ECOG-ACRIN
cancer research group
Reshaping the future of patient care

July 16, 2021

Martha Kruhm, MS RAC
Head, Protocol and Information Office
Quality Assurance Section
CTEP, DCT, NCI
6130 Executive Blvd, EPN Room 7000
Bethesda, MD 20892

Dear Ms. Kruhm:

Enclosed is Addendum #29 to EAY131-E, *MATCH Treatment Subprotocol E: AZD9291 in Patients with Tumors Having EGFR T790M Mutations or Rare Activating Mutations of EGFR*

Please replace your current copy of the protocol and Informed Consent document with these updated versions. We recommend that each institution maintain a file containing the original protocol, Informed Consent, and all subsequent revisions/versions.

IRB Review Requirements:

This addendum has been reviewed and approved by the Central IRB, which is the sole IRB of record for this study. Local IRB review and approval is unnecessary.

Implementation of this addendum must occur on the activation date. Sites are not permitted to conduct the study utilizing outdated versions of any MATCH protocol documents after the activation date of this addendum.

Re: Review of Amendment #39 of Protocol #EAY131-E: "MATCH Treatment Subprotocol E: AZD9291 in Patients with Tumors Having EGFR T790M Mutations (Except Non-Small Cell Lung Cancer) or Rare Activating Mutations of EGFR" dated 4/15/2021. The principal investigators responses appear in bold below.

I. Recommendations:

	Section	Comments
1.	Global 5.1	Within approximately 6 months the PMB-supplied investigational label AZD9291 (osimertinib) will transition to PMB-supplied commercial label osimertinib (AZD9291). There are no manufacturing differences between the investigational clinical supply and the marketed commercial supply. At the time of the next amendment please make the following administrative updates to facilitate the planned transition: • Update the primary agent name to the generic name osimertinib. The code name AZD9291 can be retained as a secondary name, such as "osimertinib (AZD9291)".

28 State Street, Suite 1100, Boston, MA 02109 p: 857.504.2900 f: 617. 589.0914 ecog-acrin.org

	Section	Comments
		Replace the entire pharmaceutical section with the updated CTEP/PMB drug monograph (attached file: Osimertinib (AZD9291) - 781254 – 1120) for consistency with the FDA approved package insert. **PI Response: This has been revised throughout the documents.**

The following revisions to the EAY131-E protocol have been made in this addendum:

	Section	Change
1.	Global	Administrative edits made throughout document.
2.	Cover Page	Updated study title.
3.	Cover Page	Updated Version Date and addendum number.
4.	2.1.2.1	Revised eligibility criteria regarding eligible mutations for study.
5.	2.1.4	First sentence, line 2; revised 'prior to registration to treatment' to "prior to registration'.
6.	2.1.10	Revised 'Male patients' to 'Patients'.
7.	3.2.2	Updated template language regarding the 'Second Cancer Reporting Requirements.'
8.	3.4	Under 'Adverse Events of Special Interest', in item 1, 1st paragraph, lines 5&6; revised 'eCRF' to 'eCRF in Medidata Rave'
9.	4	In footnote C, revised 'women' to 'patients'.
10.	5.1	Updated the primary agent name to the generic name Osimertinib throughout section.

The following revisions to the EAY131-E Informed Consent Document have been made in this addendum:

	Section	Change
1.	Global	Updated the primary agent name to the generic name Osimertinib (AZD9291) throughout document.
2.	Cover Page	Updated Version Date.

If you have any questions regarding this addendum, please contact aaagu@ecog-acrin.org or 857-504-2900.

We request review and approval of this addendum to EAY131-E so ECOG-ACRIN may activate it promptly.

Thank you.

Sincerely,

Pamela Cogliano

Senior Director of Protocol Development

ECOG-ACRIN cancer research group
Reshaping the future of patient care

EAY131-E

Molecular Analysis for Therapy Choice (MATCH)

MATCH Treatment Subprotocol E: Osimertinib (AZD9291) in Patients with Tumors Having EGFR T790M Mutations or Rare Activating Mutations of EGFR

TREATMENT SUBPROTOCOL CHAIR: Lecia V. Sequist, MD
TREATMENT SUBPROTOCOL CO-CHAIR: Helena Yu, MD
TRANSLATIONAL CHAIR: Christine Lovly, MD

Version Date: July 16, 2021
NCI Update Date: August 12, 2015

NOTE: This subprotocol (EAY131-E) should be used in conjunction with the MATCH Master Protocol (EAY131).

Rev. Add12
Rev. Add25

NOTE: As of 11/17, all protocol changes will be noted by addendum number.

SUBPROTOCOL ACTIVATION DATE

August 12, 2015 (incorporated in Addendum #1)
Update #2 – 8/15
Addendum #2 – 2/16
Addendum #3 – 5/16
Addendum #4 – 7/16
Addendum #5 – 12/16
Addendum #7 – 3/17
Addendum #12
Addendum #13
Addendum #14
Addendum #23
Addendum #25
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Addendum #29

Agent	IND#	NSC#	Supply
Osimertinib (AZD9291)	IND Sponsor: DCTD, NCI [redacted]	781254	NCI Supplied

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Schema

Cycle = 28 days
Accrual Goal: 35

1. Introduction

1.1 Osimertinib (AZ9291)

Osimertinib (AZD9291) is an irreversible, mutant specific EGFR tyrosine kinase inhibitor. It is effective in pre-clinical tumor models and clinical trials in patients with TKI sensitizing and T790M resistant tumors. It is generally well tolerated and its most common side effects are mild rash and diarrhea.

