lesion	None	None	None	Present*
Corticosteroids	Stable or decrease	Stable or decrease	Stable or decrease	Stable or increasing
Clinical Status	Stable or improved	Stable or improved	Stable or improved	Decrease*
Requirement for Response	All	All	All	Any*
NA=not applicable #: Progression occurs when any of the criteria with * is present Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration				

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. If a response recorded at one scheduled MRI does not persist at the next regular scheduled MRI, the response will still be recorded based on the prior scan, but will be designated as a non-sustained response. If the response is sustained, i.e. still present on the subsequent MRI at least four weeks later, it will be recorded as a sustained response, lasting until the time of tumor progression. Participants without measurable disease may only achieve SD or PD as their best "response."

Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started, or death due to any cause. Participants without events reported are censored at the last disease evaluation).

Duration of overall complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

12.0 END OF TREATMENT/INTERVENTION

12.1 Duration of Protocol Treatment

Patients who are in CR, PR or SD, as assessed by local radiology review, will continue on therapy until intracranial or extracranial progression of disease, excessive toxicity requiring the patient to come off of treatment, or the patient withdraws from treatment. Patients who progress in one site (i.e. intracranial or extracranial) but not the other will discontinue treatment and enter clinical follow-up. Clinical follow-up will be discontinued at the earliest occurrence of the following: withdrawal of consent from follow-up (clinical or all), disease progression in both intracranial and extracranial sites, or death. Patients who are still alive and have progressed in both intracranial and extracranial sites at once will continue to survival follow-up if consent has not been withdrawn. Please see the study calendar (Section 5.0) and the treatment section (Section 7.0) for treatment and follow-up time periods.

12.2 Criteria for Discontinuation of Protocol Treatment/Intervention

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

- Disease progression (if applicable)
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Clinical progression (if applicable)
- Patient non-compliance
- Pregnancy (if applicable)
- All women of childbearing 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 patient participating in the study.
- Termination of the study by sponsor
- The drug manufacturer can no longer provide the study agent (if applicable)
- Surgical intervention, radiotherapy, cryotherapy, ablation, etc.is performed on the primary neoplasm

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).

12.2.1 Communication of test results

Results of biomarker testing will be provided to the enrolling institution clinical research associate by email within 21 days of receipt.

12.3 Follow-up

12.3.1 Duration of Follow-up

Physical examination and staging scans are required ≤ 4 weeks from the date the patient is permanently discontinued from study treatment, then every 8 weeks for the first 2 years from registration, then every 3 months for years 3-4 from registration, then every 6 months thereafter until intracranial or extracranial disease progression (or until 5 years following registration if disease progression does not occur). Thereafter, survival information is required every 6 months until 5 years following registration.

12.3.2 Follow-up for Patients who Stop Study Treatment/Intervention Early

If the patient discontinues study agent, patients should be followed for disease progression and survival per the study calendar (Section 5.0).

12.4 Extraordinary Medical Circumstances

If, at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

- Document the reason(s) for discontinuation of therapy on data forms.
- Follow the patient for protocol endpoints as required by the Study Calendar.

12.5 Managing ineligible patients and registered patients who never receive protocol intervention

Definition of ineligible patient:

A study participant who is registered to the trial but does not meet all of the eligibility criteria is deemed to be ineligible.

Follow-up for ineligible patients who continue with protocol treatment:

Patients who are deemed ineligible after registering may continue protocol treatment, provided the treating physician, study chair, and executive officer agree there are no safety concerns if the patient continues protocol treatment. All scans, tests, and data submission are to continue as if the patient were eligible. Notification of the local IRB may be necessary per local IRB policies.

Follow-up for ineligible patients who discontinue protocol treatment:

For patients who are deemed ineligible after registering to the trial, who start treatment, but then discontinue study treatment, the same data submission requirements are to be followed as for those patients who are eligible and who discontinue study treatment.

Follow-up for patients who are registered, but who never start study treatment:

For all study participants who are registered to the trial but who never receive study intervention (regardless of eligibility), the follow-up requirements are specified below.

Baseline, off-treatment notice, and survival follow-up data submission are required. See the Data Submission Schedule accompanying the All Forms Packet.

13.0 STATISTICAL CONSIDERATIONS

13.1 Overview

This is a prospective, phase 2 study with single arm group sequential design evaluating the efficacy of CDK, PI3K, NTRK/ROS, and KRAS G12C inhibitors in patients with CDK-mutated, PI3K/AKT/mTOR-mutated, NTRK/ROS1-mutated, or KRAS G12C-mutated brain metastases. The primary endpoint per cohort is response rate (RR) as per RANO for brain metastases after starting treatment. This master protocol approach will utilize basket trial design approaches to evaluate targeted therapies within the different treatment arms.

13.2 Statistical Design and Analysis for the Primary Endpoint

13.2.1 Primary Endpoint:

The primary endpoint in each cohort is objective response rate in the brain as per RANO criteria for brain metastases (see Section 11.0). The RR is defined as the number of patients who have achieved CR or PR per RANO for brain metastases criteria during treatment with CDK, PI3K, NTRK/ROS, or KRAS G12C inhibitors divided by total number of evaluable patients within that cohort. All patients meeting eligibility criteria that have signed the consent form and started any dose of CDK, PI3K, NTRK/ROS, or KRAS G12C inhibitors will be evaluated for the analysis of the primary endpoint.

13.2.2 Statistical Design:

Primary efficacy evaluation will be carried out separately in four cohorts (defined by the treating targeted agent, and in the PI3K inhibitor arm, we will separately evaluate those with a primary histology of breast vs. other histology):

1) CDK inhibitor: any histology

2) PI3K inhibitor: any histology

3) NTRK /ROS1 inhibitor: lung

4) KRAS G12C inhibitor: any histology

Patients who harbor mutations in more than one eligible pathway will be assigned to the treatment arm for which they have not received a targeted therapy in that family of drugs (e.g. if the patient has received a PI3K inhibitor and they have a mutation in the PI3K and CDK pathway, they will receive a CDK inhibitor).

If the patient has not received any prior inhibitor used in the treatment arms, and they harbor more than one target, the patient will be assigned to the arm with the less frequent mutation as outlined below:

If a patient harbors…				… then assign the patient to:
CDK pathway	**PI3K/AKT/mTOR pathway**	**NTRK/ROS1 translocation***	**KRAS G12C**	
✓	✓	✓	✓	**NTRK/ROS1 inhibitor**
✓	✓	✓		
✓		✓	✓	
✓		✓		
	✓	✓	✓	
	✓	✓		
		✓	✓	
✓	✓		✓	**KRAS G12C inhibitor**
✓			✓	
	✓		✓	
✓	✓			**PI3K/AKT/mTOR inhibitor**
Lung Patients only,* ✓ **= *Yes (Mutation Present), " " =* *No (Mutation Absent)*				

CDK Inhibitor Design:

A single arm, two-stage phase II design with an interim analysis will be used to evaluate CNS RR in this arm regardless of the primary site. Based on historical literature, the objective response rate of targeted therapy in recurrent brain metastases is 3-10% (31-33). Thus, our null hypothesis is that the true CNS RR is at most 5% if this targeted CDK inhibitor agent is not sufficiently active. Alternatively, we hypothesize that if this targeted therapy is promising, it can improve the true CNS RR to at least 30%. To evaluate this, we will utilize a two-stage Simon minimax phase II trial design. With this design, a sample size of N=21 will provide 90% power to detect a true CNS RR of 30% or higher vs. the

null hypothesis that the true CNS RR is at most 5%, and assumes a one-sided Type I error rate of 0.025. The decision rule for this cohort requires that we observe at least 4 of the first 21 evaluable patients treated in this arm to have a CNS response in order to be considered promising in those with a CDK mutation. Otherwise, if 3 or fewer of the first 21 evaluable patients have a CNS response, then we will consider this regimen to be insufficiently active to warrant further investigation. The planned interim analysis will be conducted after the first 10 evaluable patients. If we observed at least one patient with a CNS response of these first 10 evaluable patients, then accrual will continue to the full 21 patients. Otherwise, if none of the first 10 evaluable patients have a CNS response, then we will consider this sufficient early evidence of futility and will suspend accrual to this cohort.

PI3K Inhibitor Design:

In this targeted therapy arm for PI3K, we will use a two-stage Simon minimax phase II trial design across all PI3K mutation patients regardless of their primary histology. Our assumptions follow the same literature and preliminary data used for the CDKi arm, where we hypothesize that if this PI3K inhibitor is promising in those with this target mutation, the true CNS RR will be at least 30%, vs. our null hypothesis that it is at most 5%. With N=21 patients, we will have 90% power to detect this level of difference in the CNS RR, constraining the one-sided Type I error rate to 0.025. An interim analysis is built into this design after the first 10 evaluable patients have been followed for CNS RR. If we see at least one CNS response in these first 10 patients, then we will continue accrual to the full N=21 evaluable patients. The final decision rule will require us to observe at least 4 of the first 21 evaluable patients with a CNS response in order to consider this promising and warranting further study. Otherwise, if at most 3 of the first 21 evaluable patients have a CNS response, then we will not consider this regimen to be sufficiently active in this mutation-based population. Given the assumptions and hypotheses to be tested for this cohort, this design was the best design to restrict sample size and also include an interim analysis at a meaningful and reasonable interim accrual milestone.

NTRK/ROS1 Inhibitor Cohort [note: this treatment arm was closed in January 2024]:

A single arm design with no interim analysis will be used to evaluate CNS RR within the NTRK/ROS1 inhibitor cohort of lung patients. Based on historical literature, the objective response rate of targeted therapy in recurrent brain metastases is 3-10%(31-33). Within each cohort, a maximum sample size of 10 patients will provide 83% power to compare a null response rate of 5% against an alternative of 40% with a one-sided type I error rate of 0.011.

KRAS G12C Inhibitor Design:

For this treatment arm, we will use a two-stage phase II trial design to evaluate and assess the corresponding efficacy of this targeted agent for those with KRAS G12C mutations, regardless of their primary histology. We will use a Fleming design with N=14 patients, where we will have 81% power and a Type I error constraint of 0.0274 to be able to detect a true CNS RR of 30% or higher vs. the null hypothesis that it is at most 5%. An interim analysis will be conducted after the first 7 patients are enrolled and evaluated for CNS RR. If we do not see any CNS responses in the first 7 evaluable patients, we will consider this insufficiently active in this population and will halt accrual to this treatment arm. Otherwise, accrual will continue for a total of N=14 evaluable patients. If the number of observed CNS responses is 3 or more out of these first 7 patients, this will meet the decision rules for promising early results, and we will be able to report these results early, although we will continue to enroll a total of 14 patients in order to attain better precision for

estimates and obtain more data on the toxicity profile. In the final analysis of N=14 patients, if we observe 3 or more patients with CNS response, we will consider this evidence of promising activity and that this will warrant further study. Otherwise, if at most 2 of the first 14 evaluable patients have a CNS response, this will be considered sufficient evidence of futility and this will be considered to have insufficient activity in this patient population. Given the fact that this redesign is early in accrual for this cohort, we are utilizing a Fleming design to be able to report out early results if there is sufficient promising efficacy as well as being able to stop for futility at this interim point. Given the expected percentage of patients who are eligible for this cohort and the expected accrual rate for this cohort, this design was used as the most efficient and optimal for this setting.

