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

EAY131-W

Molecular Analysis for Therapy Choice (MATCH)

MATCH Treatment Subprotocol W: Phase II Study of AZD4547 in Patients with Tumors with Aberrations in the FGFR Pathway

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AZD4547 TRANSLATIONAL CHAIR: Heather Cheng, MD, PhD

Version Date: May 16, 2018

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

Rev. Add13 **NOTE: As of 11/17, all protocol changes will be noted by addendum number. Please reference the activation memo for the addendum activation date.**

SUBPROTOCOL ACTIVATION DATE

May 31, 2016 (incorporated in Addendum #3)
Addendum #4 – 7/16
Addendum #5 – 12/16
Addendum #7 – 3/17
Addendum #13

Agent	IND#	NSC#	Supply
AZD4547		765338	NCI Supplied

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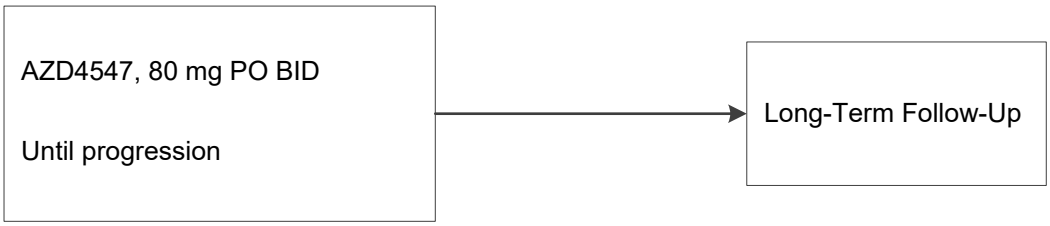
Schema



Cycle = 28 days
Accrual Goal: 70

1. Introduction

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1.1 AZD4547

Background:

AZD4547 is a selective inhibitor of the fibroblast growth factor receptor (FGFR) 1-3 kinases. It exhibits an *in vitro* IC50 of < 5nM for FGFR1-3 and has a significantly lower potency for inhibition of FGFR4 insulin-like growth factor 1 receptor (IGFIR) and kinase insert domain receptor (KFR) (i.e. vascular endothelial growth factor receptor) [VEGFR]. AZD4547 has demonstrated potent anti-tumor effects in several human cancer cell lines dependent on FGFR1-3 including KMS11, KG1a, SNU16, RT112, NCI-H2077, NCI-H716 and SUM52PE and in xenograft models derived from these cell lines.

AZD4547 has been evaluated in a phase I dose-escalation study which has recently completed accrual (NCT00979134). This study established the safety, PK and PD properties of the drug and a recommended monotherapy dose of 80 mg twice daily. Dose-expansion cohorts, which were tied to FGFR1 or FGFR2 amplification as a biomarker, demonstrated activity with a small number of responses in biomarker selected populations. AZD4547 has been evaluated in a Phase I SqNSCLC cohort and in a phase II study in advanced gastric cancer. AZD4547 is currently being evaluated in studies in the US and in Europe aimed at evaluating its efficacy in biomarker selected populations, principally subjects with FGFR1-3 amplifications, point mutations or fusions.

Pharmacokinetics of AZD4547:

Preliminary PK data are available from Studies D2610C00001 (single and multiple bid dosing of 20 mg to 200 mg AZD4547 oral suspension formulation and 120 mg to 200 mg AZD4547 tablet formulation) and D2610C00003 (a Phase I/IIa AZD4547 study in combination with exemestane or fulvestrant in estrogen receptor (ER+) breast cancer. Final reported data are available for D2610C00002 (single and multiple bid dosing of 40 to 120 mg and qd dosing of 160 mg AZD4547 oral tablet formulation in Japanese patients) and D2610C00004 (an open label Phase IIa study in AZD4547 monotherapy versus paclitaxel in advanced gastric cancer).

These studies showed that AZD4547 has a moderate rate of absorption, with a median time to maximum plasma concentration (tMax) of 1 to 4 hours. Following a single dose of AZD4547, peak plasma concentrations declined with a consistent terminal elimination half-life (t1/2) across the dose-levels; mean value approximately 30 hours. The oral clearance was approximately 50 L/h and the oral volume of distribution was greater than total body water indicating that AZD4547 was well-distributed in the tissues.

Safety:

In the dose-escalation study (Study D2610C00001), dose-limiting toxicities (DLTs) have been reported for 7 patients: raised liver function tests (80 mg bd [suspension]), mucositis (120 mg bd [tablet]), stomatitis (150 mg bd [suspension]), uncontrolled phosphate levels (160 mg bd [tablet]), renal failure (200 mg bd [suspension]), renal failure (160 mg bd [tablet]), and liver enzyme changes (200 mg bd [tablet]). The 160 mg bd dose was declared non-tolerated as 2/6 patients experienced DLTs.