1.2 Supporting Preliminary Data

Activating mutations within the epidermal growth factor receptor (EGFR) mutations are present in approximately 20% of all lung adenocarcinomas. EGFR-mutant cancers are dependent on EGFR signaling for growth and survival, making inhibition of EGFR an attractive therapeutic target. EGFR tyrosine kinase inhibitors (TKIs) including erlotinib and afatinib are FDA approved for the treatment of EGFR-mutant lung cancers based on superior responses and progression free survival compared to cytotoxic chemotherapy.[1,2] All patients that are treated with EGFR TKIs will eventually develop therapeutic resistance, on average after 10-12 months of therapy.[1,2]Tumor cells from more than half of patients with such “acquired resistance” contain a recurrent second-site mutation (T790M) in the EGFR kinase domain.[3,4] EGFR T790M is often described as a gatekeeper mutation, and this substitution results in steric hindrance that prevents drug binding and also changes the receptor affinity for ATP.[5] At present, there are no FDA approved therapies for patients with EGFR mutant lung cancer who develop acquired resistance mediated by the T790M mutation.

The first- and second- generation EGFR TKIs (erlotinib and afatinib, respectively) were designed to inhibit wild-type EGFR. Recently, a new class of pyrimidine-based EGFR TKIs has been developed which irreversibly inhibits classically sensitizing (EGFR L858R, EGFR exon 19 deletions [ex19del]) and resistant (EGFR T790M) forms of EGFR. The first drug in this class was WZ4002, and additional drugs include osimertinib (AZD9291), CO-1686, HM61713, EGF816 and ASP8273. Osimertinib (AZD9291) has a greater than 200 times selectivity for EGFR L858R/T790M over wild-type EGFR (IC50s 480 nM to 1.8 μM across different cell lines).[6] Treatment with osimertinib (AZD9291) in EGFR L858R, EGFR ex19del, EGFR L858R/T790M and EGFR ex19del/T790M xenograft tumors also led to profound tumor growth regression. Osimertinib (AZD9291) Investigator’s Brochure 2014)

The phase 1 study of osimertinib (AZD9291) (NCT01802632) has shown extremely promising activity, specifically in patients with lung adenocarcinomas that harbor EGFR T790M.[7] A total of 127 patients with centrally confirmed EGFR T790M who could be evaluated for response: the response rate was 61% (95% CI 52-70) and median PFS was 9.6 months (95% CI, 8.3 to not reached). Among all patients treated, no dose-limiting toxicities were seen at any of the doses evaluated. The most common (>10%) adverse events were diarrhea, rash/acne, nausea, decreased appetite, dry skin, pruritis, fatigue, paronychia, constipation, cough stomatitis, vomiting, anemia, dyspnea, upper respiratory tract infection, headache as presented in the Janne et al 2015 paper. Please refer to the Investigator’s Brochure for comprehensive safety data.

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As of 9th February 2015, there were 25 (2.5%) ILD-like events reported out of more than 993 patients exposed to osimertinib (AZD9291). Of these, 12 were CTCAE Grade 1-2 events, 8 were Grade 3-4 events and 3 fatal (Grade 5) events (0.3%) as outlined above. Two events haven't had a CTCAE grade reported yet. 11 patients experienced prolongation of the corrected QT (QTc) interval; none of these 11 events resulted in reduction or discontinuation of osimertinib (AZD9291). There were 7 fatal adverse events; 1/7 of these events was a pneumonia which was reported as being possibly drug-related.

The excellent responses of EGFR T790M harboring lung adenocarcinomas to osimertinib (AZD9291) provide the rationale to assess osimertinib (AZD9291) in other tumors with EGFR T790M. Osimertinib (AZD9291) is also active in pre-clinical studies against other types of EGFR mutations which suggest that the compound may provide clinical benefit in tumors with other rare EGFR mutations as well.

Comprehensive mutation profiling allows us to identify rare, potentially actionable mutations in a wide array of cancer types. Figure 1 illustrates the frequency of EGFR mutations in various tumor types demonstrating that a broad array of cancers have a low frequency of these mutations of interest. EGFR T790M and other rare variants such as vIII, G719S, L861Q, exon 19 and 20 insertions represent a small minority of these EGFR mutations. In the COSMIC database, we identified listings of EGFR T790M mutations in cancers of the upper aerodigestive tract, the biliary tract, the large intestine, the central nervous system and the skin and we suspect these mutations will be more likely to be commonly identified as comprehensive molecular testing becomes routine for all tumors.

The phase 1 study of osimertinib (AZD9291) was conducted in patients with predominantly EGFR L858R or EGFR ex19del and concurrent EGFR T790M; there is no available clinical data to indicate whether osimertinib (AZD9291) has activity against tumors with other rare EGFR mutations or with T790M alone. There is preclinical data that demonstrates activity of osimertinib (AZD9291) in cells transfected with EGFR G719S, L861Q, exon 19 insertions, EGFR variant III, and HER2 exon 20 insertions.[6] We propose studying AZD9291 in patients with EGFR T790M in cancers other than lung adenocarcinomas. We also propose assessing the activity of AZD9291 in cancers with rare EGFR mutations among which osimertinib (AZD9291) was efficacious in pre-clinical studies (providing MATCH Level 3 evidence – see MATCH Master Protocol).