We anticipate accruing an additional two patients per cohort to account for unevaluable patients, such as those who withdraw prior to receiving any therapy (cancellation) or those who withdraw prior to any disease evaluation.

13.3 Sample Size, Accrual Time and Study Duration

13.3.1 Sample Size

In the original design of this trial, separate primary histology-based cohorts were to be evaluated within the different treatment arms; however, due to accrual and screening patterns, and the ability of a targeted therapy in the context of a basket trial to evaluate patients in a histology-agnostic manner, we have modified this design. The original maximum target accrual was 186 patients (7 cohorts with 21+2 patients, one cohort with 10+2 patients, and a final cohort with 11+2 patients). In this updated design (Update #04), our maximum target accrual is 21+2=23 patients for the CDKi arm, 21+2=23 patients in the PI3Ki arm, and 14+2=16 patients in the KRAS G12Ci arm for a total of 62 evaluable patients (63 if we include the one patient enrolled on the now closed treatment arm). As of Update #04, our accrual to date vs. updated target accrual for the different arms are as follows:

Treatment Arm	Accrual as of Update #04	Updated maximum target accrual	Number of patients needed to be accrued to meet maximum target accrual
CDK inhibitor	19	21 +2 = **23**	2 +2 = **4**
PI3K inhibitor	20	21 +2 = **23**	1 +2 = **3**
NTRK/ROS1 inhibitor	1	1*	0
KRAS G12C inhibitor	2	14 +2 = **16**	12 +2 = **14**

*arm closed to accrual January 2024

As of Update #04, we have screened N=303 patients with N=42 who have gone on to receive treatment on a treatment arm. Based on these data, we expect that 12-15% of patients screened will have actionable targets and will go on to either the PI3K or the CDK inhibitor arms. For the KRAS G12C inhibitor arm, we expect 7% of screened patients to be identified as having the target mutation for this arm. Thus, we expect to screen 225 patients to achieve 16 patients with the KRAS G12C inhibitor (200 to obtain the 14 additional patients required), and that of these 200 additional patients requiring screening we should be able to identify the 7 patients (4 with CDK mutations, 3 with PI3K mutations) for the other two arms. Accounting for screen failures due to other ineligibility considerations or patient refusal of ~10%, we will need to screen about 225 additional patients.

13.3.2 Accrual Rate and Accrual Duration

Cohorts with a mutation rate of ≤15% will accrue 1 patient per month. This means that it will take approximately 12-18 months to enroll all patients onto each of the treatment arms of the trial. The individual mutation specific accrual rates are based on data from an ongoing pilot trial at Massachusetts General Hospital with an average accrual rate of six brain metastases patients per month.

13.3.3 Primary Endpoint Completion Date for [redacted] Reporting:

For purpose of [redacted] reporting, the Primary Endpoint Completion Date (PECD) for this study is the latest date for all patients based on the date a patient responded or went off-treatment (whichever comes first).

13.4 Analysis Plans

13.4.1 Primary Endpoint

The primary endpoint of CNS response rate (CNS RR) as defined in Section 13.2.1 will be evaluated for each of the treatment arms. In addition to evaluating the incidence of CNS responses by treatment arm in relation to the corresponding decision rules, we will also summarize these rates along with corresponding 95% binomial confidence intervals for each arm. Although we will not perform subset analyses based on primary histology, we will summarize and characterize these patients in each of the arms by this histology.

13.4.2 Secondary Endpoints

Systemic Response by RECIST Criteria for Extracranial Disease: Systemic response by RECIST 1.1 criteria for extracranial disease will be estimated using Systemic Response Rate (SRR) - where SRR is defined as the number of evaluable patients achieving a response (PR or CR per RECIST 1.1) during treatment with study therapy divided by the total number of evaluable patients. Point estimates will be generated for systemic response rates within each arm with corresponding 95% binomial confidence intervals [39].

Clinical Benefit Rate by RANO for CNS: Clinical Benefit Rate by RANO for brain metastases will be estimated as the number of evaluable patients achieving SD, PR or CR as their best objective response (per RANO for brain metastases) during treatment with protocol therapy divided by the total number of evaluable patients. Point estimates will be generated for clinical benefit rates within each arm with corresponding 95% binomial confidence intervals [39].

Clinical Benefit Rate by RECIST for Extracranial Disease: Clinical Benefit Rate by RECIST for extracranial disease will be estimated as the number of evaluable patients achieving SD, PR or CR as their best objective response (per RECIST for extracranial disease) during treatment with protocol therapy divided by the total number of evaluable patients. Point estimates will be generated for clinical benefit rates within each arm with corresponding 95% binomial confidence intervals [39].

Duration of Response by RANO for Brain Metastases: Duration of response by RANO for brain metastases is defined from the time measurement criteria are met for CR or PR for brain metastases until the first date that progressive CNS disease (RANO) or death is documented. Only patients who have achieved a CR or PR for brain metastases (per RANO) will be included in this analysis. Patients who fail to return for evaluation or patients who are still alive and have not progressed at the time of analysis will be censored for progression at the time of the last tumor assessment. Duration of response will be

estimated using the Kaplan-Meier method [40] within each treatment arm. Median overall survivals and survival rates will be estimated with their 95% confidence intervals. No formal comparison will be made based on primary histology.

Duration of Response by RECIST for Extracranial Disease: Duration of response by RECIST 1.1 for extracranial disease is defined from the time measurement criteria are met for CR or PR for extracranial disease until the first date that progressive disease for extracranial disease (per RECIST 1.1) or death is documented. Only patients who have achieved a CR or PR for extracranial disease (per RECIST 1.1) will be included in this analysis. Patients who fail to return for evaluation or patients who are still alive and have not progressed at the time of analysis will be censored for progression at the time of the last tumor assessment. Duration of response will be estimated using the Kaplan-Meier method [40] within each treatment arm. Median overall survivals and survival rates will be estimated with their 95% confidence intervals. No formal comparison will be made based on primary histology.

Progression Free Survival - Intracranial: progression free survival - intracranial (PFS - Intracranial) will be defined as the time from the first day of study treatment to the earliest date documentation of disease progression per RANO for brain metastases. Patients who die without documentation of disease progression will be considered to have had tumor progression at the time of their death unless there is sufficient documented evidence to conclude no progression occurred prior to death. If the patient is declared to be a major treatment violation, the patient will be censored on the date the treatment violation was declared to have occurred. Patients who are still alive and have not progressed will be censored for progression at the time of the last tumor assessment. PFS- Intracranial will be estimated using the Kaplan-Meier method [40] within each arm. Median progression free survival and survival rates will be estimated with their 95% confidence intervals. No formal comparison will be made based on primary histology.

Progression Free Survival – Extracranial: Progression free survival - Extracranial (PFS - Extracranial) will be defined as the time from the first day of study treatment to the earliest date of documentation of systemic disease progression per RECIST 1.1. Patients who die without documentation of systemic disease progression will be considered to have had systemic tumor progression at the time of their death unless there is sufficient documented evidence to conclude no progression occurred prior to death. If the patient is declared to be a major treatment violation, the patient will be censored on the date the treatment violation was declared to have occurred. Patients who are still alive and have not progressed will be censored for systemic progression at the time of the last tumor assessment. PFS-Extracranial will be estimated using the Kaplan-Meier method [40] within each arm. Median progression free survival and survival rates will be estimated with their 95% confidence intervals. No formal comparison will be made based on primary histology.

Site of First Progression: The site of first progression will be estimated descriptively within each arm within 12 and 24 months after starting protocol treatment. The first progression is defined as the first documented CNS progression per RANO or extracranial progression per RECIST, whichever occurs first. The percentage of CNS progression at first progression within 12 and 24 months after starting protocol treatment will be estimated as the number of patients who experience the first progression which is CNS progression divided by number of patients who are still at risk up to 12 and 24 months, respectively. The percentage of extracranial progression at first progression within 12 and 24 months after starting protocol treatment will be estimated as number of patients who experience the first progression which is extracranial progression divided by number of patients who are still at risk up to 12 and 24 months, respectively.

Overall Survival: Overall survival (OS) is defined as the time from the first day of study treatment to death due to all causes, and will be estimated using the Kaplan-Meier method within each arm. Median overall survivals and survival rates will be estimated with their 95% confidence intervals. No formal comparison will be made based on primary histology.

Toxicity Profile: As per NCI CTCAE, the term toxicity is defined as adverse events that are classified as possibly, probably, or definitely related to study treatment. Toxicities will be evaluated via the ordinal CTCAE standard toxicity grading. Overall toxicity incidence as well as toxicity profiles by patient and treatment arm will be explored and summarized. Frequency distributions, graphical techniques and other descriptive measures will form the basis of the analysis. No formal comparison will be made based on primary histology.

13.5 Monitoring the Study

13.5.1 Adverse Event Monitoring Rule:

The monitoring rule specified below is based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either 1) the study re-opening to accrual or 2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

The adverse event profile will be monitored by the study team (study chair, study statistician, operational office) on a monthly basis, or more frequently when it deems necessary. The overall adverse event rate will be estimated within each treatment arm (i.e., patients regardless of primary histology who receive the same inhibitor), as number of patients experienced at least one grade 4 or higher non-hematologic adverse event considered at least possibly related to study treatment (i.e., an adverse event with attribute specified as “possible”, “probable”, or “definite”) divided by patients who started any protocol treatment. If at any time the 80% two-sided confidence interval for the overall adverse event rate excludes 25% to the right (i.e., only includes values greater than 25%), the study team will conduct thorough review of all adverse event and treatment data to make the decision of enacting a protocol amendment or discontinuing the treatment arm.

13.5.2 Screening & Accrual Monitoring Rule:

The study design assumes that 1-3 patients will accrue per month to each cohort, leading to an approximate 1 to 2 year total accrual period (including leading time for sites to open the studies).

For the PI3K and CDK inhibitor cohorts:

- If less than 5 of the first 50 screened patients (of the primary disease indicated by the cohort) are found to have actionable PI3K or CDK alterations, the team will consult with CTEP about the next steps.

For the NTRK/ROS inhibitor cohorts:

- If less than 1 of the first 50 screened patients (of the primary disease indicated by the cohort) are found to have actionable NTRK/ROS alterations, the team will consult with CTEP about the next steps.

For the entire study, if less than 10 out of the first 150 screen patients are found to have actionable alterations as indicated by the protocol, then the study team will consult with CTEP about next steps.

If by 24 months post activation, less than 50% of necessary patients (who are eligible and harbor the necessary actionable mutations as defined by the protocol) have accrued then the study team will consult with CTEP about the next steps.

