NCI Protocol #: 10216
Version Date: 09/17/2024

To: CTEP Protocol and Information Office

From: Dwight Owen, M.D.

Date: TBD

Re: Amendment 19 of Protocol #10216: "A Phase Ib Study of Osimertinib (AZD9291) and Telaglenastat (CB-839) HCl in Patients with EGFR Mutant Non-Small Cell Lung Cancer"

SUMMARY OF CHANGES – Protocol

I. Comments Requiring a Response – Major Issues:

#	Section	Comments
1.	3.4.5	Updated safety guidance needs to be integrated after/before Section 3.4.4: Should participants with HIV infection be included, patients are only eligible if they meet all the following criteria: • Undetectable viral RNA load for 6 months • CD4+ count of >350 cells/μL • No history of AIDS-defining opportunistic infection within the past 12 months • Stable for at least 4 weeks on the same anti-HIV medications In patients with HIV, viral RNA load and CD4+ cell count should be monitored per local standard of care (e.g., every 3 months). **PI Response**: ***This has been added.*** **CTEP Comment:** **Because the study accrual is permanently closed, CTEP will not approve eligibility changes to this protocol.** **PI Response**: ***This has been deleted.***
2	5.5.5	Revise the Shipping Address for the EET Biobank to the following: EET Biobank 2200 International Street Columbus, OH 43228 PH: (614) 722-2865 FAX: (614) 722-2897 E-mail: BPCBank@nationwidechildrens.org **PI Response**: ***This has been corrected.***

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

#	Section	Comments
2.	13.5, 13.6	Please delete the following language from the Protocol: ***13.5 Genomic Data Sharing Plan*** The investigators and statistician and/or bioinformaticians for a study will have access to all data on mutations and variants stored in the Theradex Data Base and the GDC. This information will be sequestered from access throughout the study until it is analyzed for purposes of reporting and publishing of the study results. As specified in the CRADA for the agents used in the clinical study, the pharmaceutical collaborator will have at least 6 months, longer if needed for a regulatory filing, to review the data and or receive copies of the data once the study is completed and analyzed, or sooner, if specified for purposes of generating Intellectual Property. Once these timeframes have been exceeded, the data will be available through a Data Access Committee (DAC) in the GDC following NCI and Collaborator review of the proposals. ***13.6 Incidental/Secondary Findings Disclosure Procedure*** Given the potential clinical implications conferred by detecting a germline and/or somatic mutation in one of the proven cancer susceptibility genes, this protocol will use the following disclosure procedure, consistent with the recommendations of the American College of Medical and Genomics (ACMG) (Green *et al*., 2013 and Kalia *et al.,* 2016): The NCI Molecular Characterization Laboratory will review the mutations/variants once at the time of initial specimen evaluation according to the most recent version of the ACMG guidance on variants. The NCI Molecular Characterization Laboratory will not re-review all specimens received if a new version of the ACMG guidance is published after the initial review. For each participant with a pathogenic or likely pathogenic germline and/or somatic variant detected in the WES of blood (as defined in the ACMG guidance), the NCI Molecular Characterization Laboratory will report to the Program Director or Scientific Officer the UPID and variant(s) identified. The Program Director or Scientific Officer will contact Theradex to obtain the name of the protocol, investigator treating the patient, and the Principal Investigator of the grant. The treating physician will be contacted by phone and in writing to ask the patient whether he or she is interested in learning more about the finding. If the patient wants to know more, the physician should contact the Program Director for more information about the mutation/variant. The treating physician and a

#	Section	Comments
		medical genetics counselor should meet with the patient to discuss the importance and meaning of the finding, but not the finding itself, and notify the patient that this research finding must be confirmed by Sanger sequencing at the patient's/patient insurer's expense in a Clinical Laboratory Improvement Amendments (CLIA)-approved laboratory. The treating physician and genetic counselor should inform the patient of the confirmed result and its meaning and significance to the patient. If desired, the patient may elect to undergo genetic counseling and confirmatory CLIA-approved clinical testing on his or her own. Neither the research laboratory nor the National Cancer Institute will be responsible for the costs incurred for any confirmatory genetic testing or counseling. **PI Response:** ***This has been deleted.***
3.	Global	**Sections are numbers incorrectly.** Please revert to the original numbering. (ex. 6.1- 6.5 and 8.1- 8.1.5) **PI Response:** ***This has been updated.***
4.	6.1	**Agent Administration** Remove: All protocol therapy with CB-839 will end on 10/31/24. After that date, patients may remain on osimertinib single agent at the investigator discretion until meeting other off therapy criteria. With: All protocol therapy with Telaglenastat (CB-839) will end on 2/28/25. The clinical supply of Telaglenastat will no longer be available after the terminal lot shelf life dating of 2/28/25 is reached. After that date, patients may remain on Osimertinib single agent at the investigator discretion until meeting other off therapy criteria. **PI Response:** ***This has been updated.***

III. Recommendations:

#	Section	Comments
5.	9.2	Section 9.2 now contains the following statement: "With a total of 16 patients in MTD/RP2D (6 +10), we will have a 95% lower-limit confidence interval of 12.3% to rule out the null ORR rate of 10% when the target ORR is 30% using the exact (Clopper-Pearson) method." This statement is somewhat confusing. To help clarify, please modify the language to include the number of responses necessary to rule out a null of 0.1 at the one-sided 0.05 level (in this case, I believe that number is 5). This can be addressed at the time of the next amendment.

#	Section	Comments
		PI Response: ***This section has been updated.***
6.	5.11.1.2	For WES/RNAseq, revise this section to update the site performing correlative study: 5.11.1.2 Site(s) Performing Correlative Study WES and RNAseq will be performed on archival samples by the MoCha, Frederick National Laboratory for Cancer Research (FNLCR) under the supervision of Chris Karlovich, Ph.D. (chris.karlovich@nih.gov). **PI Response**: ***This section has been updated.***

IV. Company Comments – Requiring a Response:

#	Section	Comments
7.	3.4.5	Updated safety guidance needs to be integrated after/before Section 3.4.4: Should participants with HIV infection be included, patients are only eligible if they meet all the following criteria: • Undetectable viral RNA load for 6 months • CD4+ count of >350 cells/μL • No history of AIDS-defining opportunistic infection within the past 12 months • Stable for at least 4 weeks on the same anti-HIV medications In patients with HIV, viral RNA load and CD4+ cell count should be monitored per local standard of care (e.g., every 3 months). **PI Response**: ***This has been added.***
8.	P69	Per a recent safety update, the section on SJS and needs to be updated to include toxic epidermal necrolysis (TEN): **Erythema Multiforme, and Stevens-Johnson syndrome and Toxic epidermal necrolysis** Case reports of Erythema multiforme (EM) and toxic epidermal necrolysis have been uncommonly reported, and Stevens-Johnson syndrome (SJS) have been uncommonly and rarely reported, respectively, in association with osimertinib treatment. Before initiating treatment, patients should be advised of signs and

<table>
<tr><th>#</th><th>Section</th><th>Comments</th></tr>
<tr><td></td><td></td><td>symptoms of EM, and SJS and TEN. If signs and symptoms suggestive of EM develop, close patient monitoring and drug interruption or discontinuation of osimertinib should be considered. If signs and symptoms suggestive of SJS appear, osimertinib should be interrupted. Osimertinib should be or discontinued immediately if SJS or TEN is diagnosed.

<u>PI Response</u>: Updated as requested</td></tr>
<tr><td>9.</td><td>9.2</td><td>Additional clarity is needed about the change in power brought about by the change in sample size. The new text is OK, but if less than 5/16 (31%) respond the lower limit will cross the 10% boundary, this could perhaps be clearer. Also, the analysis of 16 rather than 21 patients is almost a 25% drop so any efficacy analysis should be treated with even more caution than previously advised. Any efficacy analysis should be treated with even more caution than previously advised.

<u>PI Response:</u> This section has been updated.</td></tr>
<tr><td>10.</td><td>5.1.1 and 5.1.2</td><td>Revise footnote #1 in each of the Specimen Collection Tables to the following:

[1]For archival tissue, a copy of the anatomic pathology report corresponding to the tissue collection procedure must be sent with the tissue and uploaded to Rave. If submitting slides, then slides must be processed in order, and numbered sequentially (e.g., H&E stained slide is created first and labeled 1, unstained slides are then created and numbered 2 – 51). Refer to section 5.3 for additional information.

<u>PI Response:</u> Updated as recommended</td></tr>
<tr><td>11.</td><td>5.5.1 and 5.5.2</td><td>Revise the beginning of Section 5.5 as shown below to clarify the forms:

5.5.1 General Shipping Information

5.5.1.1 Required Forms for Specimen Submissions

<table>
<tr><th>Specimen</th><th>Required Forms</th></tr>
<tr><td>Archival</td><td>1. Shipping List
2. Anatomic Pathology Report correspon
tissue collection procedure</td></tr>
<tr><td>Blood</td><td>1. Shipping List</td></tr>
</table>

Each document submitted with the specimen must be labeled with a label printed from the STS, or the Universal ID and Patient Study ID.

<u>Minimum required personally identifiable information:</u>
• Remove patient identifiers such as name, date of birth, medical record number, social security number, and insurance information from the pathology or other clinical reports.</td></tr>
</table>

#	Section	Comments
		• Do not remove the date of procedure, surgical pathology ID (SPID) number, block number, and diagnosis. 5.5.2 Specimen Shipping Instructions When kits are provided, the shipping container sent with kit contents should be used to ship specimens to the EET Biobank. In winter months, please include extra insulation, such as bubble wrap, inside the shipping container. • **Ambient Blood** (cfDNA Streck tubes) is shipped at room temperature on Monday through Friday. Please select Saturday delivery if shipping blood on a Friday. Ship blood in cfDNA Streck tubes shipped in ambient shipping containers provided by the EET Biobank. • **Frozen specimens** (plasma) may be shipped on Monday through Thursday. Frozen specimens are batch shipped. Shipments should contain no more than 31 cryovials so that sufficient dry ice can be included to completely encase the specimens in order to maintain specimen integrity during shipment. • **FFPE tissue block or slides** may be shipped on Monday through Thursday. Slides are shipped in containers provided by the submitting site. **PI Response:** ***Updated as recommended.***
12.	5.5.5	Revise the Contact Information for Assistance to update the EET Biobank's phone number as follows: For all queries, please use the contact information below: EET Biobank Phone: (614) 722-2865 E-mail: BPCBank@nationwidechildrens.org **PI Response:** ***Updated as recommended.***
13.	5.8	In the Biomarker Table, replace the current laboratory text for WES, WES/RNAseq, and cfDNA sequencing with the following new text: Chris Karlovich / MoCha, Frederick National Laboratory for Cancer Research (FNLCR) **PI Response:** ***Updated as recommended.***
14.	5.10.2.2 - 5.10.2.5	For WES, revise these sections to update the site performing correlative study, shipping, and shipping contact information and remove the assay information: 5.10.2.2 Site(s) Performing Correlative Study

#	Section	Comments
		WES will be performed on archival tumor and germline samples by the MoCha, Frederick National Laboratory for Cancer Research (FNLCR) under the supervision of Chris Karlovich, Ph.D. (chris.karlovich@nih.gov). ~~5.10.2.3Assay Information~~ ~~DNA libraries will be generated using the Agilent SureSelect XT Target Enrichment System and quantitated via digital droplet PCR (ddPCR). Library samples are denatured, diluted, and clustered on the cBot clonal amplification system in preparation for sequencing on the Illumina HiSeq 2500.~~ 5.10.2.3 Shipment of specimens from the EET Biobank to Site Performing Correlative Study Specimens will be shipped from the EET Biobank to: MoCha Lab, Frederick National Laboratory for Cancer Research (FNLCR) 1050 Boyles St. Bldg. 459, Rm. 125 Frederick, MD 21702 Attn: Alyssa Chapman or Ruth Thornton 5.10.2.4 Contact information for notification of specimen shipment Thomas Forbes, mochasamplereceiving@nih.gov **PI Response:** ***Updated as recommended.***
15.	5.11.1.2 - 5.11.1.5	For WES/RNAseq, revise these sections to update the site performing correlative study, shipping, and shipping contact information and remove the assay information: 5.11.1.2 Site(s) Performing Correlative Study WES and RNAseq will be performed on archival samples by the MoCha, Frederick National Laboratory for Cancer Research (FNLCR) under the supervision of Chris Karlovich, Ph.D. (chris.karlovich@nih.gov). ~~5.11.1.3 Assay Information~~ ~~WES~~ ~~DNA libraries will be generated using the Agilent SureSelect XT Target Enrichment System and quantitated via ddPCR. Library samples are denatured, diluted, and clustered on the cBot clonal amplification system in preparation for sequencing on the Illumina HiSeq 2500.~~

#	Section	Comments
		~~RNAseq~~ ~~RNA libraries will be generated using the Agilent SureSelect XT Target Enrichment System and quantitated via ddPCR. Library samples are denatured, diluted, and clustered on the cBot clonal amplification system in preparation for sequencing on the Illumina HiSeq 2500.~~ 5.11.1.3 Shipment of specimens from the EET Biobank to Site Performing Correlative Study Specimens will be shipped from the EET Biobank to: MoCha Lab, Frederick National Laboratory for Cancer Research (FNLCR) 1050 Boyles St. Bldg. 459, Rm. 125 Frederick, MD 21702 Attn: Alyssa Chapman or Ruth Thornton 5.11.1.4 Contact information for notification of specimen shipment: Thomas Forbes, mochasamplereceiving@nih.gov **PI Response:** ***Updated as recommended.***
16.	5.11.2.2 - 5.11.2.4	For cfDNA, revise these sections to update the site performing correlative study, shipping, and shipping contact information: 5.11.2.2 Site(s) Performing Correlative Study This study will be performed at the MoCha, Frederick National Laboratory for Cancer Research (FNLCR) under the supervision of Chris Karlovich, Ph.D. (chris.karlovich@nih.gov). 5.11.3.3 Shipment of specimens from the EET Biobank to Site Performing Correlative Study Specimens will be shipped from the EET Biobank to: MoCha Lab, Frederick National Laboratory for Cancer Research (FNLCR) 1050 Boyles St. Bldg. 459, Rm. 125 Frederick, MD 21702 Attn: Alyssa Chapman or Ruth Thornton 5.11.3.4 Contact information for notification of specimen shipment: Thomas Forbes, mochasamplereceiving@nih.gov

#	Section	Comments
		PI Response: ***Updated as recommended.***
17.	**9**	• The target and threshold can be easily improved. If they are updating the protocol, they should do this.- • With the current design, there is a significant risk (45%) of failing to meet the target, and the trial being a formal failure, even if the therapy works as expected / hoped. • Agreed: If we observe 5/16 (31%) then the 90% and 95% confidence intervals exclude 10%. • If the underlying rate is 30%, then we could observe 5+/16 in our data with 55% probability. Thus, if the underlying rate is 30%, there is only 55% power. • Consider one of the following alternatives: o If you increase alpha (up to 10% one-sided), then 4 or more out of 17 gives 80% power. The 95% lower-limit confidence interval with 4/17 is 10.7%. If there are 5 or more success out of 17, then you can claim significance at 5% one-sided. o If you cannot go above 16 sample size, then 4 or more out of 16 gives 75% power with alpha at 10% one-sided. The 95% lower-limit confidence interval with 4/16 is 11.3%. If there are 5 or more out of 16, then you can claim significance at 5% one-sided. o Otherwise go for an estimation approach, that is the sample size section shows the size of the confidence interval for potential results, without specifying a specific target, **PI Response:** ***Since this is a Phase 1b study to obtain preliminary efficacy data, we have updated the protocol using Option 3 from the alternatives. We stated: With a total of 16 patients at MTD/RP2D (6 + 10), we will estimate the ORR with a 95% confidence interval half-width of less than 25.4%, using the Clopper-Pearson exact method.***

V. Changes by Lead Site:

17.	Protocol Version	Updated amendment number and protocol version date.
18.	Header	Updated header version date.
19.	2.3	Section updated to include rationale for dose selection for expansion cohort.
20.	2.4.7 5.12	Removed PET criteria as The Wright Center of Imaging has moved from OSU.
21.	6.1	Section updated for expansion cohort size.
22.	9.1	Section updated for expansion cohort size.
23.	All	Deleted / Adjusted page breaks and line spacing.

24.	5.7	Updated contact information and shipping instructions for Osimertinib pharmacologist to Dr. Mitch A. Phelps at the Ohio State University
25.	Title Page	Updated Osimertinib (AZD9291) Pharmacologist Investigator from Jill Kolesar (UKY) to Mitch Phelps (OSU)

VI. Changes in Response to RRA dated 8/20/24:

25.	10.3.2	Updated AE Reporting Tables per FDA Reporting Requirements For Serious Adverse Events (21 CFR Part 312)
26.	10.1.1.2	Updated CAEPR for AZD9291 (Osimertinib, NSC 781254) (Version 2.9, May 23, 2024) Added New Risk: • Rare but Serious: Skin and subcutaneous disorders - Other (erythema dyschromicum perstans); Toxic epidermal necrolysis • Also Reported on Osimertinib Trials But With Insufficient Evidence for Attribution: Cardiac disorders - Other (atrial thrombosis); Skin hyperpigmentation Decrease in Risk Attribution: • Changed to Less Likely from Likely: Paronychia • Changed to Also Reported on Osimertinib Trials But With Insufficient Evidence for Attribution from Less Likely: Alopecia PLEASE NOTE: The specific detailed changes listed here compare the new revised CAEPR Version 2.9, and associated risk information for the ICD, to the most recent CAEPR Version 2.8. If your trial contains an older CAEPR version (i.e., does **NOT** currently contain CAEPR Version 2.8), you **MUST** include a description of any additional changes resulting from migration from the older CAEPR version.

NCI Protocol #: 10216

Local Protocol #: OSU 19016

ClinicalTrials.gov Identifier: NCT03831932

TITLE: A Phase Ib Study of Osimertinib (AZD9291) and Telaglenastat (CB-839) HCl in Patients with EGFR Mutant Non-Small Cell Lung Cancer

Corresponding Organization: LAO-OH007 / Ohio State University Comprehensive Cancer Center LAO

Principal Investigator:
Dwight Owen, M.D.
Ohio State University James Comprehensive Cancer Center
A450B Starling Loving Hall
320 W 10th Ave
Columbus, OH 43210
Tel: 614-685-2039
Fax: 614-293-1470
Dwight.Owen@osumc.edu

Investigator
Jennifer Eads, M.D.
University of Pennsylvania
3400 Civic Center Boulevard
Philadelphia, PA 19104
Tel: (215) 615-1725
Fax: (215) 349-8551
jennifer.eads@uphs.upenn.edu

Investigator
Afshin Dowlati, M.D.
Case Western Reserve University
11100 Euclid Ave
Lakeside 1200
Cleveland, OH 44106
Tel: 216-844-5181
Fax: 216-844-5234
afshin.dowlati@uhhospitals.org

Participating Organizations

LAO-11030 / University Health Network Princess Margaret Cancer Center LAO
LAO-CA043 / City of Hope Comprehensive Cancer Center LAO
LAO-CT018 / Yale University Cancer Center LAO
LAO-MA036 / Dana-Farber - Harvard Cancer Center LAO
LAO-MD017 / JHU Sidney Kimmel Comprehensive Cancer Center LAO

LAO-OH007 / Ohio State University Comprehensive Cancer Center LAO
LAO-PA015 / University of Pittsburgh Cancer Institute LAO
LAO-TX035 / University of Texas MD Anderson Cancer Center LAO
LAO-NCI / National Cancer Institute LAO
CATCHUP / Creating Access to Targeted Cancer Therapy for Underserved Populations
EDDOP / Early Drug Development Opportunity Program

Statistician:
Lai Wei, Ph.D., M.S.
Center for Biostatistics
320H Lincoln Tower, 1800 Cannon Drive
6652Columbus, OH 43210
Tel: 614-293-6449
Lai.wei@osumc.edu

Study Coordinator:
OSU Clinical Trials Office
Multi-Center Trial Coordinator
Fax: (614)-366-

Email: OSUCCC-CTO-MCTP@osumc.edu

Imaging Co-Investigator:
Investigator:
Michael Knopp, M.D., Ph.D.
Ohio State University
395 W 12th Ave, Rm 430
Columbus, OH-43210
Tel:(614) 293-9998
Fax: (614) 293-9275
knopp.16@osu.edu

Telaglenastat (CB-839) HCl Pharmacologist

Joel M. Reid, Ph.D.
Mayo Clinic Cancer Center
200 First Street SW
Rochester, MN 55905
Tel: (507) 284-0822
Fax: (507) 293-0107
reid@mayo.edu

Osimertinib (AZD9291) Pharmacologist Investigator:
Mitch A. Phelps, Ph.D.
Ohio State University
506 Riffe Building
Columbus, OH 43210
Tel: (614) 688-4370
phelps.32@osu.edu

Multi-Center Trial Program:
Clinical Trials Office
The Ohio State University Comprehensive Cancer Center
Fax: (614)-366-6652
E: OSUCCC-CTO-MCTP@osumc.edu

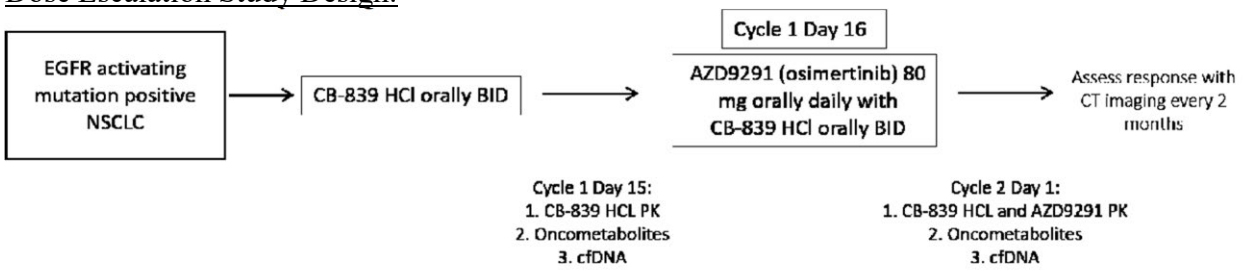
NCI-Supplied Agent(s): Telaglenastat (CB-839) HCl (NSC 795998), Osimertinib (NSC 781254)
IND #: [redacted]
IND Sponsor: DCTD, NCI

Protocol Type / Version # / Version Date:

Original / June 19, 2018
Revision 1 / August 14, 2018
Revision 2 / September 4, 2018
Revision 3 / October 5, 2018
Revision 4 / November 21, 2018
Revision 5 / December 28, 2018
Revision 6a / February 22, 2019
Amendment 1 / May 7, 2019
Amendment 2 / July 2, 2019
Amendment 3 / August 20, 2019
Amendment 4 / September 27, 2019
Amendment 5 / October 10, 2019
Amendment 6 / June 11, 2020
Amendment 7 / July 13, 2020
Amendment 8 / September 10th, 2020 (Disapproved)
Amendment 9 / September 25th, 2020
Amendment 10 / November 25, 2020
Amendment 11 / December 16, 2020
Amendment 12 / March 03, 2021
Amendment 13 / April 5, 2022
Amendment 14 / March 17, 2023
Amendment 15 / May 2, 2023
Amendment 16 / March 11, 2024 (Disapproved)
Amendment 17 / May 3, 2024 (Disapproved)
Amendment 18 / August 23, 2024 (Disapproved)
Amendment 19 / September 17, 2024

SCHEMA

Dose Escalation Study Design:



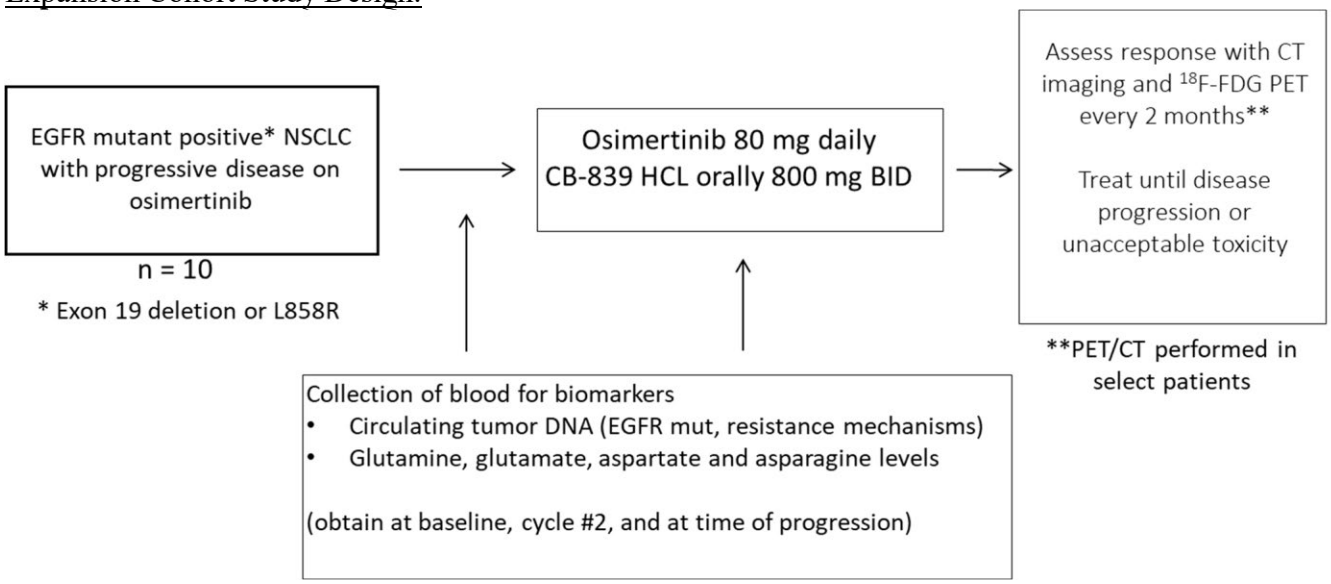
DLT period: one 28 day treatment cycle
Treat until disease progression or unacceptable toxicity

DOSE ESCALATION STRATEGY

Dose Level	CB-839 HCl (mg) BID	AZD9291 (osimertinib) (mg) daily
-1	200	80
1	400	80
2	600	80
3	800	80

EGFR: epidermal growth factor receptor; BID: twice daily; CT, computed tomography; ^{18}F-FDG-PET: fludeoxyglucose positron emission tomography; PK: pharmacokinetics; DLT: dose-limiting toxicity; NSCLC: non-small cell lung cancer

Expansion Cohort Study Design:



MTD: maximum tolerated dose. PET: positron emission tomography; RECIST: Response Evaluation Criteria In Solid Tumors. TKI: tyrosine kinase inhibitor;

Table of Contents

1. OBJECTIVES

1.1 Primary Objectives

1.1.1 To assess the safety and tolerability of Osimertinib (AZD9291) and Telaglenastat (CB-839) HCl and determine the RP2D in patients with metastatic, EGFR activating mutation-positive NSCLC.

1.2 Secondary Objectives

1.2.1 To determine toxicity profile of the combination of Osimertinib (AZD9291) and Telaglenastat (CB-839) HCl in patients with metastatic EGFR activating mutation positive NSCLC.

1.2.2 To assess the PK of Telaglenastat (CB-839) HCl and Osimertinib (AZD9291) in patients with metastatic EGFR activating mutation positive NSCLC.

1.3 Exploratory/Correlative Objectives

1.3.1 To determine the progression free survival (PFS) of Osimertinib (AZD9291) and Telaglenastat (CB-839) HCl in patients with EGFR mutation positive NSCLC who have developed PD on front-line EGFR inhibitor therapy.

1.3.2 To determine the overall survival (OS) of Osimertinib (AZD9291) and Telaglenastat (CB-839) HCl in patients with EGFR mutation positive NSCLC who have developed PD on front-line EGFR inhibitor therapy

1.3.3 To assess cell-free DNA (cfDNA) and measure changes with response to treatment as well as disease progression (EGFR sensitizing mutations, T790M resistance mutation, recognized bypass mechanisms).

1.3.4 To assess circulating levels of glutamine, glutamate, aspartate and asparagine, and measure changes with response to treatment as well as disease progression.

1.3.5 To assess ^{18}F-FDG-PET parameters at baseline and after treatment to evaluate changes with response to treatment as well as emergence of disease resistance or progression (expansion cohort, select patients only).

1.3.6 To perform molecular profiling assays on malignant and normal tissues, including, but not limited to, whole exome sequencing (WES) and RNA sequencing (RNAseq), in order to:

1.3.6.1 To identify potential predictive and prognostic biomarkers beyond any genomic alteration by which treatment may be assigned, and

1.3.6.2 To identify resistance mechanisms using genomic DNA- and RNA-based assessment platforms.

2. BACKGROUND

2.1 Study Disease(s)

Lung cancer is the second most common malignancy in both males and females with 222,500 patients diagnosed annually. It is also the leading cause of cancer related death in both men and women, with 155,870 patients dying of their disease every year (Siegel *et al.*, 2017). Amongst all lung cancers, NSCLC accounts for approximately 83% of all lung cancers, and non-squamous NSCLC (including mostly adenocarcinoma), accounts for 50-55% of lung cancers (Noone *et al.,* 2018). Within the past decade, there have been significant improvements in the treatment of NSCLC and many of the current treatment recommendations are dependent on a patients underlying genomic profile (Ettinger *et al.*, 2017). Despite these advances that allow us to provide molecularly targeted therapies for patients, there are still significant limitations, particularly for patient populations who do not harbor genomic abnormalities that allow them to fit within the algorithm for treatment with these agents. It is these patients especially who are most in need of additional treatment options.