Dose expansion cohorts included 94 subjects reporting AEs. The most commonly reported AEs (overall; all doses in all parts of the study [94 patients]) were constipation (43 [45.7%] patients); dry mouth (40 [42.6%] patients), stomatitis (39 [41.5%] patients), diarrhea (33 [35.1%] patients), alopecia (32 [34.0%] patients), decreased appetite (31 [33.0%] patients), and vomiting (31 [33.0 %] patients).

As of 04 June 2014, there have been 49 serious adverse events (SAEs) reported in 25 patients; this includes 1 SAE (respiratory distress) in 1 patient, which occurred after the 28-day follow-up period. Nineteen SAEs in 12 patients were considered by the reporting investigator to be related to treatment with AZD4547. Asthenia, blood creatinine increased, chorioretinopathy, dehydration, dyspnea, general physical health deterioration, renal failure, sepsis, and vomiting are SAE terms reported on more than one occasion.

In the gastric cancer monotherapy vs. paclitaxel study (Study D2610C00004), 40 subjects were enrolled. The most commonly reported AEs (of any grade) reported for patients receiving AZD4547 were: decreased appetite (16 [40.0%] patients), asthenia (11 [27.5%] patients), nausea (10 [25.0%] patients), constipation (10 [25.0%] patients), stomatitis (10 [25.0%] patients), abdominal pain (9 [22.5%] patients), abdominal pain upper (9 [22.5%] patients), dry mouth (9 [22.5%] patients), and vomiting (8 [20.0 %] patients). As of 05 August 2013, 12 on-treatment or post-treatment SAEs had been reported for 8 patients receiving AZD4547. AEs leading to discontinuation of study treatment were reported for 5 patients and 2 patients in the AZD4547 and paclitaxel groups, respectively. In the AZD4547 group these were: arterial disorder (1 patient; fatal; not considered by the reporting investigator to be related to treatment), blood bilirubin increased (1 patient), intestinal hemorrhage (1 patient; fatal; not considered by the reporting investigator to be related to treatment), retinal pigment epithelial detachment (RPED; 1 patient), and RPED and bile duct obstruction (both terms in 1 patient).

On the basis of these the studies, the following are considered AEs associated with AZD4547: Alopecia, blood creatinine increased, diarrhea, dysgeusia, epithelial and mucosal dryness (including palmar-plantar erythrodysesthesia syndrome), hair and eyelash disorders, hyperphosphatemia, nail disorders, retinal pigment epithelial detachment (RPED), stomatitis, and transaminases increased.

More specifically the following adverse events are expected to occur at a frequency greater than 20%: retinal detachment (usually preceded by symptoms and with good prognosis), constipation, diarrhea, dry mouth, oral mucositis, vomiting, fatigue, and anorexia. In addition, ALT and/or AST elevations and hyperphosphatemia may occur with a frequency >20%.

Less likely adverse events include xerophthalmia, keratitis, retinopathy, abdominal pain, nausea, altered taste, alopecia, dry skin, hand foot syndrome, nail discoloration and dystrophy. In addition, elevations in the ALP and serum creatinine, and decreases in the neutrophil count and ejection fraction may occur. Rarely QT prolongation may occur. Also, since AZD457 is a selective inhibitor of the fibroblast growth factor receptor and may alter bone maturation/metabolism, there is a theoretical risk that patients under 25 years of age may not reach their maximum height while taking AZD4547. This adverse event, however, has not been observed or reported as initial trials have not included patients younger than 25 years of age.

Efficacy:

There are only sparse clinical data response to AZD4547 in FGFR amplified tumours as determined by FISH. This is based on two trials that did not meet this endpoint in ORR in the relevant histologies (ASCO 2014 abstract #8035 & 2620). Responses have been documented in patients treated with JNJ42756493 or Novartis FGFR inhibitors (2 of 5 patients treated with BJG398 (Personal communication, AstraZeneca, Oct 2014). Responses in tumors harboring FGFR2 and FGFR3 fusions appear to be more robust than in tumors with FGFR gene amplifications based on early clinical data.