In the event that the boundary for any of the monitoring rules above is crossed, then the study team will consult with CTEP and evaluate whether the scientific question will be of interest at the completion of the accrual period. If it is deemed that the scientific question is likely not to have relevance at the end of the projected accrual period, the study may close. Otherwise, the study team will continue to boost the accrual rates. The accrual rate will be checked every subsequent 6 months and the likelihood that the study questions will still be of interest at the end of the trial will be evaluated. Based on this, a decision will be made whether or not to continue accrual to the study.

Note that with Update #04, we have made changes to the designs for the treatment arms in response to the fact that accrual was slower than expected to the different arms. As of Update #04, we are evaluating efficacy of each of the treatment arms regardless of primary histology. This has reduced the total numbers of patients required to assess for promising activity in each of these treatment arms.

13.6 Study Reporting

- This study will be monitored by the study team on a monthly basis upon enrollment of the first patient. Reports containing a summary of adverse events by treatment arm will be reviewed. The study team will also monitor the accrual rate.
- This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. An abbreviated report containing cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reporting time points are: January 31, April 30, July 31, and October 31.

13.7 Descriptive Factors:

None.

13.8 Minorities Distribution (sex, race, ethnicity)

This study will be available to all eligible patients, regardless of race, sex, or ethnic origin. There is no information currently available regarding differential effects of this regimen in subsets defined by race, sex, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial and sex groupings, the sample size is not increased in order to provide additional power for subset analyses.

The geographical region served by the Alliance has a population which includes approximately 7% minorities. Based on national statistics involving similar patients with brain metastases, we expect about 14% of patients will be classified as minorities by race and about 62 % of patients will be women. Expected sizes of racial by sex subsets for patients to this study are shown in the following table. Note that these values are for the maximum number of patients (501) that we expect to screen.

DOMESTIC PLANNED ENROLLMENT REPORT (SCREENING)					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	0
Asian	6	4	1	0	11
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	18	14	1	1	34
White	270	162	13	11	456
More Than One Race	0	0	0	0	0
Total	294	180	15	12	501

DOMESTIC PLANNED ENROLLMENT REPORT (TREATMENT)					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	0
Asian	0	1	0	0	1
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	3	2	0	0	5
White	26	28	1	2	57
More Than One Race	0	0	0	0	0
Total	29	31	1	2	63

14.0 CORRELATIVE AND COMPANION STUDIES

14.1 Biobanking for Future Correlative Science Studies

NOTE: Testing of banked samples will not occur until an amendment to this treatment protocol (or separate correlative science protocol) is reviewed and approved in accordance with National Clinical Trials Network (NCTN) policies. The specimens requested for optional submission for biobanking in Section 6.2 will be collected for banking only at this time.

Whole exome sequencing will be carried out in all tissue samples collected from this study to identify molecular biomarkers of response to therapy. Furthermore, cfDNA from blood will also be collected and will undergo genetic analysis; the objective will be to identify potential circulating biomarkers of response to therapy.

14.1.1 Background

Comprehensive genomic characterization of samples collected as part of our proposed clinical trial will allow us to identify biomarkers of response and provide insight into mechanisms of resistance to immunotherapy. Archived primary and brain metastatic samples and blood will be collected as part of this trial. All samples will undergo whole exome and transcriptome sequencing. Analytic tools developed for our prior studies[41-44] will be used to elucidate the genomic evolutionary profiles in matched primaries and metastases. We will analyze the association between response and other demographic and clinical features and potential genetic biomarkers in the primary tumors and the matched brain metastases.

Furthermore, liquid biopsy of metastatic cancers from blood draws has become a powerful technique enabling insight into the clonal evolution of advanced cancers that would otherwise not be accessible. We propose to exploit this in order to perform detection of clinically actionable variants in the blood. We propose to see if cfDNA from blood can serve as a less invasive, genetic surrogate of mutations detected in brain metastases, and if blood cfDNA can serve as a biomarker for response or resistance to radiation therapy.

14.1.2 Objectives

The goal is to identify genetic biomarkers from tissue and blood that will predict response to targeted therapy.

14.1.3 Methods

An unbiased comprehensive genomic approach to determine the evolutionary profiles of patients may provide insight into biomarkers of response and mechanisms of resistance to targeted therapy. Whole-exome sequencing will be performed at the using pipelines described in recent studies[41-44]. In short, DNA will be subjected to solution-phase hybrid capture followed by Illumina sequencing to >150x mean coverage. Mutations and copy-number changes will be determined using a suite of existing tools, which include the published MuTect, Indelocator, GISTIC and MutSig algorithms[42, 43, 45-49]. To understand inter- and intratumoral heterogeneity, we will perform an integrative analysis of somatic mutations and copy-number alterations. This analysis, termed Absolute[41, 50], developed by the Correlative Chair, Scott Carter, allows us to estimate the clonal architecture of tumor samples. These techniques have been refined to understand the clonal evolution across a large cohort of 101 brain metastases matched with their primary tumors[41].

RNA Sequencing from FFPE includes plating, poly-A selection and cDNA synthesis, library preparation, sequencing, sample identification QC, and data storage. Sequencing is performed using Illumina HiSeq 2000 or 2500 instruments with 76 Paired End read lengths. We will follow the analytic pipelines as previously described[51-54]. At the end of the pipeline, we will identify expression levels of genes and isoforms and detect differential expression between brain metastases and primary tumors and between responders and nonresponders.

Differences in these biomarkers between responders and non-responders will be compared with parametric or nonparametric techniques as permitted by the data. For correlative analyses, Cox proportional hazards model will be used to explore the relationship between these biomarkers measured at baseline and PFS and OS. Logistic regression will be used to explore the relationship between these biomarkers measured at baseline and the binary outcome of alive and progression-free at 6 months (APF6)

The data collected from the samples, as described above, will be sent using encrypted secure spreadsheets to the Alliance SDC A071701 Statistician to prepare analysis datasets in conjunction with the clinical/outcome data. The A071701 Statistician will then coordinate the analyses with the A071701 Correlative Science Co-Chair, Scott Carter. Analyses will be conducted using the analysis dataset used for the analysis of the clinical endpoints to ensure consistent data is reported for the primary and secondary endpoints (e.g. data associated with censoring, proper inclusion of crossover data, and data to be excluded in cases of consent withdrawals for follow-up and correlative studies).

14.2 Evaluation of Imaging Markers of Response in Brain Metastases

14.2.1. Background

Central collection of the MRI scans acquired during the study will permit exploratory studies correlating a variety of imaging markers with response. It is not feasible to perform repeated biopsies in brain metastases patients, so it is critical to identify noninvasive imaging markers that may reflect tumor response. Moreover, novel machine learning approaches hold potential to identify new ways to interpret MRI scans.

14.2.2 Objective

To perform exploratory analyses of imaging markers of response.

14.2.3 Methods

We will explore imaging parameters such as number of tumors, size of tumor, location of tumors, other radiomics features, and perfusion parameters in patients where this information is available. Since MRIs are used to assess radiographic response, we anticipate that most patients will be included in this analysis. Our initial approach will be to look at baseline features as well as the longitudinal change over time and correlate this with response. Since this is an exploratory analysis, the data will be presented in a descriptive manner. Where numbers permit, differences in biomarkers between responders and non-responders will be compared with parametric or nonparametric techniques as permitted by the data. For correlative analyses, Cox proportional hazards model will be used to explore the relationship between these biomarkers measured at baseline and PFS and OS. Logistic regression will be used to explore the relationship between these biomarkers measured at baseline and the binary outcome of alive and progression-free at 6 months (APF6).

15.0 General Regulatory Considerations and Credentialing

15.1 Institutional Credentialing

Imaging credentialing from the Imaging Core Lab at IROC Ohio will not be required for this trial. The following information is a guideline for sites.

15.1.1 IROC Ohio Institutional Requirements

Prior to the enrollment of patients, institutions should be credentialed to participate in the trial by the Imaging Core Laboratory at IROC Ohio per the Full or Conditional Approval language defined in Section 15.1.2, parts A and B respectively, below. Institutions that have previously been credentialed by the Imaging Core Laboratory at IROC Ohio to participate in imaging studies on A071102 or A071801 within the past 3 years may apply that credentialing to A071701. For institutions who have not been credentialed in the past 3 years, the ICL will provide a brief A071701 protocol refresher prior to patient enrollments. Institutions should contact the Alliance ICL directly to complete credentialing or a refresher for A071701.

Contact information for IROC Ohio can be found under protocol contacts near the title page.

15.1.2 IROC Ohio Imaging Core Credentialing

A. Full approval

i) Review and have site PI sign the Imaging Site Approval sheet obtained from IROC Ohio upon initial contact.

ii) Submit either of the following imaging data sets to IROC Ohio for a quality check:

a) MR imaging of a local patient with CNS brain metastases performed according to Appendix I, OR

b) Baseline MR imaging data of the first registered patient

In either scenario, the submitted images will be reviewed by IROC Ohio, feedback will be provided to the sites, and once a suitable imaging set is provided to IROC Ohio, full credentialing will be granted with notification of such sent to CTSU by IROC.

B. Conditional approval

Review and have site PI sign the Imaging Site Approval sheet obtained from IROC Ohio upon initial contact by the institution.

This process allows a participating site to enroll their first patient on A071701 before the site gets full approval. Full approval will be granted upon receipt of the first registered patient's baseline MRI data to IROC Ohio upon acquisition for QC.

For subsequent scans, the IROC confirms data receipt within 24 hours, performs quality check of the images with identifying any non-compliant exams that have protocol deviations, and notifies sites of the quality check report within 72 hours upon data receipt.

15.2 IRB Terminations

Until institutions receive a formal notice from the Alliance regarding termination to patient follow-up, institutions must not close this trial with the IRB of record for the study. Please contact the Alliance Regulatory team at [redacted] with any questions.

16.0 MONITORING PLAN

Use standard Alliance monitoring procedures.

17.0 REFERENCES

1. Lang, F. and R. Sawaya, *Metastatic Brain Tumors*, in *Neuro-Oncology: The Essentials*, M. Bernstein and M.S. Berger, Editors. 2008, Thieme Medical Publishers: New York. p. 367-378.
2. Brastianos, P.K., W.T. Curry, and K.S. Oh, *Clinical discussion and review of the management of brain metastases.* J Natl Compr Canc Netw, 2013. **11**(9): p. 1153-64.
3. Sperduto, P.W., et al., *A new prognostic index and comparison to three other indices for patients with brain metastases: an analysis of 1,960 patients in the RTOG database.* International journal of radiation oncology, biology, physics, 2008. **70**(2): p. 510-4.
4. Brastianos, H.C., D.P. Cahill, and P.K. Brastianos, *Systemic therapy of brain metastases.* Curr Neurol Neurosci Rep, 2015. **15**(2): p. 518.