One major decision point in selecting therapy for a patient with NSCLC is first to identify if they harbor an activating/sensitizing mutation in the *EGFR* gene. Activating mutations in the *EGFR* gene are relatively uncommon in Western countries where they occur in approximately 10% of patients (Hirsch and Bunn, 2009). The most commonly identified mutations are in either exon 19 (45%) or exon 21 (40%) (Jin *et al.*, 2016). Those who do harbor such a mutation are treated in the front-line setting with an EGFR inhibitor such as erlotinib, gefitinib, or afatinib as these agents demonstrate clinical benefit in the form of both response to therapy and PFS (Langer, 2013). More recently, based on the FLAURA study, Osimertinib (AZD9291) was approved in the first line treatment of patients with an *EGFR* exon 19 or L858R mutation (Soria *et al.*, 2018). However, many patients are still on treatment with first line TKI therapy, and Osimertinib (AZD9291) is not approved in all countries for first line therapy. Unfortunately, like most cancers, patients ultimately develop resistance to these agents and a common mechanism of resistance is the development of a T790M mutation within the *EGFR* gene, occurring in approximately 60% of patients treated with EGFR inhibitors (Pao *et al.*, 2005; Tanaka *et al.*, 2017). Currently, the management of patients who progress on first line TKI is an area of unmet clinical need.

2.2 CTEP IND Agents

2.2.1 Telaglenastat (CB-839) HCl

Telaglenastat (CB-839) HCl is a first-in-class, orally available inhibitor of glutaminase (GLS)

activity (CB-839 Investigator's Brochure, 2017). There are two GLS genes, *GLS* and *GLS2*, with the latter being primarily expressed in the liver. *GLS* is more broadly expressed and has two known splice variants, the longer kidney-type glutaminase (KGA) and the shorter glutaminase C (GAC), differing in their carboxyl-terminal. Both GLS isoforms catabolize glutamine into glutamate, and the functional differences between the two isoforms is unknown. Telaglenastat (CB-839) HCl specifically inhibits both isoforms of *GLS*, but not *GLS2*.

Telaglenastat (CB-839) HCl shows anti-tumor activity in multiple nonclinical models and has been studied in clinical trials in patients with cancer as a monotherapy and in combination with standard anticancer agents in hematological cancers, including acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), multiple myeloma (MM), and non-Hodgkin lymphoma (NHL) and solid tumors (including triple-negative breast cancer [TNBC], melanoma, NSCLC, and renal cell carcinoma [RCC]) (CB-839 Investigator's Brochure, 2017).

2.2.1.1 Mechanism of Action

Many cancer types have an altered metabolic profile and use glutamine as an energy source. GLS converts glutamine to glutamate, which can support several cellular pathways, including the tricarboxylic acid (TCA) cycle for energy production, redox balance, and amino acid synthesis (reviewed in Altman *et al.*, 2016). Many tumors have been demonstrated to overexpress GLS, particularly the shorter GAC isoform, and these tumors are sensitive to the withdrawal of glutamine from culture medium *in vitro* (Gross *et al.*, 2014; Jacque *et al.*, 2015). This overexpression of GLS can be stimulated by overexpression of Myc (Wise *et al.*, 2008; Gao *et al.*, 2009).

Telaglenastat (CB-839) HCl is a selective, allosteric, noncompetitive inhibitor of both isoforms of GLS. It has been shown to reversibly bind to the activation loop of GAC and induce the formation of inactive tetramers (Stalnecker *et al.*, 2017). This inactivation of GLS results in an increase of glutamine and a decrease of glutamate and several TCA cycle intermediates within cancer cells, leading to a decrease in cell proliferation and/or an increase in cell death (Gross *et al.*, 2014; Matre *et al.*, 2016). The decrease in cellular viability can be reversed by addition of α-ketoglutarate, suggesting that the reduction in TCA cycle intermediates is the primary mechanism by which Telaglenastat (CB-839) HCl exerts its antiproliferative and pro-apoptotic effects (CB-839 Investigator's Brochure, 2017).

2.2.1.2 Summary of Nonclinical Experience

The selectivity of Telaglenastat (CB-839) HCl was tested *in vitro* as an inhibitor of radioligand binding to 66 different receptors derived from mammalian tissue (CB-839 Investigator's Brochure, 2017). At 10 mcM Telaglenastat (CB-839) HCl, significant inhibition of radioligand binding was observed against the human adenosine A3 receptor (50%), the human *ether-à-go- go*-related gene (hERG) potassium channel (64%), and the sodium channel, site 2 (57%).
Minimal functional impact was observed with either the hERG channel (18% inhibition in a patch clamp assay) or the sodium channel (no agonist or antagonist activity in the guinea pig atrium).

In mice bearing HCC1806 tumors treated with a single dose of 200 mg/kg Telaglenastat (CB-839) HCl , the tumor and all examined tissues were exposed to Telaglenastat (CB-839) HCl, although exposure within the brain was 20-fold less than in the plasma (CB-839 Investigator's Brochure, 2017). In mice given a single dose of Telaglenastat (CB-839) HCl ranging from 2.5 to 400 mg/kg, maximum GLS inhibition, glutamine increase, and glutamate and aspartate decreases within the tumor plateaued when plasma concentrations exceeded ~300 nM, which was achieved with BID dosing of ≥100 mg/kg.

In rats, the maximum feasible dose (due to volume and solubility) of 500 mg/kg of Telaglenastat (CB-839) HCl was well tolerated during a 4-week toxicity study, and a severely toxic dose of 10% was not identified (CB-839 Investigator's Brochure, 2017). There were no clinical observations related to Telaglenastat (CB-839) HCl at the maximum dose, nor any notable findings in a gross necropsy. The concentrations of alkaline phosphatase were slightly decreased, while triglycerides and cholesterol levels were modestly increased compared to controls. While statistically significant, these were considered to be non-adverse, fully reversible, and without histology correlates. There was a 1-2 second decrease in prothrombin time, which reversed during a 14-day non-dosing recovery period.

In marmoset monkeys receiving up to 125 mg/kg BID of Telaglenastat (CB-839) HCl for 28 days, Telaglenastat (CB-839) HCl was well tolerated with no mortality, nor notable clinical observations (CB-839 Investigator's Brochure, 2017). In sporadic animals receiving the mid- and high-dose, two liver enzymes, γ-glutamyl-transpeptidase and glutamate dehydrogenase, were significantly elevated at sacrifice, while other liver function tests (LFTs) were within normal limits. This correlated with minimal to slight bile duct hyperplasia. These findings were not observed in animals which underwent a 14-day non-dosing recovery period before sacrifice. The highest non-severely toxic dose was not defined.

2.2.1.3 Summary of Clinical Experience

As of January 23, 2017, 161 patients have received Telaglenastat (CB-839) HCl as monotherapy, and 94 patients have received Telaglenastat (CB-839) HCl in combination with other agents in phase 1 and early phase 2 trials (CB-839 Investigator's Brochure, 2017). A summary of clinical data from company-sponsored Telaglenastat (CB-839) HCl trials as of January 23, 2017 is presented below. Details of all ongoing studies can be found in the most recent Telaglenastat (CB-839) HCl Investigator’s Brochure.

2.2.1.3.1 Clinical PK and Pharmacodynamics

The PK data from patients in all three monotherapy studies were collected (pre-dose, 0.5, 1, 2, 4, 6, 8 hours post-dose) on Cycle 1, Day 1 (C1D1) and C1D15 (CB-839 Investigator's Brochure, 2017). Patients treated with either 100-1000 mg of Telaglenastat (CB-839) HCl three times a day (TID) or 600-1000 mg of Telaglenastat (CB-839) HCl BID showed a high inter- and intra-patient variability in Telaglenastat (CB-839) HCl exposures, and dose proportionality could not be established with statistical significance. In general, Telaglenastat (CB-839) HCl plasma exposure (expressed as AUC from time 0 to 8 hours [$AUC_{0\text{-}8hr}$]) increased with dose over the range from 100 to 600 mg TID. However, at doses of 600 mg and above, the high variation within dose groups made it difficult to

determine exposure differences. For patients with at least three time points, the average terminal half-life ($t_{1/2}$) was ~4 hours. The median accumulation ratio was ~2.0 at C1D15 versus C1D1.

Some of the observed variability can be attributed to differences in food intake and co-administration of proton pump inhibitors (PPI) (CB-839 Investigator's Brochure, 2017). Food-effect studies comparing patients taking 600 mg of Telaglenastat (CB-839) HCl TID without food to patients receiving 600 mg of Telaglenastat (CB-839) HCl BID with meals revealed a 1.3-fold increase in $AUC_{0\text{-}8hr}$ on C1D1. Although this result was not significant, similar exposure was observed at steady-state (C1D15) in both the 600 mg BID fed and 600 mg TID fasted groups despite the daily dose being 1/3 lower on the BID schedule. Concomitant PPI administration had a significant decrease in $AUC_{0\text{-}8hr}$ in patients on the 600 mg BID schedule. The PPI effect may be due to reduced absorption at higher stomach pH because of the pH-dependent solubility of Telaglenastat (CB-839) HCl. There were no statistically significant differences in the exposure of Telaglenastat (CB-839) HCl in various demographic groups, including age, gender, race, or body weight.

Pharmacodynamic response in these trials was assessed as glutaminase (GLS) activity in platelets and peripheral blood mononuclear cells (PBMCs) 4 hours after the first dose of CB-389 HCl on C1D1, or in solid tumor biopsy samples collected on C2D1 in early dose cohorts on study CX-839-001 (CB-839 Investigator's Brochure, 2017). A greater than 90% GLS inhibition was observed in platelets when Telaglenastat (CB-839) HCl levels exceeded 250 ng/mL. In solid tumor biopsies, a 75% inhibition of GLS activity was observed. Plasma glutamine concentrations were also monitored 4 hours post-dose on C1D1 and C1D15. All dose groups showed a 1.5- to 2-fold increase in plasma glutamine levels on C1D15, confirming GLS inhibition.

2.2.1.3.2 Clinical Safety Summary

Among 59 patients who received Telaglenastat (CB-839) HCl monotherapy on the TID (fasted) schedule over a dose range of 100-1000 mg, two DLTs have been observed: one at 250 mg TID (grade 3 elevated creatinine) and one at 400 mg TID (grade 3/4 elevated LFTs) (CB-839 Investigator's Brochure, 2017). No DLTs have been reported on the monotherapy BID (fed state) schedule up to a dose of 800 mg. DLTs reported in combination cohorts have been: Grade 4 neutropenia (400 mg BID with 80 mg/m^2 intravenous [IV] paclitaxel weekly for 3 weeks in every 4 week cycle and 400 mg BID with 4 mg once daily [QD] pomalidomide for 21 days out of every 28 day cycle and 40 mg each week [QW] of dexamethasone), grade 3 pruritic rash (400 mg BID with 10 mg everolimus QD), grade 3 alanine aminotransferase (ALT) increase (800 mg BID with 240 mg IV nivolumab once every two weeks), and grade 4 platelet count decrease (600 mg dose with 60 mg cabozantinib QD). Although a maximum tolerated dose (MTD) has not been defined for either monotherapy or combination therapy, 800 mg BID is the highest dose that is confirmed to be safe and well tolerated in single-agent and combination Telaglenastat (CB-839) HCl studies.

The largest monotherapy study of Telaglenastat (CB-839) HCl, CX-839-001) included 120 patients with solid tumors, 32 receiving between 100 to 800 mg of Telaglenastat (CB-839) HCl TID without food and 88 receiving between 600 to 1000 mg of Telaglenastat (CB-839) HCl BID

with food (CB-839 Investigator's Brochure, 2017). On the BID schedule, 69.3% of patients experienced an adverse event (AE), the most common of which were fatigue, elevated LFTs, gastrointestinal (GI) AEs, and photophobia. These AEs were typically grade 1/2, reversible, and manageable without dose interruption or modification. Grade 3 LFTs were significantly reduced (2.3% of patients) on the BID schedule. One grade 3 AE of anemia was also considered to be related to Telaglenastat (CB-839) HCl.

As of the January 23, 2017, a total of 127 serious AEs (SAEs) across monotherapy and combination therapy have been recorded (CB-839 Investigator's Brochure, 2017). Seven patients experienced at least one SAE that was considered at least possibly related to Telaglenastat (CB-839) HCl treatment: increased creatinine (one patient), increased aspartate aminotransferase (AST) and/or ALT (two patients), seizure (one patient), stomatitis (one patient), dyspnea (one patient), and one patient with three concurrent SAEs of hypotension, tachycardia, and pyrexia.

2.2.1.3.3 Clinical Efficacy Summary

Patients with multiple tumor types have been included in studies with Telaglenastat (CB-839) HCl as a monotherapy or in combination with other agents (CB-839 Investigator's Brochure, 2017). In monotherapy cohorts, best overall response of stable disease (SD) or better has been observed in a variety of malignancies, including TNBC, NSCLC, RCC, MM, and leukemia. In clear cell RCC patients receiving Telaglenastat (CB-839) HCl in combination with everolimus, seven of eight (87.5%) evaluable patients achieved disease control at 16 weeks, which is notable when compared to two recent phase 3 studies of everolimus alone, where ~50% of patients had PD at 16 weeks

2.2.2 Osimertinib (AZD9291)

Osimertinib (AZD9291) is a potent irreversible TKI of both the single epidermal growth factor receptor mutation (*EGFRm*; TKI sensitivity-conferring mutation) and dual *EGFRm*/T790M (TKI resistance-conferring mutation) receptor forms of EGFR (Osimertinib (AZD9291) Investigator's Brochure, 2018). Activation of the EGFR TK triggers a cascade of intracellular downstream signaling events affecting cell proliferation, survival, angiogenesis and, potentially, metastasis.

Osimertinib (AZD9291) has shown antitumor activity *in vitro* against several lung cancer cell lines (H1975, PC9VanR, CALU3, CALU6, and H2073), and *in vivo* in murine xenograft models (H1975 [EGFR L858R/T790M] and H3255 [L858R]) (Osimertinib (AZD9291) Investigator's Brochure, 2018). Data from an AstraZeneca-sponsored study (Study D5160C001, the AURA study) in pretreated NSCLC patients with centrally-tested *EGFR* T790M mutation-positive tumors showed that treatment with Osimertinib (AZD9291) resulted in tumor shrinkage, with an investigator-assessed objective response rate (ORR) of 58.6% across all doses.

On March 30, 2017, the U.S. Food and Drug Administration (FDA) granted regular approval to Osimertinib (AZD9291) (as TAGRISSO®, AstraZeneca Pharmaceuticals) for the treatment of patients with metastatic *EGFR* T790M mutation-positive NSCLC, as detected by an FDA-approved test, whose disease has progressed on or after EGFR TKI therapy (U.S. Food and Drug Administration, 2017).

On April 18, 2018, the FDA approved Osimertinib (AZD9291) (as TAGRISSO®, AstraZeneca Pharmaceuticals) for the first-line treatment of patients with metastatic NSCLC whose tumors have *EGFR* exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test (U.S. Food and Drug Administration, 2018).

2.2.2.1 Mechanism of Action

Osimertinib (AZD9291) is kinase inhibitor of EGFR and binds irreversibly to certain mutant forms of *EGFR* (T790M, L858R, and exon 19 deletion) at approximately 9-fold lower concentrations than wild- type (Osimertinib (AZD9291) Investigator's Brochure, 2018). Activation of the EGFR tyrosine kinase (TK) triggers a cascade of intracellular downstream signaling events affecting cell proliferation, survival, angiogenesis and, potentially, metastasis. Receptor activation leads to phosphorylation of specific tyrosine residues within the cytoplasmic tail (Normanno *et al.*, 2006) These phosphorylated residues serve as docking sites for proteins containing Src homology 2 (SH2) and phosphotyrosine binding (PTB) domains, including containing (Shc), growth factor receptor binding protein 10 (Grb7), Grb2, CT10 regulator of kinase (Crk), non-catalytic region of tyrosine kinase adaptor protein 1 (Nck), the phospholipase Cγ (PLCγ), the intracellular kinases Src and phosphoinositide 3-kinase (PI3K), the protein tyrosine phosphatases Src homology-2 domain containing protein tyrosine phosphatase-1 (SHP1) and SHP2, and the Casitas B-lineage lymphoma (Cbl) E3 ubiquitin ligase (Yaffe, 2002; Marmor and Yarden, 2004; Normanno *et al.*, 2006). All ligands induce activation of the rat sarcoma/rapidly accelerated fibrosarcoma/mitogen-activated protein kinase kinase/mitogen-activated protein kinase (RAS/RAF/MEK/MAPK) pathway through either Grb2 or Shc adaptor proteins (Carpenter, 2003; Citri *et al.*, 2003; Jorissen *et al.*, 2003; Normanno *et al.*, 2006). ErbB receptors also activate PI3K by recruitment of the p85 regulatory subunit to the activated receptors (Soltoff and Cantley, 1996; Normanno *et al.*, 2006).

2.2.2.2 Summary of Nonclinical Experience

Biochemical studies showed Osimertinib (AZD9291) to be a potent and selective irreversible inhibitor of isolated mutant *EGFR*s with a margin of selectivity against wild-type *EGFR* (apparent half maximal inhibitory concentrations [IC_{50}] <12 nM for mutant vs. 184 nM for wild-type *EGFR*) (Osimertinib (AZD9291) Investigator's Brochure, 2018). Oral (PO) Osimertinib (AZD9291) treatment resulted in dose- related tumor growth inhibition in the lung cancer cell line H1975 (*EGFR* L858R/T790M) murine xenograft model, with profound regression being achieved at doses above 2.5 mg/kg after QD administration for 14 days.

The toxicological profile of Osimertinib (AZD9291) has been evaluated in rats and dogs in studies of up to 6 and 9 months duration, respectively (Osimertinib (AZD9291) Investigator's Brochure, 2018). The main findings comprised atrophic, inflammatory and/or degenerative changes affecting the epithelia of the eye (cornea), GI tract (including tongue), skin, and male and female reproductive tracts.
These findings occurred at plasma concentrations that were below those seen in patients at the 80 mg therapeutic dose. The AEs that were observed following 1 month of dosing were largely reversible within 1 month of cessation of dosing. Osimertinib (AZD9291) had marked AEs on embryonic survival plus early postnatal viability and growth when administered to pregnant or lactating rats.

2.2.2.3 Summary of Clinical Experience

As of the data cut-off date (DCO) of November 12, 2017, 3,178 patients or healthy volunteers have been exposed to study treatment (Osimertinib (AZD9291) alone [including those crossed over from comparator treatment to Osimertinib (AZD9291) monotherapy], Osimertinib (AZD9291) in combination with another treatment, or comparator) in AstraZeneca-sponsored clinical studies (Osimertinib (AZD9291) Investigator's Brochure, 2018). Of these, 3,060 were NSCLC patients and 118 were healthy volunteers. As of November 12, 2017, 2,258 patients have received Osimertinib (AZD9291) monotherapy only, 229 have received Osimertinib (AZD9291) in combination with another treatment, 167 crossed over during the study from comparator treatment to Osimertinib (AZD9291) monotherapy and 524 patients were exposed to comparator treatment only, including placebo. Hence, a total of 2654 patients or healthy volunteers have been dosed with Osimertinib (AZD9291). An additional 4743 NSCLC patients have participated in the Osimertinib (AZD9291) Early Access Program and 3020 patients participated in the real- world evidence study (ASTRIS D5160C00022).

2.2.2.3.1 Clinical PK and Pharmacodynamics

Osimertinib (AZD9291) PK parameters have been characterized in healthy subjects and NSCLC patients (Osimertinib (AZD9291) Investigator's Brochure, 2018). Based on population PK analysis, Osimertinib (AZD9291) apparent plasma clearance is 14.3 L/h, apparent volume of distribution is 918 L, and $t_{1/2}$ is approximately 44 hours. The area under the plasma concentration-time curve (AUC) and maximum serum concentration (C_{max}) of Osimertinib (AZD9291) increased dose proportionally over 20 mg to 240 mg dose range (0.25 to 3 times the recommended dosage) after PO administration and exhibited linear PK. Administration of Osimertinib (AZD9291) PO QD resulted in approximately 3-fold accumulation with steady state exposures achieved after 15 days of dosing. At steady state, the C_{max} to minimal serum concentration (C_{min}) ratio was 1.6-fold. The median time to C_{max} of Osimertinib (AZD9291) was 6 hours (range 3 to 24 hours). The absolute bioavailability of Osimertinib (AZD9291) is 70% (90% confidence interval [CI] 67, 73). Neither food nor gastric pH affects the exposure of Osimertinib (AZD9291).

Based on clinical drug-drug interaction (DDI) studies, interactions with strong CYP3A4 inhibitors are unlikely but strong CYP3A4 inducers can decrease the exposure of (Osimertinib (AZD9291) Investigator's Brochure, 2018). Osimertinib (AZD9291) may also increase the exposure of co-administered breast cancer resistance protein (BCRP) substrates. Clinical PK interactions with co- administered CYP3A4 substrates are unlikely. No clinically significant differences in the PK of Osimertinib (AZD9291) were observed based on age, sex, ethnicity, body weight, smoking status, mild or moderate or severe renal impairment (creatinine clearance [CLcr] >15 mL/min by Cockcroft- Gault) or mild or moderate hepatic impairment (mild: Child Pugh A or total bilirubin less than or equal to the upper limit of normal [ULN] and AST greater than ULN or total bilirubin between 1 to 1.5 times ULN and any AST; moderate: Child Pugh B or total bilirubin between
1.5 to 3 times ULN and any AST).

2.2.2.3.2 Clinical Safety Summary

The AstraZeneca-sponsored AURA phase 1 trial was designed to support a robust dose selection decision, with 31 pre-treated patients with advanced NSCLC in the dose escalation part of the study and 2523 in the dose expansion part receiving the capsule formulation of Osimertinib (AZD9291) across the range of doses 20, 40, 80, 160, and 240 mg (Osimertinib (AZD9291) Investigator's Brochure, 2018). Of these, 103 patients (6 patients in the dose escalation cohort and 97 patients in the dose expansion cohort) were dosed at the recommended daily dose of 80 mg PO. No DLTs were reported at any dose level in the escalation cohorts of AURA phase 1 during the 21-day DLT evaluation period, and therefore a MTD has not been defined. The most commonly reported AEs were rash (grouped terms) (78%), diarrhea (73%), dry skin (grouped terms) (58%), paronychia (grouped terms) (50%) and stomatitis (47%). Osimertinib (AZD9291) appeared less tolerable at doses above 80 mg; an approximate doubling in the incidence of skin disorders, nail effects and diarrhea were observed at doses higher than 80 mg, with severe Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥3 instances of these events occurring more frequently at the 160 mg and 240 mg doses. Additionally, a substantive increase in dose reductions due to AEs was observed at doses of 160 mg (20.3%) and 240 mg (57.1%), compared to 80 mg (1.0%).

FLAURA was a randomized phase 3 study designed to test efficacy of Osimertinib (AZD9291) in patients with *EGFR*-mutated NSCLC *vs.* Standard of Care first line TKI (Osimertinib (AZD9291) Investigator's Brochure, 2018; Soria *et al.*, 2018). AEs were reported in the majority of patients in both treatment arms: 273 (97.3%) with Osimertinib (AZD9291) and 271 (97.8%) with Standard of Care. A similar proportion of patients in both arms had AEs assessed by investigators to be possibly related to study treatment: Osimertinib (AZD9291), 253 (90.7%) patients, Standard of Care, 255 (92.1%) patients. AEs were predominantly mild or moderate severity, with a lower incidence of AEs of CTCAE Grade ≥3 in the Osimertinib (AZD9291) arm compared with Standard of Care: CTCAE Grade ≥3 AEs were reported in 95 (34.1%) patients in the Osimertinib (AZD9291) arm compared with 124 (44.8%) patients in the Standard of Care arm. A similar proportion of patients in the 2 treatment arms reported SAEs, and AEs with an outcome of death (CTCAE Grade 5) were reported in a low but numerically higher proportion of patients in the Standard of Care arm. A lower proportion of patients had AEs leading to drug discontinuation in the Osimertinib (AZD9291) arm compared with the Standard of Care arm.

Serious AEs occurred in a similar proportion of patients in the 2 treatment arms. The most frequently reported SAEs in the Osimertinib (AZD9291) arm (≥1% of patients) were pneumonia (7 [2.5%] patients), ILD and pulmonary embolism (4 [1.4%] each), and pleural effusion (3 [1.1%) (Osimertinib (AZD9291) Investigator's Brochure, 2018; Soria *et al.*, 2018). The most frequently reported SAEs in the Standard of Care arm (≥1% of patients) were: pneumonia (7 [2.5%] patients), vomiting (5 [1.8%]), diarrhea (4 [1.4%]), and ILD, pleural effusion, dyspnea, sepsis, and drug- induced liver injury (3 [1.1%] each). Serious AEs were considered to be possibly related to study treatment by the investigator in a similar proportion of patients in the 2 treatment arms (Osimertinib (AZD9291): 22 [7.9%]; Standard of Care: 23 [8.3%]).

The proportion of patients who had CTCAE Grade ≥3 AEs was lower in the Osimertinib (AZD9291) arm (95 [34.1%] patients) compared with the Standard of Care arm (124 [44.8%] patients) (Osimertinib (AZD9291) Investigator's Brochure, 2018; Soria *et al.*, 2018). CTCAE

Grade ≥3 events were reported in a wide range of preferred terms covering multiple system organ classes (SOCs); most AEs were single events. The only CTCAE Grade ≥3 events reported by more than 5 patients in the Osimertinib (AZD9291) arm were decreased appetite (7 [2.5%] patients) and diarrhea, pneumonia and electrocardiogram interval measured from the beginning of the Q wave, R wave, S Wave (QRS) complex to the end of the T wave (ECG QT) prolonged (each in [2.2%] patients). AEs led to discontinuation of treatment in a lower proportion of patients in the Osimertinib (AZD9291) arm (37 [13.3%]) than in the Standard of Care arm (49 [17.7%]), indicating that Osimertinib (AZD9291) was at least as well tolerated as the Standard of Care comparator.

2.2.2.3.3 Clinical Efficacy Summary

In the dose expansion population of AURA phase 1, clinical activity was observed in patients with T790M mutation positive tumors (92/157 patients with a confirmed objective response) at all doses investigated (20 mg to 240 mg dose range), without any apparent trend (Mok *et al.*, 2017; Osimertinib (AZD9291) Investigator's Brochure, 2018). ORRs based on investigator assessment ranged from 50.0% to 65.6%, with highest ORR of 65.6% (95% CI: 52.3, 77.3) being observed at the 80 mg dose. Doses of 160 mg and higher appeared unlikely to provide any additional efficacy benefit. Responses were durable across all doses, with a median DoR of 11.1 months (38.0% maturity) and a median PFS of 10.9 months (42.9% maturity). In pre-treated patients with centrally-tested *EGFR* T790M mutation negative tumors in the AURA phase 1 component; investigator assessed analyses, the ORR was 24.6% (95% CI: 15.1, 36.5) in 17 of 69 EGFR patients. Median PFS was 3.0 months (95% CI: 2.1, 4.2; 88.4% maturity) in patients with centrally confirmed T790M mutation negative NSCLC.

In the AURA3 phase 3 study, the median duration of PFS was significantly longer with Osimertinib (AZD9291) than with platinum therapy plus pemetrexed (10.1 months vs. 4.4 months; HR; 0.30; 95% CI, 0.23 to 0.41; P<0.001) (Mok *et al.*, 2017; Osimertinib (AZD9291) Investigator's Brochure, 2018).

The ORR was significantly better with Osimertinib (AZD9291) (71%; 95% CI, 65 to 76) than with platinum therapy plus pemetrexed (31%; 95% CI, 24 to 40) (odds ratio for objective response, 5.39; 95% CI, 3.47 to 8.48; P<0.001). Among 144 patients with metastases to the central nervous system (CNS), the median duration of PFS was longer among patients receiving Osimertinib (AZD9291) than among those receiving platinum therapy plus pemetrexed (8.5 months vs. 4.2 months; hazard ratio [HR], 0.32; 95% CI, 0.21 to 0.49).

In the FLAURA phase 3 study, the median PFS was significantly longer with Osimertinib (AZD9291) than with standard EGFR TKIs (18.9 months vs. 10.2 months; HR for disease progression or death, 0.46; 95% CI, 0.37 to 0.57; P<0.001) (Osimertinib (AZD9291) Investigator's Brochure, 2018; Soria *et al.*, 2018). The ORR was similar in the two groups: 80% with Osimertinib (AZD9291) and 76% with standard EGFR TKIs (odds ratio, 1.27; 95% CI, 0.85 to 1.90; P=0.24). The median duration of response was 17.2 months (95% CI, 13.8 to 22.0) with Osimertinib (AZD9291) versus 8.5 months (95% CI, 7.3 to 9.8) with standard EGFR-TKIs. In a subsequent report on the final analysis of overall survival from the FLAURA trial, Ramalingam et al reported that the median overall survival was 38.6 months (95% confidence interval [CI], 34.5 to 41.8) in the osimertinib group and 31.8 months (95% CI, 26.6

to 36.0) in the comparator group (hazard ratio for death, 0.80; 95.05% CI, 0.64 to 1.00; P = 0.046) (Ramalingam *et al*, 2019)).