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1.2 Supporting Preliminary Data

While FGFR1-3 gene amplifications had been widely recognized prior to the initiation of clinical studies of AZD4547, multiple newer studies have also described FGFR gene point mutations and translocations across a diverse array of cancer types. Currently, there are preclinical data that tumors with FGFR2 and FGFR3 point mutations and FGFR3/TACC3 fusions are responsive to AZD4547; Responses in tumors harboring FGFR2 and FGFR3 fusions appear to be more robust than in tumors with FGFR gene amplifications based on early clinical data. Based on the TCGA dataset, the prevalence of FGFR point mutations is above 10% in bladder cancer, uterine cancer, cholangiocarcinoma and melanoma and 5-10% in lung adenocarcinoma, lung squamous cell carcinoma, gastric and pancreas cancer. Although the prevalence of FGFR fusions continues to be defined, fusions have been described in lung, head and neck and bladder cancer as well as GBM and cholangiocarcinoma. Moreover, clinical activity of FGFR inhibitors has been reported in patients whose cancers contain FGFR fusions.

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

2.1 Eligibility Criteria

_____ 2.1.1 Patients 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).

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_____ 2.1.2 Patients must have FGFR 1-3 mutation or translocation as determined by the MATCH screening assessment. See Appendix II for a list of the FGFR gene alterations and corresponding Levels of Evidence.

_____ 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):

Date of ECG: _____

_____ 2.1.4 Patients must not have known hypersensitivity to AZD4547 or compounds of similar chemical or biologic composition.

_____ 2.1.5 Patients must have an ECHO or a nuclear study (MUGA or First Pass) within 4 weeks prior to registration to treatment 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: _____

_____ 2.1.6 Patients must have a pre-study eye exam by an ophthalmologist. See Section 3.4.2. Patients with current evidence of corneal or retinal disorder/keratopathy are excluded.

_____ 2.1.7 Patients must not have received prior FGFR specific inhibitors (e.g. BGJ398, erdafitinib, BAY1163877, LY2874455). Prior non-selective FGFR inhibitor treatment (e.g. Pazopanib, dovitinib, ponatinib, brivanib, lucitanib, lenvatinib) will be allowed.

_____ 2.1.8 Patients must not have any history of or current evidence of renal or endocrine alterations of calcium/phosphate homeostasis, or history of or current evidence of extensive tissue calcification (by evaluation of the clinician), including but not limited to, the soft tissue, kidneys, intestine, myocardium and lung with the exception of calcified lymph nodes and asymptomatic vascular calcification per investigators' judgment.

_____2.1.9 Patients must not be currently using medications that can elevate serum phosphorous and/or calcium levels.

2.1.9.1 Medications that increase serum calcium should be avoided. Over the counter calcium supplements, antacids that contain calcium (Tums) and Vitamin D supplements (cholecalciferol and ergocalciferol) should be avoided. Prescription medications including lithium, hydrochlorothiazide and chlorthalidone must be used with caution.

2.1.9.2 Medications that increase serum phosphate should be avoided. Over the counter laxatives that contain phosphate such as Fleets Oral or Fleets enema and Miralax should be avoided.

_____ _____

Physician Signature Date

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

3. AZD4547 Treatment Plan

3.1 Administration Schedule

Patients who meet the eligibility criteria and provided a signed informed consent form will receive AZD4547 at 80 mg PO BID continuously. Dosing is irrespective of body weight.

A cycle is defined as 28 days.

Repeat cycles until progression or unacceptable toxicity.

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 – Subprotocol W

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.

EAY131 – Subprotocol W 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 subject is on AZD4547, or within 28 days of the subject's last dose of AZD4547, 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 – Subprotocol W specific expedited reporting exceptions:

For Subprotocol W, 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 to ECOG-ACRIN using Medidata Rave

- **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 via CTEP-AERS at http://ctep.cancer.gov

     Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, or c.) treatment related secondary malignancy
  3. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP confirming the diagnosis.
  4. 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.

3.3 Comprehensive Adverse Events and Potential Risks List (CAEPR) for AZD4547 (NSC 765338)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, 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 via CTEP-AERS (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 168 patients*. Below is the CAEPR for AZD4547.

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 2.2, May 24, 2016[1]

Adverse Events with Possible Relationship to AZD4547 (CTCAE 4.0 Term) [n= 168]			**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)***
EYE DISORDERS			
	Dry eye		
	Keratitis		
Eye disorders - Other (retinal pigment epithelium detachment)[2]			***Eye disorders - Other (retinal pigment epithelium detachment)[2]***
	Retinopathy		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
Constipation			***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 2)***
Dry mouth			***Dry mouth (Gr 2)***
Mucositis oral			***Mucositis oral (Gr 2)***
	Nausea		
Vomiting			***Vomiting (Gr 2)***
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)***