5. Eichler, A.F., et al., *The biology of brain metastases-translation to new therapies.* Nat Rev Clin Oncol, 2011. **8**(6): p. 344-56.
6. Garraway, L.A., J. Verweij, and K.V. Ballman, *Precision oncology: an overview.* J Clin Oncol, 2013. **31**(15): p. 1803-5.
7. Baselga, J., *Bringing precision medicine to the clinic: from genomic profiling to the power of clinical observation.* Ann Oncol, 2013. **24**(8): p. 1956-7.
8. Maillet, D., et al., *Ineffectiveness of crizotinib on brain metastases in two cases of lung adenocarcinoma with EML4-ALK rearrangement.* J Thorac Oncol, 2013. **8**(4): p. e30-1.
9. Musolino, A., et al., *Multifactorial central nervous system recurrence susceptibility in patients with HER2-positive breast cancer: epidemiological and clinical data from a population-based cancer registry study.* Cancer, 2011. **117**(9): p. 1837-46.
10. Weickhardt, A.J., et al., *Local ablative therapy of oligoprogressive disease prolongs disease control by tyrosine kinase inhibitors in oncogene-addicted non-small-cell lung cancer.* J Thorac Oncol, 2012. **7**(12): p. 1807-14.
11. Brastianos, P.K., et al., *Genomic Characterization of Brain Metastases Reveals Branched Evolution and Potential Therapeutic Targets.* Cancer Discov, 2015.
12. Van Allen, E.M., et al., *Whole-exome sequencing and clinical interpretation of FFPE tumor samples to guide precision cancer medicine.* Nature Medicine, In Press.
13. Van Allen, E.M., et al., *Whole-exome sequencing and clinical interpretation of formalin-fixed, paraffin-embedded tumor samples to guide precision cancer medicine.* Nat Med, 2014. **20**(6): p. 682-8.
14. Brastianos, P.K., et al., *Abstract: Genomic characterization of 101 brain metastases and paired primary tumors reveals patterns of clonal evolution and selection of driver mutations*, in *AACR*. 2014: San Diego.
15. Drilon, A., et al., *A Next-Generation TRK Kinase Inhibitor Overcomes Acquired Resistance to Prior TRK Kinase Inhibition in Patients with TRK Fusion-Positive Solid Tumors.* Cancer Discov, 2017. **7**(9): p. 963-972.
16. Patil, T., et al., *The incidence of brain metastases in stage IV ROS1-rearranged non-small cell lung cancer and rate of central nervous system progression on crizotinib.* J Thorac Oncol, 2018.
17. Shaw, A.T., et al., *Crizotinib versus chemotherapy in advanced ALK-positive lung cancer.* N Engl J Med, 2013. **368**(25): p. 2385-94.
18. Kim, J., et al., *Recurrent fusion transcripts detected by whole-transcriptome sequencing of 120 primary breast cancer samples.* Genes Chromosomes Cancer, 2015. **54**(11): p. 681-91.
19. Lezcano, C., et al., *Primary and Metastatic Melanoma With NTRK Fusions.* Am J Surg Pathol, 2018. **42**(8): p. 1052-1058.
20. Stransky, N., et al., *The landscape of kinase fusions in cancer.* Nat Commun, 2014. **5**: p. 4846.
21. Vaishnavi, A., et al., *Oncogenic and drug-sensitive NTRK1 rearrangements in lung cancer.* Nat Med, 2013. **19**(11): p. 1469-1472.
22. Pietrantonio, F., et al., *ALK, ROS1, and NTRK Rearrangements in Metastatic Colorectal Cancer.* J Natl Cancer Inst, 2017. **109**(12).
23. Koshy, M., et al., *Improved survival time trends for glioblastoma using the SEER 17 population-based registries.* J Neurooncol, 2012. **107**(1): p. 207-12.
24. Lagerwaard, F.J., et al., *Identification of prognostic factors in patients with brain metastases: a review of 1292 patients.* Int J Radiat Oncol Biol Phys, 1999. **43**(4): p. 795-803.
25. Brastianos, P.K. and D.P. Cahill, *Management of brain metastases in the era of targeted and immunomodulatory therapies.* Oncology (Williston Park), 2015. **29**(4): p. 261-3.
26. Cagney, D.N., et al., *Incidence and prognosis of patients with brain metastases at diagnosis of systemic malignancy: A population-based study.* Neuro Oncol, 2017.
27. Dagogo-Jack, I., S.L. Carter, and P.K. Brastianos, *Brain Metastasis: Clinical Implications of Branched Evolution.* Trends Cancer, 2016. **2**(7): p. 332-337.

28. Dagogo-Jack, I., et al., *Treatment of brain metastases in the modern genomic era.* Pharmacol Ther, 2017. **170**: p. 64-72.
29. Ray, S., et al., *Comparative analysis of survival, treatment, cost and resource use among patients newly diagnosed with brain metastasis by initial primary cancer.* J Neurooncol, 2013. **114**(1): p. 117-25.
30. Mehta, M.P., et al., *The role of chemotherapy in the management of newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline.* J Neurooncol, 2010. **96**(1): p. 71-83.
31. Bhangoo, S.S., M.E. Linskey, and S.N. Kalkanis, *Evidence-based guidelines for the management of brain metastases.* Neurosurg Clin N Am, 2011. **22**(1): p. 97-104, viii.
32. Gaspar, L.E., et al., *The role of whole brain radiation therapy in the management of newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline.* J Neurooncol, 2010. **96**(1): p. 17-32.
33. Johung, K.L., et al., *Extended Survival and Prognostic Factors for Patients With ALK-Rearranged Non-Small-Cell Lung Cancer and Brain Metastasis.* J Clin Oncol, 2016. **34**(2): p. 123-9.
34. Chubachi, S., et al., *A Case of Non-Small Cell Lung Cancer with Possible "Disease Flare" on Nivolumab Treatment.* Case Rep Oncol Med, 2016. **2016**: p. 1075641.
35. Sleeman, J. and P.S. Steeg, *Cancer metastasis as a therapeutic target.* Eur J Cancer, 2010. **46**(7): p. 1177-80.
36. Brastianos, P.K., et al., *Genomic Characterization of Brain Metastases Reveals Branched Evolution and Potential Therapeutic Targets.* Cancer Discov, 2015. **5**(11): p. 1164-77.
37. Okada, H., et al., *Immunotherapy response assessment in neuro-oncology: a report of the RANO working group.* Lancet Oncol, 2015. **16**(15): p. e534-42.
38. Lin, N.U., et al., *Response assessment criteria for brain metastases: proposal from the RANO group.* Lancet Oncol, 2015. **16**(6): p. e270-8.
39. Clopper, C.J. and E.S. Pearson, *The use of confidence or fiducial limits illustrated in the case of the binomial.* Biometrika, 1934. **26**: p. 404-413.
40. Kaplan, E.L. and P. Meier, *Nonparametric-Estimation from Incomplete Observations.* Journal of the American Statistical Association, 1958. **53**(282): p. 457-481.
41. Brastianos, P.K., et al., *Abstract: Genomic characterization of 101 brain metastases and paired primary tumors reveals patterns of clonal evolution and selection of driver mutations.* AACR, 2014.
42. Brastianos, P.K., et al., *Genomic sequencing of meningiomas identifies oncogenic SMO and AKT1 mutations.* Nat Genet, 2013. **45**(3): p. 285-9.
43. Brastianos, P.K., et al., *Exome sequencing identifies BRAF mutations in papillary craniopharyngiomas.* Nat Genet, 2014.
44. Shankar, G.M., et al., *Sporadic hemangioblastomas are characterized by cryptic VHL inactivation.* Acta Neuropathol Commun, 2014. **2**(1): p. 2.
45. Lawrence, M.S., et al., *Mutational heterogeneity in cancer and the search for new cancer-associated genes.* Nature, 2013. **499**(7457): p. 214-8.
46. Ye, K., et al., *Pindel: a pattern growth approach to detect break points of large deletions and medium sized insertions from paired-end short reads.* Bioinformatics, 2009. **25**(21): p. 2865-71.
47. McKenna, A., et al., *The Genome Analysis Toolkit: a MapReduce framework for analyzing next-generation DNA sequencing data.* Genome research, 2010. **20**(9): p. 1297-303.
48. Cibulskis, K., et al., *Sensitive detection of somatic point mutations in impure and heterogeneous cancer samples.* Nat Biotechnol, 2013. **31**(3): p. 213-9.
49. Berger, M.F., et al., *The genomic complexity of primary human prostate cancer.* Nature, 2011. **470**(7333): p. 214-20.
50. Carter, S.L., et al., *Absolute quantification of somatic DNA alterations in human cancer.* Nature biotechnology, 2012.

51. Dobin, A., et al., *STAR: ultrafast universal RNA-seq aligner.* Bioinformatics, 2013. **29**(1): p. 15-21.
52. Li, B. and C.N. Dewey, *RSEM: accurate transcript quantification from RNA-Seq data with or without a reference genome.* BMC Bioinformatics, 2011. **12**: p. 323.
53. DeLuca, D.S., et al., *RNA-SeQC: RNA-seq metrics for quality control and process optimization.* Bioinformatics, 2012. **28**(11): p. 1530-2.
54. Brooks, A.N., et al., *Conservation of an RNA regulatory map between Drosophila and mammals.* Genome Res, 2011. **21**(2): p. 193-202.
55. Kaufmann, T.J., et al., *Consensus recommendations for a standardized brain tumor imaging protocol for clinical trials in brain metastases (BTIP-BM).* Neuro Oncol, 2020.
56. Kaufmann, T.J., et al., *Consensus recommendations for a standardized brain tumor imaging protocol for clinical trials in brain metastases.* Neuro Oncol, 2020. **22**(6): p. 757-772.
57. Ellingson, B.M., et al., *Consensus recommendations for a standardized Brain Tumor Imaging Protocol in clinical trials.* Neuro Oncol, 2015. **17**(9): p. 1188-98.
58. Yamada, K., et al., *Effect of intravenous gadolinium-DTPA on diffusion-weighted images: evaluation of normal brain and infarcts.* Stroke, 2002. **33**(7): p. 1799-802.

APPENDIX I REQUIRED CONSENSUS MRI ACQUISITION PARAMETERS

The MRI acquisition protocols defined in the following table have been defined by an international consensus panel. These parameters have been reviewed and adopted by the National Cancer Institute (NCI), and these acquisition parameters are required for all national drug-registration trials. The specific acquisition parameters, the sequence of imaging acquisition, and the plane of imaging are all required as explicitly stated in these protocols. Additionally, individual patients should be consistently imaged at the same field strength as their baseline registration scan.