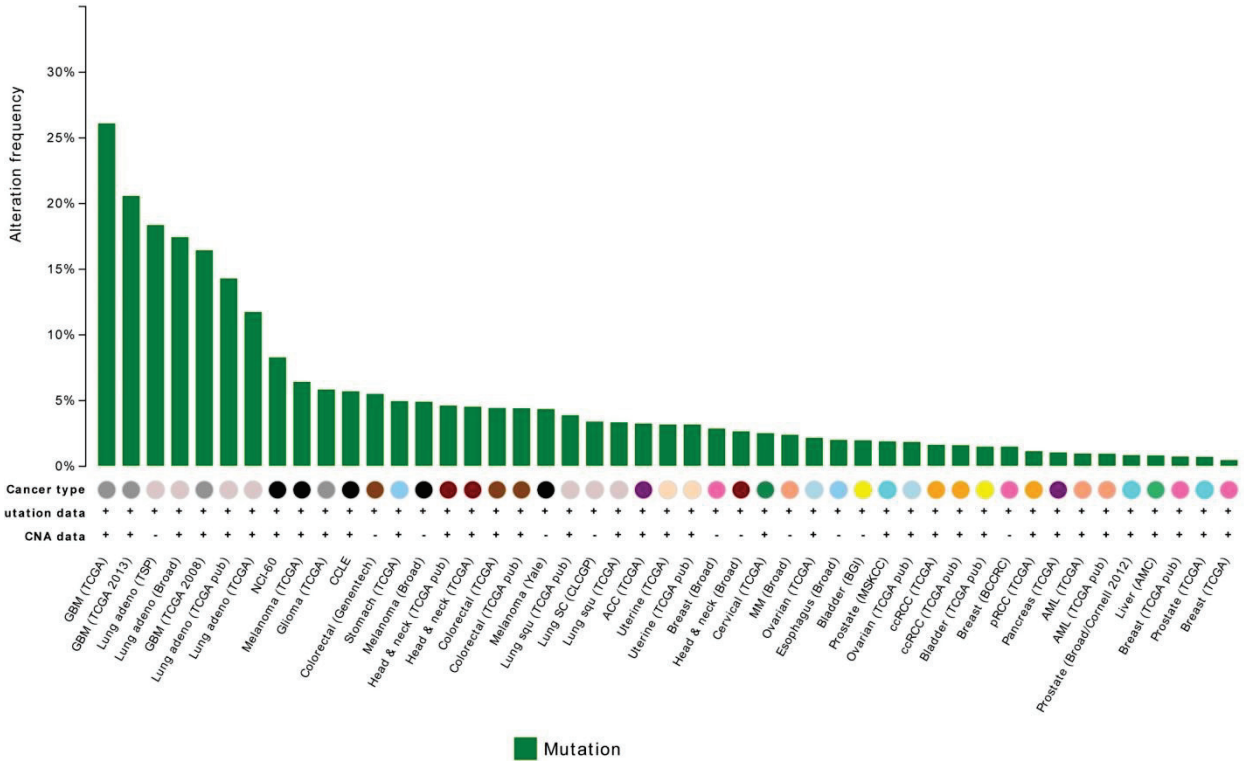

Figure 1

Figure 1: Frequency of EGFR mutations in tumor types derived from the cBIO portal (http://www.cbioportal.org/public-portal/). The X-axis denotes the tumor type and the genomic study from which the data was derived. The Y-axis represents the frequency of the EGFR alterations in the studies represented on the X-axis.

Rev. Add29 **2. Selection of Patients**

Each of the criteria in the checklist that follows must be met, along with the eligibility in the MATCH Master Protocol, in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

ECOG-ACRIN Patient No. _____

Patient's Initials (L, F, M) _____

Physician Signature and Date _____

NOTE: Policy does not allow for the issuance of waivers to any protocol specified criteria (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm). Therefore, all eligibility criteria listed in Section 2 must be met, without exception. The registration of individuals who do not meet all criteria listed in Section 2 can result in the participant being censored from the analysis of the study, and the citation of a major protocol violation during an audit. All questions regarding clarification of eligibility criteria must be directed to the Group's Executive Officer (EA.Execofficer@jimmy.harvard.edu) or the Group's Regulatory Officer (EA.RegOfficer@jimmy.harvard.edu).

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration/randomization by the treating physician.

NOTE: All patients must have signed the relevant treatment consent form.

Rev. Add29 2.1 Eligibility Criteria

Rev.2/16 _____2.1.1 Patient must fulfill all eligibility criteria outlined in Section 3.1 of MATCH Master Protocol (excluding Section 3.1.6) at the time of registration to treatment step (Step 1, 3, 5, 7).

Rev. Add13 _____2.1.2 Patients must have either of the below, or another aberration, as determined via the MATCH Master Protocol and according to Appendix IV:

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2.1.2.1 Any malignancy except NSCLC withEGFR T790M identified in their tumor, with or without an activating mutation

OR

2.1.2.2 Any malignancy harboring any of the following mutations: EGFR G719A, G719C, G719D, G719S EGFR L861Q, S786I or an EGFR exon 19 in frame insertion mutation.

See Appendix IV for information on the targeted mutations and corresponding Levels of Evidence.

Rev. Add13 _____ 2.1.3 Patients must have an electrocardiogram (ECG) within 8 weeks prior to treatment assignment and must have no clinically important abnormalities in rhythm, conduction or morphology of resting ECG e.g. complete left bundle branch block, third degree heart block, and second-degree heart block.

Date of ECG: _____

Rev. 2/16 _____ 2.1.4 **P**atients must have an ECHO or a nuclear study (MUGA or First Pass) within 4 weeks prior to registration and must not have a left ventricular ejection fraction (LVEF) < institutional lower limit of normal (LLN). If the LLN is not defined at a site, the LVEF must be > 50% for the patient to be eligible.

Date of ECHO/Nuclear Study: _____

Rev. Add13 _____ 2.1.5 Patients must not have known hypersensitivity to osimertinib (AZD9291) or compounds of similar chemical or biologic composition or any of the inactive excipients of the tablets.

_____ 2.1.6 Patient must not have received osimertinib (AZD9291), WZ4002, CO-1686, HM61713, EGF816 or ASP8273 previously.

_____ 2.1.7 Patients known to harbor germline EGFR T790M mutations are excluded from the study. Prospective testing for germline mutations is not required.