	Blood bilirubin increased		
	Creatinine increased		***Creatinine increased (Gr 2)***
	Ejection fraction decreased		
		Electrocardiogram QT corrected interval prolonged	
	Neutrophil count decreased		
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 2)***
Metabolism and nutrition disorders - Other (hyperphosphatemia)			***Metabolism and nutrition disorders - Other (hyperphosphatemia) (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Dysgeusia		***Dysgeusia (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		***Alopecia (Gr 2)***
	Dry skin		***Dry skin (Gr 2)***
	Palmar-plantar erythrodysesthesia syndrome		
	Skin and subcutaneous tissue disorders - Other (nail disorders)[3]		***Skin and subcutaneous tissue disorders - Other (nail disorders)[3] (Gr 2)***

[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]Retinal Pigment Epithelium Detachment (RPED) is characterized as RPED, detachment of macular retinal pigment epithelium, subretinal fluid, serous retinal detachment.

[3]Nail disorders include nail discoloration, and/or dystrophy.

Adverse events reported on AZD4547 trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that AZD4547 caused the adverse event:

CARDIAC DISORDERS - Pericardial effusion; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia

EYE DISORDERS - Retinal detachment

GASTROINTESTINAL DISORDERS - Dyspepsia; Dysphagia; Hemorrhoids; Oral pain

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema limbs; Fever; Malaise

HEPATOBILIARY DISORDERS - Hepatobiliary disorders - Other (bile duct obstruction); Hepatobiliary disorders - Other (hepatomegaly); Hepatobiliary disorders - Other (jaundice)

INFECTIONS AND INFESTATIONS - Paronychia; Sepsis; Upper respiratory infection; Urinary tract infection

INVESTIGATIONS - Cardiac troponin T increased; GGT increased; Investigations - Other (increase in LVEF)

METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperkalemia; Hypocalcemia; Hypokalemia; Hyponatremia; Hypophosphatemia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Musculoskeletal and connective tissue disorder - Other (groin pain); Pain in extremity

NERVOUS SYSTEM DISORDERS - Lethargy; Peripheral sensory neuropathy

PSYCHIATRIC DISORDERS - Insomnia

RENAL AND URINARY DISORDERS - Acute kidney injury

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Dyspnea; Epistaxis; Nasal congestion; Pleural effusion; Pleuritic pain; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (breath sounds abnormal)

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Rash maculo-papular

VASCULAR DISORDERS - Hypotension

NOTE: AZD4547 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.

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).

The dose of AZD4547 should be modified according to the dose modification guidelines in Section 3.4.1 if any of the following toxicities occur:

1. Grade 4 neutropenia (ANC < 500/ mm^3)
2. Grade 3 neutropenia (ANC< 1000/ mm^3) in the presence of mucositis or for more than 7 days
3. Febrile neutropenia
4. Grade 3 or greater thrombocytopenia (platelet count < 50,000/mm^3 (50 x 10^9/L)) in the presence of grade 2 or greater bleeding events.
5. Grade 4 thrombocytopenia (platelet count < 25,000/mm^3 (25 x 10^9/L)).
6. Grade 3 or 4 nausea, vomiting, or diarrhea if persistent, despite optimal anti-emetic and/or anti-diarrheal therapy.
7. Hyperphosphatemia >7.5 mg/dL.
8. Any other Grade 4 or unmanageable Grade 3 toxicity.
9. Refer below (Section 3.4.2) for management of ocular toxicities.

3.4.1 AZD4547 Dose Modifications

Occurrence	Action to be Taken
First	Withhold study drug up to 3 weeks until recovery to Grade ≤ 1 or baseline; may restart at 60 or 80 mg PO BID. If restart at 60 mg PO BID, an effort should be made to increase dose to 80 mg PO BID within 4 weeks.
Second	Withhold study drug until recovery to Grade ≤1 or baseline; restart at 60 mg PO BID. No effort should be made to increase dose at 80 mg PO BID.
Third	Discontinue AZD4547 permanently

Dose reductions to 60 mg PO BID are allowed. Dose reductions to lower dose levels are not allowed.