Metastatic Brain Tumor Imaging Protocol (version February 12, 2020)[55-57]

Table 1: "Ideal" Recommended 3T Metastatic Brain Tumor Imaging Protocol

	3D T1w TSE Pre[b]	Ax 2D FLAIR[j,q]	Ax 2D DWI[p,v]	Contrast Injection [a]	DSC[a] Perfusion (Optional)	Ax 2D T2w[h,i,q]	3D T1w TSE Post[b]
Sequence	TSE[s]	TSE[c,s]	SS-EPI[g]		GE-EPI	TSE[c,s]	TSE[s]
Plane	Sagittal or Axial	Axial	Axial		Axial	Axial	Sagittal or Axial
Mode	3D	2D	2D		2D	2D	3D
TR [ms]	550-750	>6000	>5000		1000-1500	>2500	550-750
TE [ms]	Min	100-140	Min		25-35ms	80-120	Min
TI [ms]		2000-2500[k]					
Flip Angle	Default[t]	90º/≥160º	90º/180º		30º	90º/≥160º	Default[t]
Frequency	256	≥256	128		≥96	≥256	256
Phase	256	≥256	128		≥96	≥256	256
NEX	≥1	≥1	≥1		1	≥1	≥1
FOV	256mm	240mm	240mm		240mm	240mm	256mm
Slice Thickness	1mm	3mm	3mm		3-5mm as needed to cover tumor	3mm	1mm
Gap/Spacing	0	0	0		0-1mm as needed to cover tumor	0	0
Other Options			b = 0, 500, 1000 s/mm^2 ≥3 directions		30-60 pre-bolus time points; >120 total time points		
Parallel Imaging	Up to 3x[u]	Up to 2x	Up to 2x		Up to 2x	Up to 2x	Up to 3x[u]

[a] 0.1 mmol/kg dose injection with a Gadolinium chelated contrast agent. Use of a power injector is desirable at an injection rate of 3-5cc/sec. (Note: If DSC perfusion is collected, contrast injection is performed after starting DSC acquisition. DSC perfusion can be performed with the "Ideal" protocol at 3T as well as with the Minimum Standard protocols at 3T and 1.5T.)

[b] Post-contrast 3D T1-weighted images should be collected with equivalent parameters to pre-contrast 3D T1-weighted images

[c] TSE = turbo spin echo (Siemens & Philips) is equivalent to FSE (fast spin echo; GE, Hitachi, Toshiba)

[d] FL2D = two-dimensional fast low angle shot (FLASH; Siemens) is equivalent to the spoil gradient recalled echo (SPGR; GE) or T1- fast field echo (FFE; Philips), fast field echo (FastFE; Toshiba), or the radiofrequency spoiled steady state acquisition rewound gradient echo (RSSG; Hitachi). A fast gradient echo sequence without inversion preparation is desired.

[e] IR-GRE = inversion-recovery gradient-recalled echo sequence is equivalent to MPRAGE = magnetization prepared rapid gradient-echo (Siemens & Hitachi) and the inversion recovery spoiled gradient-echo (IR-SPGR or Fast SPGR with inversion activated or BRAVO; GE), 3D turbo field echo (TFE; Philips), or 3D fast field echo (3D Fast FE; Toshiba).
[f] A 3D acquisition without inversion preparation will result in different contrast compared with MPRAGE or another IR-prepped 3D T1-weighted sequences and therefore should be avoided.
[g] In the event of significant patient motion, a radial acquisition scheme may be used (e.g. BLADE [Siemens], PROPELLER [GE], MultiVane [Philips], RADAR [Hitachi], or JET [Toshiba]); however, this acquisition scheme is can cause significant differences in ADC quantification and therefore should be used only if EPI is not an option. Further, this type of acquisition takes considerable more time.
[h] Dual echo PD/T2 TSE is optional for possible quantification of tissue T2. For this sequence, PD is recommended to have a TE < 25ms.
[i] Advanced sequences can be substituted into this time slot, so long as 3D post-contrast T1-weighted images are collected between 4 and 8 min after contrast injection and this timing is constant across all MR exams performed in each patient.
[j] 3D FLAIR is an optional alternative to 2D FLAIR, with sequence parameters as follows per EORTC guidelines: 3D TSE/FSE acquisition; TE=90-140ms; TR=6000-10000ms; TI=2000-2500ms (chosen based on vendor recommendations for optimized protocol and field strength); GRAPPA≤2; Fat Saturation; Slice thickness ≤ 1.5mm; Orientation Sagittal or Axial; FOV ≤ 250 mm x 250 mm; Matrix ≥ 244x244.
[k] Choice of TI should be chosen based on the magnetic field strength of the system (e.g. TI ≈ 2000ms for 1.5T and TI ≈ 2500ms for 3T).
[l] In order to ensure comparable SNR older 1.5T MR systems can use contiguous (no interslice gap) images with 5mm slice thickness or increase NEX for slice thickness ≤4mm.
[m] For Siemens and Hitachi scanners. GE, Philips, and Toshiba scanners should use a TR = 5-15ms for similar contrast.
[n] For Siemens and Hitachi scanners. GE, Philips, and Toshiba scanners should use a TI = 400-450ms for similar contrast.
[p] Older model MR scanners that are not capable of >2 *b*-values should use $b = 0$ and 1000 s/mm^2.
[q] Axial 2D T2-weighted FLAIR and Axial 2D T2-weighted images can be interchanged pre- and post-contrast.
[r] Sites may choose to perform the 3D T1w IR-GRE sequence prior to the 2D T1w TSE/SE because of the potential risk of patient movement and to help with patient comfort. However, there is less inherent lesion conspicuity in the 3D T1w IR-GRE sequence, so delaying this sequence to the end may be efficacious.
[s] Acceptable 3D T1w TSE sequences include CUBE (GE), SPACE (Siemens), VISTA (Philips), isoFSE (Hitachi), or 3D MVOX (Canon)
[t] Flip angles for 3D TSE sequences (including CUBE and SPACE) are complicated because many utilize variable flip angle refocusing radiofrequency pulses to produce the desired image contrast. Investigators are encouraged to work with their scanner vendors to determine the ideal parameters.
[u] Investigators are encouraged to work with their scanner vendors to determine the best parallel imaging strategies, which may include simultaneous multislice imaging (SMS), controlled aliasing in parallel imaging resulting in higher acceleration (CAIPI), iPAT, GRAPPA, as well as turbo or other acceleration factors.
[v] While some sites may choose to collect DWI post-contrast, studies have suggested this can lower ADC measurements as much as 3% [58].

Table 2: Minimum Standard 3T Metastatic Brain Tumor Imaging Protocol [56, 57]

	3D T1w Pre[b]	Ax 2D FLAIR[j,q]	Ax 2D DWI[p,u]	Contrast Injection [a]	Ax 2D T2w[h,i,q]	2D SE T1w Post[r,s]	3D T1w Post[b,r]
Sequence	IR-GRE[d,e,f]	TSE[c]	SS-EPI[g]		TSE[c]	TSE/SE	IR-GRE [d,e,f]
Plane	Sagittal or Axial	Axial	Axial		Axial	Axial and/or Coronal	Sagittal or Axial
Mode	3D	2D	2D		2D	2D	3D
TR [ms]	2100[m]	>6000	>5000		>2500	< 500	2100[m]
TE [ms]	Min	100-140	Min		80-120	Min	Min
TI [ms]	1100[n]	2000-2500[k]					1100[n]
Flip Angle	10º-15º	90º/≥160º	90º/180º		90º/≥160º	90º/≥160º	10º-15º
Frequency	256	≥256	128		≥256	≥256	256
Phase	256	≥256	128		≥256	≥256	256
NEX	≥1	≥1	≥1		≥1	≥1	≥1
FOV	256mm	240mm	240mm		240mm	240mm	256mm
Slice Thickness	1mm	3mm	3mm		3mm	3mm	1mm
Gap/Spacing	0	0	0		0	0	0
Other Options			*b* = 0, 500, 1000 s/mm^2 ≥3 directions			Fat Saturation Encouraged	
Parallel Imaging	Up to 3x [t]	Up to 2x	Up to 2x		Up to 2x	Up to 2x	Up to 3x [t]

[a] 0.1 mmol/kg dose injection with a Gadolinium chelated contrast agent. Use of a power injector is desirable at an injection rate of 3-5cc/sec. (Note: If DSC perfusion is collected, contrast injection is performed after starting DSC acquisition. DSC perfusion can be performed with the "Ideal" protocol at 3T as well as with the Minimum Standard protocols at 3T and 1.5T.)

[b] Post-contrast 3D T1-weighted images should be collected with equivalent parameters to pre-contrast 3D T1-weighted images

[c] TSE = turbo spin echo (Siemens & Philips) is equivalent to FSE (fast spin echo; GE, Hitachi, Toshiba)

[d] FL2D = two-dimensional fast low angle shot (FLASH; Siemens) is equivalent to the spoil gradient recalled echo (SPGR; GE) or T1- fast field echo (FFE; Philips), fast field echo (FastFE; Toshiba), or the radiofrequency spoiled steady state acquisition rewound gradient echo (RSSG; Hitachi). A fast gradient echo sequence without inversion preparation is desired.

[e] IR-GRE = inversion-recovery gradient-recalled echo sequence is equivalent to MPRAGE = magnetization prepared rapid gradient-echo (Siemens & Hitachi) and the inversion recovery spoiled gradient-echo (IR-SPGR or Fast SPGR with inversion activated or BRAVO; GE), 3D turbo field echo (TFE; Philips), or 3D fast field echo (3D Fast FE; Toshiba).

[f] A 3D acquisition without inversion preparation will result in different contrast compared with MPRAGE or another IR-prepped 3D T1-weighted sequences and therefore should be avoided.

[g] In the event of significant patient motion, a radial acquisition scheme may be used (e.g. BLADE [Siemens], PROPELLER [GE], MultiVane [Philips], RADAR [Hitachi], or JET [Toshiba]); however, this acquisition scheme is can cause significant differences in ADC quantification and therefore should be used only if EPI is not an option. Further, this type of acquisition takes considerable more time.

[h] Dual echo PD/T2 TSE is optional for possible quantification of tissue T2. For this sequence, PD is recommended to have a TE < 25ms.

[i] Advanced sequences can be substituted into this time slot, so long as 3D post-contrast T1-weighted images are collected between 4 and 8 min after contrast injection.

[j] 3D FLAIR is an optional alternative to 2D FLAIR, with sequence parameters as follows per EORTC guidelines: 3D TSE/FSE acquisition; TE=90-140ms; TR=6000-10000ms; TI=2000-2500ms (chosen based on vendor recommendations for optimized protocol and field strength); GRAPPA≤2; Fat

Saturation; Slice thickness ≤ 1.5mm; Orientation Sagittal or Axial; FOV ≤ 250 mm x 250 mm; Matrix ≥ 244x244.

[k] Choice of TI should be chosen based on the magnetic field strength of the system (e.g. TI ≈ 2000ms for 1.5T and TI ≈ 2500ms for 3T).

[l] In order to ensure comparable SNR older 1.5T MR systems can use contiguous (no interslice gap) images with 5mm slice thickness or increase NEX for slice thickness ≤4mm.

[m] For Siemens and Hitachi scanners. GE, Philips, and Toshiba scanners should use a TR = 5-15ms for similar contrast.

[n] For Siemens and Hitachi scanners. GE, Philips, and Toshiba scanners should use a TI = 400-450ms for similar contrast.

[p] Older model MR scanners that are not capable of >2 *b*-values should use $b = 0$ and 1000 s/mm^2.