2.3 Rationale

Osimertinib (AZD9291) is a third generation EGFR inhibitor that has demonstrated activity in patients with *EGFR* activating mutation positive NSCLC who progressed on front-line EGFR inhibitor therapy despite the acquisition of a T790M gene mutation, indicating that it is able to overcome this resistance to therapy. As such, it has been approved for the treatment of *EGFR* activating mutation positive and T790M mutation positive NSCLC in the second-line setting (Janne *et al.*, 2015; Mok *et al.*, 2017). More recently, based on the FLAURA trial mentioned above, Osimertinib (AZD9291) has received FDA approval in the first line treatment of metastatic *EGFR*-positive NSCLC (Soria *et al.*, 2018). Although the improvement in overall survival is encouraging, unfortunately, eventually all patients progress on front-line EGFR inhibitor therapy with osimertinib. As such, the objective of this clinical trial is to identify a way to overcome resistance to front-line EGFR inhibitor therapy. To date, no single mechanism of resistance has been identified in these patients, although the most commonly described findings at time of osimertinib progression including *MET* amplification and *EGFR* amplification, as well as EGFR independent pathways including *BRAF* as well as histologic transformation (Romero *et al*, 2020; Roper *et al*, 2020). Preclinical studies have demonstrated that HIF-1 signaling pathway, PI3K-Akt pathway, and oxidative phosphorylation are upregulated in osimertinib resistant NSCLC cell lines, while glycolysis/gluconeogenesis is downregulated (Ma *et al*, 2020).

It has been shown that many cancer cells rely on two major pathways of metabolism for growth: glucose metabolism, which is driven by the EGFR pathway, and glutamine metabolism (Wise *et al.*, 2008; Gao *et al.*, 2009; Wang *et al.*, 2010; Gross *et al.*, 2014). While cellular growth may be inhibited by blocking glucose metabolism (and is the reason why EGFR inhibition is effective in the presence of EGFR activating mutations), there is no therapeutic intervention that additionally address the glutamine pathway which, if inhibited, may also result in growth inhibition. It is therefore our hypothesis that in patients who have received front-line EGFR inhibitor therapy and developed resistance, the addition of an agent that inhibits the glutamine pathway will overcome this resistance and that dual pathway inhibition will result in enhanced cellular toxicity. Lastly, given the role of glutamine in HIF-1 signaling (Ma *et al*, 2020) and oxidative phosphorylation (Chen *et al*, 2020), the addition of CB-839 to osimertinib may prolong disease control in these patients.

It has been shown in preclinical studies that synergy exists when NSCLC cells are treated with a combination of an EGFR inhibitor and a glutaminase inhibitor (Telaglenastat (CB-839) HCl) (Momcilovic *et al.*, 2017). As erlotinib has been the most commonly used agent for the front-line treatment of NSCLC, many of the preclinical studies assessing the combination have been performed with erlotinib. In a NSCLC cell line (HCC827, an *EGFR* activating mutation positive cell line) study, cell survival was found to be diminished with the administration of erlotinib (as would be expected) as well as with single agent Telaglenastat (CB-839) HCl. However, combinatorial administration of erlotinib and Telaglenastat (CB-839) HCl resulted in an even greater decrease in cell survival in a dose dependent manner. This combination was found to be synergistic (see Figure 1 below) suggesting that dual inhibition of the glucose and glutamine

metabolic pathways is more efficacious that inhibition of a single metabolic pathway.

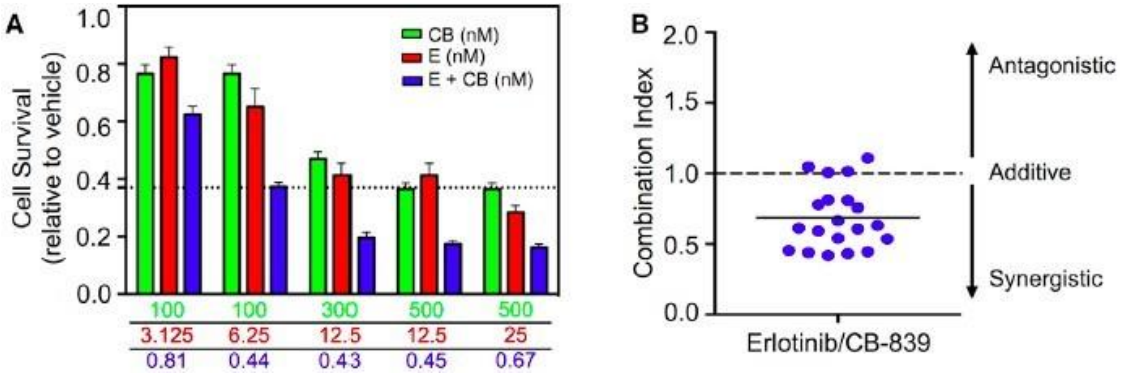


Figure 1: Erlotinib and Telaglenastat (CB-839) HCl Cooperate to Inhibit Growth of *EGFR* Mutant Cell Lines *In Vitro* (From Momcilovic *et al.*, 2017).

This was further evidenced in a xenograft model where mice with HCC827 NSCLC tumor xenografts were treated with single agent erlotinib, single agent Telaglenastat (CB-839) HCl or the combination (Momcilovic *et al.*, 2017). Single-agent Telaglenastat (CB-839) HCl did not generate a significant change in tumor growth while single-agent erlotinib did result in tumor shrinkage. In mice receiving the combination of erlotinib and Telaglenastat (CB-839) HCl, however, there was a significantly greater decrease in the size of the tumor xenograft as compared to mice treated with either erlotinib or Telaglenastat (CB-839) HCl as a single agent control. The fact that the combination was better than erlotinib alone is significant as this suggests improved disease control with combinatorial treatment as compared to standard single agent EGFR inhibition therapy.

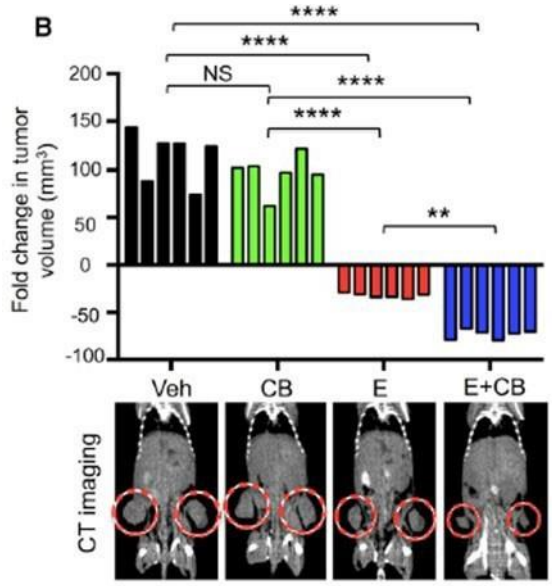


Figure 2: Erlotinib and Telaglenastat (CB-839) HCl Cooperate to Inhibit Growth of *EGFR* Mutant Xenografts *In Vivo* (From Momcilovic *et al.*, 2017).

Recently, the FLAURA trial, a randomized phase 3 trial of Osimertinib (AZD9291) vs. Standard of Care treatment with EGFR inhibitor therapy for first-line treatment of patients with *EGFR* activating mutation positive NSCLC, reported an improved PFS of 18.9 months with Osimertinib (AZD9291) compared to the Standard of Care (median PFS 10.2 months, HR 0.46, P<0.001) (Soria *et al.*, 2018). Given these positive results demonstrating superiority with Osimertinib (AZD9291), Osimertinib (AZD9291) has replaced erlotinib (and other earlier generation EGFR inhibitors) as the front-line treatment of choice for metastatic *EGFR* activating mutation positive NSCLC. As such, preclinical data assessing the combination of Osimertinib (AZD9291) and Telaglenastat (CB-839) HCl were conducted (Figure 3, Calithera internal, unpublished data). The synergistic activity of Osimertinib (AZD9291) and Telaglenastat (CB-839) HCl was assessed in two *EGFR* mutation positive NSCLC cell lines, HCC827 (T790M mutation negative) and H1975 (T790M mutation positive). In both of these studies, cell growth inhibition was observed in a dose-dependent manner and synergistic activity was observed in both the T790M mutation-positive and -negative groups.

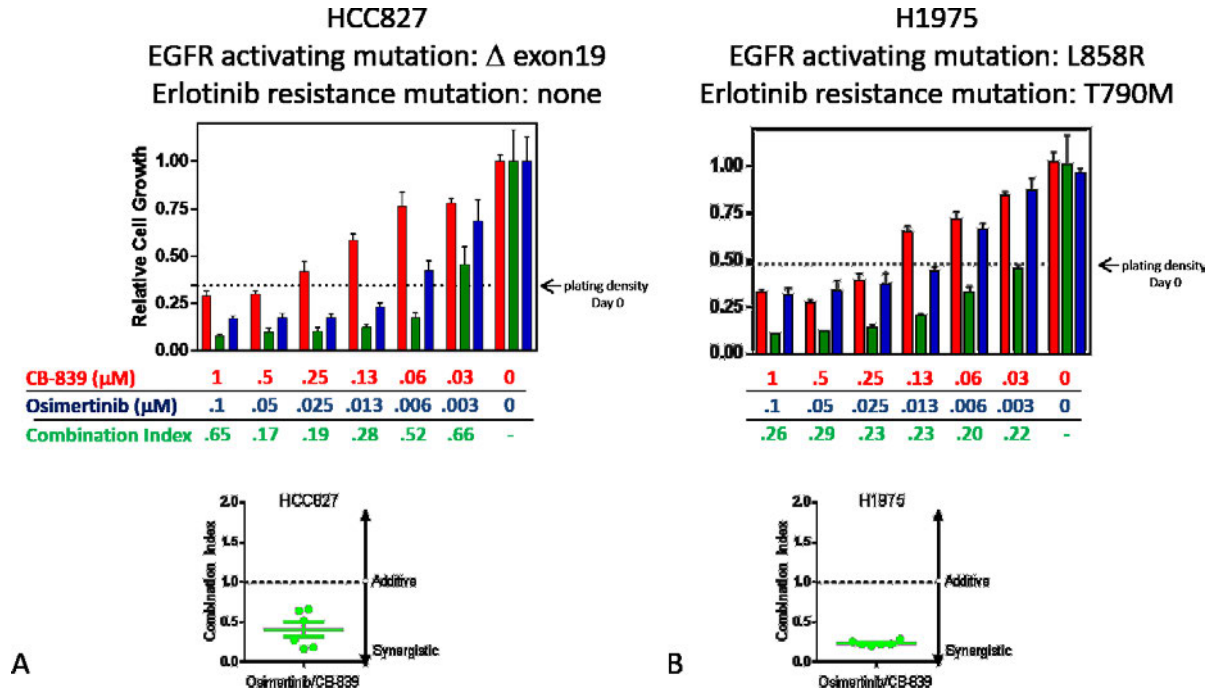


Figure 3: Synergistic activity of Osimertinib (AZD9291) and Telaglenastat (CB-839) HCl in HCC827 (A) and H1975
(B) cell lines. This synergy was seen in T790M positive and negative lines (From Calithera internal, unpublished data).

These studies provide additional preclinical data that the combination of an EGFR inhibitor and Telaglenastat (CB-839) HCl is synergistic, particularly when Osimertinib (AZD9291) is used as the EGFR inhibitor, and that this combination is efficacious even in T790M mutation negative NSCLC. Finally, to evaluate whether combination therapy could induce responses *in vivo*, mouse xenograft studies were performed which showed synergistic activity for Telaglenastat (CB-839) HCl and Osimertinib (AZD9291) (Figure 4A and 4B).

Based on the above preclinical data demonstrating synergistic activity between EGFR inhibitors

(including Osimertinib (AZD9291)) and the glutaminase inhibitor, Telaglenastat (CB-839) HCl, this phase 1/2 study is proposed to assess this drug combination in patients with metastatic *EGFR* activating mutation positive NSCLC who have progressed on front-line EGFR inhibitor therapy and are known to be T790M mutation-negative. We hypothesize that this combination will be more efficacious as compared to the historical control of Osimertinib (AZD9291) alone in this patient population.

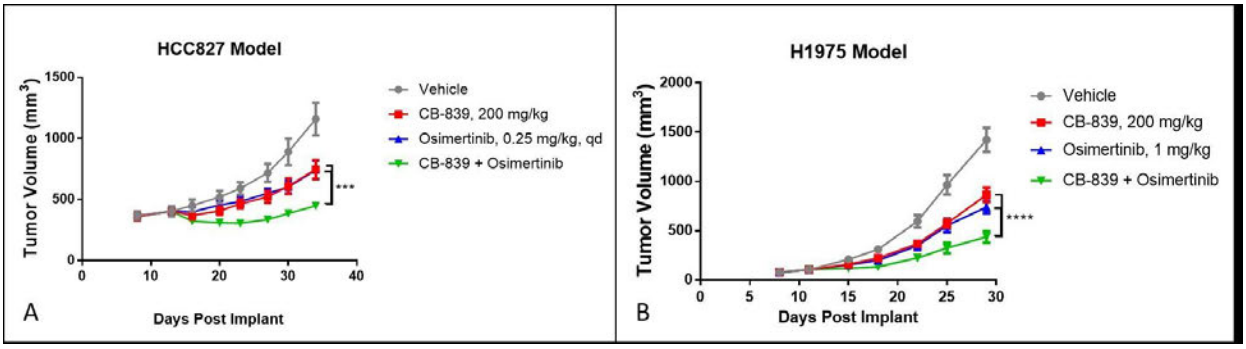


Figure 4: Synergistic activity of Osimertinib (AZD9291) and Telaglenastat (CB-839) HCl in HCC827 (A) and H1975
(B) xenograft models. A) Female scid/bg mice were implanted subcutaneously with 5 x 106 HCC827 lung adenocarcinoma cells. On Day 14 post-implant, mice were randomized into groups of n=10/group to receive the following: 1) Vehicle (25% hydroxypropyl-B-cyclodextrin) orally BID; 2) Telaglenastat (CB-839) HCl at 200 mg/kg orally BID; 3) Osimertinib (AZD9291) at 0.25 mg/kg orally once daily; or 4) Telaglenastat (CB-839) HCl at 200 mg/kg PO BID and Osimertinib (AZD9291) orally once daily. Tumors were measured with calipers three times per week and tumor volume calculated using the formula tumor volume (mm3) = (a x b2/2) where 'b' is the smallest diameter and 'a' is the largest perpendicular diameter. ***P <0.001 (ANOVA) versus both monotherapies. B) Female scid/bg mice were implanted subcutaneously with 2.5 x 10^6 H1975 lung adenocarcinoma cells. On Day 12 post-implant, mice were randomized into groups of n=10/group to receive the following: 1) Vehicle (25% hydroxypropyl-B-cyclodextrin) orally BID; 2) Telaglenastat (CB-839) HCl at 200 mg/kg orally BID; 3) Osimertinib (AZD9291) at 1 mg/kg orally once daily; or 4) Telaglenastat (CB-839) HCl at 200 mg/kg PO BID and Osimertinib (AZD9291) orally once daily. Tumors were measured with calipers three times per week and tumor volume calculated using the formula tumor volume (mm^3) = (a x b^2/2) where 'b' is the smallest diameter and 'a' is the largest perpendicular diameter. ****P <0.0001 (ANOVA) *versus* both monotherapies.

Pharmacokinetics of Osimertinib (AZD9291) and Telaglenastat (CB-839) HCl

Since Telaglenastat (CB-839) HCl is a substrate of efflux pumps, co-administration of Telaglenastat (CB-839) HCl and Osimertinib (AZD9291), an efflux pump inhibitor, may increase intracellular concentrations of Telaglenastat (CB-839) HCl and result in lower plasma concentrations. Both Osimertinib (AZD9291) and Telaglenastat (CB-839) HCl are oral agents with Osimertinib (AZD9291) administered QD (regardless of presence/absence of food) and Telaglenastat (CB-839) HCl administered BID with food. Given that both agents are absorbed within the gut, under these differing conditions and utilizing an overlapping pump mechanism, a DDI that may affect the absorption and blood levels of either of these agents could be possible and to date has not been explored. The question of whether these agents can be co-administered without affecting absorption of either Telaglenastat (CB-839) HCl or Osimertinib (AZD9291) is therefore relevant and as such, a phase 1 component is necessary to evaluate this drug combination and to obtain thorough PK information at a number of dose levels.

Rationale for expansion cohort

In order to gain additional data regarding safety and tolerability of combination Telaglenastat (CB-839) HCl and Osimertinib (AZD9291), as well as to confirm PK findings above, an expansion cohort of 10 patients treated at RP2D will be conducted. This expansion cohort will include only patients who have experience disease progression on first line Osimertinib (AZD9291) which has become the standard first line treatment for *EGFR* mutation positive NSCLC. The expansion cohort will allow for additional analysis of biospecimens to understand the metabolic and molecular changes that occur during treatment with CB-839 and osimertinib. Lastly, the expansion cohort will provide additional information regarding preliminary efficacy of the combination in these patients.

Rationale for dose selection for expansion cohort

In the expansion cohort, patients will receive combination Telaglenastat (CB-839) HCl at 800 mg orally twice daily and Osimertinib (AZD9291) 80 mg orally daily. This is based on results of the dose escalation cohort where combination Telaglenastat (CB-839) HCl and Osimertinib (AZD9291) at these doses were associated with acceptable safety and toxicity profile. In total, 12 patients were treated with combination Telaglenastat (CB-839) HCl and Osimertinib (AZD9291) in the dose escalation study, with one patient experiencing DLT at dose level 3 (grade 3 mucositis and grade 2 pneumonitis, which is protocol defined DLT). Both mucositis and pneumonitis are known toxicities with osimertinib, and both resolved with supportive care and withholding of study therapy. Treatment related serious adverse events (TRSAE) occurred in 2 patients, including grade 3 lymphocyte count decreased (attributed to osimertinib) in one patient as well as grade 3 fatigue (attributed as possibly related to both study agents and likely related to disease), and grade 3 failure to thrive (attributed as possibly related to CB-839 and definitely related to disease). The most common treatment related adverse events of any grade were nausea (n=6, 50%, all grade 1 or 2), fatigue (n=4, 33%), and decreased white blood cell count (n=4, 33%). Best response was complete response (CR) in 1 patient, stable disease (SD) in 7 patients, and disease progression in 4 patients. Of note, all 6 patients treated at the highest dose level tested had stable disease as best response after experiencing progression on osimertinib. As 800 mg BID is the highest dose that is confirmed to be safe and well tolerated in single-agent and combination Telaglenastat (CB-839) HCl studies, and there were no new safety concerns as well as evidence of clinical activity seen in the dose escalation cohort, Telaglenastat (CB-839) HCl at 800 mg orally twice daily and Osimertinib (AZD9291) 80 mg orally daily was chosen for the expansion cohort.

2.4 Correlative Studies Background

The molecular landscape of cancer is just beginning to be defined. However, we do not know enough about the genomic and molecular landscape of tumors from patients who enter early phase clinical trials. With this study, we will attempt to learn more about specific molecular features of cancers from this patient subgroup. It is particularly important to learn, as early as possible, if there are molecular features within a particular malignant histology or across malignant histologies that can inform about potential response or resistance to treatments in early phase clinical trials. Such knowledge will be used to design more efficient later stage clinical trials for more efficient and more effective drug development.

2.4.1 *EGFR* Mutational Status (Integral, Standard of Care)

Given the importance of *EGFR* genotyping in predicting the activity of all TKI therapy including Osimertinib (AZD9291), genotyping for *EGFR* mutational status will performed on all patients on study. This is considered routine practice upon progressive disease on first line TKI.

EGFR mutational status will be assessed in local/referral Clinical Laboratory Improvement Amendments (CLIA)-certified laboratories as part of the Standard of Care procedures for patients with NSCLC.

2.4.2 Quantification of Plasma Glutamine, Glutamate, Aspartate, and Asparagine Concentrations (Integrated)

Telaglenastat (CB-839) HCl is a selective, allosteric, noncompetitive inhibitor of both isoforms of GLS. This inactivation of GLS results in an increase of glutamine and a decrease of glutamate and several TCA cycle intermediates within cancer cells, leading to a decrease in cell proliferation and/or an increase in cell death (Gross *et al.*, 2014; Matre *et al.*, 2016). The plasma levels of glutamine, glutamate, aspartate, and asparagine will be measured at various time points to determine the changes as a result of Telaglenastat (CB-839) HCl monotherapy or Telaglenastat (CB-839) HCl and Osimertinib (AZD9291) combination therapy. The changes in the systemic levels of these metabolites provide key pharmacodynamic information on the effects of glutaminase inhibition.

Measurement of plasma concentrations of glutamine, glutamate, aspartate, and asparagine will be performed using validated liquid chromatography tandem-MS (LC/MS/MS) assays by the Mayo Clinic Cancer Center's Metabolomics Resource Core under the direction of Dr. Ian Lanza.

2.4.3 Whole Exome Sequencing to Confirm *EGFR* Mutational Status (Integrated)

The importance of *EGFR* testing is outline above in Section 2.4.1. In order to confirm *EGFR* mutational status, including sensitizing and resistance mutations (*i.e.,* T790M), whole exome sequencing (WES) will be performed on archival tumor as an integrated biomarker at the Frederick National Laboratory for Cancer Research (FNLCR), Molecular Characterization Laboratory (MoCha).

2.4.4 Pharmacokinetics (Integrated)

Blood levels of Osimertinib (AZD9291) and Telaglenastat (CB-839) HCl will be assessed to evaluate drug-drug interactions, and to compare to established pharmacokinetic profiles from prior single-agent trials. Since Telaglenastat (CB-839) HCl is a substrate of efflux pumps, co-administration of Telaglenastat (CB- 839) HCl and Osimertinib (AZD9291), the efflux pump inhibitor, may increase intracellular concentrations of Telaglenastat (CB-839) HCl and result in lower plasma concentrations.

2.4.5 Whole Exome Sequencing / RNA sequencing (Exploratory)

In order to determine possible biomarkers for response to treatment with Osimertinib (AZD9291) and Telaglenastat (CB-839) HCl, WES and RNA sequencing (RNAseq) will be

performed on the archival/baseline tumor specimen. Recent studies have demonstrated the importance of co- mutations in *EGFR*-mutated NSCLC, and potential primary resistance mechanisms to Osimertinib (AZD9291) have been elucidated, including regulators of cell cycle such as *CDK4/6* (Blakely *et al.*, 2017) as well as additional *EGFR* mutations L718 and L792 (Yang *et al.*, 2018). Evaluation for these and other mutations at baseline will be performed to identify biomarkers associated with drug activity.

2.4.6 Cell-Free DNA Analysis (Exploratory)

cfDNA will be assessed for *EGFR* mutational status, T790M mutational status and resistance mechanisms at different time points in this study. Peripheral blood will be collected for cfDNA at baseline, after one month of treatment, and at time of progression. In the phase 1 study, cfDNA will also be collected on C1D15 after single agent Telaglenastat (CB-839) HCl prior to initiation of combination therapy. cfDNA for *EGFR* status will be compared with archival/baseline specimen for concordance. Blood based assays for detection of resistance mechanisms are widely used in clinical practice, and have also yielded information about resistance mechanisms to treatment (Blakely *et al.*, 2017).

3. PATIENT SELECTION

3.1 Overall Eligibility Criteria

3.1.1 Histologically confirmed, Stage IV NSCLC, with advanced or metastatic disease.

3.1.2 Activating mutation present in the *EGFR* gene (L858R or exon 19 deletion, alone or in combination with other *EGFR* mutations) as per local assessment of a tissue biopsy/cytology specimen. The tissue biopsy must have been obtained since the time of disease progression on most recent targeted therapy. “Liquid” (i.e.blood based) biopsies cannot be used for eligibility determination.

3.1.3 Patients must have had progressive disease on prior EGFR inhibitor therapy (gefitinib, erlotinib, afatinib, or osimertinib). There is no limit to lines of prior TKI therapy. Prior Osimertinib (AZD9291) therapy is permitted.

3.1.4 Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥20 mm (≥2 cm) by chest X-ray or as ≥10 mm (≥1 cm) with CT scan, magnetic resonance imaging (MRI), or calipers by clinical exam. See Section 12 for the evaluation of measurable disease.

3.1.5 Age >18 years. NSCLC is exceedingly rare in patients <18 years of age. Because no dosing or AE data are currently available on the use of Telaglenastat (CB-839) HCl in combination with Osimertinib (AZD9291) in patients <18 years of age, children are

excluded from this study.

3.1.6 Eastern Cooperative Oncology Group (ECOG) performance status ≤2 (Karnofsky ≥60%, see Appendix A).

3.1.7 Must be able to swallow pills.

3.1.8 Life expectancy >3 months.

3.1.9 Patients must have adequate organ and marrow function as defined below:

– leukocytes	≥3,000/mcL
– absolute neutrophil count	≥1,500/mcL
– platelets	≥100,000/mcL
– hemoglobin	≥90 g/L
– total bilirubin	≤1.5 × institutional ULN and up to 3 mg/dL for patients with Gilbert's disease
– AST(SGOT)/ALT(SGPT)	≤2.5 × institutional ULN and ≤5 × institutional ULN for patients with liver metastases
– creatinine	within 1.5 × ULN OR
– glomerular filtration rate (GFR)	≥50 mL/min/1.73 m^2 [measured or calculated by Cockcroft and Gault equation] —confirmation of creatinine clearance is only required for patients with creatinine levels above institutional upper limit of normal.

3.1.10 Should participants with HBV infection be included, patients are only eligible if they meet all the following criteria:

- Demonstrated absence of HCV co-infection or history of HCV co-infection *(Note that the sponsor's 3.1.11 is more lenient because it allows for history of HBC)*
- Demonstrated absence of HIV infection
- Participants with active HBV infection are eligible if they are:

  Receiving anti-viral treatment for at least 6 weeks prior to study treatment, HBV DNA is suppressed to <100 IU/mL and transaminase levels are below ULN.

  Participants with a resolved or chronic infection HBV are eligible if they are:

  Negative for HBsAg and positive for hepatitis B core antibody [anti-HBc IgG]. In addition, patients must be receiving anti-viral prophylaxis for 2-4 weeks prior to study treatment and 6-12 months (TBD by hepatologist) post treatment
  Or
  Positive for HBsAg, but for > 6 months have had transaminases levels below ULN and HBV DNA levels below <100 IU/mL (i.e., are in an inactive carrier state). In addition, patients must

be receiving anti-viral prophylaxis for 2-4 weeks prior to study treatment and 6-12 months (TBD by hepatologist) post treatment. Refer to section 3.4.

3.1.11 If history of hepatitis C virus (HCV) infection, must be treated and have an undetectable HCV viral load.

3.1.12 Patients with **treated brain metastases** are eligible if follow-up brain imaging after central nervous system (CNS)-directed therapy shows no evidence of progression.

3.1.13 Patients with **new or progressive brain metastases** (active brain metastases) or **leptomeningeal disease** are eligible if the treating physician determines that immediate CNS specific treatment is not required and is unlikely to be required during the first cycle of therapy. Patients on corticosteroids for the treatment of brain metastases will be permitted as long as the dose is is ≤ 10 mg of prednisone-equivalent and has not been increased within 2 weeks of screening.

3.1.14 Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.

3.1.15 Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, patients should be class 2B or better.

3.1.16 Ability to understand and the willingness to sign a written informed consent document. Participants with impaired decision-making capacity (IDMC) who have a legally-authorized representative (LAR) and/or family member available will also be eligible.

3.2 Exclusion Criteria

3.2.1 Patients who have not recovered from AEs due to prior systemic anti-cancer therapy (*i.e.*, have residual toxicities > grade 1), with the exception of alopecia. Note: Subjects with irreversible toxicity that in the opinion of the treating physician is not reasonably expected to be exacerbated by the investigational treatment may be included (e.g., hearing loss, hormone deficiency requiring replacement therapy).

3.2.2 Previous enrollment in the present study.

3.2.3 Past medical history of interstitial lung disease, drug-induced interstitial lung disease, radiation pneumonitis requiring steroid treatment, or any evidence of clinically active interstitial lung disease.

3.2.4 Patients who are receiving any other investigational agent within five half-lives of the compound or 3 months, whichever is greater. Patients who have received prior immunotherapy may be included only if time from last immunotherapy is at least 3 months (ie 90 days).

3.2.5 Spinal cord compression, symptomatic and unstable brain metastases except for those patients who have completed definitive therapy, and have had a stable neurological status for at least 2 weeks after completion of definitive therapy. Patients may be on corticosteroids (≤ 10 mg of prednisone-equivalent) to control brain metastases if they have been on a stable dose for 2 weeks (14 days) prior to the start of study treatment and are clinically asymptomatic."