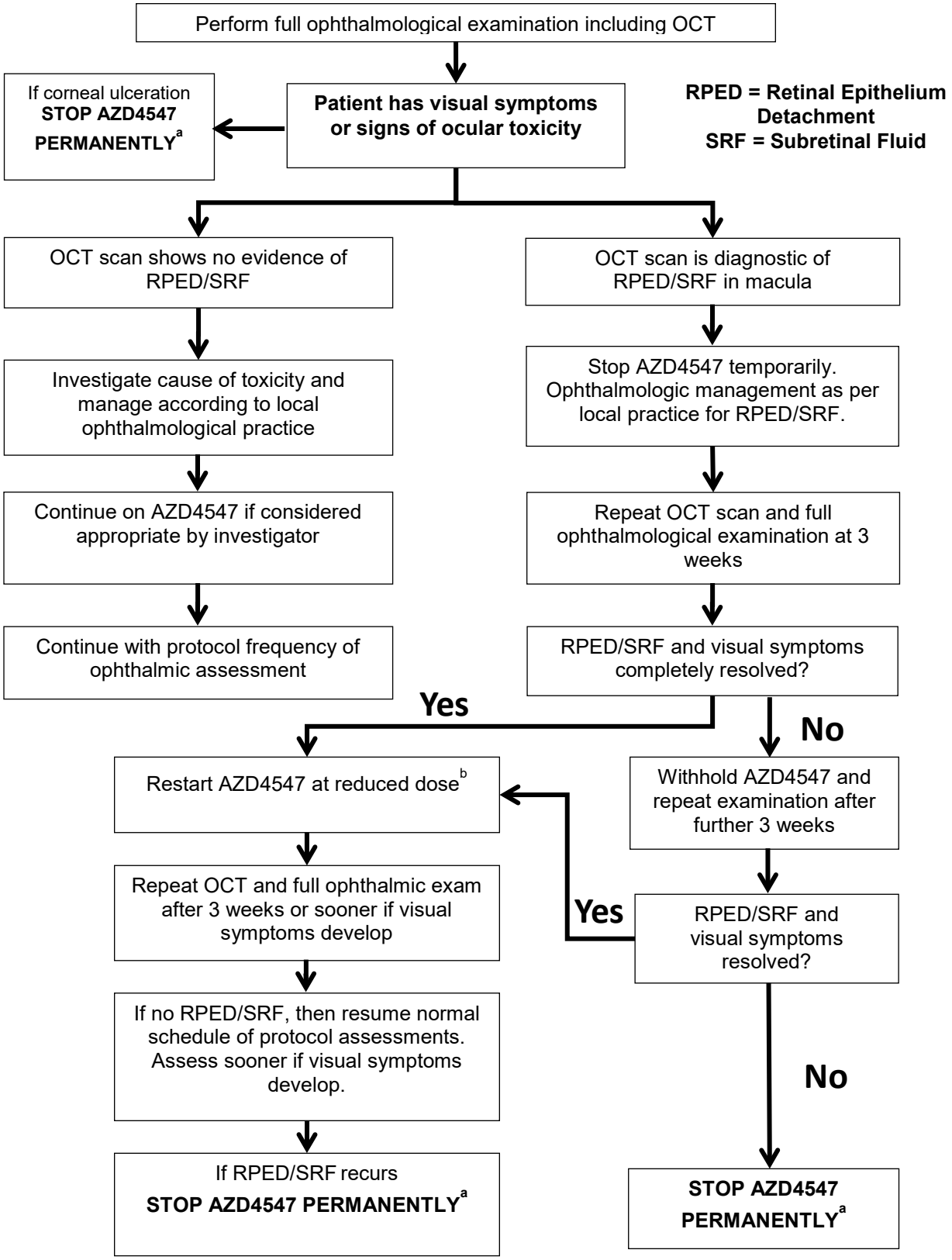
Missed doses should be recorded and considered missed; no effort should be made to make up for missed doses.

Treatment can be withheld due to adverse events up to twice up to 3 weeks in each occurrence.

Treatment will be permanently discontinued if treatment has to be held for toxicity for the third time or for more than 3 weeks.

3.4.2 Dose Modifications for Ocular Toxicities:

Figure 1: Management guidelines for patients with visual symptoms of ocular toxicity



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Footnotes Figure 1:

A full ophthalmologic evaluation by an ophthalmologist should involve at least assessment of the visual acuity and an optical coherence tomography (OCT) scan plus the following evaluations at the discretion of the ophthalmologist:

1. Amsler grid
2. Schirmer test without anesthesia
3. Slit lamp exam
4. Fundoscopy with attention to retinal abnormalities especially retinal pigment detachment (RPED) and subretinal fluid accumulation (SRF)
5. Corneal examination