[q] Axial 2D T2-weighted FLAIR and Axial 2D T2-weighted images can be interchanged pre- and post-contrast.

[r] Sites may choose to perform the 3D T1w IR-GRE sequence prior to the 2D T1w TSE/SE because of the potential risk of patient movement and to help with patient comfort. However, there is less inherent lesion conspicuity in the 3D T1w IR-GRE sequence, so delaying this sequence to the end may be efficacious.

[s] Adding FLAIR to this T1-weighted imaging at 3T could be considered for CSF suppression.

[t] Investigators are encouraged to work with their scanner vendors to determine the best parallel imaging strategies, which may include simultaneous multislice imaging (SMS), controlled aliasing in parallel imging resulting in higher acceleration (CAIPI), iPAT, GRAPPA, as well as turbo or other acceleration factors.

[u] While some sites may choose to collect DWI post-contrast, studies have suggested this can lower ADC measurements as much as 3% [58].

Table 3: Minimum Standard 1.5T Metastatic Brain Tumor Imaging Protocol[56, 57]

	3D T1w Pre[b]	Ax 2D FLAIR[j,q]	Ax 2D DWI[p,t]	Contrast Injection[a]	Ax 2D T2w[h,i,q]	2D SE T1w Post[r]	3D T1w Post[b,r]
Sequence	IR-GRE[d,e,f]	TSE[c]	SS-EPI[g]		TSE[c]	TSE/SE	IR-GRE[d,e,f]
Plane	Sagittal or Axial	Axial	Axial		Axial	Axial and/or Coronal	Sagittal or Axial
Mode	3D	2D	2D		2D	2D	3D
TR [ms]	2100[m]	>6000	>5000		>3500	400-600	2100[m]
TE [ms]	Min	100-140	Min		80-120	Min	Min
TI [ms]	1100[n]	2000-2500[k]					1100[n]
Flip Angle	10º-15º	90º/≥160º	90º/180º		90º/≥160º	90º/≥160º	10º-15º
Frequency	≥172	≥256	128		≥256	≥256	≥172
Phase	≥172	≥256	128		≥256	≥256	≥172
NEX	≥1	≥1	≥1		≥1	≥1	≥1
FOV	256mm	240mm	240mm		240mm	240mm	256mm
Slice Thickness	≤1.5mm	≤4mm[l]	≤4mm[l]		≤4mm[l]	≤4mm[l]	≤1.5mm
Gap/Spacing	0	0	0		0	0	0

Other Options			b = 0, 500, 1000 s/mm^2 ≥3 directions			Fat Saturation Encouraged	
Parallel Imaging	Up to 2x[s]	Up to 2x	Up to 2x		Up to 2x	Up to 2x	Up to 2x[s]

[a] 0.1 mmol/kg dose injection with a Gadolinium chelated contrast agent. Use of a power injector is desirable at an injection rate of 3-5cc/sec. (Note: If DSC perfusion is collected, contrast injection is performed after starting DSC acquisition)
[b] Post-contrast 3D T1-weighted images should be collected with equivalent parameters to pre-contrast 3D T1-weighted images
[c] TSE = turbo spin echo (Siemens & Philips) is equivalent to FSE (fast spin echo; GE, Hitachi, Toshiba)
[d] FL2D = two-dimensional fast low angle shot (FLASH; Siemens) is equivalent to the spoil gradient recalled echo (SPGR; GE) or T1- fast field echo (FFE; Philips), fast field echo (FastFE; Toshiba), or the radiofrequency spoiled steady state acquisition rewound gradient echo (RSSG; Hitachi). A fast gradient echo sequence without inversion preparation is desired.
[e] IR-GRE = inversion-recovery gradient-recalled echo sequence is equivalent to MPRAGE = magnetization prepared rapid gradient-echo (Siemens & Hitachi) and the inversion recovery spoiled gradient-echo (IR-SPGR or Fast SPGR with inversion activated or BRAVO; GE), 3D turbo field echo (TFE; Philips), or 3D fast field echo (3D Fast FE; Toshiba).
[f] A 3D acquisition without inversion preparation will result in different contrast compared with MPRAGE or another IR-prepped 3D T1-weighted sequences and therefore should be avoided.
[g] In the event of significant patient motion, a radial acquisition scheme may be used (e.g. BLADE [Siemens], PROPELLER [GE], MultiVane [Philips], RADAR [Hitachi], or JET [Toshiba]); however, this acquisition scheme is can cause significant differences in ADC quantification and therefore should be used only if EPI is not an option. Further, this type of acquisition takes considerable more time.
[h] Dual echo PD/T2 TSE is optional for possible quantification of tissue T2. For this sequence, PD is recommended to have a TE < 25ms.
[i] Advanced sequences can be substituted into this time slot, so long as 3D post-contrast T1-weighted images are collected between 4 and 8 min after contrast injection.
[j] 3D FLAIR is an optional alternative to 2D FLAIR, with sequence parameters as follows per EORTC guidelines: 3D TSE/FSE acquisition; TE=90-140ms; TR=6000-10000ms; TI=2000-2500ms (chosen based on vendor recommendations for optimized protocol and field strength); GRAPPA≤2; Fat Saturation; Slice thickness ≤ 1.5mm; Orientation Sagittal or Axial; FOV ≤ 250 mm x 250 mm; Matrix ≥ 244x244.
[k] Choice of TI should be chosen based on the magnetic field strength of the system (e.g. TI ≈ 2000ms for 1.5T and TI ≈ 2500ms for 3T).
[l] In order to ensure comparable SNR older 1.5T MR systems can use contiguous (no interslice gap) images with 5mm slice thickness or increase NEX for slice thickness ≤4mm.
[m] For Siemens and Hitachi scanners. GE, Philips, and Toshiba scanners should use a TR = 5-15ms for similar contrast.
[n] For Siemens and Hitachi scanners. GE, Philips, and Toshiba scanners should use a TI = 400-450ms for similar contrast.
[p] Older model MR scanners that are not capable of >2 b-values should use b = 0 and 1000 s/mm^2.
[q] Axial 2D T2-weighted FLAIR and Axial 2D T2-weighted images can be interchanged pre- and post-contrast.
[r] Sites may choose to perform the 3D T1w IR-GRE sequence prior to the 2D T1w TSE/SE because of the potential risk of patient movement and to help with patient comfort. However, there is less inherent lesion conspicuity in the 3D T1w IR-GRE sequence, so delaying this sequence to the end may be efficacious.
[s] Investigators are encouraged to work with their scanner vendors to determine the best parallel imaging strategies, which may include simultaneous multislice imaging (SMS), controlled aliasing in parallel

imging resulting in higher acceleration (CAIPI), iPAT, GRAPPA, as well as turbo or other acceleration factors.

[t] While some sites may choose to collect DWI post-contrast, studies have suggested this can lower ADC measurements as much as 3% [58].

APPENDIX II CENTRAL LABORATORY BIOMARKER TESTING PROCEDURES

Integral Molecular Testing

The SNAPSHOT NGS assay and the Solid Fusion NGS assay are fully validated clinical tests designed and developed at the MGH Center for Integrated Diagnostics (MGH CID) and are performed in a CLIA-certified laboratory. These assays combine anchored-multiplex PCR with next-generation sequencing for detection of single nucleotide variants, insertions/deletions, and copy number variants (SNAPSHOT NGS Assay) or gene fusions (Solid Fusion NGS assay) across a number of known cancer genes. Testing is performed on genomic DNA (SNAPSHOT NGS Assay) or RNA (Solid Fusion NGS assay) derived from diagnostic tumor specimens. These assays have been clinically validated, and standard operating procedures have been created. While these two assays interrogate a number of genes, only alterations in a subset of these genes will be evaluated for determining patient eligibility and reported to the site and to the Alliance (see table below).

Samples Testing

All Cancer Types: Under this A071701 study, it is **MANDATORY** that both the **metastatic tumor** specimen and an **extracranial tumor specimen** undergo SNAPSHOT NGS testing if both tissue types are available. Intracranial tissue alone is sufficient if there is no extracranial tissue available. Therefore, it is essential to receive an adequate number of tissue sections to reduce the chance of test failure, particularly with older tumor specimens.

Primary Lung Cancer and Melanoma: The Solid Fusion NGS assay will be performed together with the SNAPSHOT NGS assay ONLY for patients with primary Lung cancer or Melanoma, as eligible gene fusions are exceedingly rare in other malignancies. It is also **MANDATORY** that both the **metastatic tumor specimen** and an **extracranial tumor specimen** undergo testing if both tissue types are available. Intracranial tissue alone is sufficient if there is no extracranial tissue available.

As of January 2024, the solid fusion NGS assay will not be performed, as the entrectinib arm is now closed.

Methodology

Nucleic Acid Extraction: As the first step in prospective testing for eligible biomarker evaluation, total nucleic acids consisting of both DNA and RNA will be co-extracted from diagnostic formalin-fixed, paraffin-embedded tumor tissue. This will be accomplished using a clinically validated method that comprises the nucleic acid extraction platform used in our clinical tumor mutational profiling program.

Genotyping Using the SNAPSHOT Assay: Total nucleic acid samples will subsequently undergo prospective tumor genotyping using the clinical SNAPSHOT NGS assay for single nucleotide variant (SNV) and copy number variant (CNV) detection. Double-stranded DNA contained within the total nucleic acid sample will be used to produce adapter-ligated DNA libraries for sequencing in a high-throughput manner. This will include fragmentation of the DNA, repair of the DNA strands to produce blunt ended strands, phosphorylation of the 5' ends of the DNA, attachment of dATPs at the 3' ends, ligation of uniquely indexed adapter sequences to both ends of the DNA followed by two rounds of nested PCR for enrichment amplification of the gene exons of interest. SPRI bead clean-up steps are incorporated within these procedures. Adapter-ligated DNA libraries will be quantified by qPCR and then sequenced on an Illumina MiSeq or NextSeq genomic sequencer (both the positive and negative strand).

Gene Fusion Testing Using the Solid Fusion NGS Assay: The RNA within the total nucleic acid sample will undergo first- and second-strand complementary DNA (cDNA) synthesis. This double-stranded cDNA (and also genomic DNA) will undergo end repair and then adenylation to allow ligation with a universal half-functional adapter. Following SPRI bead clean-up, target enrichment is achieved through nested PCR using a primer complementary to a portion of the ligated universal adapter and a reverse primer to the target gene fusion region. A second round of nested PCR is used to incorporate Illumina sequencing adapters and to further enrich the target gene fragments, some of which would contain the gene fusion region. The resulting library will be quantified by qPCR using the Kapa Illumina kit and then sequenced on an Illumina MiSeq or NextSeq genomic sequencer (both the positive and negative strand).