3.2.6 Patients with an uncontrolled intercurrent illness.

3.2.7 Patients with psychiatric illness/social situations that would limit compliance with study requirements.

3.2.8 History of allergic reactions attributed to compounds of similar chemical or biologic composition to Telaglenastat (CB-839) HCl, Osimertinib (AZD9291), or other agents used in study. Patients with hypersensitivity to to any of the inactive excipients thereof should also be excluded.

3.2.9 Currently receiving (or unable to stop use prior to receiving the first dose of study treatment) medications or herbal supplements known to be potent inducers of CYP3A4 (wash-out periods vary; see Appendix D [Guidance Regarding Potential Interactions with Concomitant Medications]) All patients must try to avoid concomitant use of any medications, herbal supplements and/or ingestion of foods with known inducer effects on CYP3A4.

3.2.10 Pregnant women are excluded from this study because Telaglenastat (CB-839) HCl is a glutaminase inhibitor with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for AEs in nursing infants secondary to treatment of the mother with Telaglenastat (CB-839) HCl and Osimertinib (AZD9291), breastfeeding should be discontinued if the mother is treated with Telaglenastat (CB-839) HCl and Osimertinib (AZD9291). Breastfeeding patients will be excluded. These potential risks may also apply to other agents used in this study.

3.2.11 Patients with a significant history of cardiovascular disease (e.g., MI, thrombotic or thromboembolic event in the last 6 months).

3.2.12 Any of the following cardiac criteria:

a) Mean resting corrected QT interval (QTc using Fredericia's formula [QTcF]) >470 msec (Fridericia's Criteria for Corrected QT interval [QTc] Calculation: Fridericia's formula QTcF = (QT/RR0.33). RR is the time from the interval of 1 QRS complex to the next measured in seconds and is commonly calculated as (60/HR) (Hosmane *et al.,* 2006)
b) Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG (*e.g.*, complete left bundle branch block, third degree heart block, second degree heart block)
c) Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, electrolyte abnormalities (including: Serum/plasma

potassium < LLN; Serum/plasma magnesium < LLN; Serum/plasma calcium < LLN , congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years of age in first degree relatives, or any concomitant medication known to prolong the QT interval and cause Torsades de Pointes.

d) Left ventricular ejection fraction (LVEF) < lower limit of normal (LLN) as assessed by either multigated acquisition (MUGA) scan or echocardiogram (ECHO).

3.2.13 Patients with active malignancies other than NSCLC or patients with prior curatively treated malignancy at high risk of relapse during the study period with the exception of localized squamous or basal cell skin cancers, ductal carcinoma in-situ (DCIS), or indolent cancer currently on observation (*i.e.* CLL or low-risk prostate cancer).

3.2.14 Any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension and active bleeding diatheses, which in the investigator's opinion makes it undesirable for the patient to participate in the trial or which would jeopardise compliance with the protocol, or active infection with human immunodeficiency virus (HIV). Screening for chronic conditions is not required.

3.2.15 Patients with symptomatic CNS metastases who are neurologically unstable.

3.2.16 Patients who are at risk for impaired absorption of oral medication including, but not limited to, refractory nausea and vomiting, chronic gastrointestinal diseases, inability to swallow the formulated product or previous significant bowel resection that would preclude adequate absorption of Telaglenastat (CB-839) HCl and Osimertinib (AZD9291).

3.2.17 Judgment by the investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions and requirements.

3.2.18 Involvement in the planning and/or conduct of the study (applies to both Investigator staff and/or staff at the study site).

3.3 Expansion Cohort Specific Inclusion Criteria

3.3.1 Patients must have had progressive disease on prior first line EGFR inhibitor therapy with osimertinib.

3.4 Restrictions

3.4.1 Telaglenastat (CB-839) HCl is a weak *in vitro* inhibitor of CYP2C9. Therefore, patients receiving any medications or substances that are substrates of CYP2C9 are eligible but should use caution with substrates that have a narrow therapeutic index. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated medical reference. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product.

3.4.2 The effects of Telaglenastat (CB-839) HCl and Osimertinib (AZD9291) on the developing human fetus are unknown. For this reason and because glutaminase inhibitor and EGFR TKI agents are known to be teratogenic, women of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and up to 6 weeks after receiving last dose of study treatment. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 4 months after completion of Telaglenastat (CB-839) HCl and Osimertinib (AZD9291) administration. For further details please refer to Appendix F (Definition of Women of Childbearing Potential and Acceptable Contraceptive Methods).

3.4.3 Patients who have received prior treatment with immune-oncology (IO) therapies should be closely monitored for an appropriate period of time after the last dose of the IO treatment, in accordance with the respective IO label, as immune mediated adverse reactions with the IO therapy may occur at any time during or after discontinuation of therapy. The stop date of the prior IO drug therapy should be captured in the case report forms.

3.4.4 In patients with resolved or chronic hepatitis B infection (inactive carrier state) or active controlled HBV infection on treatment with osimertinib:

a. Recommend monthly monitoring of ALT/AST, HBV DNA levels and HBsAg (if negative at baseline)
b. Where liver signs and symptoms of viral reactivation appear (HBV DNA levels exceeding 10-fold from baseline or ≥100 IU/ml (if baseline HBV DNA levels are undetectable) or conversion of HBsAg negative to positive):

Expert hepatologist/specialist oversight of the patient is required. Consider interruption

or discontinuation of study treatment, based on risk-benefit assessment

3.4.5 In terms of reproductive restrictions, the use of osimertinib in the approved setting needs to follow the current approved local safety guidance.

3.4.6 Once enrolled all patients must try to avoid concomitant use of medications, herbal supplements and/or ingestion of foods that are known to be strong inducers of CYP3A4 whenever feasible, but patients may receive any medication that is clinically indicated for treatment of adverse events. Such drugs must have been discontinued for an appropriate period before they enter screening and for a period of 3 months after the last dose of Osimertinib (AZD9291). All concomitant medications should be captured on the eCRF. Guidance on medicines to avoid, medications that require close monitoring and on washout periods is provided (see Appendix A).

If medically feasible, patients taking regular medication, with the exception of potent inducers of CYP3A4 (see above), should be maintained on it throughout the study period. Patients taking concomitant medications whose disposition is dependent upon BCRP and/or P-glycoprotein (P-gp) and which have a narrow therapeutic index should be closely monitored for signs of changed tolerability as a result of increased exposure of the concomitant medication whilst receiving Osimertinib (AZD9291). Guidance on medications to avoid, medications that require close monitoring and on washout periods is provided (seeAppendix D “Guidance regarding Potential Interactions with Concomitant Medications”).

Patients taking rosuvastatin should have creatine phosphokinase levels monitored (due to BCRP-mediated increase in exposure). If the patient experiences any potentially relevant AEs suggestive of muscle toxicity including unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever, rosuvastatin must be stopped and any appropriate further management should be taken.

3.5 Inclusion of Women and Minorities

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

4. REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

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

RCR utilizes five person registration types.

- IVR: MD, DO, or international equivalent,
- NPIVR: advanced practice providers (*e.g.*, NP or PA) or graduate level researchers (*e.g.*, PhD),
- AP: clinical site staff (*e.g.*, RN or CRA) with data entry access to CTSU applications (*e.g.*, Roster Update Management System [RUMS], OPEN, Rave,),
- Associate (A): other clinical site staff involved in the conduct of NCI-sponsored trials, and
- Associate Basic (AB): individuals (*e.g.*, pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

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

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

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

In addition, all investigators act as the Site-Protocol PI, consenting/treating/drug shipment, or as the CI on the DTL must be rostered at the enrolling site with a participating organization (*i.e.*, Alliance).

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

4.2 Site Registration

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

IRB Approval

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

In addition, the Site-Protocol PI (*i.e.*, the investigator on the IRB/REB approval) must meet the following five criteria to complete processing of the IRB/REB approval record:

- Holds an Active CTEP status,
- Rostered at the site on the IRB/REB approval (*applies to US and Canadian sites only*) and on at least one participating roster,
- If using NCI CIRB, rostered on the NCI CIRB Signatory record,
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile, and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional requirements to obtain an approved site registration status include:

- An active Federalwide Assurance (FWA) number,
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization, and

Compliance with all protocol-specific requirements (PSRs).

4.2.1 Downloading Regulatory Documents

Download the site registration forms from the protocol-specific page located on the CTSU members'

website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a Participating Organization on the protocol.

- Log on to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password,
- Click on *Protocols* in the upper left of your screen
    - 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 LAO-OH007, and protocol number 10240,

- Click on *Documents*, select *Site Registration*, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load automatically to the CTSU as described above.)

4.2.2 Requirements For NCI 10216 Site Registration

- Site Initiation Teleconference
- Specimen Tracking System Training Requirement:
    - All data entry users (Clinical Research Associate role) at each participating site will need to complete the Theradex-led training.
    - Theradex will provide a certificate of completion, which will need to be submitted to the CTSU through the Regulatory Submission Portal.
    - The training is a one-time only requirement per individual. If an individual has previously completed the training for another ETCTN study, the training does not need to be completed again nor does the certificate of completion need to be resubmitted to the CTSU. However, new versions of the Specimen Tracking System may require new training.
    - This training will need to be completed before the first patient enrollment at a given site.
    - Please contact STS Support at Theradex for the training (STS.Support@theradex.com, Theradex phone: 609-799-7580).

4.2.3 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal, log on to the CTSU members' website → Regulatory → Regulatory Submission.

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

4.2.4 Checking **Site** Registration Status

You can verify your site's registration status on the members' side of the CTSU website.

- Log on to the CTSU members' website
- Click on *Regulatory* at the top of your screen
- Click on *Site Registration*
- Enter your 5-character CTEP Institution Code and click on Go

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

4.3 Patient Registration

4.3.1 OPEN/IWRS

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the Lead Protocol Organization (LPOs) registration/randomization systems or 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:

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

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

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

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

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

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

4.3.2 Special Instructions for Patient Enrollment

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

- All biospecimens collected for this trial must be submitted using the ETCTN Specimen Tracking System (STS) unless otherwise noted.
- The system is accessed through special Rave user roles: "CRA Specimen Tracking" for data entry at the treating institutions and "Biorepository" for users receiving the specimens for processing and storage at reference labs and the Biorepository.
- Please refer to the Medidata Account Activation and Study Invitation Acceptance link on the CTSU website under the Rave/DQP tab.

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

For trials with slot reservation requirements, OPEN will connect to IWRS at enrollment initiation to check slot availability. Registration staff should ensure that a slot is available and secured for the patient before completing an enrollment. OSU will register all patients, including subsite patients, using IWRS.

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

Patients will be registered after meeting all entry requirements, clearance by the Protocol Coordinator, and signing of the informed consent.

OSU patients will be registered by the OSU research coordinator, as per their standard practice.

Subsite patients will have eligibility verified and will be entered on study centrally at the Ohio State University by the Multi-Institution Program Coordinator. All subsites must email the Multi-Institution Program Coordinator to verify slot availabilities prior to consenting patients.

The required forms, including Eligibility Criteria Checklist and Registration Form, can be found in the Supplemental Forms Document.

To register a subsite patient, the following documents must be completed by the subsite research team and faxed or securely e-mailed to the Multi-Institution Program Coordinator:

- Copy of all baseline tests required per the protocol calendar. Tests must be within the specified window.
- Signed Patient Consent Form
- Signed Patient HIPAA Authorization Form
- Consent Documentation Note

- Completed & Signed Eligibility Checklist (refer to Supplemental Forms Document)
- Registration Form (refer to Supplemental Forms Document)
- Source documents verifying every inclusion & exclusion criteria
  - Note: every inclusion and exclusion criteria must be documented in the patient's medical record

Upon receipt of registration documents, the Multi-Institution Program Coordinator will send an email confirmation of receipt. If confirmation of receipt is not received within 1 hour of submission, please call or page the Multi-Institution Program Coordinator.

Upon receipt of all required registration documents and upon verification the subsite patient meets all eligibility criteria, the Multi-Institution Program Coordinator will:

- Assign the patient a study sequence ID
- Register the patient on the study
- Fax and/or e-mail to the subsite the completed Registration Form with the assigned study sequence ID as confirmation of patient registration

Each participating institution will order study agents directly. Agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded to the Multi- Institution Program Coordinator.

Patient sequence IDs will be assigned in the following fashion:

- A-BCD
  - A = CTEP Site ID
  - BCD = sequential numbers by order of enrollment

For the ETCTN Biobanking and Molecular Characterization Initiative, the following information will be requested:

- Protocol Number
- Investigator Identification
  - Institution and affiliate name
  - Investigator's name

Eligibility Verification: Patients must meet all the eligibility requirements listed in Section 3.

- Additional Requirements:
  - Patients must provide a signed and dated, written informed consent form.

Upon enrolling a patient, IWRS will communicate with OPEN, assigning two separate and unique identification numbers to the patient, a Universal patient ID (UPID) and a Treatment patient ID. The UPID is associated with the patient and used each and every time the patient engages with the ETCTN Biobanking and Molecular Characterization portion of this protocol. The UPID contains no information or link to the treatment protocol. IWRS will maintain an association between the UPID for ETCTN biobanking and molecular characterization and any

treatment protocols the patient participates in, thereby allowing analysis of the molecular characterization results with the clinical data.

Immediately following enrollment, the institutional anatomical pathology report for the diagnosis under which the patient is being enrolled must be uploaded into Rave. The report must include the surgical pathology ID (SPID) and the IWRS-assigned UPID for this trial. **Important: Remove any personally identifying information, including, but not limited to, the patient's name, initials, and patient ID# for this treatment trial, from the institutional pathology report prior to submission.**

4.4 General Guidelines

Following registration, patients should begin protocol treatment within 5 days. Issues that would cause treatment delays should be discussed with the PI. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

5. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

5.1 Summary Table for Biospecimen Collection

5.1.1 Dose Escalation Summary Table

Time Point	Specimen	Send Specimens To:
Archival[1]		
	Formalin-fixed paraffin-embedded (FFPE) tumor tissue block (preferred) If a block is not available, then submit (cut sequentially): • One (1) H&E stained slide • 30-50, 5-10 micron, unstained, air-dried, uncharged slides	EET Biobank
Baseline		
	• 3 mL blood in purple top EDTA tubes processed for plasma at site (oncometabolites) • 20 mL whole blood in cfDNA Streck tubes	EET Biobank (oncometabolites, cfDNA)
	• 3 mL blood in purple top EDTA tube processed for plasma at the site (Telaglenastat (CB-839) HCl PK)	Lab of Dr. Joel Reid, Mayo Clinic Cancer Center (Telaglenastat (CB-839) HCl PK)
Cycle 1, Day 15 (C1D15)		
PK time points: Pre-Dose / 0 hours 30 Minutes 1 Hour 2 Hours 4 Hours 8 Hours	• 3 mL blood in purple top EDTA tube at each time point – processed for plasma at the site (Telaglenastat (CB-839) HCl PK)	Lab of Dr. Joel Reid, Mayo Clinic Cancer Center (Telaglenastat (CB-839) HCl PK)
Pre-dose / 0 hours	• 20 mL whole blood in cfDNA Streck tubes	EET Biobank
	• 3 mL blood in purple top EDTA tubes processed for plasma at site (oncometabolites)	EET Biobank (oncometabolites)
Cycle 2, Day 1 (C2D1)		
Pre-dose / 0 hours 30 Minutes 1 Hour 2 Hours 4 Hours	• 3 mL blood in purple top EDTA tube at each time point – processed for plasma at the site (Telaglenastat (CB-839) HCl PK)	Lab of Dr. Joel Reid, Mayo Clinic Cancer Center (Telaglenastat (CB-839) HCl PK)

8 Hours	• 6 mL blood in purple top EDTA tube at each time point – processed for plasma at the site (Osimertinib (AZD9291) PK)	Lab of Dr. Mitch Phelps, Ohio State University (Osimertinib (AZD9291) PK)

Time Point	**Specimen**	**Send Specimens To:**
Pre-dose / 0 hours	• 3 mL blood in purple top EDTA tubes processed for plasma at site (oncometabolites) • 20 mL whole blood in cfDNA Streck tubes	EET Biobank
Cycle 2, Day 2 (optional)		
Pre-dose / 0 hours	• 3 mL blood in purple top EDTA tube processed for plasma at the site (Telaglenastat (CB-839) HCl PK)	Lab of Dr. Joel Reid, Mayo Clinic Cancer Center (Telaglenastat (CB-839) HCl PK)
	• 6 mL blood in purple top EDTA tube processed for plasma at the site (Osimertinib (AZD9291) PK)	Lab of Dr. Mitch Phelps, Ohio State University (Osimertinib (AZD9291) PK)
Day 1 of each cycle onward starting with Cycle 3		
Pre-dose / 0 hours	• 3 mL blood in purple top EDTA tube processed for plasma at the site (Telaglenastat (CB-839) HCl PK)	Lab of Dr. Joel Reid, Mayo Clinic Cancer Center (Telaglenastat (CB-839) HCl PK)
	• 6 mL blood in purple top EDTA tube processed for plasma at the site (Osimertinib (AZD9291) PK)	Lab of Dr. Mitch Phelps, Ohio State University (Osimertinib (AZD9291) PK)
Progression	• 3 mL blood in purple top EDTA tube processed for plasma at the site (oncometabolites) • 20 mL blood in cfDNA Streck tubes	EET Biobank

[1]For archival tissue, **a copy of the anatomic pathology report corresponding to the tissue collection procedure must be sent with the tissue and uploaded to Rave**. If submitting slides, then slides must be processed in order, and numbered sequentially (*e.g.*, H&E stained slide is created first and labeled 1, unstained slides are then created and numbered 2 – 51). Refer to section 5.3 for additional information .

5.1.2 Expansion Cohort Summary Table

Time Point	Specimen and Quantity	Send Specimens to:
Archival[1]		
	Formalin-fixed paraffin-embedded (FFPE) tumor tissue block (preferred) If a block is not available, then submit (cut sequentially): • One (1) H&E stained slide • 30-50, 5-10 micron unstained air-dried uncharged slides	EET Biobank
Baseline		

Time Point	Specimen and Quantity	Send Specimens to:
	• 3 mL blood in purple top EDTA tubes processed for plasma at site (oncometabolites) • 20 mL blood in cfDNA Streck tubes	EET Biobank (oncometabolites, cfDNA)
	• 3 mL blood in purple top EDTA tube processed for plasma at the site (Telaglenastat [CB- 839 HCl] PK)	Lab of Dr. Joel Reid, Mayo Clinic Cancer Center (Telaglenastat [CB- 839] HCl PK)
	• 6 mL blood in purple top EDTA tube processed for plasma at the site (Osimertinib (AZD9291) PK)	Lab of Dr. Mitch Phelps, Ohio State University (Osimertinib (AZD9291) PK)
Cycle 2, Day 1 (C2D1)		
Pre-dose / 0 hours	• 3 mL blood in purple top EDTA tube processed for plasma at site (oncometabolites) • 20 mL blood in cfDNA Streck tubes (cfDNA)	EET Biobank (oncometabolites, cfDNA)
	• 3 mL blood in purple top EDTA tube processed for plasma at the site (Telaglenastat [CB- 839] HCl PK)	Lab of Dr. Joel Reid, Mayo Clinic Cancer Center (Telaglenastat [CB- 839 HCl] PK)
	• 6 mL blood in purple top EDTA tube processed for plasma at the site (Osimertinib (AZD9291) PK)	Lab of Dr. Mitch Phelps, Ohio State University (Osimertinib (AZD9291) PK)
Day 1 of each cycle onward starting with Cycle 3		
Baseline / 0 hours	• 3 mL blood in purple top EDTA tube processed for plasma at the site (Telaglenastat [CB- 839 HCl] PK)	Lab of Dr. Joel Reid, Mayo Clinic Cancer Center (Telaglenastat [CB- 839] HCl PK)
	• 6 mL blood in purple top EDTA tube at each time point – processed for plasma at the site (Osimertinib (AZD9291) PK)	Lab of Dr. Mitch Phelps, Ohio State University (Osimertinib (AZD9291) PK)
Progression/Relapse		
	• 3 mL blood in purple top EDTA tube processed for plasma at site (oncometabolites) • 20 mL blood in cfDNA Streck tubes	EET Biobank
[1]For archival tissue, **a copy of the anatomic pathology report corresponding to the tissue collection procedure must be sent with the tissue and uploaded to Rave**. If submitting		

slides, then slides must be processed in order, and numbered sequentially (*e.g.*, H&E stained slide is created first and labeled 1, unstained slides are then created and numbered 2 – 51). Refer to section 5.3 for additional information.

5.2 Specimen Procurement Kits and Scheduling

5.2.1 Specimen Shipping Kits from the EET Biobank

Kits for collection and shipment of specimens to the EET Biobank can be ordered online via the Kit Management System: https://kits.bpc-apps.nchri.org/.

Users at the clinical sites will need to set up an account in the Kit Management system and select a specific clinical trial protocol to request a kit. Please note that protocol may include more than one type of kit. Each user may order two kit types per protocol per day (daily max = 6 kits). Kits are shipped ground, so please allow 5-7 days for receipt. A complete list of kit contents for each kit type is located on the Kit Management system website.

Note: Kits or supplies are only provided for specimens shipped to the Biorepository. Institutional supplies must be used for all other specimen collection and processing.

5.2.2 Scheduling of Specimen Collections

Blood in cfDNA Streck tubes may be collected and shipped to the EET Biobank on Monday through Friday. Please select "Saturday Delivery" if shipping blood on a Friday. If Streck tubes cannot be shipped immediately, then they should be stored at room temperature until shipment.

Frozen plasma can be shipped to the EET Biobank on Monday through Thursday. Do not send frozen specimens for Saturday delivery. Processed plasma specimens must be stored in a -70 to -80°C freezer until shipment.

Formalin-fixed paraffin-embedded (FFPE) tissue block or slides can be shipped to the EET Biobank on Monday through Thursday. FFPE specimens should be stored at room temperature until shipment.

5.3 Specimen Collection, Processing, and Submission

5.3.1 Collection and Processing of Tumor Tissue

- FFPE tumor tissue block(s) must be submitted. The optimal block is at least 70% tumor. Specimen size requirement is as follows:
  - Surface area: 25 mm^2 is optimal. Minimum is 5 mm^2.
  - Volume: 1 mm^3 optimal. Minimum volume is 0.2 mm^3, however the success of DNA extraction decreases at suboptimal tissue volume.

If an existing block cannot be submitted, the following are requested, if available:

- One (1) H&E slide
- Thirty to fifty (30-50) 5-10 micron unstained air-dried uncharged slides

5.3.2 Collection and Processing of Whole Blood in EDTA for Pharmacokinetic Analysis (Telaglenastat [CB- 839] HCL and Osimertinib (AZD9291)).

1. Refer to the Summary Table for Biospecimen Collection (Section 5.1) for the time points for this collection.
2. All "pre-dose / 0 hour" or "baseline" samples should be collected after at least 8 hours of fasting. Instruct patients to bring dose to the clinic and take dose (with food) after the baseline PK sample has been obtained on all days where PK sampling will occur.
3. Label both 3 mL (for Telaglenastat (CB-839) HCl samples) and 6 mL (for Osimertinib (AZD9291) samples) EDTA (purple top) tubes.
4. Collect blood in pre-labeled tube and gently invert tube to mix. Place on wet ice (or store at 4°C) until processing.
5. Blood must be processed for plasma isolation within 20 minutes of collection. The time at which the sample was collected from the patient and the time at which the plasma was stored in an aliquot at -80°C must be recorded in the Specimen Tracking System, for every sample to ensure adequate handling.
6. Centrifuge blood at 1000 – 1300 x g (relative centrifugal force [RCF]) for 10 minutes in a refrigerated centrifuge kept at 4°C.
7. Following centrifugation, remove the plasma (top yellowish or clearish layer) and create 1 mL aliquots in labeled 2 mL screw-top cryovials. Refer to Section 5.4 for labeling instructions.
8. Tube labels must contain the information indicated in Section 5.4.1.2. These data should also be recorded in nurse's notes, on the flow sheet, and on the pharmacology reporting form that is to be sent with the samples
9. Freeze vials immediately upright in a -70 to -80°C freezer until shipment to the Mayo Clinical Cancer Center (Telaglenastat (CB-839) HCl PK specimens) and/or Ohio State University (Osimertinib (AZD9291) HCl PK specimens). See Sections 5.6 and 5.7 for shipping instructions and addresses.

5.3.3 Collection and Processing of Whole Blood in EDTA for Oncometabolite Analysis

1. Peripheral blood will be collected at: baseline, C2D1, and at time of disease progression.
2. Label a 3 mL EDTA tube.
3. Collect 3 mL of blood into the pre-labeled tube and gently invert tube to mix. Place on wet ice (or store at 4°C) until processing.
4. The peripheral blood sample must be centrifuged within 30 to 60 minutes of collection at 4°C with a centrifuge speed of 2000 x g for 15 minutes.
5. After centrifugation, remove plasma (top yellowish or clearish layer) and create 0.5 mL aliquots in labeled 2 mL screw-top cryovials. Refer to Section 5.4 for labeling instructions.
6. Immediately freeze the aliquots upright in a -70 to -80°C freezer until shipment to the EET Biobank according to the instructions below. The time at which the sample was collected from the patient and the time at which the plasma was stored in an aliquot at -80°C must be recorded in the Specimen Tracking System for every sample to ensure adequate handling.

5.3.4 Collection of Whole Blood in cfDNA Streck Tubes

1. Label two cfDNA Streck tubes. Refer to Section 5.4 for labeling instructions.
2. Invert tube to mix. **Note: blood must be thoroughly mixed to ensure preservation of the specimen.**
3. After collection, blood in cfDNA Streck tubes should never be refrigerated as this will compromise the specimens. Blood collected in cfDNA Streck tubes is stable at room temperature.
4. Ship on day of collection (whenever possible) to the EET Biobank according to instructions below.

5.4 Specimen Tracking System Instructions

5.4.1 Specimen Tracking System Overview and Enrollment Instructions

For the ETCTN STS, the following information will be requested:

- Protocol Number
- Investigator Identification
  - Institution and affiliate name
  - Investigator's name
- Eligibility Verification: Patients must meet all the eligibility requirements listed in Section 3..
- Additional Requirements:
  - Patients must provide a signed and dated, written informed consent form.

Upon enrolling a patient, IWRS will communicate with OPEN, assigning two separate and unique identification numbers to the patient, a Universal patient ID (UPID) and a Treatment patient ID. The UPID is associated with the patient and used each and every time the patient engages with the portion of this or any other protocol that uses the ETCTN Specimen Tracking System. The UPID contains no information or link to the treatment protocol. IWRS will maintain an association between the UPID for ETCTN biobanking and molecular characterization and any treatment protocols the patient participates in, thereby allowing analysis of the molecular characterization results with the clinical data.

Immediately following enrollment, the institutional anatomical pathology report for the diagnosis under which the patient is being enrolled must be uploaded into Rave. The report must include the surgical pathology ID (SPID), collection date, block number, and the IWRS-assigned UPID and patient study ID for this trial. For newly acquired biopsies, the radiology and operative report(s) must also be uploaded into Rave. **Important: Remove any personally identifying information, including, but not limited to, the patient's name, date of birth, initials, medical record number, and patient contact information from the institutional pathology report prior to submission.**

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

For questions regarding the Specimen Tracking System, please contact STS Support at

STS.Support@theradex.com.

The Shipping List report **must** be included with all sample submissions.

5.4.2 Specimen Labeling

5.4.2.1 Tissue Labels
Include the following on all tissue specimens or containers (*e.g.*, formalin jar):

- Patient Study ID
- Universal Patient ID (UPID)
- Specimen ID (automatically generated by Rave)
- Time point
- Specimen type (*e.g.*, formalin-fixed paraffin-embedded [FFPE] Block, Formalin Fixed Tissue, Fresh Tissue in Media, *etc.*)
- Tissue type (P for primary, M for metastatic or N for normal)
- Surgical pathology ID (SPID) number (when applicable)
- Block number from the corresponding pathology report (archival only)
- Collection date (to be added by hand)

5.4.2.2 Blood Specimen Labels

Include the following on blood specimens (including whole blood and frozen, processed blood products – like serum and plasma):

- Patient Study ID
- Universal Patient ID (UPID)
- Specimen ID (automatically generated by Rave)
- Time point
- Specimen type (*e.g.*, blood, serum)
- Collection date and time (to be added by hand)

Label plasma samples for PK (all collections and processed/shipping samples) and oncometabolites (all collections) with:

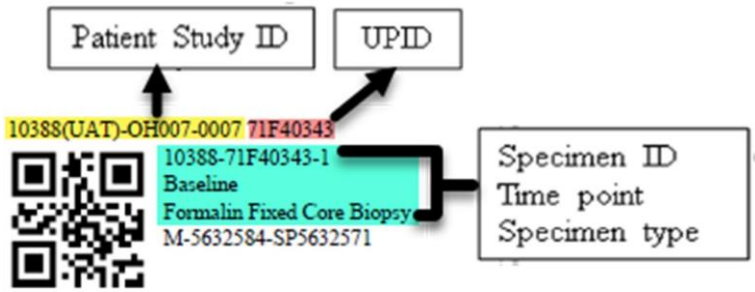
- Patient study ID
- Universal Patient ID (UPID)
- Specimen ID (automatically generated by Rave)
- Time point (*i.e.*, baseline, 0, 1, 2, 4, and 8 hours after the PO dose of Telaglenastat (CB-839) HCl)
- Specimen type (*e.g.*, blood, plasma)
- Collection date and time (to be added by hand)(*i.e.*, C1D1 0.5 hour)

These same data should be recorded in nurse's notes, on the flow sheet, and on the pharmacology reporting form that is to be sent with the samples. The pharmacology reporting form that is to be sent with the samples should also contain patient's Age, Height, Weight, Dose level and Actual Dose given. The Specimen labels should be taped on to the sample vials.