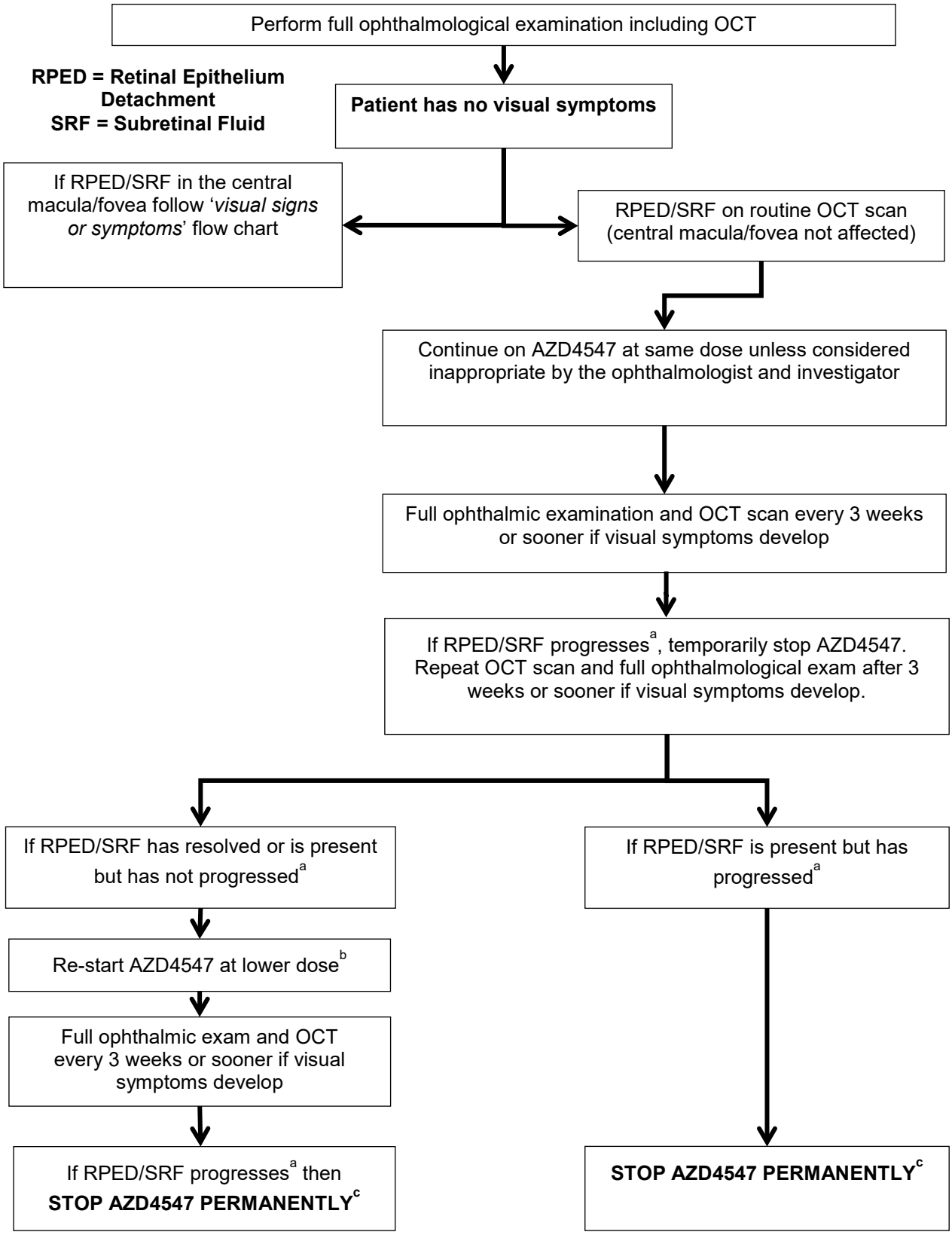
If an active ophthalmologic disease is identified (e.g. retinal detachment), no further testing is required per protocol since the patient is ineligible for the study (see Section 2.1.7); the ophthalmologist can proceed with further testing and treatment at his/her discretion.

a: After permanent discontinuation of AZD4547 due to ocular toxicity, patients should be managed according to local clinical practice.

b: Only 1 dose reduction allowed for management of RPED or SRF.

MedDRA Medical Dictionary for Regulatory Activities; OCT Optical-coherence-tomography; RPED or SRF This grouped term includes RPED (MedDRA preferred terms of detachment of retinal pigment epithelium and detachment of macular retinal pigment epithelium), MedDRA preferred term subretinal fluid, MedDRA preferred term serous detachment, MedDRA preferred term retinal detachment (MedDRA lower level term: serous retinal detachment); SRF Subretinal fluid

Figure 2: Toxicity management guidelines for patients with no visual symptoms of ocular toxicity



Rev. 12/16

Footnotes Figure 2:

A full ophthalmologic evaluation by an ophthalmologist should involve at least assessment of the visual acuity and an optical coherence tomography (OCT) scan plus the following evaluations at the discretion of the ophthalmologist:

1. Amsler grid
2. Schirmer test without anesthesia
3. Slit lamp exam
4. Fundoscopy with attention to retinal abnormalities especially retinal pigment detachment (RPED) and subretinal fluid accumulation (SRF)
5. Corneal examination

If an active ophthalmologic disease is identified (e.g. retinal detachment), no further testing is required per protocol since the patient is ineligible for the study (see Section 2.1.7); the ophthalmologist can proceed with further testing and treatment at his/her discretion.

a: Progression of RPED or SRF is defined as development of visual symptoms, extension from para-macular to macula, or increase in the number of lesions.

b: Only 1 dose reduction allowed for management of RPED or SRF.

c: After permanent discontinuation of AZD4547 due to ocular toxicity, patients should be managed according to local clinical practice.