Rev. Add13 _____ 2.1.8 Patients must not have a history of interstitial lung disease, idiopathic pulmonary fibrosis, organizing pneumonia (eg, bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, radiation pneumonitis requiring steroids, or evidence of active pneumonitis on screening chest computerized tomography (CT) scan. History of radiation pneumonitis in the radiation field (fibrosis) is permitted.

Rev. Add13 _____ 2.1.9 Patients must not currently be receiving treatment with potent CYP3A4 inducters or medications “known to prolong” the QT interval as defined in Appendix II. Drugs that “may possibly prolong” the QT interval, as defined in Appendix II, are permitted if the patient has been stable on therapy for the period indicated for the specific medication.

Rev. Add13 _____ 2.1.10 Patients must agree to not donate sperm from the start of protocol treatment until at least 4 months after the last dose of protocol treatment.

_____ _____

Physician Signature Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

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3. Osimertinib (AZD9291) Treatment Plan

3.1 Administration Schedule

Osimertinib (AZD9291) is given orally. The dose will be 80mg orally once daily continuously. A cycle is defined as 28 days.

Patients should be instructed that if they vomit after taking a dose, then they must not "make it up" with an extra dose, but instead, resume subsequent doses as prescribed. Any missed dose should be skipped and dosing resumed with subsequent doses.

3.2 Adverse Event Reporting Requirements

The Adverse Event Reporting Requirements for all EAY131 subprotocols are outlined in the MATCH MASTER protocol. Please refer to those guidelines when determining if an event qualifies as a Serious Adverse Event (SAE) and requires expedited reporting via CTEP's Adverse Event Reporting System (CTEP-AERS).

In addition, the following section outlines agent specific requirements and must be followed to ensure all reporting requirements are met.

3.2.1 Additional instructions, requirements and exceptions for protocol EAY131-E

Additional Instructions

For instructions on how to specifically report events that result in persistent or significant disability/incapacity, congenital anomaly, or birth defect events via CTEP-AERS, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497. This will need to be discussed on a case-by-case basis.

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EAY131-E specific expedited reporting requirements:

- **Pregnancies**: Pregnancies and suspected pregnancies (including a positive or inconclusive pregnancy test, regardless of age or disease state) occurring while the female patient is on osimertinib (AZD9291), or within 28 days of the female patient's last dose of osimertinib (AZD9291), are considered immediately reportable events. The pregnancy, suspected pregnancy, or positive/ inconclusive pregnancy test must be reported via CTEP-AERS within 24 hours of the Investigator's knowledge. Please refer to Appendix VIII in MATCH Master Protocol for detailed instructions on how to report the occurrence of a pregnancy as well as the outcome of all pregnancies.

EAY131-E specific expedited reporting exceptions:

For study Subprotocol E, the adverse events listed below **do not** require expedited reporting via CTEP-AERS:

- If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ***ONLY*** be reported via CTEP-AERS if the grade being reported exceeds the grade listed in the parentheses next to the event.

3.2.2 Second Primary Cancer Reporting Requirements

All cases of second primary cancers, including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), that occur following treatment on NCI-sponsored trials must be reported as follows.

- **A second malignancy is a cancer that is UNRELATED to any prior anti-cancer treatment (including the treatment on this protocol). Second malignancies require ONLY routine reporting as follows:**
  1. Complete a Second Primary Form in Medidata Rave within 14 days.
  2. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave confirming the diagnosis.
  3. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave.
- **A secondary malignancy is a cancer CAUSED BY any prior anti-cancer treatment (including the treatment on this protocol). Secondary malignancies require both routine and expedited reporting as follows:**
  1. Complete a Second Primary Form in Medidata Rave within 14 days
  2. Report the diagnosis on the Adverse Event Form or Late Adverse Event Form in the appropriate Treatment Cycle or Post Registration folder in Medidata Rave

     Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, or c.) treatment related secondary malignancy

     NOTE: When reporting attribution on the AE Form, assess the relationship between the secondary malignancy and the current protocol treatment ONLY (and NOT relationship to any anti-cancer treatment received either before or after protocol treatment).
  3. Report the diagnosis via CTEP-AERS at http://ctep.cancer.gov
  4. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP confirming the diagnosis.
  5. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP.

NOTE: The Second Primary Form and the CTEP-AERS report should not be used to report recurrence or development of metastatic disease.

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the Second Primary Form must be submitted for the most recent trial. ECOG-ACRIN must be provided with a copy of the form and the associated pathology report and cytogenetics report (if available) even if ECOG-ACRIN was not the patient's most recent trial.

NOTE: Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted via CTEP-AERS or by the Second Primary Form.

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3.3 Comprehensive Adverse Events and Potential Risks List (CAEPR) for Osimertinib (AZD9291) (osimertinib, 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 1342 patients*. Below is the CAEPR for Osimertinib (AZD9291).

NOTE: If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ***ONLY*** be reported via CTEP-AERS if the grade being reported exceeds the grade listed in the parentheses next to the event in the SPEER.