5.4.2.3 Example of Specimen Label Generated by STS

STS includes a label printing facility, accessed via the Print Label CRF in the All Specimens folder. A generated PDF is emailed to the user as a result of saving that form.

The following image is an example of a tissue specimen label printed on a label that is 0.5" high and 1.28" wide.



The QR code in the above example is for the Specimen ID shown on the second line.

Labels may be printed on a special purpose label printer, one label at a time, or on a standard laser printer, multiple labels per page. Theradex recommends the use of these low temperature waterproof labels for standard laser printers: https://www.labtag.com/shop/product/cryo-laser-labels-1-28-x-0-5-cl-23-colors-available/

The last line item on the label includes the following data points joined together:

1. Tissue only: Primary (P), Metastatic (M), Normal (N) tissue indicated at the beginning of the specimen ID; this field is blank if not relevant (*e.g.*, for blood)
2. Block ID or blank if not relevant
3. SPID (Surgical Pathology ID) or blank if none
4. An optional alpha-numeric code that is protocol specific and is only included if the protocol requires an additional special code classification

Space is provided at the bottom of the label for the handwritten date and optional time. The last line on the example label is for the handwritten date and optional time.

5.4.3 Overview of Process at Treating Site

5.4.3.1 OPEN Registration

All registrations will be performed using the Oncology Patient Enrollment Network (OPEN) system. OPEN communicates automatically with the Interactive Web Response System (IWRS) which handles identifier assignments, any study randomization, and any prescribed slot assignments. If specimen analysis is required to determine eligibility, the protocol will be setup with multi-step registration.

Registration without eligibility specimen analysis:

1. Site enters registration data into OPEN during one or more steps.
2. IWRS receives data from OPEN, generates the Patient Study ID and the Universal Patient ID, both of which are sent back to OPEN.
3. IWRS sends all applicable registration data directly to Rave at the end of the final registration step.

Any data entry errors made during enrollment should be corrected in Rave.

5.4.3.2 Rave Specimen Tracking Process Steps

Step 0: Log into Rave via your CTEP-IAM account, then navigate to the appropriate participant.

Step 1: Complete the **Histology and Disease** form (but do not upload reports until a specimen label can be applied to them) and the Baseline forms regarding **Prior Therapies**. Enter the initial clinical specimen data:

- **Specimen Tracking Enrollment** CRF: Enter Time Point, Specimen Category, Specimen Type, Block number, Tissue type, Surgical Path ID, and number of labels needed (include extra labels to apply to reports to be uploaded). CRF generates unique Specimen ID.

Step 2: Print labels using the **Print Labels** CRF located in the All Specimens folder, then collect specimen.

- Label specimen containers and write collection date and time on each label. After collection, store labeled specimens as described in Section 5.4.2.
- Apply an extra specimen label to *each* report before scanning. Return to the **Histology and Disease** form to upload any initial Pathology, Radiology, Molecular Reports (up to 4), and Surgical (or Operative) reports. Return to **Specimen Tracking Enrollment** CRF to upload any molecular report (one per specimen) and/or specimen specific pathology or related report (one per specimen) and/or the Tissue Biopsy Verification form (when applicable). Uploaded reports should have protected health information (PHI) data, like name, date of birth, mailing address, medical record number or social security number (SSN), redacted. **Do not redact SPID, block number, diagnosis or relevant dates (such as collection date), and include the UPID and patient study ID on each document** (either by adding a label or hand-writing).

Step 3: Complete specimen data entry.

- **Specimen Transmittal** Form: Enter collection date and time and other required specimen details.

Step 4: When ready to ship, enter shipment information.

- **Shipping Status** CRF: Enter tracking number, your contact information, recipient, number of sample containers and ship date once for the first specimen in a shipment.
- **Copy Shipping** CRF: In the specimen folders for additional specimens (if any) that will be shipped with the initial specimen, please use the **Copy Shipping** form to derive common data into additional **Shipping Status** forms. A few unique fields will still need to be entered in

Shipping Status.

Step 5: Print shipping list report and prepare to ship.

- Shipping List report is available at the site level.
- Print two copies of the shipping list, one to provide in the box, the other for your own records.
- Print pathology or other required reports to include in the box. Be sure the printed copy includes the specimen label.

Step 6: Send email notification.

- For only one of the specimens in the shipment, click "Send Email Alert" checkbox on the **Shipping Status** CRF to email recipient.

Step 7: Ship the specimen(s).

Step 8: Monitor the Receiving Status form located in each specimen folder for acknowledgment of receipt and adequacy.

5.5 Shipping of Specimen(s) from Clinical Sites to the EET Biobank

5.5.1 General Shipping Information

5.5.1.1 Required Forms for Specimen Submissions

Tissue	**Required Forms**
Archival	1. Shipping List 2. Corresponding Pathology Report
Blood	1. Shipping List

Each document submitted with the specimen must be labeled with a label printed from the STS, or the Universal ID and Patient Study ID.

Minimum required personally identifiable information:

- Remove patient identifiers such as name, date of birth, medical record number, social security number, and insurance information from the pathology or other clinical reports.
- Do not remove the date of procedure, surgical pathology ID (SPID) number, block number, and diagnosis.

5.5.2 Schedule of Shipment

When kits are provided, the shipping container sent with kit contents should be used to ship specimens to the EET Biobank. In winter months, please include extra insulation, such as bubble

wrap, inside the shipping container.

- **Ambient Blood** (cfDNA Streck tubes) is shipped at room temperature on Monday through Friday. Please select Saturday delivery if shipping blood on a Friday. Ship blood in cfDNA Streck tubes shipped in ambient shipping containers provided by the EET Biobank.

- **Frozen specimens** (plasma) may be shipped on Monday through Thursday. Frozen specimens are batch shipped. Shipments should contain no more than 31 cryovials so that sufficient dry ice can be included to completely encase the specimens in order to maintain specimen integrity during shipment.

- **FFPE tissue block or slides** may be shipped on Monday through Thursday. Slides are shipped in containers provided by the submitting site.

5.5.3 Packaging Instructions for Blood (Streck Tubes) in an Ambient Shipper

1. Before packaging specimens, verify that each specimen is labeled according to the instructions above and that the lids of all primary receptacles containing liquid are tightly sealed.
2. Prepare the SAF-T-TEMP Gel Pak for shipment. *Note: If contents of the Pak are crunchy, place Pak in a warm water bath until gel is smooth.* ***Do not refrigerate, freeze, or microwave.***
3. Place the SAF-T-TEMP Pak in bottom of insulated chest. Note: The insulated chest must be shipped inside the provided cardboard box(es).
4. Place the blood collection tubes in zip-lock bags.
5. Next, place blood into a biohazard envelope with absorbent material. Expel as much air as possible and seal the envelope securely.
6. Place the biohazard envelope into a Tyvek envelope. Expel as much air as possible and seal securely.
7. Place packaged blood collection tube(s) and a copy of the shipping manifest from the Sample Tracking System on top of the SAF-T-TEAP Pak.
8. Place the lid on the insulated chest.
9. Close the outer flaps of the shipping box and tape shut.
10. Attach a shipping label to the top of the shipping container.
11. Attach an Exempt Human Specimen sticker to the side of the box.
12. Ship specimens *via* overnight courier to the address listed below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.

5.5.4 Packaging Instructions for Frozen Plasma

Frozen plasma samples should be batch shipping in a Single Chambered Specimen Procurement Kit. No more than 21 cryovials of plasma should be included in each Single Chambered Kit.

1. Place the plasma specimens in zip-lock bags. Use a separate zip-lock bag for eachtime point and collection time (*i.e.,* oncometabolites).
2. Place the zip-lock bags in a biohazard envelope containing absorbent material. Expel as

much air as possible and seal the envelope.
3. Put the secondary envelope into a Tyvek envelope. Expel as much air as possible and seal the envelope.
4. Place the Tyvek envelope in the kit compartment filled with dry ice. Layer the bottom of the compartment with dry ice until it is approximately one-third full. Place the Tyvek envelope containing frozen specimens on top of the dry ice. Cover the specimens with the dry ice until the compartment is almost completely full.
5. Insert a copy of the specimen manifest from the Specimen Tracking System into a plastic bag and place in the kit chamber.
6. Place the Styrofoam lid on top to secure specimens during shipment. Do not tape the inner chamber shut.
7. Close the outer lid of the Specimen Procurement Kit and tape it shut with filament or other durable sealing tape. Do not completely seal the container.
8. Complete a FedEx air bill and attach to top of shipping container.
9. Complete a dry ice label.
10. Attach the dry ice UN1845 label and an Exempt Human Specimen sticker or UN3373 sticker to the side of the shipping container.
11. Arrange for courier pickup. Note: FedEx Priority Overnight is strongly recommended for next day delivery to prevent delays in package receipt.

5.5.5 Shipping Instructions and Addresses

Ship specimens to the address below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt. Do not ship specimens the day before a holiday.

Revise the Shipping Address for the EET Biobank to the following:
EET Biobank
2200 International Street
Columbus, OH 43228
PH: (614) 722-2865
FAX: (614) 722-2897
E-mail: BPCBank@nationwidechildrens.org

FedEx Priority Overnight service is very strongly preferred. There is no central Courier account for this study. Sites are responsible for all costs for overnight shipment per sample shipment to the EET Biobank, utilizing the site screening and base intervention payments.

NOTE: The EET Biobank FedEx Account will not be provided to submitting institutions.

Contact Information for Assistance

For all queries, please use the contact information below:

EET Biobank
Phone: (614) 722-2865
E-mail: BPCBank@nationwidechildrens.org

5.6 Shipping of Telaglenastat (CB-839) HCl Pharmacokinetics (PK) Plasma from Clinical Sites to Mayo Clinic Cancer Center

5.6.1 Schedule of Shipment

- **Frozen specimens** (plasma) may be shipped on Monday through Thursday. Frozen specimens are batch shipped.

5.6.2 Packing Instructions for Frozen Plasma

Frozen plasma samples should be batch shipped at the completion of each patient cycle using the instructions below:

1. Place the plasma specimens in zip-lock bags. Use a separate zip-lock bag for each time point and collection.
2. Place the zip-lock bags in a biohazard bag containing absorbent material. Expel as much air as possible and seal the bag.
3. Layer the bottom of a Styrofoam container with dry ice until it is approximately one-third full. Place the biohazard bag containing frozen specimens on top of the dry ice. Cover the specimens with the dry ice until the compartment is almost completely full.
4. Insert a copy of the specimen manifest from the Specimen Tracking System into a plastic bag and place in the container.
5. Place the Styrofoam lid on top to secure specimens during shipment. Do not seal the Styrofoam container.
6. Place the Styrofoam container into a card board box. Close the card board lid with durable sealing tape.
7. Complete a FedEx air bill and attach to top ofshipping container.
8. Complete a dry ice label.
9. Attach the dry ice UN1845 label and an Exempt Human Specimen sticker or UN3373 sticker to the side of the shipping container.
10. Arrange for courier pickup. Note: FedEx Priority Overnight is strongly recommended for next day delivery to prevent delays in packagereceipt.

5.6.3 Shipping Address and Contact Information

Ship plasma for PK analysis overnight courier on dry ice to the Mayo Clinic Cancer Center Pharmacology Shared Resource for processing and storage. Please ship samples Mondays to Thursday only and send an email to reid@mayo.edu prior to shipment to alert us of a shipment.

Attn: Joel Reid, Ph.D.
Mayo Clinic
221 4th Avenue SW
Guggenheim- 17-37
Rochester, MN 55905
Phone: (507) 284-0822
Fax: (507) 293-0107

Email: reid@mayo.edu

5.7 Shipping of Osimertinib (AZD9291) Pharmacokinetics (PK) Plasma from Clinical Sites to Ohio State University

5.7.1 Schedule of Shipment

- **Frozen specimens** (plasma) may be shipped on Monday through Wednesday. For study sub-sites, plasma samples may be shipped in batches but preferably no longer than 3 months after sample collection.

5.7.2 Packing Instructions for Frozen Plasma

Frozen plasma samples should be batch shipped using the instructions below:

1. Specimen should be stored through the end of collection for each participant and shipped as a batch, on dry ice, by participant (more than one participant / shipment is acceptable).
2. The OSU PhASR lab may contact the study team to request shipment off-schedule.
3. Please ship only 1 aliquot to the OSU PhASR laboratory within each shipment. Once receipt is confirmed, the back-up aliquot(s) may also be shipped. The back-up aliquots can be shipped at a later date with subsequent batches of samples for other participants.

Preparing the Specimen Shipment:

1. Samples should be stored in cardboard boxes (5 1/8" x 5 1/8" x 2", LxWxH) with dividers.
2. Please organize the samples by Patient and Timepoint in the box.
3. Do not store in plastic bags (they break on dry ice and labels will detach).
4. A copy of each of the pharmacokinetic sample collection forms (Appendix X) for the respective patients or a sample list/manifest should be included with each shipment.
5. To prevent problems with illegible writing on tubes, consider numbering them (in addition to a sample label) and numbering samples on the sample list/manifest. The RAVE system does provide unique sample identifiers which are useful for these purposes.
6. Note the study number, PI, and the drugs used/to be measured.
7. A name, phone number and email address should be included with samples so that receipt can be acknowledged.
8. Please notify the lab by email (phasr@osumc.edu) at least 24 hours prior to shipment
9. Place the box in a Styrofoam container filled with dry ice. Layer the bottom with dry ice until it is approximately one-third full. Place the box containing frozen specimens on top of the dry ice. Cover the specimens with the dry ice until the compartment is almost completely full.
10. Insert a copy of the specimen manifest from the Specimen Tracking System into a plastic bag and place in the container.
11. Place the Styrofoam lid on top to secure specimens during shipment.
12. Close the lid with filament or other durable sealing tape. Do not completely seal the container.
13. Complete a FedEx air bill and attach to top of shipping container.
14. Complete a dry ice label.
15. Attach the dry ice UN1845 label and an Exempt Human Specimen sticker or UN3373 sticker to the side of the shipping container.
16. Arrange for courier pickup. Note: FedEx Priority Overnight is strongly recommended for next

day delivery to prevent delays in package receipt.

5.7.3 Shipping Address and Contact Information

Ship plasma for PK analysis overnight courier on dry ice to the Ohio State University for processing and storage.

The OSUCCC Pharmacoanalytical Shared Resource
Attn: Nicole Abbott, Ph.D.
441 Biomedical Research Tower
460 West 12th Avenue
Columbus, OH 43210
Phone: (614)688-0578

Contact Information for Assistance

OSUCCC PhASR Lab
PhASR@osumc.edu
Nicole Abbott, PhD can be reached at (614) 688-0578
Mitch Phelps, PhD can be reached at (614) 832-2547

5.8 Biomarker Plan

List of Biomarker Assays in Order of Priority

Note for participating sites: Please see Section 5.1 for details on specimens to collect. The specimens tested are not always the same specimens that are submitted by the site, as processing of blood and tissue will occur at the Biobank prior to testing

Priority	Biomarker Name	Biomarker Assay	Biomarker Type and Purpose	M/O	Timing	Specimen	Quantity Needed	Laboratory
1	*EGFR* mutational status	Any approved assay in tissue	Integral Eligibility criteria	M	Baseline	Archival tumor tissue	Per local guidelines	Local CLIA-certified labs (Standard of Care)
2	Quantification of plasma glutamine, glutamate, aspartate and asparagine concentrations	LC/MS/MS	Integrated To measure the pharmacodynamic effect of Telaglenastat (CB-839) HCl on systemic levels of TCA cycle metabolites.	M	Baseline, C1D15 (Dose escalation cohort only), C2D1, and at the time of disease progression.	Peripheral blood	3 mL blood in purple top EDTA tubes processed for plasma at site. 3 samples	Ian Lanza / Mayo Clinic Cancer Center (Mayo) Metabolomics Resource Core
3	WES	NGS	Integrated To confirm *EGFR* mutational status in tissue.	M	Baseline	DNA and cDNA from Archival tumor tissue	FFPE block or One (1) H&E slide, thirty to fifty (30-50) 5-10 micron unstained, air-dried, uncharged slides	Chris Karlovich / MoCha, Frederick National Laboratory for Cancer Research (FNLCR)

Priority	Biomarker Name	Biomarker Assay	Biomarker Type and Purpose	M/O	Timing	Specimen	Quantity Needed	Laboratory
4	PK for Telaglenastat (CB-839) HCl	LC/MS/MS	Integrated To assess the PK of Telaglenastat (CB-839) HCl when administered in combination with Osimertinib (AZD9291).	M	<u>All patients</u>: Baseline <u>Dose escalation only</u>: C1D15 following the AM dose of Telaglenastat (CB-839) HCl (pre-dose / 0 hr, 0.5 hr, 1 hr, 2 hr, 4 hr, 8 hr). C2D1 following the AM dose of Telaglenastat (CB-839) HCl and Osimertinib (AZD9291) (0 hr, 0.5 hr, 1 hr, 2 hr, 4 hr, 8 hr, 24 hr[a]). <u>Expansion cohort</u>: C2D1 pre-dose. <u>All patients</u>: A specimen will also be collected on Day 1 of each treatment cycle, starting with Cycle 3.	Peripheral blood	3 mL blood in purple top EDTA tube at each time point processed for plasma at the site. At least 14 samples for a total of 42 mL of blood (including the C2D1 sample)	Dr. Joel Reid / Mayo Clinic Cancer Center (Mayo) Pharmacology Shared Resource

Priority	Biomarker Name	Biomarker Assay	Biomarker Type and Purpose	M/O	Timing	Specimen	Quantity Needed	Laboratory
5	PK for Osimertinib (AZD9291)	LC/MS/MS	Integrated To assess the PK of Osimertinib (AZD9291) when administered in combination with Telaglenastat (CB-839) HCl.	M	Dose escalation only: C2D1 following the AM dose of Telaglenastat (CB-839) HCl and Osimertinib (AZD9291) (0 hr, 0.5 hr, 1 hr, 2 hr, 4 hr, 8 hr, 24 hr[a]). Expansion cohort only: Baseline and C2D1 pre-dose All patients: A specimen will also be collected on day 1 of each treatment cycle starting with Cycle 3.	Peripheral blood	6 mL blood in purple top EDTA tube at each time point processed for plasma at the site. At least 6 samples for a total of 36 mL of blood	Dr. Mitch Phelps, Ohio State University
6	WES / RNAseq	NGS	Exploratory To identify biomarkers of response (hypothesis generating).	M	Baseline	DNA, cDNA, and RNA from Archival Tumor tissue	N/A (Collected as part of specimen collection for WES integrated biomarker)	Chris Karlovich / MoCha, Frederick National Laboratory for Cancer Research (FNLCR)
7	cfDNA sequencing	NGS	Exploratory To assess cfDNA for assessment of *EGFR* mutational status, T790M mutational status and resistance mechanisms.	M	Baseline, C1D15 (phase 1 only), C2D1, and at the time of disease progression	Germline DNA from blood in cfDNA Streck tube	20 mL blood in cfDNA Streck tube 4 samples (phase 1); 3 samples (phase 2)	Chris Karlovich / MoCha, Frederick National Laboratory for Cancer Research (FNLCR)

CLIA, Clinical Laboratory Improvement Amendments, LC/MS,Liquid Chromatography-Mass Spectrometry and Liquid Chromatography- Tandem Mass Spectrometry; WES, whole exome sequencing; NGS, next-generation sequencing; PK, pharmacokinetics; cfDNA, cell-free DNA; EDTA, ethylenediaminetetraacetic acid; RNAseq, RNA sequencing.
[a] The 24 hour PK timepoint is optional.

5.9 Integral Laboratory or Imaging Studies

5.9.1 *EGFR* Mutational Status (Standard of Care)

EGFR mutational status will be assessed in local laboratories as part of the Standard of Care procedures for patients with NSCLC on a CLIA-certified assay. This is considered routine practice upon progressive disease on first line TKI. *EGFR* mutational status will later be confirmed retrospectively at the NCI MoCha laboratory using WES.

5.10 Integrated Correlative Studies

5.10.1 Quantification of Plasma Glutamine, Glutamate, Aspartate, and Asparagine Concentrations

The plasma levels of glutamine, glutamate, aspartate, and asparagine will be measured at various time points to determine the changes as a result of Telaglenastat (CB-839) HCl monotherapy or Telaglenastat (CB-839) HCl and Osimertinib (AZD9291) combination therapy. The changes in the systemic levels of these metabolites provide key pharmacodynamic information on the effects of glutaminase inhibition.

5.10.1.1 Specimen Receipt and Processing at the EET Biobank

Upon receipt at the EET Biobank, frozen aliquots of plasma will be received, barcoded, and stored in a -80°C freezer until distribution for testing. Samples will then be distributed to the testing site.

5.10.1.2 Site(s) Performing Correlative Study

This test will be performed at the Mayo Clinic Metabolomics Core (Lab PI: Ian Lanza), which is one of six NIH-funded state of the art metabolomics facilities with special expertise in measuring these levels via liquid chromatography/mass spectrometry (LC-MS).

5.10.2 Whole Exome Sequencing (WES) to Confirm *EGFR* Mutational Status

In order to provide centralized confirmation of *EGFR* mutational status, WES will be performed on archival tumor as an integrated biomarker.

5.10.2.1 Specimen Receipt and Processing at the EET Biobank

Archival formalin-fixed paraffin-embedded tissue (block or slides) will be used for this assay. If a block is received, then the EET Biobank will cut and H&E stain slides. A pathology quality control review to assess tumor content and annotate slides for macrodissection will be completed for all tissue received. Unstained slides will be macrodissected, if needed, and scraped for DNA and RNA co-extraction. DNA will be banked in a stock vial and RNA will be divided into 5 aliquots; all nucleic acids will be stored in a -80°C freezer until distribution for testing.

Any additional FFPE tissue blocks or slides will banked at room temperature.

DNA will be extracted from blood collected in cfDNA Streck tubes at the baseline time point, following plasma processing. DNA will be stored in a -80°C freezer until distribution for testing.

5.10.2.2 Site(s) Performing Correlative Study

WES will be performed on archival tumor and germline samples by the MoCha, Frederick National Laboratory for Cancer Research (FNLCR) under the supervision of Chris Karlovich, Ph.D. (chris.karlovich@nih.gov).

5.10.2.3 Shipment of specimens from the EET Biobank to Site Performing Correlative Study

Specimens will be shipped from the EET Biobank to:

MoCha Lab, Frederick National Laboratory for Cancer Research (FNLCR)
1050 Boyles St.
Bldg. 459, Rm. 125
Frederick, MD 21702
Attn: Alyssa Chapman or Ruth Thornton

5.10.2.4 Contact information for notification of specimen shipment

Thomas Forbes, mochasamplereceiving@nih.gov

5.10.3 Telaglenastat (CB-839) HCl Pharmacokinetics

Blood levels of Osimertinib (AZD9291) and Telaglenastat (CB-839) HCl will be assessed to evaluate for drug- drug interactions, and to compare with established pharmacokinetic profiles from prior single- agent trials. Since Telaglenastat (CB-839) HCl is a substrate of efflux pumps, co-administration of Telaglenastat (CB-839) HCl and Osimertinib (AZD9291), the efflux pump inhibitor, may increase intracellular concentrations of Telaglenastat (CB-839) HCl and result in lower plasma concentrations.

5.10.3.1 Hypothesis and Rationale

In those patients with inadequate drug exposure, inhibition of glutaminase activity and other cellular effects of glutaminase inhibition as described in Section 2.2.1 will be limited. These studies are necessary to characterize the PK and drug exposure of Telaglenastat (CB-839) HCl when used in combination with Osimertinib (AZD9291) in patients with metastatic *EGFR* activating mutation positive NSCLC, to assess pharmacodynamic relationships with plasma oncometabolites such as glutamate, glutamine, aspartate, asparagine and clinical response endpoints, and to determine the effect of Osimertinib (AZD9291) on the Telaglenastat (CB-839) HCl PK.

5.10.3.2 Assay Validity and Appropriateness for Study

Plasma concentrations of Telaglenastat (CB-839) HCl will be measured by LC/MS/MS methods developed in the Mayo Clinic Cancer Center Pharmacology Shared Resource. The Shared Resource, directed by Dr. Joel Reid, is fully equipped to carry out pharmacologic investigations, including two exquisitely sensitive Xevo TQ-S mass spectrometers with Accuity UPLC systems to carry out the bioanalytical measurements and licenses for Phoenix WINNONLIN, NONMEM and PsN Pirana to carry out standard and population PK/pharmacodynamics analyses. The laboratory has developed or modified assays for more than 85 antitumor agents, served as a central analytical and PK resource laboratory for 9 published NCI-sponsored phase 1 and phase 2 trials with vorinostat (for example: Galanis *et al.*, Fouladi *et al.*, and Lee *et al.*) and serves as one of the pharmacology resource laboratories for the Children's Oncology Group (Galanis *et al.*, 2009; Fouladi *et al.*, 2010; Lee *et al.*, 2012). The approach to assay development and implementation of criteria for system suitability, quality assurance, and ongoing evaluation of specific assay data are consistent with recommendations from two FDA-sponsored conferences on analytical methods validation (Shah *et al.*, 1991; Shah *et al.*, 2000) that are described in a recent FDA guidance document "Guidance for Industry: Bioanalytical Method Validation" (Draft Guidance, 2013). In particular, as the lab develops a specific high-performance liquid chromatography (HPLC) or other method for measurement of drug and relevant metabolites, they incorporate standard assessments of drug extraction efficiency, sensitivity, linearity, precision, accuracy, storage stability, and other parameters relevant to the particular method.
Assay performance is thoroughly validated before implementation in the clinical trial and monitored on a routine basis during the course of the clinical trial by inclusion of appropriate quality assurance samples.

5.10.3.3 Specimen Receipt and Processing at the Mayo Clinic Cancer Center

Frozen plasma aliquots will be received at the Mayo Clinical Cancer Center. Upon receipt, plasma will be accessioned, barcoded, and stored in a -80°C freezer until distribution for testing.

5.10.3.4 Site(s) Performing Correlative Study

Samples will be analyzed in the Pharmacology Core of the Mayo Clinic Cancer Center, which has developed validated assays for over 85 separate anticancer drugs during the course of its existence. This assay will be performed under the direction of Dr. Joel Reid.

5.10.4 Osimertinib (AZD9291) Pharmacokinetics

5.10.4.1 Hypothesis and Rationale

Osimertinib (AZD9291) is a moderate inhibitor of BCRP and Telaglenastat (CB-839) HCl is a substrate of efflux pumps. Therefore, the most likely drug interaction is increased plasma concentration of Telaglenastat (CB-839) HCl. However, since both drugs are orally administered, an impact on Osimertinib (AZD9291) pharmacokinetics cannot be ruled out without pharmacokinetic studies. The primary endpoint will be comparing the $AUC_{0\text{-}8hr}$ in this study to a prior ETCTN single agent Osimertinib (AZD9291) study (9903). C_{ss} concentrations

of Cycle 2 Day 1 and subsequent cycles will also be evaluated as potential biomarkers of efficacy and toxicity.

5.10.4.2 Assay Validity and Appropriateness for Study

LC/MS/MS is the analytical standard for quantitation of drug plasma concentrations due to its sensitivity and accuracy. A LC/MS/MS assay for the analysis of Osimertinib (AZD9291), AZ5104, and AZ7550 was developed and validated based on a previously published method (Rood *et al.*, 2016). Following SALLE extraction, samples were analyzed with a Shimadzu Nexera X2 series interfaced with a Sciex QTRAP® 6500+ MS/MS. Liquid chromatography was performed using a Waters® Acquity UPLC® BEH C8 column. MS/MS data was obtained in positive ion mode (ESI+) with Osimertinib (AZD9291) at m/z 500.118 → 72.092, AZ5104 at m/z 486.761 → 72.092, AZ7550 at m/z 486.761 → 430.178, and pazopanib at m/z 438.717 → 358.146.

Stock solutions of 100 mcg/mL of Osimertinib (AZD9291) were used to obtain nine validation samples in human heparin plasma (1000, 800, 500, 200, 100, 50, 3, and 1 ng/mL). Each sample was measured analytically on three separate days. The standard curve was linear from 1 – 1000 ng/mL, $R^2 = 0.987$ with an inter-day variability of 3.74% for high standard (1000 ng/mL), n = 3 and 12.46%for low standard (1 ng/mL), n = 3 over three days. The lower limit of quantification (LLOQ) was 3 ng/mL and limit of detection (LOD) was 1 ng/mL.