Bioinformatic Variant Analysis: Sequencing data generated through SNAPSHOT or Solid Fusion testing will be processed through the clinically-validated MGH bioinformatics pipeline. First, the sequencing (FASTQ) data will be demultiplexed, aligned to the human reference genome, and the resultant binary files (BAM) generated. This step will be used to identify gene fusions. Secondly, somatic mutations in the patient samples will be deciphered and annotated using the Mutect and Oncotator bioinformatics tools developed at the BROAD institute. Quality assessment includes the incorporation of molecular barcoding and a minimum sequencing depth threshold.

Target Mutations

The following genetic alterations are considered eligible when identified in the metastatic brain lesion:

	SNAPSHOT NGS ASSAY**				SOLID FUSION NGS ASSAY
	Eligible Variants		**CNV**		**Eligible Fusions**
Arm	Oncogene	Tumor Suppressor	Amplification	Deletion	Translocation
Abemaciclib	n/a	**CDKN2A** *(Nonsense, indel, frameshift, splice site mutations)*	***CDK4*** ***CDK6*** ***CCND1*** ***CCND2*** ***CCND3*** ***CCNE1***	***CDKN2A***	n/a
Paxalisib	***AKT1*** c.49G>A ***PIK3CA*** p.R88Q (c.263G>A) p.E542K (c.1624G>A) p.E542Q (c.1624G>C) p.E545K (c.1633G>A) p.E545Q (c.1633G>C) p.E545A (c.1634A>C) p.E545G (c.1634A>G) p.E545V (c.1634A>T) p.Q546K (c.1636C>A) p.Q546E (c.1636C>G) p.Q546P (c.1637A>C) p.Q546R (c.1637A>G) p.Q546L (c.1637A>T) p.H1047Y (c.3139C>T) p.H1047R (c.3140A>G) p.H1047L (c.3140A>T) p.G1049R (c.3145G>C) p.G1049S (c.3145G>A)	***PTEN*** ***(Nonsense, indel, frameshift, splice site mutations)*** **p.C124R (c.370T>C)** **p.C124S (c.370T>A)** **p.C124S (c.371G>C)** **p.G129E (c.386G>A)** **p.G129R (c.385G>A)** **p.G129R (c.385G>C)** **p.G129V (c.386G>T)** **p.R130G (c.388C>G)** **p.R130L (c.389G>T)** **p.R130P (c.389G>C)** **p.R130Q (c.389G>A)** **p.C136R (c.406T>C)** **p.C136Y (c.407G>A)** **p.R173C (c.517C>T)**	***PIK3CA***	***PTEN***	n/a
Entrectinib	n/a	n/a	n/a	n/a	***ROS1*** **fusions** (exons 31-37) **NTRK1 fusions** (exons 8, 10-13) **NTRK2 fusions** (exons 11-17) **NTRK3 fusions** (exons 13-16)

MRTX849	KRAS p.Gly12Cys(c34G>T)	n/a	n/a	n/a	n/a

**Other mutations in these target genes when identified during patient sample testing will be compared to the COSMIC database of known somatic mutations and reported if found. If these additional mutations are determined to be potentially actionable, they will be considered for eligibility.

Assay Protocol

1. The SNAPSHOT and the Solid Fusion assays will be performed in a CLIA-certified laboratory at the MGH Center for Integrated Diagnostics (MGH CID). While these assays detect genetic alterations across a number of cancer genes, only alterations in *AKT1, CDK4, CDK6, CCND1, CCND2, CCND3, CCNE1, CDKN2A, PIK3CA, PTEN, NTRK1, NTRK2, NTRK3, ROS1, and KRAS* will be reported.

2.Quality assurance measures will require that each trial sample is submitted with two identifiers and are accompanied by the required pathology reports. The MGH TRL program coordinator will verify that the sample received matches the information provided by the site, as recorded on the upper portion of the "Alliance A071701 Biomarker Results Form" that must be included with the specimen. Sample acceptability will be determined based on shipping and received condition and sample identifiers will be confirmed before initiating the testing process. Testing will be delayed in the event of improper sample submission, sample labeling, or completion of the "Alliance A071701 Biomarker Results Form".

3.Samples received into the MGH CID for testing will be annotated into a laboratory database and a chain of custody sheet will be initiated to track and record each step of the testing process, the staff member conducting the process, the quantity of sample that was utilized during testing, the testing result(s), and reporting.

4. The H&E stained slide will be reviewed by the study pathologist for tumor percentage. The pathologist will circle the tumor area to be extracted and designate the amount of unstained slides needed for extraction.

5. The designated number of sections of tumor tissue will be macroscopically dissected according to the pathologist's marked H&E slide. Nucleic acid will be extracted in accordance with a clinically-validated protocol. Double-stranded DNA and RNA concentrations will be independently determined using Qubit fluorometric quantitation.

6.Samples undergoing SNAPSHOT and/or Solid Fusion assay testing will be sequenced on an Illumina MiSeq or NextSeq genome sequencer. The assays have been clinically validated and standard operating procedures have been documented.

7.Sequencing data generated will be processed through a validated bioinformatics pipeline developed at MGH where the sequencing (FASTQ) data is demultiplexed, aligned to the human reference genome and the resultant binary files (BAM) generated. Somatic mutations in the patient samples will additionally be deciphered and annotated using the MGH CIDer bioinformatics tool. Quality assessment includes the incorporation of molecular barcoding and a minimum sequencing depth threshold.

8.Sequencing results will be reviewed by a pathologist (John Iafrate) and the presence of an eligible genetic alteration will be called using established criteria. Final reporting will be communicated through the "Alliance A071701 Biomarker Results Form" emailed to the site contact listed on the form and to the Alliance. If NO eligible mutation was identified during testing, the site and the Alliance will be notified of biomarker ineligibility. For the purposes of record keeping, electronic signatures will be considered identical to original wet signatures.

9.Expected turnaround time for testing and reporting is 14 days from the date of receiving acceptable FFPE tumor recuts for both the primary tumor and the metastatic tumor, a de-identified pathology report for each of the 2 samples, and a properly completed "Alliance A071701 Biomarker Results Form" into the MGH CID. Inadequate or poor quality sample that requires sample resubmission or that requires repeat testing due to inadequate read depth will delay reporting.

APPENDIX III: PATIENT MEDICATION DIARIES

The following medication diaries are included within this appendix:

Appendix III-A: Patient medication diary – Paxalisib

Appendix III-B: Patient medication diary – Entrectinib

Appendix III-C: Patient medication diary – Abemaciclib

Appendix III-D: Patient medication diary – MRTX849 (Adagrasib)

Appendix III-A: Patient medication diary – <u>Paxalisib</u>

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each 4 week-period while you take **paxalisib**.
2. You will take your dose of **paxalisib** <u>once daily.</u>
3. Record the date, the number of capsules you took, and when you took them. Record doses as soon as you take them; do <u>not</u> batch entries together at a later time.
4. If a dose is missed, do not make up that dose; resume dosing with the next scheduled dose.
5. Capsules should not be opened or crushed.
6. If you have any comments or notice any side effects, please record them in the Comments column. If you make a mistake while you write, please cross it out with one line, put your initials next to it, and then write the corrected information next to your initials. Example: ~~10:30 am~~ SB 9:30 am
7. Please return this form to your physician when you go for your next appointment.

Day	Date	Time of AM dose	# of capsules taken	Comments
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				

21				
22				
23				
24				
25				
26				
27				
28				
Patient's Signature				Date

Physician's Office will complete this section:

1. Date patient started protocol treatment
   _____

2. Date patient was removed from study
   _____

3. Total number of capsules taken this month (each size)
   _____

4. Physician/Nurse/Data Manager's Signature

   _____

Appendix III-B: Patient medication diary – <u>Entrectinib</u>

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each 4 week-period while you take **Entrectinib**.
2. You will take your dose of **<u>Entrectinib</u>** <u>daily.</u>
3. Record the date, the number of capsules you took, and when you took them. Record doses as soon as you take them; do <u>not</u> batch entries together at a later time.
4. If a dose is missed, do not make up that dose; resume dosing with the next scheduled dose.
5. Capsules should not be opened or crushed.
6. If you have any comments or notice any side effects, please record them in the Comments column. If you make a mistake while you write, please cross it out with one line, put your initials next to it, and then write the corrected information next to your initials. Example: ~~10:30 am~~ SB 9:30 am
7. Please return this form to your physician when you go for your next appointment.

Day	Date	Time of daily dose	# of capsules taken	Comments
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				

21				
22				
23				
24				
25				
26				
27				
28				
Patient's Signature				Date

Physician's Office will complete this section:

1. Date patient started protocol treatment
   _____

2. Date patient was removed from study
   _____

3. Total number of capsules taken this month (each size)
   _____

4. Physician/Nurse/Data Manager's Signature

   _____

Appendix III-C: Patient medication diary – Abemaciclib

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each 4 week-period while you take **Abemaciclib**.
2. You will take your dose of **Abemaciclib** twice daily.
3. Record the date, the number of tablets you took, and when you took them. Record doses as soon as you take them; do not batch entries together at a later time.
4. If a dose is missed, do not make up that dose; resume dosing with the next scheduled dose.
5. Tablets should not be crushed.
6. If you have any comments or notice any side effects, please record them in the Comments column. If you make a mistake while you write, please cross it out with one line, put your initials next to it, and then write the corrected information next to your initials. Example: ~~10:30 am~~ SB 9:30 am
7. Please return this form to your physician when you go for your next appointment.

Day	Date	Time of daily dose 1	# of tablets taken	Time of daily dose 2	# of tablets taken	Comments
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
17						
18						

19						
20						
21						
22						
23						
24						
25						
26						
27						
28						
Patient's Signature						Date

Physician's Office will complete this section:

1. Date patient started protocol treatment
   _____
2. Date patient was removed from study
   _____
3. Total number of capsules taken this month (each size)
   _____
4. Physician/Nurse/Data Manager's Signature
   _____

Appendix III-D: Patient medication diary – MRTX849 (Adagrasib)

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each 4 week-period while you take **MRTX849**.
2. MRTX849 should be taken with or without food.
3. MRTX849 should be taken with at least 240 mL (8 ounces) of **water**.
4. Swallow the MRTX849 pill whole and not chew them. Tablets should not be opened or crushed.
5. If vomiting occurs after dosing, MRTX849 doses should not be replaced.
6. You will take your dose of MRTX849 **twice daily** (approximately every 12 hours).
7. Record the date, the number of tablets you took, and when you took them. Record doses as soon as you take them; do not batch entries together at a later time.
8. If a dose is missed, the dose should be skipped if >4 hours has elapsed from the expected dosing time. Dosing may resume the following day.
9. If you have any comments or notice any side effects, please record them in the Comments column. If you make a mistake while you write, please cross it out with one line, put your initials next to it, and then write the corrected information next to your initials. Example: ~~10:30 am~~ SB 9:30 am
10. On the days of pharmacokinetic (PK) blood collection, the first doses of the day should be taken in the clinic.
11. Please return this form to your physician when you go for your next appointment.