Version 2.7, October 19, 2020[1]

Adverse Events with Possible Relationship to AZD9291 (osimertinib) (CTCAE 5.0 Term) [n= 1342]			**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)***
CARDIAC DISORDERS			
		Heart failure	
EYE DISORDERS			
		Dry eye	
		Eye disorders - Other (thinning of the front layer of the eye)	
		Keratitis	
GASTROINTESTINAL DISORDERS			
Diarrhea			***Diarrhea (Gr 2)***
Mucositis oral			***Mucositis oral (Gr 2)***
	Nausea		
	Vomiting		
INFECTIONS AND INFESTATIONS			
Paronychia			***Paronychia (Gr 2)***
INVESTIGATIONS			
	Creatinine increased		

Adverse Events with Possible Relationship to AZD9291 (osimertinib) (CTCAE 5.0 Term) [n= 1342]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Ejection fraction decreased	
	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			
	Epistaxis		
	Respiratory, thoracic and mediastinal disorders - Other (interstitial lung disease)[2]		***Respiratory, thoracic and mediastinal disorders - Other (interstitial lung disease)[2] (Gr 2)***
		Pulmonary edema	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		
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 (skin fissures)		
		Stevens-Johnson syndrome	

[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 AZD9291 (osimertinib) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that AZD9291 (osimertinib) caused the adverse event:

CARDIAC DISORDERS - Atrial fibrillation; Atrial flutter; Cardiac arrest; Myocardial infarction; Supraventricular tachycardia

EYE DISORDERS - Vision decreased

GASTROINTESTINAL DISORDERS - Constipation; Dry mouth; Dyspepsia; Dysphagia; Gastritis; Gastrointestinal disorders - Other (intestinal ischemia); Pancreatitis

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Death NOS; Fatigue; Fever[2]; Flu like symptoms; Generalized edema; Non-cardiac chest pain

INFECTIONS AND INFESTATIONS - Folliculitis; Lung infection; Nail infection; Papulopustular rash; Rash pustular; Shingles; Upper respiratory infection

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Other (drug eruption)

INVESTIGATIONS - Alanine aminotransferase increased; Aspartate aminotransferase increased; CPK increased; 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 - Cough[2]; Dyspnea[2]; Hypoxia; Pleural effusion; Respiratory failure

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Eczema; Palmar-plantar erythrodysesthesia syndrome; Skin and subcutaneous tissue disorders - Other (skin erosion)

VASCULAR DISORDERS - Hematoma; Thromboembolic event

NOTE: AZD9291 (osimertinib) 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.

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3.4 Dose Modifications

All toxicity grades below are described using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

If there is a clinically-significant AE or unacceptable toxicity of any kind (grade 3 of greater), the primary treatment strategy should be dose interruption and supportive care aimed at the AE. The patient may resume osimertinib (AZD9291) dosing once the AE has resolved to grade 2 or less (see exceptions below). Dosing may resume at 80mg QD or 40mg QD at the discretion of the investigator provided the AE resolved to grade 2 or less within 21 days of dose interruption. If the toxicity does not resolve within 21 days to grade 2 or less, the patient should be removed from the protocol and followed until resolution.

Upon resolution of toxicity within 21 days and resumption of study drug:

- If a further episode of the same AE subsequently requires dose interruption, osimertinib (AZD9291) must restart at 40mg QD.
- If a different AE subsequently requires dose interruption, osimertinib (AZD9291) may restart at either 80mg QD or 40mg QD at the investigator's discretion

Adverse Events of Special Interest

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1. Ophthalmic Events

   Full ophthalmic assessment, including slit lamp examination, is required if a patient experiences any visual symptoms (including blurring of vision) (grade 2 or greater), with additional tests if clinically indicated. Any clinically significant findings, including those confirmed by the ophthalmologist must be reported as an event on the eCRF in Medidata Rave. Ophthalmology examination results should be collected in the eCRF in Medidata Rave. Patient will be advised to consult the clinic promptly if they have any concerns.

   Keratitis

   Keratitis was reported in 0.7% (n=6) of the 833 patients treated with osimertinib 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.

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2. Interstitial lung disease

   If new or worsening pulmonary symptoms (eg, dyspnea) or radiological abnormality suggestive of interstitial lung disease is observed, an interruption in study treatment dosing is required as well as a full diagnostic workup to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. In the presence of confirmatory High Resolution CT scans where other causes of respiratory symptoms have been excluded, a diagnosis of interstitial lung disease should

be considered and study treatment permanently discontinued. In the absence of a diagnosis of interstitial lung disease study treatment may be restarted following consultation with the study subprotocol PI's.

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3. Cardiovascular effects

Exclusion criteria for unstable cardiac conditions and risk factors for QT prolongations are included in the clinical study protocol. Concomitant use of regular medications that may prolong the QT interval will be restricted whenever feasible, but patients may receive any medication that is clinically indicated for the treatment of AEs. Electrolyte and vital sign assessments, including pulse rate and blood pressure, will be monitored regularly throughout the study. ECG will be performed at enrollment and prior to each treatment cycle. The investigator or designated physician will review each ECG prior to discharge from the clinic and may refer to a local cardiologist if appropriate for immediate management of the patient. A paper copy should be filed in the patient's medical records. If an abnormal ECG finding at screening or baseline is considered to be clinically significant by the investigator, it should be reported as a concurrent condition.

QTc Prolongation

Patients with QTcF prolongation fulfilling the following criteria (i.e., confirmed QTcF prolongation to > 500 msec absolute or a > 60 msec increase from baseline) should have osimertinib (AZD9291) interrupted and regular ECGs performed until resolution to baseline. If the toxicity does not resolve to < grade 1 within 3 weeks the patient will be permanently withdrawn from osimertinib (AZD9291) treatment.

Changes in Cardiac Contractility

Across clinical trials, Left Ventricular Ejection Fraction (LVEF) decreases greater than or equal to 10% and a drop to less than 50% occurred in 4.0% (26/655) of patients treated with osimertinib who had baseline and at least one follow-up LVEF assessment. Based on the available clinical trial data, a causal relationship between effects on changes in cardiac contractility and osimertinib has not been established. In patients with cardiac risk factors and those with conditions that can affect LVEF, cardiac monitoring, including an assessment of LVEF at baseline and during treatment, should be considered. In patients who develop relevant cardiac signs/symptoms during treatment, cardiac monitoring including LVEF assessment should be considered.