We will use a validated LC/MS/MS assay for the analysis of Osimertinib (AZD9291) and metabolites analysis. As these are blood samples, obtaining the samples represents minimal risk however, careful consideration to patient inconvenience for sample collection was conducted. Given the large body of Osimertinib (AZD9291) PK information and the small likelihood of a drug interaction effecting Osimertinib (AZD9291) plasma concentrations, as described above, the $AUC_{0\text{-}8hr}$ will be used as the primary endpoint, to minimize subject sampling burden.

5.10.4.3 Specimen Receipt and Processing at the Ohio State University

Frozen plasma aliquots will be received at the Ohio State University. Upon receipt, plasma will be accessioned, barcoded, and stored in a -80°C freezer until distribution for testing.

5.10.4.4 Site(s) Performing Correlative Study

Dr. Mitch Phelps' lab at the Ohio State University, will conduct the proposed studies. Mitch A. Phelps, PhD is Director of the OSU Comprehensive Cancer Center Pharmacoanalytical Shared Resource, which supports pharmacokinetic (PK)/pharmacodynamic (PD) study design and conduct for pre-clinical and clinical drug development. Dr. Phelps has directed PK/PD studies in preclinical disease models and in early phase clinical trials for nearly ten years. His research group focuses on development of small molecule and oligonucleotide anticancer and immune-modulatory agents here at OSU, using statistical modeling and simulation of PK/PD data to understand how genetic and other factors contribute to differences in therapy outcomes among individuals.

5.11 Exploratory/Ancillary Correlative Studies

5.11.1 Whole Exome Sequencing / RNA sequencing

In order to determine possible biomarkers for response to treatment with Osimertinib (AZD9291) and Telaglenastat (CB-839) HCl, WES and RNA sequencing will be performed on the archival/baseline tumor specimen. Recent studies have demonstrated the importance of co-mutations in *EGFR*-mutated NSCLC, and potential primary resistance mechanisms to Osimertinib (AZD9291) have been elucidated, including regulators of cell cycle such as *CDK4/6* (Blakely *et al.*, 2017) as well as additional *EGFR* mutations L718 and L792 (Yang *et al.*, 2018). Evaluation for these and other mutations at baseline will be performed to identify biomarkers associated with drug activity

5.11.1.1 Specimen Receipt and Processing at the EET Biobank

Archival formalin-fixed paraffin-embedded tissue (block or slides) will be used for this assay. If a block is received, then the EET Biobank will cut and H&E stain slides. A pathology quality control review to assess tumor content and annotate slides for macrodissection will be completed for all tissue received. Unstained slides will be macrodissected, if needed, and scraped for DNA and RNA co-extraction. DNA will be banked in a stock vial and RNA will be divided into 5 aliquots; all nucleic acids will be stored in a -80°C freezer until distribution for testing.
Any additional FFPE tissue blocks or slides will banked at room temperature.

DNA will be extracted from blood collected in cfDNA Streck tubes at the baseline time point, following plasma processing. DNA will be stored in a -80°C freezer until distribution for testing.

5.11.1.2 Site(s) Performing Correlative Study

WES and RNAseq will be performed on archival samples by the MoCha, Frederick National Laboratory for Cancer Research (FNLCR) under the supervision of Chris Karlovich, Ph.D. (chris.karlovich@nih.gov).

5.11.1.3 Shipment of Specimens from the EET Biobank to Site Performing Correlative Study

Specimens will be shipped from the EET Biobank to:

MoCha Lab, Frederick National Laboratory for Cancer Research (FNLCR)
1050 Boyles St.
Bldg. 459, Rm. 125
Frederick, MD 21702
Attn: Alyssa Chapman or Ruth Thornton

5.11.1.4 Contact information for notification of specimen shipment:

Thomas Forbes, mochasamplereceiving@nih.gov

5.11.2 Cell-Free DNA Analysis

Peripheral blood will be collected to assess cfDNA for *EGFR* mutational status, T790M mutational status, and resistance mechanisms. cfDNA for *EGFR* status will be compared with archival/baseline specimen for concordance. Blood based assays for detection of resistance mechanisms are widely used in clinical practice, and have also yielded information about resistance mechanisms to treatment (Blakely *et al.*, 2017).

5.11.2.1 Specimen Receipt and Processing at the EET Biobank

Blood received in cfDNA Streck tubes will be processed for plasma upon receipt at the EET Biobank. The baseline cfDNA Streck tube will also be processed for DNA (to be used for other correlative studies), and the buffy coat from other time points will also be processed and stored. Plasma will be stored in 1 mL aliquots in a -80°C freezer until distribution for testing. Buffy coat will also be stored in a -80°C freezer.

5.11.2.2 Site(s) Performing Correlative Study

This study will be performed at the MoCha, Frederick National Laboratory for Cancer Research (FNLCR) under the supervision of Chris Karlovich, Ph.D. (chris.karlovich@nih.gov).

5.11.3.3 Shipment of specimens from the EET Biobank to Site Performing Correlative Study

Specimens will be shipped from the EET Biobank to:

MoCha Lab, Frederick National Laboratory for Cancer Research (FNLCR)
1050 Boyles St.
Bldg. 459, Rm. 125
Frederick, MD 21702
Attn: Alyssa Chapman or Ruth Thornton

5.11.3.4 Contact information for notification of specimen shipment:

Thomas Forbes, mochasamplereceiving@nih.gov

6 TREATMENT PLAN

6.1 Agent Administration

Treatment will be administered on an outpatient basis. Reported AEs and potential risks are described in Section 10. Appropriate dose modifications are described in Section 7. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Dose Escalation Treatment Plan: A single arm dose escalation portion of the study will first be performed to determine the optimal dosing strategy where three dose levels will be assessed. Extensive PK studies will also be conducted to assess for any potential drug-drug interactions through the obtaining of peripheral blood. Eligible patients will initially receive treatment with single agent Telaglenastat (CB-839) HCl BID according to the dose escalation strategy and PK sampling will be done on Day 15. Starting on Day 16, patients will then go on to receive both Osimertinib (AZD9291) 80 mg PO QD as well as Telaglenastat (CB-839) HCl PO BID at the same dose as initially provided during the monotherapy portion of the study and a second set of PK analyses will be conducted on Day 1 of Cycle 2 for both Osimertinib (AZD9291) and Telaglenastat (CB-839) HCl (see table below). Peripheral blood will also be obtained for a PK assessment at the beginning of each 28- day treatment cycle starting with Cycle 2. An assessment for response to treatment will be conducted with a CT of the chest, abdomen, and pelvis (C/A/P) every 2 months as is standard practice.
Patients will continue to receive treatment until the time of disease progression, unacceptable toxicity, or treatment is discontinued based on patient/physician preference.

Patients enrolled to the dose escalation portion of the study will be treated according to a dose escalation schedule where three different dose levels will be assessed. For all dose levels, the Osimertinib (AZD9291) dose will be set at 80 mg PO QD. The dose levels of Telaglenastat (CB-839) HCl are as follows:
1) 400 mg PO BID; 2) 600 mg PO BID; 3) 800 mg PO BID. Dose Level -1 will be 200 mg Telaglenastat (CB- 839) HCl BID.

Phase 1 Dose Escalation Schedule		
Dose Level	**Dose***	
	Telaglenastat (CB-839) HCl (mg) orally BID	**Osimertinib (AZD9291) (mg) orally daily**
Level -1	200 mg	80 mg
Level 1 (Starting Dose)	400 mg	80 mg
Level 2	600 mg	80 mg
Level 3	800 mg	80 mg
BID = twice daily, QD = once daily **Dosing is given orally on a continuous schedule*		

Regimen Description					
Agent	**Premedications**	**Dose***	**Route**	**Schedule**	**Cycle Length**
Telaglenastat (CB-839) HCl	None	Varying** (400-800 mg, 2-4 tablets)	PO BID with food	Continuous	28 days (4 weeks)
Osimertinib (AZD9291)	None	80 mg (1 tablet)	PO QD	Phase 1: Continuous starting on C1D16 Phase 2: Continuous	

PO = by mouth, QD = once daily, BID = twice daily
** Dosing is given orally on a continuous schedule*
***Doses as appropriate for assigned dose level.*

Expansion Cohort Treatment Plan: A 10-patient expansion cohort study will then be performed at the maximum tolerated dose (MTD) identified in the dose escalation study. Eligible patients will receive Osimertinib (AZD9291) 80 mg PO QD as well as Telaglenastat (CB-839) HCl PO BID at doses determined during the phase 1 portion of the study. An assessment for response to treatment will be conducted with a CT C/A/P every 2 months. Peripheral blood specimens will be collected at baseline, one-month post-treatment and at the time of RECIST progression to assess cfDNA for *EGFR* mutational status, T790M mutational status and *EGFR* resistance mechanisms as well as to assess changes in the metabolites glutamine, glutamate, aspartate and asparagine. Patients will continue with treatment until the time of disease progression, unacceptable toxicity, or treatment is discontinued based on patient/physician preference.

Patients enrolled to the expansion cohort of the study will be treated with Osimertinib (AZD9291) 80 mg PO QD as well as Telaglenastat (CB-839) HCl PO BID at 800mg BID which was evaluated in the dose escalation portion of the study and found to be safe. The initial dose of Osimertinib (AZD9291) 80 mg QD can be reduced to 40 mg QD for patients enrolled to the phase 2 study as detailed in Section 7. Patients will be treated until the time of disease progression, unacceptable toxicity, or treatment is discontinued per patient/physician preference. Patients will be followed for 30 days after completion of therapy unless treatment related toxicities have not resolved to grade 1 in which case they will be followed until toxicities have resolved to grade 1.

Patients will be requested to maintain a medication diary of each dose of medication. The medication diary (Appendix G) will be returned to clinic staff at the end of each course.

All protocol therapy with Telaglenastat (CB-839) will end on 2/28/25. The clinical supply of Telaglenastat will no longer be available after the terminal lot shelf life dating of 2/28/25 is reached. After that date, patients may remain on Osimertinib single agent at the investigator discretion until meeting other off therapy criteria.

6.1.1 Telaglenastat (CB-839) HCl

When taken with food, Telaglenastat (CB-839) HCl has demonstrated a slightly higher (~1.3 fold) absorption, and patients have experienced significantly fewer incidences of elevated LFTs compared to the fasted state. Telaglenastat (CB-839) HCl should be taken with breakfast and dinner, roughly 12 hours apart.

6.1.2 Osimertinib (AZD9291)

Based on the results from the definitive food effect study and supporting results from the exploratory study, it is recommended that Osimertinib (AZD9291) can be taken with or without food.

6.1.3 Other Modalities or Procedures

N/A

6.2 Definition of Dose-Limiting Toxicity

The DLT period will be 28 days (of combined treatment) and patients will continue therapy until the time of disease progression, unacceptable toxicity, or per patient/physician preference. To be evaluable for a DLT, patients must have started the combination therapy portion of the study. Patients who complete the DLT period and receive at least 75% of scheduled days of treatment will be evaluable for safety endpoints. Patients who discontinue combined treatment during the 28-day evaluation period for any reason other than treatment-related or dose-limiting toxicity will not be evaluable. Non-evaluable patients will be replaced. A DLT will be defined as any AE that cannot be determined to be unrelated to study treatment, occurs within the first 28 days of combination treatment, and that meets at least one of the following criteria. Non-hematologic DLTs will be defined as grade 3 or higher toxicities according to the CTCAE version 5.0 except the following— grade 3 nausea, vomiting, or diarrhea lasting <48 hours and controlled by optimal antiemetic/antidiarrheal therapy; clinical laboratory abnormalities that are reversible to ≤grade 1 or baseline status within 72 hours with outpatient care and/or monitoring or that are not considered clinically significant by the PI. Grade 3 rash attributed to the combination will be considered a DLT if grade 3 despite maximal medical management (including oral antibiotic, topical or oral steroids) for >72 hours. Hematologic DLTs will be defined as the following— grade 4 or higher neutropenia [absolute neutrophil count (ANC) < 0.5 x 10^9/L]; grade 3 or higher febrile neutropenia (ANC <1.0 x 10^9/L with a fever ≥ 38.3 °C); grade 4 or higher thrombocytopenia (<25.0 x 10^9/L); and grade 3 or higher thrombocytopenia associated with grade 3 or higher bleeding. Patients will be followed for 30 days after completion of therapy unless treatment-related toxicities have not resolved to grade 1 in which case they will be followed until toxicities have resolved to grade 1. Any grade of pneumonitis will also be considered a DLT.

Dose escalation will proceed within each cohort according to the following scheme. DLT is defined above.

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter 3 patients at the next dose level.
≥2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
1 out of 3	Enter at least 3 more patients at this dose level. • If 0 of these 3 patients experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
≤1 out of 6 at highest dose level below the maximally administered dose	This is generally the RP2D. At least 6 patients must be entered at the RP2D.

6.3 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of Telaglenastat (CB-839) HCl and Osimertinib (AZD9291) with other concomitantly administered drugs, the Case Report Form (CRF) must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The PI should be alerted if the patient is taking any agent known to affect or with the potential for drug interactions. The potential targets for drug interaction can involve, but are not limited to CYP450, glucuronidation, P-glycoprotein, protein binding, or reduced absorption from proton- pump inhibitors. Check the study agent Investigator's Brochure for potential sources of drug interactions. The study team should check a frequently-updated medical reference for a list of drugs to avoid or minimize use of. Appendix B (Patient Drug Information Handout and Wallet Card) should be provided to patients if available, and Appendix D (Guidance Regarding Potential Interactions with Concomitant Medications) for additional information on concurrent medications.

6.3.1 Radiotherapy

Radiotherapy will be permitted if deemed clinically beneficial by the treating physician for palliation of painful bone disease or in cases of symptomatic CNS disease amenable to stereotactic radiation. Whole brain radiation and radiation of target lesions is not permitted. Study treatment should be held for 3 days before and after radiotherapy.

6.3.2 Osimertinib (AZD9291), CYP 3A4 and BCRP

Because there is a potential for interaction of Osimertinib (AZD9291) with other concomitantly administered drugs, the CRF must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The PI should be alerted if the patient is taking any agent known to affect or with the potential for drug interactions. *In vitro* studies demonstrate that Osimertinib (AZD9291) and its active metabolites are primarily metabolized by CYP 3A4 enzymes. Potent inducers of CYP 3A4 are therefore contraindicated and a wash-out period is required (duration of wash-out varies, See Appendix D [Guidance Regarding Potential Interactions With Concomitant Medications]).

Patients taking rosuvastatin should have creatine phosphokinase levels monitored (due to BCRP-

mediated increase in exposure). If the patient experiences any potentially relevant AEs suggestive of muscle toxicity including unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever, rosuvastatin must be stopped and any appropriate further management should be taken.

6.3.3 Telaglenastat (CB-839) HCl and CYP2C9

Telaglenastat (CB-839) HCl is metabolized by human hepatocytes primarily through amide hydrolysis. Telaglenastat (CB-839) HCl does not appear to induce CYP drug-metabolizing enzymes and only weakly inhibits CYP2C9 (~40-50% inhibition at 5 mcM) *in vitro*. Although Telaglenastat (CB-839) HCl is not expected to inhibit CYP2C9 at the exposure levels planned, caution is warranted when administering Telaglenastat (CB-839) HCl to patients taking drugs that are highly dependent on CYP2C9 for metabolism and have a narrow therapeutic index. A list of medications that are CYP2C9 substrates is provided in Appendix C (Cytochrome P450 [CYP] 2C9 Substrates).

6.3.4 Telaglenastat (CB-839) HCl and Proton Pump Inhibitors

Preliminary PK data generated in single agent phase 1 studies indicate that concomitant use of PPIs may reduce absorption of Telaglenastat (CB-839) HCl, resulting in decreased systemic exposure. Although patients are not required to discontinue their use of these agents, the strong preference is for patients to discontinue PPIs prior to joining the study. Antagonists of the H2 histamine receptor (*e.g.*, ranitidine, famotidine, *etc.*) may be substituted for PPIs. For patients unable to discontinue PPI therapy or that require restarting PPI therapy while on study, administration of Telaglenastat (CB-839) HCl with an acidic beverage (*e.g.*, orange juice) or supplement (*e.g.*, citric acid) may be an option. If an acidic beverage/oral supplement is administered along with the Telaglenastat (CB-839) HCl dose, it should be recorded on the appropriate electronic CRF (eCRF), including the identity of the beverage/supplement, dosage, and start and stop dates of administration.

To aid absorption, it is recommended that Telaglenastat (CB-839) HCl is taken at least 2 hours before or at least 10 hours after H2 receptor agonist therapy, or at least 2 hours before or at least 2 hours after other antacid therapy.

6.4 Duration of Therapy

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

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable AE(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
- Patient non-compliance
- Pregnancy
    - All women of child bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (*e.g.*, missed or late menstrual period) at any time during study participation.
    - The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a patient participating in the study.
- Termination of the study by sponsor
- The drug manufacturer can no longer provide the study agent

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

6.5 Duration of Follow-Up

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

7 DOSING DELAYS/DOSE MODIFICATIONS

Telaglenastat (CB-839) HCl

Based on available data, AEs that are most likely to be observed with Telaglenastat (CB-839) HCl treatment include fatigue, GI events (nausea, vomiting, anorexia), photophobia, and elevated LFTs. Careful application of the dose-escalating rules and close observation of the subjects should minimize the potential risk of dosing with Telaglenastat (CB-839) HCl. The study personnel must be able to recognize and diagnose these potential AEs and initiate prompt intervention. In general, grade 1 events should be managed with appropriate supportive care, dosing can be interrupted for persistent drug-related grade 2 events, and the dose should be reduced for most Telaglenastat (CB-839) HCl-related grade 3/4 toxicities. In particular, regular monitoring of LFTs is recommended. Grade >2 elevations in ALT or total bilirubin should lead to an interruption of study drug and grade ≥3 events should lead to dose reduction upon restarting Telaglenastat (CB-839) HCl.

Blood Bilirubin Increase	**Management/Next Dose for Telaglenastat (CB-839) HCl**	**Management/Next Dose for Osimertinib (AZD9291)**
Grade 1	No change in dose.	No change in dose
Grade 2	Hold until ≤ grade 1. Resume at same dose level.	Hold until ≤ grade 1. Resume at same dose level.
Grade 3	Hold* until ≤ grade 1. Resume at one dose level lower, if indicated.**	Hold* until ≤ grade 1. Resume at one dose level lower, if indicated.**
Grade 4	Hold* until ≤ grade 1. Resume at one dose level lower, if indicated.**	Hold* until ≤ grade 1. Resume at one dose level lower, if indicated.**

*Patients requiring a delay of >2 weeks should go off protocol therapy.
**Patients requiring > 2 dose reductions of Telaglenastat (CB-839) HCl or > 1 dose reduction in Osimertinib (AZD9291) must go off protocol therapy.

Alanine Aminotransferase Increased	**Management/Next Dose for Telaglenastat (CB-839) HCl**	**Management/Next Dose for Osimertinib (AZD9291)**
Grade 1	No change in dose.	No change in dose
Grade 2	Hold until ≤ grade 1. Resume at same dose level.	Hold until ≤ grade 1. Resume at same dose level.
Grade 3	Hold* until ≤ grade 1. Resume at one dose level lower, if indicated.**	Hold* until ≤ grade 1. Resume at one dose level lower, if indicated.**
Grade 4	Hold* until ≤ grade 1. Resume at one dose level lower, if indicated.**	Hold* until ≤ grade 1. Resume at one dose level lower, if indicated.**
*Patients requiring a delay of >2 weeks should go off protocol therapy.		

Alanine Aminotransferase Increased	**Management/Next Dose for Telaglenastat (CB-839) HCl**	**Management/Next Dose for Osimertinib (AZD9291)**
** Patients requiring > 2 dose reductions of Telaglenastat (CB-839) HCl or > 1 dose reduction in Osimertinib (AZD9291) must go off protocol therapy.		

Other AEs	**Management/Next Dose for Telaglenastat (CB-839) HCl**	**Management/Next Dose for Osimertinib (AZD9291)*** **
Grade 1	No change in dose. Administer standard supportive care.	No change in dose
Grade 2	For persistent grade 2 toxicity****: Hold until ≤ grade 1. Resume at same dose level.	For persistent grade 2 toxicity****: Hold until ≤ grade 1. Resume at same dose level.
Grade 3	Reduce dose by one level if event is related to Telaglenastat (CB-839) HCl.*	Hold* until ≤ grade 1. Resume at one dose level lower, if indicated.**

Grade 4	Reduce dose by one level if event is related to Telaglenastat (CB-839) HCl.*	Hold* until ≤ grade 1. Resume at one dose level lower, if indicated.**

*Patients requiring a delay of >2 weeks should go off protocol therapy.
** Patients requiring > 2 dose reductions of Telaglenastat (CB-839) HCl or > 1 dose reduction in Osimertinib (AZD9291) must go off protocol therapy.
***Osimertinib (AZD9291) must be permanently discontinued for ILD/pneumonitis or QTc interval prolongation with signs/symptoms of serious arrhythmia
****Persistent grade 2 toxicities include those that do not resolve within 7 days despite optimal supportive care or result in treatment delay > 14 days

Osimertinib (AZD9291)

Dose Adjustments for Osimertinib (AZD9291):

Dose Level	Osimertinib (AZD9291) Dose (QD)
Starting Dose	80 mg
Dose Reduction	40 mg

All patients in the phase 2 study will commence treatment with Osimertinib (AZD9291) at 80 mg daily. If a patient experiences a persistent drug-related grade 2 event or any CTCAE grade 3 or higher and/or unacceptable toxicity (any grade), where the clinician considers the event of concern to be specifically associated with Osimertinib (AZD9291) (and not attributable to the disease or disease-related processes for which patient is being treated), dosing will be interrupted, and supportive therapy administered as required in accordance with local practice/guidelines. If a toxicity resolves or reverts to ≤CTCAE grade 2 within 3 weeks of onset, treatment with Osimertinib (AZD9291) may be restarted at the same dose (80 mg) or a lower dose (40 mg) using the rules indicated in the above table for dose modifications and with discussion and agreement with the Sponsor Study Team Physician as needed. There will be no individual modifications to dosing schedule in response to toxicity, only potential dose reduction or dose interruption. If the toxicity does not resolve to ≤CTCAE grade 2 after 3 weeks, then the patient should be withdrawn from the study and observed until resolution of the toxicity.

Dose adjustment for AEs should be in accordance with the following table:

Dose Adjustment Information for Adverse Reactions		
Target Organ	**Adverse Reaction**	**Dose Modification**

Pulmonary	ILD/Pneumonitis	Permanently discontinue Osimertinib (AZD9291)
Cardiac	QTc interval greater than 500 msec on at least 2 separate ECGs	Withold Osimertinib (AZD9291) until QTc interval is less than 481 msec or recovery to baseline if baseline QTc is greater than or equal to 481 msec, then restart at a reduced dose (40 mg) or at 80 mg (at the discretion of the investigator, to allow for situations where causality in relation to osimertinib may be difficult to determine).
	QTc interval prolongation with signs/symptoms of serious arrhythmia	Permanently discontinue Osimertinib (AZD9291)
Other	Grade 3 or higher adverse reaction	Withhold Osimertinib (AZD9291) for up to 3 weeks
	If grade 3 or higher adverse reaction improves to grade 0-2 after withholding of Osimertinib (AZD9291) for up to 3 weeks	Osimertinib (AZD9291) may be restarted at the same dose (80 mg) or a lower dose (40 mg)
	Grade 3 or higher adverse reaction that does not improve to grade 0-2 after withholding for up to 3 weeks	Permanently discontinue Osimertinib (AZD9291)

On resolution of toxicity within 3 weeks:

- If an AE subsequently requires dose interruption, Osimertinib (AZD9291) may restart at the same dose or the reduced dose, on resolution/improvement of the AE at the discretion of the Investigator.

Patients experiencing any of the following AEs will not be permitted to restart study treatment:

- Interstitial Lung Disease (ILD)
- QTc interval prolongation with signs/symptoms of serious arrhythmia

There is no dose reduction allowed below 40 mg. If a patient experiences toxicity such that 40 mg is no longer considered tolerable, the patient should discontinue study treatment.

It is recommended that all patients follow a program of sun protective measures while receiving study drug and for 3 to 4 weeks after discontinuing study drug.

Interstitial Lung Disease (ILD)/Pneumonitis-like toxicity:

If new or worsening pulmonary symptoms (e.g., dyspnea) or radiological abnormality suggestive of interstitial lung disease is observed, an interruption in study treatment dosing is recommended, and the AstraZeneca study team should be informed. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis,

infection, allergy, cardiogenic edema or pulmonary hemorrhage. The results of full diagnostic workup (including high resolution computed tomography (HRCT), blood and sputum culture, hematological parameters) will be captured by eCRF. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of interstitial lung disease should be considered and study treatment permanently discontinued

Management of Keratitis

Keratitis was reported in 0.7% (n=6) of the 833 patients treated with Osimertinib (AZD9291) in the AURA studies. Patients presenting with signs and symptoms suggestive of keratitis such as acute or worsening: eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain, and/or red eye should be referred promptly to an ophthalmology specialist.

Management of QTC Prolongation

For QTc interval greater than 500 msec on at least 2 separate ECGs, withhold Osimertinib (AZD9291) until QTc interval is less than 481 msec, or until recovery to baseline if baseline QTc is greater than or equal to 481 msec. Osimertinib (AZD9291) can then be restarted at a reduced dose. If the toxicity does not resolve to grade ≤2 within 21 days, the patient will be permanently withdrawn from study treatment.

For QTc interval prolongation with signs/symptoms of serious arrhythmia, Osimertinib (AZD9291) must be permanently discontinued.

Changes in Cardiac Contractility

An Echocardiogram or MUGA scan to assess LVEF will be performed at screening (prior to first dose of Osimertinib (AZD9291)) and at end of treatment. Per the FDA label, echocardiogram is indicated at baseline and during treatment for patients with cardiac risk factors, or if clinically indicated.

The modality of the cardiac function assessments must be consistent within a patient i.e. if echocardiogram is used for the screening assessment then echocardiogram should also be used for subsequent scans. The patients should also be examined using the same machine and operator whenever possible, and quantitative measurements should be taken. A 28-day follow-up assessment will be required if an on-treatment assessment was abnormal at the time of discontinuation of study therapy, to confirm reversibility of the abnormality.

Erythema Multiforme, and Stevens-Johnson syndrome and Toxic epidermal necrolysis

Case reports of Erythema multiforme (EM) and toxic epidermal necrolysis have been uncommonly reported, and Stevens-Johnson syndrome (SJS) have been uncommonly and rarely reported, respectively, in association with osimertinib treatment. Before initiating treatment, patients should be advised of signs and symptoms of EM, and SJS and TEN. If signs and symptoms suggestive of EM develop, close patient monitoring and drug interruption or discontinuation of osimertinib should be considered. If signs and symptoms suggestive of SJS appear, osimertinib should be interrupted. Osimertinib should be or discontinued immediately if SJS or TEN is diagnosed.

Aplastic Anemia

Rare reports of aplastic anemia have been reported in association with osimertinib treatment. Some cases had a fatal outcome. Before initiating treatment, patients should be advised of signs and symptoms of aplastic anemia including but not limited to persistent fever, bruising, bleeding, and/or pallor. If signs and symptoms suggestive of aplastic anemia develop, close patient monitoring and drug interruption or discontinuation of osimertinib should be considered. Osimertinib should be discontinued in patients with confirmed aplastic anemia.

Dose Modifications and Supportive Care for Diarrhea

Severity (CTCAE v5.0 Grading)	**Description**	**Intervention concerning Osimertinib (AZD9291) treatment**	**Specific intervention**
Mild (Grade 1)	Increase of <4 stools per day over baseline; mild increase in ostomy output compared with baseline	Continue same dose	Stop laxatives and advise patient to drink at least 8-10 glasses of water of clear fluids per day. Consider adding loperamide. 4 mg (2 tablets) of loperamide to be taken immediately, followed by 2 mg (1 tablet) after each loose stool until bowel movements cease for 12 hours.
Moderate (Grade 2)	Increase of 4-6 stools per day over baseline; IV fluids indicated <24 hours; moderate increase in ostomy output compared with baseline; not interfering with ADL	Continue same dose with medical management unless investigator determines clinically significant and persists >72 hours. Then interrupt Osimertinib (AZD9291) until grade ≤1 and consider a dose reduction.	Start loperamide if patient not already taking per dosing above. 4 mg (2 tablets) of loperamide to be taken immediately, followed by 2 mg (1 tablet) after each loose stool until bowel movements cease for 12 hours. If already on loperamide, consider adding diphenoxylate/atropine (lomotil) and/or tincture of opium.

Severe (Grade 3)	Increase of ≥7 stools per day over baseline; incontinence; IV fluids >24 hours; hospitalization; severe increase in ostomy output compared with baseline; interfering with ADL	Dose interruption until recovered to ≤grade 1 followed by dose reduction.	See grade 2; plus: Consider an infectious process. Aggressive IV fluid replacement; consider hospitalization to monitor progress.
Life threatening (Grade 4)	Life-threatening consequences (*e.g.,* haemodynamic collapse)	Dose interruption until recovered to ≤ grade 1 followed by dose reduction	See grade 3

Appropriate management of diarrhea, including dose adjustments for AEs of diarrhea that are of CTCAE grade ≥3 or that are clinically significant and/or intolerable and considered by the Investigator to be causally related to Osimertinib (AZD9291), should be undertaken as per standard practice and guidelines for dose adjustments above. Changes in CTCAE grade of diarrhea will be captured in the AE eCRF.