Day	Date	Time of daily dose 1	# of tablets taken	Time of daily dose 2	# of tablets taken	Comments
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						

14						
15						
16						
17						
18						
19						
20						
21						
22						
23						
24						
25						
26						
27						
28						
Patient's Signature						Date

Physician's Office will complete this section:

1. Date patient started protocol treatment
   _____
2. Date patient was removed from study
   _____
3. Total number of tablets taken this month (each size)
   _____
4. Physician/Nurse/Data Manager's Signature
   _____

APPENDIX IV: PATIENT DRUG INFORMATION HANDOUT AND WALLET CARDS

The following patient drug information handout and wallet cards are included within this appendix:

Appendix IV-A: Patient drug information and wallet card – Paxalisib

Appendix IV-B: Patient drug information and wallet card – Entrectinib

Appendix IV-C: Patient drug information and wallet card – Abemaciclib

Appendix IV-D: Patient drug information and wallet card – MRTX849 (Adagrasib)

Appendix IV-A: Patient Drug Information Handout and Wallet Card – Paxalisib

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

[Note to authors: This appendix consists of an "information sheet" to be handed to the patient at the time of enrollment. Use or modify the text as appropriate for the study agent, so that the patient is aware of the risks and can communicate with their regular prescriber(s) and pharmacist. A convenient wallet-sized information card is also included for the patient to clip out and retain at all times. If you choose to use them, please note that the information sheet and wallet card will require IRB approval before distribution to patients.]

The patient _____ is enrolled on a clinical trial using the experimental study drug, ***paxalisib.*** This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a healthcare provider need to know:

Paxalisib interacts with *a certain specific enzyme in your liver*.

- The enzyme in question is Cytochrome P450 CYP3A4. Use of medications that block CYP3A4 with *paxalisib* may increase the amount of *paxalisib* in the body. Use of medications that speed up the activity of *paxalisib* may decrease the amount of *paxalisib* in the body.

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

Paxalisib may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

Paxalisib must be used very carefully with other medicines that use certain ***liver enzymes.*** 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 ***strong inducers/inhibitors*** of ***Cytochrome CYP3A4.***

- 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.
- 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. Your study doctor's name is

_____ and he or she can be contacted at

_____.

STUDY DRUG INFORMATION WALLET CARD

You are enrolled on a clinical trial using the experimental study drug, **paxalisib.** This clinical trial is sponsored by the NCI. **Paxalisib** may interact with drugs that are *processed by your liver*. Because of this, it is very important to:

- Tell your doctors if you stop taking any medicines or if you start taking any new medicines.
- Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

Paxalisib interacts with a specific liver enzyme ***called CYP3A4*** and must be used very carefully with other medicines that interact with ***this enzyme.***

- 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 ***strong inducers/inhibitors of CYP3A4.***
- Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is _____

  and can be contacted at _____.

Appendix IV-B: Patient Drug Information Handout and Wallet Card – Entrectinib

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

[Note to authors: This appendix consists of an "information sheet" to be handed to the patient at the time of enrollment. Use or modify the text as appropriate for the study agent, so that the patient is aware of the risks and can communicate with their regular prescriber(s) and pharmacist. A convenient wallet-sized information card is also included for the patient to clip out and retain at all times. If you choose to use them, please note that the information sheet and wallet card will require IRB approval before distribution to patients.]

The patient _____ is enrolled on a clinical trial using the experimental study drug, ***Entrectinib.*** This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a healthcare provider need to know:

Entrectinib interacts with *certain specific enzyme(s) in your liver*.*

- *The enzymes in question are ***Cytochrome P450 CYP3A, CYP2C9 and CYP2D6***. Use of medications that block CYP3A with *entrectinib* may increase the amount of *entrectinib* in the body. Use of medications that speed up the activity of *entrectinib* may decrease the amount of *entrectinib* in the body. *Entrectinib* may increase the amount of other medications in the body that use the CYP2C9 and CYP2D6 enzymes.

Entrectinib has the potential to cause a reaction to light (photo-reactive). This means that your body could experience side effects (such as a sunburn) through sunlight exposure after taking the drug. You should be careful with sun exposure by using daily sunscreen, lip balm, and wearing protective clothing, sunglasses, and a hat when going outdoors.

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

Entrectinib may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal supplements such as St. John's Wort. It is

helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

Entrectinib has the potential to cause a reaction to light (photo-reactive). You should be careful with sun exposure by using daily sunscreen, lip balm, and wearing protective clothing, sunglasses, and a hat when going outdoors.

Entrectinib must be used very carefully with other medicines that use certain ***liver enzymes***. 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 ***strong inducers/inhibitors of CYP3A or substrates of CYP3A, CYP22C9 and CYP2D6.***

- 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.
- 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. Your study doctor's name is

_____ and he or she can be contacted at

_____.

STUDY DRUG INFORMATION WALLET CARD	
You are enrolled on a clinical trial using the experimental study drug, **Entrectinib.** This clinical trial is sponsored by the NCI. **Entrectinib** may interact with drugs that are ***processed by your liver***. Because of this, it is very important to: ➢ Tell your doctors if you stop taking any medicines or if you start taking any new medicines. ➢ Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial. ➢ Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.	**Entrectinib** interacts with ***specific liver enzymes called CYP3A, CYP2C9 and CYP2D6***, and must be used very carefully with other medicines that interact with ***these enzymes.*** ➢ 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 ***strong inducers/inhibitors of CYP3A or substrates of CYP3A, CYP2C9 or CYP2D6.*** ➢ Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor. ➢ Your study doctor's name is _____ and can be contacted at _____.

Appendix IV-C: Patient Drug Information Handout and Wallet Card – Abemaciclib

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

[Note to authors: This appendix consists of an "information sheet" to be handed to the patient at the time of enrollment. Use or modify the text as appropriate for the study agent, so that the patient is aware of the risks and can communicate with their regular prescriber(s) and pharmacist. A convenient wallet-sized information card is also included for the patient to clip out and retain at all times. If you choose to use them, please note that the information sheet and wallet card will require IRB approval before distribution to patients.]

The patient _____ is enrolled on a clinical trial using the experimental study drug, ***Abemaciclib***. This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a healthcare provider need to know:

Abemaciclib interacts with *a certain specific enzyme in your liver**.

- ***The enzyme in question is ***Cytochrome P450 CYP3A.*** Use of medications that block CYP3A with *abemaciclib* may increase the amount of *abemaciclib* in the body. Use of medications that speed up the activity of *abemaciclib* may decrease the amount of *abemaciclib* in the body.

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

Abemaciclib may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

Abemaciclib must be used very carefully with other medicines that use certain ***liver enzymes***. 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 ***strong inducers/inhibitors*** of ***CYP3A.***

- 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.
- 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. Your study doctor's name is

_____ and he or she can be contacted at

_____.

STUDY DRUG INFORMATION WALLET CARD

You are enrolled on a clinical trial using the experimental study drug, **Abemaciclib.** This clinical trial is sponsored by the NCI.
Abemaciclib may interact with drugs that are ***[processed by your liver.*** Because of this, it is very important to:

- Tell your doctors if you stop taking any medicines or if you start taking any new medicines.
- Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

Abemaciclib interacts with a ***specific liver enzyme called CYP3A*** and must be used very carefully with other medicines that interact with ***this enzyme.***

- 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 ***strong inducers/inhibitors of CYP3A.***
- Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is _____

  and can be contacted at _____.

Appendix IV-D: Patient Drug Information Handout and Wallet Card – MRTX849 (Adagrasib)

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

[Note to authors: This appendix consists of an "information sheet" to be handed to the patient at the time of enrollment. Use or modify the text as appropriate for the study agent, so that the patient is aware of the risks and can communicate with their regular prescriber(s) and pharmacist. A convenient wallet-sized information card is also included for the patient to clip out and retain at all times. If you choose to use them, please note that the information sheet and wallet card will require IRB approval before distribution to patients.]

The patient _____ is enrolled on a clinical trial using the experimental study drug, ***MRTX849***. This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a healthcare provider need to know:

MRTX849 interacts with *certain specific enzymes in your liver**.

- *The enzymes in question are ***Cytochrome P450 CYP3A4, CYP2B6, and CYP2C9.***

  Use of medications that block CYP3A4 may increase the blood levels of MRTX849 in the body. Use of medications that speed up the activity of CYP3A4 may decrease the blood levels of MRTX849 in the body. Use of medications that block or speed up CYP3A4 should be avoided.

  MRTX849 is a strong inhibitor of CYP3A4 and may increase the blood levels of other medications in the body that use CYP3A4 and use of these medications is to be avoided. MRTX849 is a moderate inhibitor of CYP2C9 and has the potential to block CYP2B6 enzymes and drugs that use CYP2C9 and CYP2B6 should be used with caution.

In addition, *MRTX849* may interact with other medications and dietary substances:

- **Gastric acid reducing medications**: Because MRTX849 is best absorbed in acidic conditions, drugs that reduce gastric acid secretion may decrease MRTX849 exposure which may reduce MRTX849 efficacy. Proton pump inhibitors (PPIs) should be avoided. As an alternative to PPIs, preference should be given first to antacids administered more than 2 hours before and more than 2 hours after dosing with MRTX849, and second to an H2 antagonist with dosing separated by more than 2 hours from of MRTX849 dosing (eg, MRTX849 at 8AM and 8PM, and a short-acting H2 blocker at 10AM and 10PM).

- An abnormal heartbeat finding called **QT prolongation** has been associated with MRTX849. Therefore, medications known to prolong QTc and pose risk of a condition called Torsades de Pointes should be avoided.

- **Herbal medications** and preparations should be avoided throughout the study. Herbal medications include, but are not limited to: St. John's wort, green tea, milk thistle, turmeric/curcumin, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe (yohimbine), saw palmetto, ginseng, quercetin and Schisandra extract

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

MRTX849 may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

MRTX849 must be used very carefully with other medicines that use certain ***liver enzymes***. 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 ***strong inducers or inhibitors*** of ***CYP3A, substrates of CYP3A with narrow therapeutic index, known to prolong QT,*** *or* ***proton pump inhibitors. These medicines are to be avoided.*** *Drugs that are substrates of CY2B6, CYP2C9 or P-glycoprotein are to be used with caution.*

- 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.

- 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. Your study doctor's name is

_____ and he or she can be contacted at

_____.

STUDY DRUG INFORMATION WALLET CARD

You are enrolled on a clinical trial using the experimental study drug**, MRTX849.** This clinical trial is sponsored by the NCI. **MRTX849** may interact with drugs that are ***processed by your liver or are processed by a other organs***. Because of these potential drug interactions, it is very important to:

- Tell your doctors if you stop taking any medicines or if you start taking any new medicines.
- Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

MRTX849 interacts with ***specific liver enzymes called CYP3A, CYP2B6 and CYP2C9***, and as well as an enzyme called P-gp. MRTX849 must be used very carefully with other medicines that interact with ***these enzymes.***

- 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 ***strong inducers/inhibitors of CYP3A or substrates of CYP3A, CYP2B6, CYP2C9 or P-gp***, ***reduce stomach acid***, or cause a heartbeat abnormality called ***QT prolongation***.
- Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is _____

  and can be contacted at _____.