3.5 Supportive Care

All supportive measures consistent with optimal patient care will be given throughout the study.

3.6 Duration of Agent-specific treatment

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

- Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued. In this event submit forms according to the instructions in the MATCH Forms Packet.

- Patient withdraws consent.
- Patient experiences unacceptable toxicity.
- Non-protocol therapies are administered.
- Disease progression

3.7 Duration of Follow-Up

Refer to the MATCH Master Protocol for specifics on the duration of follow-up.

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4. Study Parameters

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4.1 Therapeutic Parameters for Osimertinib (AZD9291) Treatment

NOTE: In addition to the study parameters listed in the MATCH Master Protocol, the below parameters must also be performed for patients on osimertinib (AZD9291) treatment.

NOTE: All assessments required prior to registration to treatment should be done ≤ 4 weeks prior to registration to Steps 1, 3, 5, 7, excluding the radiologic evaluation and electrocardiogram (ECG).

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Test/Assessment	Prior to Registration to Treatment	Treatment		End of Treatment	Follow Up[F]
		Every Cycle, prior to treatment	Every 2 Cycles		
H&P, Weight, Vital signs[A]	X	X[J]			X
Performance status	X	X[J]			X
CBC w/diff, plts[B]	X	X[J]			X
Serum chemistry[B]	X	X[J]			X
Radiologic evaluation[D]	X		X[D]		X[F]
β-HCG[C]	X				
Toxicity Assessment[G]		X		X	X[F]
Pill Count/Diary[H]		X		X	
ECG[K]	X	X[I]			
ECHO/Nuclear Study	X				
Rev. 3/17 Tumor biopsy and blood sample for MATCH Master Protocol[E]			X	X	
Rev. Add13 Eye evaluation[L]	X				

A. History and physical, including vital signs and weight at the start of each cycle (up to 3 days before start of new cycle).

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B. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, creatinine, glucose, phosphorus, potassium, SGOT[AST], SGPT[ALT], sodium, magnesium and serum tumor markers (including LDH, PSA if appropriate). For eligibility purposes, participants with creatinine levels above institutional normal, Cockcroft-Gault will be used to calculate creatinine clearance. CBC w/diff, platelets and serum chemistries should be performed on cycle 1, day 1 (or up to 7 days prior), and at the start of each subsequent cycle (up to 3 days before start of new cycle). CBC with differential will be performed more frequently in patients with grade 4 neutropenia or thrombocytopenia until resolution to ≤ grade 3. CBC and serum chemistries are only required in follow-up until values return to pre-treatment levels or until progressive disease.

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C. Blood pregnancy test (patients of childbearing potential) required prior to beginning treatment.

Rev. 2/16 D. Disease measurements are repeated every 2 cycles for the first 26 cycles, and every 3 cycles thereafter until PD or start of another MATCH treatment step. The baseline evaluation should be performed as closely as possible to the beginning of treatment and never more than 6 weeks before registration to treatment step. For multiple myeloma patients, please refer to Section 6.4 of the MATCH Master Protocol for additional
Rev. 3/17 information on myeloma response criteria and the required disease assessments. Documentation (radiologic) must be provided for patients removed from study for progressive disease.

Rev. Add13 E. Additional blood specimens and/or biopsies are to be submitted from consenting patients per Section 9.3.2 of the MATCH Master Protocol. Submit at the following time points, as applicable:

- Blood specimens are to be submitted at the end of Cycle 2 (prior to start of Cycle 3 treatment). If patient progresses or treatment is discontinued prior to Cycle 3, collect the blood at that time instead. On-treatment kits for blood sample collections will be automatically shipped to sites upon registration to the treatment step.
- Screening biopsies for additional aMOI assessments after registration to appropriate screening step, if applicable (Step 2 or Step 4).
- At end of all MATCH study treatments, blood specimens and/or research biopsy after consent and registration to Step 8

Please refer to Section 4 of the MATCH Master Protocol to determine whether the patient proceeds to the next screening step or to follow-up (with a potential end of treatment biopsy for research purposes on Step 8). Samples are to be submitted as outlined in Section 9 of the MATCH Master Protocol. To order Step 2/4 Screening or Step 8 kits, complete the EAY131 Collection and Shipping Kit Order Form (See Appendix XII of the MATCH Master Protocol) and fax to 713-563-6506.

Rev. 2/16 F. Every 3 months if patient is < 2 years from study entry, and every 6 months for year 3. Toxicity assessments and radiologic evaluations are not required to be done during Follow Up if progression has been previously reported; however if an adverse event occurs post treatment that meets the SAE reporting requirements, it still must be reported via CTEP-AERS, even if progression has occurred.

G. Site personnel should evaluate for toxicity and discuss treatment compliance with the patient in order to ensure the medication is taken correctly; this evaluation may be conducted by telephone or in person. The Toxicity Assessment is not required prior to Cycle 1, but is required every subsequent cycle.

H. The pill calendar will be collected at the end of every cycle. The Pill Count/Diary is not required prior to Cycle 1, but is required every subsequent cycle.

Rev. 2/16 I. An electrocardiogram must be done on C1D1 approximately 2 hours after receiving the first dose of osimertinib (AZD9291), on C1D8, and then on D1 of each subsequent cycle.

J. For Cycle 1, if the following tests/assessments occurred within 7 days of Day 1, they do not need to be repeated at this timepoint: H&P, Weight, Vital Signs; Performance Status; CBC w/diff, plts; Serum chemistry; Concomitant Medications.

K. Within 8 weeks of treatment assignment.

Rev. Add13 L. Patients should be asked about eye symptoms at baseline. Patients with unexplained eye symptoms should be referred to an ophthalmologist for a full ophthalmic assessment.

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5. Drug Formulation and Procurement

This information has been prepared by the ECOG-ACRIN Pharmacy and Nursing Committees.