Nausea, vomiting, or both may be controlled with anti-emetic therapy per local practice..

8 PHARMACEUTICAL INFORMATION

A list of the AEs and potential risks associated with the investigational agents administered in this study can be found in Section 10.1.

8.1 CTEP IND Agents

8.1.1 Telaglenastat (CB-839) HCl (NSC 795998)

Chemical Name: N-[5-[4-[6-[[2-[3-(trifluoromethoxy)phenyl]acetyl]amino]-3-pyridazinyl]butyl]-1,3,4-thiadiazol-2-yl]-2-pyridineacetamide

Classification: Glutaminase Inhibitor

Molecular Formula: $C_{26}H_{24}F_3N_7O_3S$ **M.W.: 571.57**

Mode of Action: Telaglenastat (CB-839) HCl is a potent and selective reversible inhibitor of glutaminase activity. It is an allosteric and noncompetitive inhibitor of both GAC ("glutaminase C") and KGA ("kidney glutaminase") isoforms of glutaminase (GLS), but does not inhibit glutaminase-2.

How Supplied: Telaglenastat (CB-839) HCl is supplied as 200 mg white to off-white oval coated tablets. Each tablet contains 200 mg Telaglenastat (CB-839) HCl salt which is equivalent to 188 mg of CB-839 free base. Tablet excipients include microcrystalline cellulose, lactose monohydrate, sodium starch glycolate, magnesium stearate, and Opadry II White (coating). The approximate dimensions (L x W x H) are 14.5 mm x 6.9 mm x 6.0 mm (0.57" x 0.273" x 0.236"). Each 50-count bottle is sealed with a tamper-evident seal and a child-proof cap. Tablets can be transferred to another bottle per institutional procedure prior to dispensing.

In late 2021 PMB will transition to a new formulation of telaglenastat (CB-839) HCl. This new telaglenastat (CB-839) HCl formulation is supplied as 200 mg purple, oval, coated tablets embossed with the letters "TEL" on one side of the tablet. Each tablet contains 200 mg CB-839 HCL salt which is equivalent to 188 mg of CB-839 free base. Tablet excipients include microcrystalline cellulose, lactose monohydrate, sodium starch glycolate, magnesium stearate, and Opadry® II 85F90035 Purple (coating). This color is free from potentially allergenic dyes and is an approved color for US and EU markets. The approximate dimensions (L x W x H) are 14.5 mm x 6.9 mm x 6.0 mm (0.57" x 0.273" x 0.236").

Each 240-count bottle is sealed with a tamper-evident seal and a child-proof cap. The packaging consists of white opaque high-density polyethylene (HDPE) plastic bottles closed with a child resistant cap (CRC) and sealed with a tamper-evident induction seal. No rayon in bottle. Tablets can be transferred to another bottle per institutional procedure prior to dispensing.

Storage: Store at room temperature (20°C-25°C). Excursions +/- 5°C are permitted.

If a storage temperature excursion is identified, promptly return Telaglenastat (CB-839) HCl to (20°C-25°C) and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to for determination of suitability.

Stability: Stability studies are ongoing.

Route of Administration: PO, approximately 12 hours apart, with food. Administer the first dose immediately after breakfast, the second dose approximately 12 hours later. Doses should be taken at approximately the same times each day. Missed doses may be taken if it is not more than three hours past the scheduled administration time for the missed dose. Vomited doses should not be made up.

Metabolism: In *in vitro* studies, Telaglenastat (CB-839) HCl is metabolized by amide hydrolysis and to a lesser extent, P450-mediated hydroxylation.

Potential Drug Interactions: In *in vitro* data, Telaglenastat (CB-839) HCl is a weak inhibitor of CYP2C9; therefore, concomitant medications that are metabolized by CYP2C9 should either be given with caution (including closely monitoring for signs of toxicity or altered efficacy) or substituted with a non-CYP2C9 substrate. Telaglenastat (CB-839) HCl is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C19, CYP2D6, and CYP3A4 nor

an inducer of CYP1A2, CYP2B6, and CYP3A4.

Telaglenastat (CB-839) HCl requires low pH conditions for optimal solubilization. Concomitant use of PPIs should be avoided due to significantly reduced exposure to Telaglenastat (CB- 839) HCl. Patients may be switched to shorter acting agents such as histamine H2 receptor antagonists (H2RA) and as-needed antacid buffering agents (e.g. calcium carbonate, magnesium hydroxide and aluminum hydroxide) since, based on limited clinical data, they do not appear to result in a significant reduction of Telaglenastat (CB-839) HCl exposure. It is recommended that Telaglenastat (CB-839) HCl be dosed at least 2 hours before and at least 10 hours after treatment with H2RA therapy, and at least 2 hours before or at least 2 hours after other antacid therapy.

Patient Care Implications: Women of child-bearing potential must have a negative pregnancy test prior to starting Telaglenastat (CB-839) HCl and use two forms of effective birth control while receiving Telaglenastat (CB-839) HCl.

Availability

Telaglenastat (CB-839) HCl is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

Telaglenastat (CB-839) HCl is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 13.4).

8.1.2 Osimertinib (AZD9291) (NSC 781254)

Chemical Name: N-(2-{[2-(Dimethylamino)ethyl](methyl)amino}-4-methoxy-5-{[4-(1-methyl-1H-indol-3-yl)pyrimidin-2-yl]amino}phenyl)prop-2-enamide methanesulfonate

Other Names: Tagrisso™, AZD9291 mesylate

Classification: Epidermal growth factor receptor (EGFR) inhibitor

Molecular Formula: C28H33N7O2.CH4O3S **M.W.:** 595.71 (mesylate salt)
499.61 (free base)

Approximate Solubility: The solubility of osimertinib free base has been measured as 7.2 mg/mL in Simulated Gastric Fluid (pH 1.4) and 0.2 mg/mL in Fasted State Simulated Intestinal Fluid (pH 6.5).

Mode of Action: Osimertinib (AZD9291) is a potent, oral, irreversible, tyrosine kinase inhibitor (TKI) of epidermal growth factor receptor (EGFR) mutation-positive (EGFRm) and T790M mutation-positive forms of EGFR.

Description: Osimertinib mesylate is a crystalline powder.

How Supplied: Osimertinib (AZD9291) tablets are supplied by AstraZeneca and

distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI. Tablets are packaged in 30-count bottles with mannitol, microcrystalline cellulose, low-substituted hydroxypropyl cellulose and sodium stearyl fumarate as inactive ingredients in the following strengths:

- 80 mg tablets: beige, oval and biconvex tablet marked with "AZ 80" on one side and plain on the reverse.
- 40 mg tablets: beige, round and biconvex tablet marked with "AZ 40" on one side and plain on the reverse.

The tablet coating contains polyvinyl alcohol, titanium dioxide, macrogol 3350, talc, ferric oxide yellow, ferric oxide red and ferric oxide black.

Storage: Store at room temperature 20° to 25°C (68° to 77°F), excursions permitted between 15 to 30°C (59 to 85°F).

If a storage temperature excursion is identified, promptly return osimertinib (AZD9291) to controlled room temperature and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability: Refer to the package label for expiration.

Route of Administration: Take by mouth with or without food. If a dose of osimertinib (AZD9291) is missed or vomited, do not make up the missed dose and take the next dose as scheduled.

Potential Drug Interactions: The main metabolic pathways of osimertinib (AZD9291) are oxidation (predominantly CYP3A4) and dealkylation in vitro. Avoid concomitant use of strong CYP3A4 inducers. CYP3A4 inhibitors are not likely to affect the exposure of osimertinib (AZD9291). Based on in vitro studies, osimertinib (AZD9291) is a competitive inhibitor of CYP 3A4/5 but not CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6 and 2E1 at clinically relevant concentrations. Osimertinib (AZD9291) is an inducer of CYP1A2. Use caution with coadministration of CYP 3A4/5 and 1A2 substrates.

Osimertinib (AZD9291) is a substrate of BCRP and P-gp but is unlikely to result in clinically relevant drug interactions. Osimertinib (AZD9291) is not a substrate of OATP1B1 and OATP1B3 and does not inhibit OAT1, OAT3, OATP1B1, OATP1B3, OCT2, MATE1 and MATE2K at clinically relevant concentrations. Based on in vitro data, osimertinib (AZD9291) is an inhibitor of BCRP and may increase the exposure of BCRP substrates. Osimertinib (AZD9291) does not inhibit P-gp at clinically relevant concentrations but has the potential to increase exposure of sensitive substrates.

Avoid use of osimertinib (AZD9291) in patients with congenital long QT syndrome. For patients with normal QT interval at the trial enrollment, avoid use of concomitant drugs that are known to prolong QT interval and use caution with drugs that may prolong QT interval. Refer to a frequently updated drug information reference and to the protocol for appropriate cardiac monitoring.

8.1.3 Agent Ordering and Agent Accountability

NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead participating investigator at that institution.

In general, sites may order initial agent supplies when a subject is being screened for enrollment onto the study.

Submit agent requests through the Pharmaceutical Management Branch (PMB) Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP IAM account and the maintenance of an "active" account status, a "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

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

8.1.4 Investigator Brochure Availability

The current versions of the Investigator's Brochures (IBs) for the agents will be accessible to site investigators and research staff through the PMB OAOP application. Access to OAOP requires the establishment of a CTEP IAM account and the maintenance of an "active" account status, a "current" password, and active person registration status. Questions about IB access may be directed to the PMB IB Coordinator via email.

8.1.5 Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB OAOP application: https://ctepcore.nci.nih.gov/OAOP
- CTEP IAM account: https://ctepcore.nci.nih.gov/iam/
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- IB Coordinator: IBCoordinator@mail.nih.gov

- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

9 STATISTICAL CONSIDERATIONS

9.1 Study Design/Endpoints

The dose escalation component of this study is a dose-escalation trial of Telaglenastat (CB-839) HCl and Osimertinib (AZD9291) in patients with metastatic *EGFR* activating mutation positive NSCLC. It has been designed to define the RP2D of Telaglenastat (CB-839) HCl and Osimertinib (AZD9291). Assuming DLT rate is as few as 30% at MTD, a traditional 3+3 dose escalation design will be adopted and 3-6 evaluable patients will be treated at each dose level. Dose escalation rules are defined in Section 6.2. An evaluable patient for a DLT is defined as the patient who must have started the combination therapy portion of the study. Patients who discontinue combined treatment during the 28-day evaluation period for any reason other than treatment-related or dose-limiting toxicity will not be evaluable. Non-evaluable patients will be replaced. Nine to eighteen patients are expected to be enrolled depending on the number of dose escalations and assuming that a total of 6 patients will be treated at the final RP2D level. The DLT period will be set at 28 days of combination therapy.

In the 10 patient expansion cohort, we will gain additional experience and understanding regarding the safety, tolerability, and efficacy of combination Telaglenastat (CB-839) HCl and Osimertinib (AZD9291) in patients with *EGFR* activating mutation positive NSCLC who have progressed on first line EGFR TKI with osimertinib.

In the expansion cohort component of the study, a safety monitoring scheme will also be implemented by including a stopping rule based on the number of DLTs among the first 10 patients in the expansion cohort. Enrollment may be paused if the lower bound of the 1-sided 80% exact binomial confidence interval of the estimated DLT excludes 30%. After the first 10 patients have been evaluated for DLT, the study will be stopped for safety if at least 5 patients with DLTs are observed. The study will continue if no more than 4 patients experience DLTs.

Integral testing for *EGFR* status will be completed locally but an integrated *EGFR* test will also be completed centrally for confirmation of *EGFR* status. In case a patient is deemed to be *EGFR* mutant by the local test but *EGFR* wild-type by the central test, that patient will not be included in the primary analysis.

All toxicities will be summarized as the percentage of patients experiencing each type and grade of event according to dose level. Patients who receive at least one dose of treatment will be included in the analysis.

The ORR will be calculated as the proportion of patients who achieve a response to therapy divided by the total number of evaluable patients. An evaluable patient is defined as an eligible patient who has received at least one dose of therapy and has centralized confirmation of positive *EGFR* mutation status. All evaluable patients will be included in calculating the ORR for the study along with corresponding 95% binomial CIs (assuming that the number of patients who respond is binomially distributed). Separately, all patients treated at the RP2D in either the dose expansion or the expansion cohort will be analyzed.

Definition of Primary Endpoints

- Safety, tolerability and RP2D of combination therapy with Telaglenastat (CB-839) HCl and Osimertinib (AZD9291) in patients with metastatic *EGFR* activating mutation positive NSCLC.

Definition of Secondary Endpoints

- DLTs as assessed by CTCAE version 5.0 of the combination of Telaglenastat (CB-839) HCl and Osimertinib (AZD9291) in patients with metastatic *EGFR* activating mutation positive NSCLC.
- PFS of patients with metastatic *EGFR* activating mutation positive NSCLC who have progressed on front-line EGFR inhibitor therapy following treatment with Telaglenastat (CB-839) HCl and Osimertinib (AZD9291). PFS is defined as the time from initiation of therapy to documented progression or death without progression.
- OS of patients with metastatic *EGFR* activating mutation positive NSCLC who have progressed on front-line EGFR inhibitor therapy following treatment with Telaglenastat (CB-839) HCl and Osimertinib (AZD9291). OS is defined as the time from initiation of therapy to death from any cause.

Definition of Correlative Endpoints

- Post-Telaglenastat (CB-839) HCl PK as assessed by Telaglenastat (CB-839) HCl drug levels following both single agent therapy as well as combination therapy with Telaglenastat (CB-839) HCl and Osimertinib (AZD9291) in patients with metastatic *EGFR* activating mutation positive NSCLC.
- Post-Osimertinib (AZD9291) PK as assessed by Osimertinib (AZD9291) drug levels following combination therapy with Telaglenastat (CB-839) HCl and Osimertinib (AZD9291) in patients with metastatic *EGFR* activating mutation positive NSCLC.
  Changes in *EGFR* mutational status as assessed by cfDNA in patients with metastatic *EGFR* activating mutation positive NSCLC who have progressed on front- line EGFR inhibitor therapy.
- Changes in circulating levels of glutamine, glutamate, aspartate, and asparagine as assessed by plasma concentrations of these compounds in patients with metastatic *EGFR* activating mutation positive NSCLC who have progressed on front- line EGFR inhibitor therapy.

9.2 Sample Size/Accrual Rate

This study plans to accrue a minimum of 9 and a maximum of 28 patients. Estimated accrual rate is 5 patients/month.

Sample Size Justification:

For the dose escalation portion of the study, the trial will be conducted using a standard 3+3 dose escalation design. As there are three dose levels to be assessed, a total of 9 to 18 patients are expected to be enrolled depending on the number of dose escalations and assuming that a total of 6 patients will be treated at the final MTD/RP2D level.

In the expansion cohort component of the study, we plan to obtain additional data regarding safety and tolerability as well as preliminary efficacy of combination CB-839 and osimertinib. With a total of 16 patients at MTD/RP2D (6 + 10), we will estimate the ORR with a 95% confidence interval half-width of less than 25.4%, using the Clopper-Pearson exact method.

PLANNED ENROLLMENT REPORT

This patient population represents a fraction of the entire NSCLC population, especially since this study is limited to the second line setting. Given the small numbers involved in this study, it is impossible to predict precise accrual patterns, but they should be reflective of the demographic areas of each accruing center. All patients with metastatic NSCLC who meet eligibility criteria will be eligible for this study.

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**

Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
Asian	1	2	0	0	**3**
Native Hawaiian or Other Pacific Islander	1	0	0	0	**1**
Black or African American	1	1	0	0	**1**
White	10	5	3	2	**15**
More Than One Race	1	0	0	1	**2**

Total	**14**	**8**	**3**	**3**	**22**

9.3 Stratification Factors

This is a non-randomized study and therefore no stratification will be performed.

9.4 Analysis of Secondary and Exploratory Endpoints

Frequency and severity of AEs and tolerability of the regimen will be collected and summarized by descriptive statistics. The maximum grade for each type of toxicity will be recorded for each patient, and frequency tables will be reviewed to determine toxicity patterns. All patients who have received at least one dose of the therapeutic agents will be evaluable for toxicity and tolerability.

We will explore PK endpoints such as C_{ss}, AUC, C_L, V_d, and $t_{1/2}$ computed using non-compartmental and compartmental methods. We will use graphical analyses as well as repeated measure models (linear or nonlinear mixed models, generalized estimating equations [GEE]) to assess the PK and PD markers described above in relation to clinical treatment outcomes, recognizing some inherent limitations due to sample size.

OS will be defined as time from initiation of therapy to death. PFS will be defined as the time from initiation of therapy to the time of RECIST progression or death. Survival will initially be modeled using Kaplan-Meier methods, resulting in median survival times with 95% CI, assuming sufficient events have occured.

All exploratory studies will be performed on specimens obtained from patients treated at MTD including the expansion cohort portion of the study. Graphical analyses will be largely used to assess potential patterns and relationships. cfDNA and circulating levels of glutamine, glutamate, aspartate, and asparagine will be summarized at baseline, after one month of treatment, and at time of progression. All continuous measurements will be summarized using mean +/- SEM, range, and median at each time point. Changes in these measurements from baseline to after treatment, or baseline to progression will be assessed using paired Wilcoxon tests. Adjustments for multiple comparisons or multiple outcomes will be performed using Bonferroni correction. ^{18}F-FDG-PET parameters will also be summaried at baseline and after treatment using mean +/- SEM, range, and median. The changes in the FDG-PET/CT parameter measurements from baseline to after treatment will be compared between responders and non-responders using two sample t-test or Wilcoxon test, whichever is appropriate. Fisher's exact test will be used to assess the association between biomarkers, genetic alterations and response to study drugs. Logistics regression model might also be used to identify potential predictive and prognostic biomarkers beyond any genomic alteration with response to study drugs. Initially, data will be presented as summary statistics and upon sufficent accural, a more detailed analytical plan will be developed. Given the small sample size, these analyses will be dependent on there being a sufficient number of responders with samples available.

9.5 Reporting and Exclusions

9.5.1 Evaluation of Toxicity

All patients will be evaluable for toxicity from the time of their first treatment with Telaglenastat (CB-839) HCl and Osimertinib (AZD9291).

9.5.2 Evaluation of Response

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) CR; 2) partial response (PR); 3) SD; 4) PD; 5) early death from malignant disease; 6) early death from toxicity; 7) early death because of other cause; or 9) unknown (not assessable, insufficient data). (Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.)

All the patients who met the eligibility criteria (with the exception of those who received no study medication, or patients who are found to be *EGFR* wild-type by the central confirmation test) should be included in the main analysis of the ORR. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the ORR. Precise definitions for categories 4-9 will be protocol specific.

All conclusions should be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (*e.g.*, early death due to other reasons, early discontinuation of treatment, major protocol violations, *etc*.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% CI should also be provided.

10 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

AE monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 10.1) and the characteristics of an observed AE (Sections 10.2 and 10.3) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) **in addition** to routine reporting.

10.1 Comprehensive Adverse Events and Potential Risks Lists (CAEPRs)

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

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

10.1.1 CAEPRs for CTEP IND Agents

10.1.1.1 CAEPR for Telaglenastat (CB-839) HCl

Below is the CAEPR for Telaglenastat (CB-839) HCl. Frequency is based on 161 patients.

Version 2.2, July 21, 2019[1]

Adverse Events with Possible Relationship to Telaglenastat (CB-839) HCl (CTCAE 5.0 Term) [n= 161]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		
EYE DISORDERS			
	Photophobia		
GASTROINTESTINAL DISORDERS			
	Nausea		***Nausea (Gr 2)***
	Vomiting		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 2)***
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 2)***
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 2)***
	GGT increased		
	Platelet count decreased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		

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

Adverse events reported on Telaglenastat (CB-839) HCl trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Telaglenastat (CB-839) HCl caused the adverse event:

CARDIAC DISORDERS - Sinus tachycardia
GASTROINTESTINAL DISORDERS - Constipation; Mucositis oral; Oral pain
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Death NOS; Fever
INFECTIONS AND INFESTATIONS - Hepatitis viral; Meningitis
INVESTIGATIONS - Blood bilirubin increased; Creatinine increased; Lymphocyte count decreased; Neutrophil count decreased

METABOLISM AND NUTRITION DISORDERS - Hyperglycemia; Hyponatremia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Myositis
NERVOUS SYSTEM DISORDERS - Seizure
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Dyspnea; Hypoxia
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Rash maculo-papular
VASCULAR DISORDERS - Hypertension; Hypotension

Note: Telaglenastat (CB-839) HCl in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

10.1.1.2 CAEPR for AZD9291 (Osimertinib, NSC 781254)

Comprehensive Adverse Events and Potential Risks list (CAEPR) for Osimertinib (AZD9291, NSC 781254)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 4734 patients*. Below is the CAEPR for Osimertinib (AZD9291).

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

Version 2.9, May 23, 2024[1]

Adverse Events with Possible Relationship to Osimertinib (AZD9291) (CTCAE 5.0 Term) [n= 4734]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 2)***
		Blood and lymphatic system disorders - Other (aplastic anemia)	
CARDIAC DISORDERS			
		Heart failure	
EYE DISORDERS			
		Dry eye Eye disorders - Other (thinning of the front layer of the eye)	
		Keratitis	
GASTROINTESTINAL DISORDERS			
	Constipation		
	Diarrhea		***Diarrhea (Gr 2)***
	Mucositis oral Nausea		***Mucositis oral (Gr 2)***

Adverse Events with Possible Relationship to Osimertinib (AZD9291) (CTCAE 5.0 Term) [n= 4734]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Vomiting		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Fatigue		
INFECTIONS AND INFESTATIONS			
	Paronychia		***Paronychia (Gr 2)***
INVESTIGATIONS			
	Electrocardiogram QT corrected interval prolonged		***Electrocardiogram QT corrected interval prolonged (Gr 3)***
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 2)***
	Neutrophil count decreased		***Neutrophil count decreased (Gr 2)***
	Platelet count decreased		***Platelet count decreased (Gr 2)***
	White blood cell decreased		***White blood cell decreased (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough[2]		
		Pulmonary edema	
	Respiratory, thoracic and mediastinal disorders - Other (interstitial lung disease)[2]		***Respiratory, thoracic and mediastinal disorders - Other (interstitial lung disease) (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Dry skin		***Dry skin (Gr 2)***
		Erythema multiforme	
	Nail changes[3]		***Nail changes[3] (Gr 2)***
	Pruritus		***Pruritus (Gr 2)***
	Rash acneiform		***Rash acneiform (Gr 2)***
	Rash maculo-papular		***Rash maculo-papular (Gr 2)***
		Skin and subcutaneous tissue disorders - Other (erythema dyschromicum perstans)	
		Stevens-Johnson syndrome	
		Toxic epidermal necrolysis	

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

[2]Interstitial lung disease includes the terms pneumonitis and interstitial lung disease. Dyspnea, cough and fever may be indicative of interstitial lung disease/pneumonitis.

[3]Nail changes may include the terms nail bed disorders, nail discoloration, nail disorder, nail loss, nail pigmentation, nail toxicity, nail dystrophy, nail ridging, onychoclasis, onycholysis, and onychomadesis.

Adverse events reported on Osimertinib (AZD9291) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Osimertinib (AZD9291) caused the adverse event:

CARDIAC DISORDERS - Atrial fibrillation; Atrial flutter; Cardiac arrest; Cardiac disorders - Other (atrial thrombosis); Myocardial infarction; Supraventricular tachycardia
EYE DISORDERS - Eye disorders - Other (corneal epithelium defect); Eye disorders - Other (corneal erosion); Eye disorders - Other (eyelids pruritus); Vision decreased
GASTROINTESTINAL DISORDERS - Dry mouth; Dyspepsia; Dysphagia; Gastritis; Gastrointestinal disorders - Other (intestinal ischemia); Pancreatitis
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Death NOS; Fever[2]; Flu like symptoms; Generalized edema; Malaise; Non-cardiac chest pain
INFECTIONS AND INFESTATIONS - Folliculitis; Infections and infestations - Other (pustule); Lung infection; Nail infection; Papulopustular rash; Rash pustular; Shingles; Upper respiratory infection
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Injury, poisoning and procedural complications - Other (drug eruption)
INVESTIGATIONS - Alanine aminotransferase increased; Aspartate aminotransferase increased; CPK increased; Creatinine increased; Ejection fraction decreased; GGT increased; Investigations - Other (electrocardiogram QT interval abnormal); Weight loss
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperglycemia; Hypermagnesemia; Hypokalemia; Hyponatremia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Generalized muscle weakness; Neck pain
NERVOUS SYSTEM DISORDERS - Dizziness; Headache; Ischemia cerebrovascular; Stroke
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Dyspnea[2]; Epistaxis; Hypoxia; Pleural effusion; Respiratory failure
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Eczema; Palmar-plantar erythrodysesthesia syndrome; Skin and subcutaneous tissue disorders - Other (onychalgia); Skin and subcutaneous tissue disorders - Other (skin fissures); Skin and subcutaneous tissue disorders - Other (onychomalacia); Skin and subcutaneous tissue disorders - Other (skin erosion); Skin hyperpigmentation; Urticaria
VASCULAR DISORDERS - Hematoma; Thromboembolic event

Note: Osimertinib (AZD9291) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

10.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 10.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.

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

10.3 Expedited Adverse Event Reporting

10.3.1 Rave-CTEP-AERS Integration

The Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) integration enables evaluation of post-baseline AEs entered in Rave to determine whether they require expedited reporting, and facilitates entry in CTEP-AERS for those AEs requiring expedited reporting.

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 Clinical Research Associate (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 Event 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 (fields added to the form during study build do not need to be query-free for the integration call with CTEP-AERS to be a success).

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 301-897-7497. Once Internet connectivity is restored, the 24-hour notification that was phoned in must be entered immediately into CTEP-AERS using the deep 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.

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

NCI Guidelines for Investigators: Adverse Event Reporting Requirements is available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

Distribution of Adverse Event Reports

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

10.3.2 Expedited Reporting Guidelines

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

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

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

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

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

NOTE: Investigators **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.

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10.3.3 Additional Protocol-Specific Expedited Adverse Event Reporting

All SAEs (Serious Adverse Events), regardless of causality, must be reported to the OSU PI and Multi-Institution Coordinator within 24 hours of knowledge of the event. Initial 24-hour notification using secure email or fax is acceptable.

For SAEs not requiring expedited reporting via CTEP-AERS, a complete report accompanied by the SAE Submission Form (refer to Supplemental Forms Document) must be submitted to the OSU PI and Multi-Institution Coordinator via secure email or fax within 5 days of knowledge of the event.

All sites will directly report SAEs requiring expedited reporting to CTEP as outlined in the previous sections: AstraZeneca will receive any CTEP assessed SAE event reports, directly from CTEP.

If the study is being conducted in multiple countries or multiple sites, Investigators or other site personnel inform sponsor representatives of the SAE. Sponsor/Investigators must inform the local authority of any SAE within 24 hours in accordance with the local regulations and report SAEs to IRB/IEC in the time per local requirements.

10.4 Routine Adverse Event Reporting

All AEs (Adverse Events) **must** be reported in routine study data submissions. **AEs reported expeditiously through CTEP-AERS must also be reported in routine study data submissions.**

AE 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. AEs are reported in a routine manner at scheduled times during the trial using Medidata Rave. For this trial the AE CRF is used for routine AE reporting in Rave.

10.5 Pregnancy

Although not an AE in and of itself, pregnancy as well as its outcome must be documented via **CTEP-AERS, and in Medidata Rave**. In addition, the ***Pregnancy Information Form*** included within the NCI Guidelines for Adverse Event Reporting Requirements must be completed and submitted to CTEP. Any pregnancy occurring in a patient or patient's partner from the time of consent to 90 days after the last dose of study drug must be reported and then followed for outcome. Newborn infants should be followed until 30 days old. Please see the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" (at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm) for more details on how to report pregnancy and its outcome to CTEP.

All pregnancies and outcomes of pregnancy should be reported to the Sponsor and the Company during the course of the study and within 6 weeks of the last dose of Osimertinib (AZD9291).

Maternal exposure

Should a pregnancy still occur, the investigational product should be discontinued immediately and the pregnancy reported to the Sponsor and the Company

If a subject becomes pregnant during the course of the study Osimertinib (AZD9291) should be discontinued immediately.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the subject was discontinued from the study.

If any pregnancy occurs in the course of the study or within 6 weeks of the final dose of the investigational product, then the Investigator or other site personnel informs the appropriate Sponsor/Sponsor representatives within 1 day i.e., immediately but no later than 24 hours of when he or she becomes aware of it.

The designated Sponsor representative works with the Investigator to ensure that all relevant information is provided to the Sponsor data entry site within 1 or 5 calendar days for SAEs (see Section 10.3) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

Paternal exposure

Pregnancy of the subject's partners is not considered to be an adverse event. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should if possible be followed up and documented.