MedDRA Medical Dictionary for Regulatory Activities; OCT Optical-coherence-tomography; RPED or SRF This grouped term includes RPED (MedDRA preferred terms of detachment of retinal pigment epithelium and detachment of macular retinal pigment epithelium), MedDRA preferred term subretinal fluid, MedDRA preferred term serous detachment, MedDRA preferred term retinal detachment (MedDRA lower level term: serous retinal detachment); SRF Subretinal fluid.

3.5 Supportive Care

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

3.5.2 The following supportive measures are specific for AZD4547 related adverse events:

Organ/toxicity	Severity	Action
Eye		
Xerophthalmia and keratitis	Grade 1and 2	Lubricating eye drops and replacement tears
	Grade 3	Withhold AZD4547 until resolution
RPED*	Found on routine ophthalmology monitoring and no visual impairment	See algorithm for ocular toxicity
Renal		
Hyperphosphatemia	Doubling of phosphate from baseline or Corrected calcium x phosphate > 4.5 $mmol^2/L^2$	Start phosphate chelation therapy (sevelamer at 800 mg PO TID) Weekly chemistry assessments until resolution of the parameter to below the intervention limit Educate patient of low phosphate diet Consult Nephrology to assist in the prescription and/or titration of phosphate chelators (sevelamer up to 1600mg PO TID) Continue chelation therapy regardless of the resolution to below intervention criteria. If no resolution after 14 days of chelation therapy, dose reduce to 60mg PO BID, except if already at that dose then permanently discontinue AZD4547
	Phosphate levels > 7.5 mg/dL	Withhold AZD4547 as outlined in Section 3.4 and start chelation therapy as mentioned above.
Creatinine elevation	Grade 1 or 2	Continue treatment; encourage oral hydration
	Grade 3 or 4	Withhold treatment as outlined in Section 3.4.

*RPED includes retinal pigmented epithelial detachment, central serous retinopathy, central serous choriodopathy, serous detachment.

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

4.1 Therapeutic Parameters for AZD4547 Treatment

NOTE: In addition to the study parameters listed in the MATCH Master Protocol, the below parameters must also be performed for patients receiving AZD4547 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).

Test/Assessment	Prior to Registration to Treatment	Treatment			End of Treatment	Follow Up[F]
		Every Cycle, prior to treatment	Cycle 1, Day 15	Every 2 Cycles		
H&P, Weight, Vital signs[A]	X	X[J]	X		X	X
Performance status	X	X[J]			X	X
CBC w/diff, plts[B]	X	X[J]	X			X
Serum chemistry[B]	X	X[J]	X			X
Radiologic evaluation[D]	X			X[D]		X[F]
β-HCG[C]	X					
Toxicity Assessment[G]		X	X		X	X[F]
Pill Count/Diary[H]		X			X	
ECG[K]	X	X[I]	X[I]			
Echocardiogram or Nuclear Study (MUGA or First Pass)	X	X[I]				
Tumor biopsy and blood sample for MATCH Master Protocol[E]				X	X	
Ophthalmic Exam	X			X[I]		

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

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.

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

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 the treatment step. For multiple myeloma patients, please refer to Section 6.4 of the MATCH Master Protocol for additional information on myeloma response criteria and the required disease assessments. Documentation (radiologic) must be provided for patients removed from study for progressive disease.

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.

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.

I. As clinically indicated. For eye exam, only when indicated by eye-related symptoms.

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 **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 the 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).

Rev. 12/16 **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.

Rev. 3/17 **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

5.1 AZD4547 (NSC 765338)

5.1.1 Other Names

None

5.1.2 Classification

Fibroblast growth factor receptor (FGFR) inhibitor

5.1.3 Mode of Action

AZD4547 is potent and selective inhibitor of the fibroblast growth factor receptor (FGFR) -1, 2 and 3 receptor tyrosine kinases and a weak inhibitor of both insulin-like growth factor 1 receptor (IGF1R) and kinase insert domain receptor (KDR).

5.1.4 Storage and Stability

Store 20 to 25° C (68 to 77° F) in the original container until use.