Availability

NO STARTER SUPPLIES MAY BE ORDERED. Subjects must be enrolled and assigned to the treatment subprotocol prior to submitting the clinical drug request to PMB.

Drug Ordering: NCI supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that drug be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained – see general information) 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 investigator at that institution.

Submit agent requests through the PMB Online Agent Order Processing (OAOP) application (https://ctepcore.nci.nih.gov/OAOP). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam/) and the maintenance of an “active” account status, a “current” password, and an active person registration status.

NCI Supplied Agent(s) – General Information

Questions about drug orders, transfers, returns, or accountability should be addressed to the PMB by calling 240-276-6575 Monday through Friday between 8:30 AM and 4:30 PM Eastern Time or email PMBAfterHours@mail.nih.gov anytime.

Drug Returns: All undispensed drug supplies should be returned to the PMB. When it is necessary to return study drug (e.g., sealed bottles remaining when PMB sends a stock recovery letter), investigators should return the study drug to the PMB using the NCI Return Agent Form available on the NCI home page (http://ctep.cancer.gov).

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Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of agent received from the PMB using the NCI Investigational Agent Accountability Record Form for Oral Agents available on the NCI home page (http://ctep.cancer.gov). Maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator.

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Investigator Brochure Availability: The current versions of the IBs for PMB-supplied agents will be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an “active” account status, a “current” password, and active person registration status. Questions about IB access may be directed to the PMB IB coordinator at IBCoordinator@mail.nih.gov.

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5.1 Osimertinib (AZD9291) (NSC #781254)

5.1.1 Other Names

Tagrisso™, AZD9291 mesylate

5.1.2 Classification

Epidermal growth factor (EGFR) inhibitor

5.1.3 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

5.1.4 Storage and Stability

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

5.1.5 Dose Specifics

The dose will be 80mg orally once daily continuously.

5.1.6 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.

5.1.7 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.

5.1.8 Incompatibilities

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.

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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.

5.1.9 Side Effects

See Section 3.3 for side effects.

5.1.10 Patient Care Implications

Advise patients of reproductive potential to use effective methods of contraception. Patients of child-bearing potential must use an appropriate double barrier method of birth control (such as female use of a diaphragm, intrauterine device (IUD), sponge and spermicide, in addition to the male use of a condom) or involve female use of prescribed “birth control pills” or a prescribed birth control implant. Both double barrier contraception and birth control pill or implants must be used for at least one week prior to the start of the study and continuing for 16 weeks after the last dose of the study drugs.

Male patients must use barrier contraceptives (i.e., by use of condoms) from the start of study and continue for 16 weeks after the least dose of the study drugs. Male patients should also refrain from donating sperm from the start of study treatment until 4 months after discontinuing study treatment

6. Translational Studies

Please refer to the MATCH Master Protocol for information on the Translational Studies.

7. References

1. Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. The Lancet Oncology 2012;13:239-46.
2. Sequist LV, Yang JC, Yamamoto N, O'Byrne K, Hirsh V, Mok T, et al. Phase III Study of Afatinib or Cisplatin Plus Pemetrexed in Patients With Metastatic Lung Adenocarcinoma With EGFR Mutations. Journal of Clinical Oncology 2013; 31(27):3327-34.
3. Sequist LV, Waltman BA, Dias-Santagata D, et al. Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. Science Translational Medicine 2011;3:75ra26.
4. Yu H, Arcila ME, Rekhtman N, Sima CS, Zakowski MF, Pao W, et al. Analysis of Mechanisms of Acquired Resistance to EGFR TKI therapy in 155 patients with EGFR-mutant Lung Cancers. Clinical Cancer Research 2013; 19(8):2240-7.
5. Yun CH, Mengwasser KE, Toms AV, et al. The T790M mutation in EGFR kinase causes drug resistance by increasing the affinity for ATP. Proceedings of the National Academy of Sciences of the United States of America 2008;105:2070-5.
6. Cross DA, Ashton SE, Ghiorghiu S, Eberlein C, Nebhan CA, Spitzler PJ, et al. AZD9291, an irreversible EGFR TKI, overcomes T790M-mediated resistance to EGFR inhibitors in lung cancer. Cancer Discovery 2014; Sep;4(9):1046-61.
7. Janne PA et al N Engl J Med. 2015 Apr 30;372(18):1689-99.

Molecular Analysis for Therapy Choice (MATCH)
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Appendix I

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Patient Pill Calendar

Pill Calendar Directions

1. Take your scheduled dose of each tablet.
2. If you forget, the missed tablets will not be taken later.
3. Please bring the empty bottle or any leftover tablets and your pill calendar to your next clinic visit.
4. Take AZD9291 once daily by mouth, with or without food.
5. Swallow tablets whole. Do not crush or chew tablets.
6. Store tablets at room temperature.

Patient Pill Calendar

This is a calendar on which you are to record the time and number of tablets you take each day. You should take your scheduled dose of each tablet. **Note the times and the number of tablets that you take each day.** If you develop any side effects, please record them and anything you would like to tell the doctor in the space provided. Bring any unused tablets and your completed pill calendar to your doctor's visits.

AZD9291

DAY	Date: Month	Day	Year	Time tablets taken	Dose taken	Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)
1						
2						
3						
4						
5						
6						
7						
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12						
13						
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15						
16						
17						
18						
19						
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22						
23						
24						
25						
26						
27						
28						

Patient Signature: _____ Date: _____

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Appendix II

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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

Osimertinib is metabolised by CYP3A4 and CYP3A5 enzymes.

A drug-drug interaction study of osimertinib evaluated in patients showed that there is potential for osimertinib being a victim when co-administered with strong inducers of CYP3A4 (osimertinib 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.