To capture information about a pregnancy from the partner of a male subject, the male subject's partner consent must be obtained to collect information related to the pregnancy and outcome; the male subject should not be asked to provide this information. A consent form specific to this

situation must be used. The outcome of any conception occurring from the date of the first dose until 4 months after dosing ends should be followed up and documented.

10.6 Overdose

In the context of a clinical study, an overdose is any dose which exceeds the daily dose that is defined in the clinical study protocol. A maximum tolerated dose has not been established for Osimertinib (AZD9291).

Overdoses should be recorded as follows:

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module
- An overdose without associated symptoms is only reported on the Overdose eCRF module

There is no specific treatment in the event of Osimertinib (AZD9291) overdose, and symptoms of overdose are not established. In the event of an overdose, physicians should follow general supportive measures and should treat symptomatically.

If an overdose on a Company study drug occurs in the course of the study, then the Investigator or other site personnel inform the appropriate Sponsor representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated Sponsor representative works with the Investigator to ensure that all relevant information is provided to the Sponsor data entry site.

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 10.3. For other overdoses, reporting must occur within 30 days.

10.7 Secondary Malignancy

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

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

- Leukemia secondary to oncology chemotherapy (*e.g.*, 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.

For this trial, use the Adverse Event CRF in Rave.

10.8 Second Malignancy

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

11 STUDY CALENDAR

Baseline evaluations are to be conducted within 14 days prior to start of protocol therapy. Scans and X-rays must be done ≤4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy. During emergency situations, some visits may be conducted remotely or by the local healthcare team, with the approval of the study chair.

11.1 Study Calendar

	Cycle 1				Cycle 2			Cycle 3 onwards	Off Study[f]
	Pre-Study	D1[a]	D15[p]	D16	D1	D2	D15[p]	D1	
Telaglenastat (CB-839) HCl		A ---------- A							
Osimertinib (AZD9291) – Dose escalation				B[b]	B---------- B				
Osimertinib (AZD9291) – Expansion Cohort		B ---------- B							
Informed consent	X								
Inclusion/Exclusion	X	X							
Telaglenastat (CB-839) HCl disbursement and reconciliation		X			X			X	
Osimertinib (AZD9291) disbursement and reconciliation – Dose escalation			X		X			X	
Osimertinib (AZD9291) disbursement and reconciliation – Expansion Cohort		X			X			X	
Demographics	X								
Medical history	X								
Concurrent meds	X	X	X		X			X	X
Physical exam	X	X	X		X			X	X
Vital signs	X	X	X		X			X	X
Height	X								
Weight	X	X	X		X			X	X
Performance status	X	X	X		X			X	X
CBC w/diff, plts	X	X	X		X			X	
Serum chemistry[c]	X	X	X		X			X	
Urinalysis[l]	X				X			X[d]	
12-lead EKG[m,d]	X				X				X
Echocardiography/MUGA for LVEF[k]	X								X
Full ophthalmic assessment[k]									
Adverse event evaluation[o]	X	X	X		X		X[o]	X	
B-HCG	X[e]								
Tumor Biopsy (archival)	X								
Plasma from peripheral blood (Oncometabolites)		X[g]	X[g]		X[g]				X[g]

Whole blood in cfDNA Streck tubes		X_g	X_g		X_g				X_g
	Cycle 1				**Cycle 2**			**Cycle 3 onwards**	**Off Study[f]**
	Pre-Study	D1[a]	D15	D16	D1	D2	D15	D1	
Plasma from peripheral blood (Pharmacokinetics – Dose escalation)		X_h	X_h		X_h	X_h		X_h	
Plasma from peripheral blood (Pharmacokinetics – Expansion Cohort)		X_i			X_i			X_i	
Tumor Imaging[n]	X_n	Tumor measurements are repeated every 8 weeks until progression. Documentation (radiologic) must be provided for patients removed from the study for progressive disease.							

A: Telaglenastat (CB-839) HCl: Dose as assigned; Dose escalation starts at 400 mg PO BID continuously
B: Osimertinib (AZD9291): Dose as assigned; 80 mg PO QD continuously
a: All days are +/- 5 days to account for patient and clinic schedules, holidays, etc.
b. Osimertinib (AZD9291) is added to Telaglenastat (CB-839) HCl treatment starting on D16 of Cycle 1.
c: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, blood creatine phosphokinase, BUN, calcium, chloride, creatinine, glucose, LDH, magnesium, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium. Important note: In case a subject shows an AST or ALT ≥3xULN or total bilirubin ≥ 2xULN please refer to Appendix E 'Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law', for further instructions.
* Electrolyte abnormalities (hypokalaemia, hypomagnesaemia, hypocalcaemia) must be corrected to be within normal ranges prior to first dose and electrolyte levels monitored during study treatment.
d. To be repeated if clinically indicated
e: Serum pregnancy test (women of childbearing potential).
f: Off-study evaluation.
g: Peripheral blood and plasma for cfDNA and oncometabolite studies will be collected at baseline, C1D15 (escalation only), C2D1, and progression.
h: Peripheral blood samples for dose escalation cohort PK analysis will be collected at the following timepoints: 1) baseline/pre-dose; 2) C1D15 before the morning dose of Telaglenastat (CB-839) HCl (0 min) and at 30 min, 1 hour, 2 hours, 4 hours, and 8 hours following this dose; and 3) C2D1 before the morning dose of Telaglenastat (CB-839) HCl and Osimertinib (AZD9291) (0 min) and at 30 min, 1 hour, 2 hours, 4 hours, and 8 hours following this dose. A 24 hour (C2D2, pre-dose) PK collection is optional but encouraged (escalation cohort only). Peripheral blood samples (baseline / 0 hours) will also be collected on Day 1 of each treatment cycle starting with Cycle 3. There is no window for pre-dose research labs as long as done on the same calendar day. Window for post-dose labs is +/- 15 minutes.
i: Peripheral blood samples for phase 2 PK analysis (baseline / 0 hours) will be collected at baseline and on Day 1 of each treatment cycle starting with Cycle 2.
j. To be performed during screening end of treatment. Per the FDA label, echocardiogram is indicated at baseline and during treatment for patients with cardiac risk factors, or if clinically indicated.
k. Full ophthalmic assessment, including slit lamp examination, should be performed if a patient experiences any visual symptoms (including blurring of vision), with additional tests if clinically indicated. Ophthalmology examination results should be collected in the eCRF. Any clinically significant findings, including those confirmed by the ophthalmologist must be reported as an AE.
l. Urinalysis (dipstick) includes: Hb/Erythrocytes/Blood; Protein/Albumin; Glucose
m. Twelve-lead ECGs will be obtained after the patient has been resting semi-supine for at least 5 minutes prior to assessment. All ECGs should be recorded with the patient in the same physical position. For each time point three ECG recordings should be taken at about 2 minute intervals. QTc is assessed using Fredericia's formula. If there is a clinically significant abnormal ECG finding during the Treatment period, this should be recorded on the AE eCRF, according to standard adverse events collection and reporting processes. A 28-day follow-up assessment will be required if an on treatment assessment was abnormal at the time of discontinuation of study therapy, to confirm reversibility of the abnormality.
n. Tumor measurements are repeated every 8 weeks until progression. Documentation (radiologic) must be provided for patients removed from study for progressive disease

o. The investigator will contact the patient by telephone at C2D15 for adverse event assessment following completion of defined DLT period.
p. C1D15 visit and C2D15 telephone visit not required in the expansion cohort

12 MEASUREMENT OF EFFECT

Although the clinical benefit of these drugs have not yet been established, the intent of offering this treatment is to provide a possible therapeutic benefit, and thus the patient will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability. Patients with measurable disease will be assessed by standard criteria. For the purposes of this study, patients should be re-evaluated every 8 weeks. In addition to a baseline scan, confirmatory scans will also be obtained at least 4 weeks following initial documentation of an objective response.

CT Imaging: The purpose of CT imaging in this trial is to assess response by RECIST v1.1. CT imaging and correlate changes with response to treatment as well as disease progression. CT of the chest, abdomen, and pelvis will be obtained on an every 2-month basis to assess response by RECIST v1.1.

12.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained at least 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 revised 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.

12.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with Telaglenastat (CB-839) HCl and Osimertinib (AZD9291).

RECIST evaluable for objective response. Only those patients 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 RECIST response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients 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.

12.1.2 Disease Parameters

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 (≥2 cm) by chest X-ray or as

≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. Tumor lesions that are situated in a previously irradiated area may only be considered measurable if they are growing on pre-treatment imaging.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). 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 [<1 cm] or pathological lymph nodes with ≥10 to <15 mm [≥1 to <1.5 cm] short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as 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 patient, 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.

12.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

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 (≥1 cm) 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 slice thickness is 5 mm (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), the minimum size for 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.

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 date 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 at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy. The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following CR or surgical resection is an endpoint.

Tumor markers. Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both cancer antigen 125 (CA-125) response (in recurrent ovarian cancer) and prostate-specific antigen (PSA) response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology. These techniques can be used to differentiate between PRs and CRs in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

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 SD is mandatory to differentiate between response or SD (an effusion may be a side effect of the treatment) and PD.

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:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. 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.
c. 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.

12.1.4 Response Criteria

12.1.4.1 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 (<1 cm).

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 (0.5 cm). (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.

12.1.4.2 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 [<1 cm] short axis).

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

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 PI).

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

Note: Patients 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 Patients 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 'SD' 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

12.1.5 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 PD is objectively documented (taking as reference for PD the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that PD is objectively documented.

Duration of stable disease: SD 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.

12.1.6 Progression Free Survival (PFS)

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

13 STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

AE lists, guidelines, and instructions for AE reporting can be found in Section 10 (Adverse Events: List and Reporting Requirements).

13.1 Study Oversight

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

For the dose escalation portion of this study, all decisions regarding dose escalation/expansion/de- escalation require sign-off by the Protocol PI through the CTMS/IWRS. In addition, for the dose escalation portion, the Protocol PI will have at least monthly, or more frequently, conference calls with the Study Investigators and the CTEP Medical Officer(s) to review accrual, progress, and AEs and unanticipated problems.

For the expansion cohort, enrollment to the expansion cohort portion of the trial will not begin until a protocol amendment has been submitted which summarizes the phase 1 results, the RP2D, and the rationale for selecting it. The amendment must be reviewed and approved by CTEP before enrollment to the expansion cohort can begin.

During the expansion cohort of the study, the Protocol PI will have, at a minimum, quarterly conference calls with the Study Investigators and the CTEP Medical Officer(s) to review accrual, progress, and pharmacovigilance. Decisions to proceed to the second stage of the expansion cohort will require sign-off by the Protocol PI and the Protocol Statistician.

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

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

13.2 Data Reporting

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments. To access Rave via iMedidata:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account, and
- Assigned one of the following Rave roles on the relevant Lead Protocol Organization (LPO) or Participating Organization roster at the enrolling site: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator. Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.
  - To hold Rave CRA or Rave CRA (Lab Admin) role, site staff must hold a minimum of an AP registration type,
  - To hold Rave Investigator role, the individual must be registered as an NPIVR or IVR, and
  - To hold Rave Read Only role, site staff must hold an Associates (A) registration type.

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

link will display under the study name.

Site staff that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Rave section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

13.2.1 Method

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at: http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. On-site audits will be conducted on an 18-36 month basis as part of routine cancer center site visits. More frequent audits may be conducted if warranted by accrual or due to concerns regarding data quality or timely submission. For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609)-619-7862 or by email at CTMSSupport@theradex.com for additional support with Rave and completion of CRFs.

13.2.2 Responsibility for Data Submission

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

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

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

An End of Study CRF is to be completed by the PI and is to include a summary of study endpoints not otherwise captured in the database, such as (for phase 1 trials) the RP2D and a description of any DLTs. CTMS will utilize a core set of eCRFs that are Cancer Data Standards Registry and Repository (caDSR) compliant (http://cbiit.nci.nih.gov/ncip/biomedical-informatics-resources/interoperability-and-semantics/metadata-and-models). Customized eCRFs will be included when appropriate to meet unique study requirements. The PI is encouraged to review the eCRFs, working closely with CTMS to ensure prospectively that all required items are appropriately captured in the eCRFs prior to study activation. CTMS will prepare the eCRFs with built-in edit checks to the extent possible to promote data integrity.

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

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

13.3 Data and Safety Monitoring

The data and safety monitoring plan will involve the continuous evaluation of safety, data quality and data timeliness. Investigators will conduct continuous review of data and patient safety at their regular Disease Group meetings (at least monthly). For each dose level, the PI, study coordinator, and statistician, in consultation with treating physicians as appropriate will review all toxicities at a given dose level to inform the model for dose level adjustments and to determine if the risk/benefit ratio of the trial changes. Frequency and severity of adverse events will be reviewed by the PI and compared to what is known about the agent/device to determine if the trial should be terminated before completion. Serious adverse events will be reviewed by the OSUCCC Data and Safety Monitoring Committee (DSMC). The PI will also submit progress reports that will be reviewed by the committee per the DSMC plan.

Safety and trial review teleconferences will be scheduled and moderated by the Multi-Center Trial Program (MCTP). All sites involved in the study should have a representative present for every call to review and discuss patients on study and other applicable agenda items. Teleconferences will be held monthly and may be held more frequently, as needed. For studies closed to accrual with patients expected to remain on long-term treatment and/or follow-up, teleconferences may be extended to occur every two months or quarterly. Decreasing frequency of teleconferences requires OSU PI and MCTP approval.

In the expansion cohort component of the study, a safety monitoring scheme will also be implemented by including a stopping rule based on the number of DLTs among the first 21 patients in the first stage. Enrollment may be paused if the lower bound of the 1-sided 80% exact binomial confidence interval of the estimated DLT excludes 30%. At the end of the first stage, the study will be stopped for safety if at least 5 patients with DLTs are observed. The study will continue if no more than 4 patients experience DLTs.

13.4 Collaborative Agreements Language

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

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

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

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

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

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

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

3. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group

studies, or PI for other studies) of Collaborator's wish to contact them.

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

5. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected.

   Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release.

   Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

   Email: ncicteppubs@mail.nih.gov

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

13.5 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, and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

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

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

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

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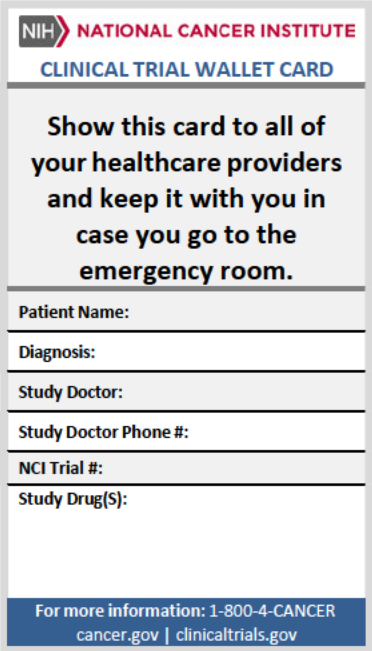
APPENDIX A PERFORMANCE STATUS CRITERIA

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

APPENDIX B PATIENT CLINICAL TRIAL WALLET CARD



NIH NATIONAL CANCER INSTITUTE

CLINICAL TRIAL WALLET CARD

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

Patient Name:

Diagnosis:

Study Doctor:

Study Doctor Phone #:

NCI Trial #:

Study Drug(S):

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

APPENDIX C CYTOCHROME P450 (CYP) 2C9 SUBSTRATES

CYP2C9 Substrates with a narrow therapeutic index*

- S-Warfarin (anticoagulant)
- Phenytoin (antiepileptic)

*Narrow therapeutic index is defined as "CYP *substrates with narrow therapeutic range* refers to drugs whose exposure-response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns (*e.g.*, Torsades de Pointes)."

http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm

Other CYP2C9 Substrates

- NSAIDs (analgesic, antipyretic, anti-inflammatory)
  - celecoxib
  - lornoxicam
  - diclofenac
  - ibuprofen
  - naproxen
  - ketoprofen
  - piroxicam
  - meloxicam
  - suprofen
- fluvastatin (statin)
- sulfonylureas (antidiabetic)
  - glipizide
  - glibenclamide
  - glimepiride
  - tolbutamide
  - glyburide
- irbesartan (to treat hypertension)
- losartan (to treat hypertension)
- sildenafil (in erectile dysfunction)
- terbinafine (antifungal)
- amitriptyline (tricyclic antidepressant)
- fluoxetine (SSRI antidepressant)
- nateglinide (antidiabetic)
- rosiglitazone (antidiabetic)
- tamoxifen (SERM)
- torasemide (loop diuretic)
- ketamine

APPENDIX D GUIDANCE REGARDING POTENTIAL INTERACTIONS WITH CONCOMITANT MEDICATIONS

The use of any natural/herbal products or other "folk remedies" should be discouraged, but use of these products, as well as use of all vitamins, nutritional supplements, and all other concomitant medications must be recorded in the electronic case report form (eCRF).

1. Drugs Inducing CYP3A4 Metabolism That AstraZeneca Strongly Recommend Are Not Combined With Osimertinib (AZD9291)

Osimertinib (AZD9291) is metabolised by CYP3A4 and CYP3A5 enzymes.

A drug-drug interaction study of Osimertinib (AZD9291) evaluated in patients showed that there is potential for Osimertinib (AZD9291) being a victim when co-administered with strong inducers of CYP3A4 (Osimertinib (AZD9291) concentrations are decreased when co-dosed with rifampicin).

The following potent inducers of CYP3A4 must not be used during this study for any patient receiving Osimertinib (AZD9291).

D1 Drugs Inducing CYP3A4

Contraindicated drugs	Withdrawal period prior to Osimertinib (AZD9291) start
Carbamazepine, phenobarbital, phenytoin, rifampicin, rifabutin, rifapentine, St John's Wort	3 weeks
Phenobarbitone	5 weeks

This list is not intended to be exhaustive, and a similar restriction will apply to other agents that are known to strongly modulate CYP3A4 activity. Appropriate medical judgment is required. Please contact AstraZeneca with any queries you have on this issue.

2. Medicines Whose Exposures May be Affected by Osimertinib (AZD9291) That AstraZeneca Considers May be Allowed With Caution

Osimertinib (AZD9291) may increase the concentration of sensitive BCRP and P-gp substrates (concentration of the sensitive BCRP substrate, rosuvastatin and sensitive P-gp substrate, fexofenadine, are increased).

D2 Exposure, Pharmacological Action and Toxicity May be Increased by Osimertinib (AZD9291)

Warning of possible interaction	Advice
Rosuvastatin Sulfasalazine Doxorubicin	Drugs are permitted but caution should be exercised and patients monitored closely for possible drug interactions. Please refer to full prescribing information for all drugs prior to co-administration with Osimertinib (AZD9291).

Warning of possible interaction	Advice
Topotecan	
Dabigatran	
Aliskiren	
Digoxin	

3. Drugs That May Prolong QT Interval

The drugs listed in this section are taken from information provided by The Arizona Center for Education and Research on Therapeutics website: https://www.crediblemeds.org/ . The website categorizes drugs based on the risk of inducing Torsades de Pointes (TdP).

During screening the drugs that patients are currently prescribed should be checked opposite the ArizonaCert website.

4. Drugs with a known risk of Torsades de Pointes

The following drugs prolong the QT interval and are clearly associated with a known risk of TdP, even when taken as recommended. These drugs must have been discontinued prior to the start of administration of study treatment in accordance with guidance provided in Table 3 and should not be co-administered with study treatment (osimertinib) and for a period of two weeks after discontinuing study treatment. **The list of drugs may not be exhaustive and is subject to change as new information becomes available. As such investigators are recommended to search the website to provide the most up to date information**.

Table 3 Drugs with a known risk of TdP

Drug name	Withdrawal period prior to osimertinib treatment start
Aclarubicin, Anagrelide, ciprofloxacin, clarithromycin, cocaine, droperidol, erythromycin, levofloxacin, ondansetron, papaverine hydrochloride, procainamide, sulpiride, sultopride, terfenadine terlipressin	2 days
Cilostazol, Cisapride, disopyramide, dofetilide, domperidone, flecainide, gatifloxacin, grepafloxacin, ibutilide, moxifloxacin, oxaliplatin, propofol, quinidine, roxithromycin, sevoflurane, sotalol, sparfloxacin, thioridazine	7 days

Azithromycin bepridil, citalopram, chlorpromazine, dronedarone, escitalopram, fluconazole, halofantrine, haloperidol, levomepromazine, levosulpiride, mesoridazine	14 days
Donepezil, terodiline	3 weeks
Levomethadyl, methadone, pimozide	4 weeks
Arsenic trioxide*, Ibogaine	6 weeks
Pentamidine	8 weeks
Astemizole, Probucol, vandetanib	4 months
Amiodarone, chloroquine	1 year

* Estimated value as pharmacokinetics of arsenic trioxide has not been studied

This list should be checked against the full and most current list presented in the CredibleMeds® website (https://www.crediblemeds.org/).

Values determined from comprehensive review (internal to AZ) of each compounds PK half-life and determination of the washout period.

Other TdP risk Categories
Patients receiving drugs that prolong QT interval or may increase the risk of TdP from other TdP risk categories can be enrolled, notwithstanding other exclusions and restrictions, if these drugs are considered essential for patient management and the patient has been stable on therapy. Close monitoring with ECGs and electrolytes is recommended.

Patients with **congenital long QT syndrome (CLQTS) are excluded** from this study.

Guidance regardless of TdP risk category
Following study treatment initiation if it is considered essential for patient management to give drugs known to prolong QTc interval, **regardless of TdP risk category**, close monitoring with ECGs and electrolytes is recommended.

APPENDIX E ACTIONS REQUIRED IN CASES OF INCREASES IN LIVER BIOCHEMISTRY AND EVALUATION OF HY'S LAW

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries. Specific guidance on the managing liver abnormalities can be found in Section 7 of the protocol.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with Sponsor clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

Definitions

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) **together with** total bilirubin (TBL) ≥ 2xULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

Hy's Law (HL)

AST or ALT ≥ 3x ULN **together with** TBL ≥ 2xULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (i.e. on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3xULN
- AST ≥ 3xULN

- TBL ≥ 2xULN

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Determine whether the patient meets PHL criteria (see
- Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

Follow-up

Potential Hy's Law Criteria not met

If the patient does not meet PHL criteria the Investigator will:

- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment (See Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment)
- Notify the Sponsor/Company

The Sponsor contacts the Investigator, to provide guidance, discuss and agree on approach for the study patients' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated.
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Company.
- Complete the three Liver CRF Modules as information becomes available
- If at any time (in consultation with the Sponsor) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

Review and Assessment of Potential Hy's Law Cases

The instructions in this Section should be followed for all cases where PHL criteria are met. No later than 3 weeks after the biochemistry abnormality was initially detected, the Company contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The Sponsor Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF.
- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Report an SAE (report term 'Hy's Law') according to standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply.
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review, amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment

This section is applicable to patients with liver metastases who meet PHL criteria on study treatment having previously met PHL criteria at a study visit prior to starting study treatment. At the first on study treatment occurrence of PHL criteria being met the Investigator will:

- Determine if there has been a significant change in the patients' condition[#] compared with the last visit where PHL criteria were met[#]
  - If there is no significant change no action is required
  - If there is a significant change notify the Sponsor representative, who will inform the Company, then follow the subsequent process described in Potential Hy's Law Criteria met of this Appendix

[#] A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Company if there is any uncertainty.

Actions Required for Repeat Episodes of Potential Hy's Law

This section is applicable when a patient meets PHL criteria on study treatment and has already met PHL criteria at a previous on study treatment visit.
The requirement to conduct follow-up, review and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.
The Investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

- Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study e.g. chronic or progressing malignant disease, severe infection or liver disease, or did the patient meet PHL criteria prior to starting study treatment and at their first on study treatment visit as described in Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment?

If No: follow the process described in Potential Hy's Law Criteria met of this Appendix
If Yes:
Determine if there has been a significant change in the patient's condition[#] compared with when PHL criteria were previously met

- If there is no significant change no action is required
  If there is a significant change follow the process described above ("Potential Hy's Law Criteria Met")

[#]A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the Company if there is any uncertainty.

References

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

APPENDIX F DEFINITION OF WOMEN OF CHILDBEARING POTENTIAL AND ACCEPTABLE CONTRACEPTIVE METHODS

Definition of Women of Childbearing Potential

Women of Childbearing Potential (WoCBP):
Women between menarche and menopause who have not been permanently or surgically sterilised and are capable of procreation.

Women NOT of Childbearing Potential:
Women who are permanently or surgically sterilised or postmenopausal (definitions below):

Permanent sterilisation includes hysterectomy and/or bilateral oophorectomy and/or bilateral salpingectomy but excludes bilateral tubal occlusion. Tubal occlusion is considered a highly effective method of birth control but does not absolutely exclude possibility of pregnancy. (The term occlusion refers to both occluding and ligating techniques that do not physically remove the oviducts).

- Women who have undergone tubal occlusion should be managed on trials as if they are of WoCBP (e.g. undergo pregnancy testing etc., as required by the study protocol)
- Women will be considered postmenopausal if they are amenorrhoeic for 12 months without an alternative medical cause. The following age-specific requirements apply:
  - Women under 50 years old will be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatments and with luteinizing hormone and follicle-stimulating hormone levels in the postmenopausal range
  - Women over 50 years of age will be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatments

Acceptable Contraception Methods:

Highly effective method of birth control is defined in Note 3 in International Conference on Harmonisation Guidance M3 (Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals) as one that results in a low failure rate (e.g., less than 1 percent per year) when used consistently and correctly.
Note that women should have been stable on their chosen method of birth control for a minimum of 2 weeks before entering the trial. Generic names and examples of trade names are given. As trade names may vary, Investigators should check the generic name of any contraception to ensure suitability.

Acceptable contraception methods are:

- Total sexual abstinence (abstinence must be for the total duration of the trial and the follow-up period)
- Vasectomised sexual partner plus male condom (with participant assurance that partner received post-vasectomy confirmation of azoospermia)
- Tubal occlusion plus male condom

- Intra-uterine device – provided coils are copper-banded, plus male condom
- Intra-uterine system (IUS) levonorgestrel IUS (e.g., Mirena), plus male condom
- Medroxyprogesterone injections (Depo-Provera) plus male condom
- Etonogestrel implants (e.g., Implanon, Norplan) plus male condom
- Normal and low dose combined oral contraceptive pills, plus male condom
- Norelgestromin / ethinylestradiol transdermal system plus male condom
- Intravaginal device (e.g., ethinylestradiol and etonogestrel) plus male condom
- Cerazette (desogestrel) plus male condom (Cerazette is currently the only highly efficacious progesterone based pill)

Unacceptable Contraception Methods:

The following methods are considered not to be highly effective and are therefore not acceptable contraceptive methods in AstraZeneca clinical trials:

- Triphasic combined oral contraceptives
- All progesterone only pills except, Cerazette
- All barrier methods, if intended to be used alone
- Non-copper containing intra-uterine devices
- Fertility awareness methods
- Coitus interruptus

APPENDIX G PATIENT DIARY

CTEP-assigned Protocol # 10216
Local Protocol # _____

PATIENT'S MEDICATION DIARY – PAGE 1 of 2

Today's date _____ **Agents** Telaglenastat (CB-839) HCl and Osimertinib (AZD9291)

Patient Name_____(*initials acceptable)* **Patient Study ID**_____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for every 4 weeks.
2. You will take your dose of Telaglenastat (CB-839) HCl **twice daily** by mouth, approximately 12 hours apart, **in the morning and in the evening**. You will take____200 mg tablet(s), every day. **Take Telaglenastat (CB-839) HCl with food,** immediately after breakfast and after dinner. Doses should be taken at approximately the same times each day. Missed doses may be taken if it is not more than 3 hours past the scheduled administration time for the missed dose. Vomited doses should not be made up.
3. You will take your dose of Osimertinib (AZD9291) **once daily** by mouth, at approximately the same time every day. You will take_____of mg tablet(s), every day. If you are in the dose escalation portion, you will only be taking Osimertinib (AZD9291) from Day 16 of Cycle 1. You may take Osimertinib (AZD9291) with or without food. If a dose of Osimertinib (AZD9291) is missed or vomited, do not make up the missed dose and take the next dose as scheduled.
4. Record the date, the number of tablets you took, and when you took them.
5. If you have any comments or notice any side effects, please record them in the Comments column.
6. Please return the forms to your physician when you go for your next appointment.

Day	Date	Telaglenastat (CB-839) HCl				Osimertinib (AZD9291)		Comments
		What time was dose taken?		# of 200 mg tablets taken		What time was dose taken?	# of____mg tablets taken	
		AM	PM	AM	PM			
1								
2								
3								
4								
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10								
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19								

PATIENT'S MEDICATION DIARY – PAGE 2 of 2

Day	Date	Telaglenastat (CB-839) HCl				Osimertinib (AZD9291)		Comments
		What time was dose taken?		# of 200 mg tablets taken		What time was dose taken?	# of____mg tablets taken	
		AM	PM	AM	PM			
20								
21								
22								
23								
24								
25								
26								
27								
28								

Physician's Office will complete this section:

1. Date patient started protocol treatment _____
2. Date patient was removed from study _____
3. Patient's planned total daily dose _____
4. Total number of pills taken this month_____
5. Physician/Nurse/Data Manager's Signature _____