D1 Drugs Inducing CYP3A4

Contraindicated drugs	Withdrawal period prior to osimertinib start
Carbamazepine, phenobarbital, phenytoin, rifampicin, rifabutin, rifapentin	3 weeks
St John's Wort	
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.

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

Osimertinib may increase the concentration of sensitive breast cancer resistance protein (BCRP) substrates (concentration of the sensitive BCRP substrate, rosuvastatin, is increased).

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

Warning of possible interaction	Advice
Rosuvastatin	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.
Sulfasalazine	
Doxorubicin	
Daunorubicin	
Topotecan	

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 and The Critical Path Institute, Tucson, Arizona and Rockville, Maryland. Ref: http://www.arizonacert.org/medical-pros/drug-lists/drug lists.htm.

3.1 Drugs known to prolong QT interval

The following drugs are known to prolong QT interval or induce Torsades de Pointes and should not be combined with osimertinib. Recommended withdrawal periods following cessation of treatment with these agents are provided in the table.

D3 Drugs Prolonging QT Interval

Contraindicated drug	Withdrawal period prior to osimertinib start
Clarithromycin, droperidol, erythromycin, procainamide	2 days
Cisapride, disopyramide, dofetilide, domperidone, ibutilide, quinidine, sotalol, sparfloxacin, thioridazine	7 days
Bepridil, chlorpromazine, halofantrine, haloperidol, mesoridazine	14 days
Levomethadyl, methadone, pimozide	4 weeks
Arsenic trioxide	6 weeks [a]
Pentamidine	8 weeks
Amiodarone, chloroquine	1 year

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

3.2 Drugs that may possibly prolong QT interval

The use of the following drugs is permitted (notwithstanding other exclusions and restrictions) provided the patient has been stable on therapy for the periods indicated.

D4 Drugs That May Prolong QT Interval

Drug	Minimum treatment period on medication prior to osimertinib start
Alfuzosin, chloral hydrate, ciprofloxacin, dolasetron, foscarnet, galantamine, gemifloxacin, isridipine, ketoconazole, levofloxacin, mexiletine, nicardipine, octreotide, ofloxacin, ondansetron, quetiapine, ranolazine, telithromycin, tizanidine, vardenafil, venlafaxine, ziprasidone	2 days
Amantadine, amitriptyline, amoxapine, clozapine, doxepin, felbamate, flecainide, fluconazole, fosphenytoin, gatifloxacin, granisetron, imipramine, indapamide, lithium, moexipril/HCTZ, moxifloxacin, risperidone, roxithromycin, sertraline, trimethoprin-sulfa, trimipramine, voriconazole	7 days

Drug	Minimum treatment period on medication prior to osimertinib start
Azithromycin, citalopram, clomipramine, itraconazole, nortriptyline, paroxetine, solifenacin, tacrolimus	14 days
Fluoxetine	5 weeks
Protriptyline	6 weeks
Tamoxifen	8 weeks

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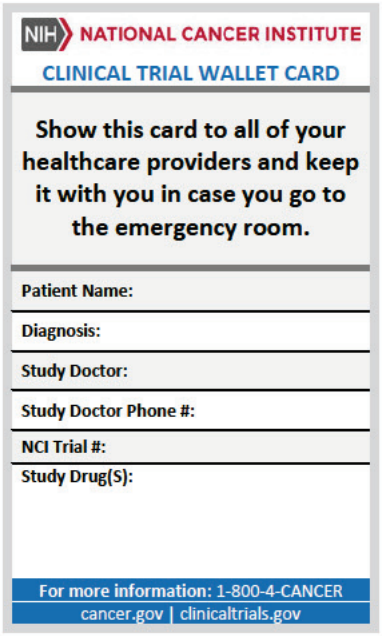
Appendix III

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

Molecular Analysis for Therapy Choice (MATCH)
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Appendix IV

Actionable Mutations for Sub-Protocol EAY131-E

A function has been implemented in MATCHBOX to identify any in-frame insertions in exon 19 of the EGFR gene at Level of Evidence code 3. Please refer to Section 1.4.2 of the MATCH Master Protocol for more information.

Gene Name	Variant ID	Variant Type	Level of Evidence Code	aMOI
EGFR	COSM6240	SNV	2	p.T790M
EGFR	COSM6252	SNV	3	p.G719S
EGFR	COSM6253	SNV	3	p.G719C
EGFR	COSM18425	SNV	3	p.G719D
EGFR	COSM6239	SNV	3	p.G719A
EGFR	COSM6213	SNV	3	p.L861Q
EGFR	COSM18441	MNV	3	p.G719C
EGFR	COSM6241	SNV	3	p.S768I
EGFR	COSM12423	Large Indel	3	p.V738_K739insKIPVal
EGFR	COSM26443	Large Indel	3	p.V738_K739insKIPVal
EGFR	COSM26444	Large Indel	3	p.I740_P741insPValKV
EGFR	COSM255152	Large Indel	3	p.I740_P741insPValKT
EGFR	COSM26720	Large Indel	3	p.A763_Y764insFQEA
EGFR	MVAR181	Large Indel	3	p. D770_N771insNPG
EGFR	COSM392166	Large Indel	3	p.V769_D770insASV
EGFR	COSM13428	Large Indel	3	p.D770_N771insSVD
EGFR	MVAR190	Large Indel	3	p.N771_P772insPGD
EGFR	COSM35508	SNV	3	p.R222C
EGFR	COSM13006	SNV	2	p.V774M
EGFR	EGFR-SEPT14.E24S10	Fusion	3	EGFR-SEPT14.E24S10

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Appendix V

Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

1. Introduction

   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 3.4 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.

2. Definitions

   2A. 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).

   2B. 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.

3. 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