Shelf-life studies are ongoing. Dispense tablets in the original, unopened containers. Do not repackage tablets in pharmacy bottles per the manufacturer's instructions.

If a storage temperature excursion is identified, promptly return AZD4547 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.

5.1.5 Dose Specifics

AZD4547 is administered at 80 mg PO BID continuously on a 28-day cycle. Dose reductions to 60 mg PO BID continuously on a 28-day cycle are allowed.

5.1.6 Preparation

AstraZeneca supplies and CTEP, DCTD, NCI distributes AZD4547 as beige, round, biconvex, film-coated tablets in 20 mg and 80 mg strengths. Tablets are packed in high-density polyethylene (HDPE) bottles. Each 20-count bottle is secured with an induction sealed membrane and child-resistant closure.

Each tablet contains active drug substance and the following excipients: microcrystalline cellulose, mannitol, magnesium carbonate, hydroxypropyl cellulose, sodium starch glycolate and glyceryl dibehenate. The film coating contains polyvinyl alcohol, titanium dioxide, polyethylene glycol 3350, talc, iron oxide yellow, iron oxide red and iron oxide black.

5.1.7 Route of Administration

Oral. Take without regard to meals.

5.1.8 Incompatibilities

In vitro studies demonstrate that AZD4547 is mainly metabolized by CYP 3A4/5, 2D6 and 1A1 enzymes. Use caution in patients who are taking potent inhibitors or inducers of 3A4/5, 2D6 and 1A1. Smokers

may experience reduced drug exposure since tobacco induces CYP1A1 activity. AZD4547 is also mainly glucuronidated by UGT1A8 and 9 isoforms; however, studies indicate a number of other CYP and UGT isoforms may be responsible for AZD4547 metabolism.

In vitro studies demonstrate that AZD4547 is a substrate of OATP1B1, does not inhibit p-glycoprotein (P-gp) and is a weak inhibitor of OATP1B1 and OCT2.

In vivo, AZD4547 is a reversible and time-dependent inhibitor of CYP 3A4/5. Use caution when combining AZD4547 with CYP3A4/5 substrates known to have a narrow therapeutic window.

5.1.9 Side Effects

See Section 3.3 for side effects.

6. Translational Studies

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

7. References

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7. Singh D, Chan JM, Zoppoli P, et al. Transforming fusions of FGFR and TACC genes in human glioblastoma. Science 2012;337:1231-5.
8. Tan L, Wang J, Tanizaki J, et al. Development of covalent inhibitors that can overcome resistance to first-generation FGFR kinase inhibitors. Proceedings of the National Academy of Sciences of the United States of America 2014;111:E4869-77.
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Molecular Analysis for Therapy Choice (MATCH)
MATCH Treatment Subprotocol W: AZD4547

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Appendix I

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Patient Pill Calendar

Storage: Store at Room Temperature

Pill Calendar Directions

1. Take your scheduled dose of each tablet.
2. If you forget, the missed tablets will not be taken later.
3. If you vomit after taking your scheduled dose, it will not be made up or re-taken. You will continue to receive the next scheduled doses as prescribed
4. Twice daily doses should be taken at approximately the same time each morning and evening approximately 12 hours apart, without regard to meals.
5. Swallow tablets whole. Do not crush or chew tablets.
6. Please bring the empty bottle or any leftover tablets and your pill calendar to your next clinic visit.
7. Do not take over the counter calcium supplements, antacids that contain calcium (e.g. Tums; Alka-Seltzer Chews; Alcalak; Antacid Calcium Extra Strength; Cal-Gest Antacid: Calcium Antacid Extra Strength: Calcium Antacid Ultra Max St; Maalox Childrens and some other Maalox formulations; Rolaids; and Titralac), Vitamin D supplements (cholecalciferol and ergocalciferol), or laxatives (Fleets Oral, Fleets enema and Miralax) without first checking with the Study Doctor.
8. Avoid consumption of grapefruit, grapefruit hybrids, pumellos, star-fruit, Seville oranges or products containing the juice of each within 7 days prior to starting study treatment and throughout study treatment.
9. Do not use tobacco (smoke or chew) while taking this medication – this will make the medication less effective.

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.

AZD4547

DAY	Date			Time tablets taken		Number of tablets 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.)
	Month	Day	Year	AM	PM	AM	PM	
1								
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
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28								

Patient Signature: _____ Date: _____

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Appendix II

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Actionable Mutations for Sub-Protocol EAY131-W

Gene Name	Variant ID	Variant Type	Variant Description	Level of Evidence Code
FGFR1	COSM4771556	SNV	p.K656M	3
FGFR1	COSM35673	SNV	p.K656E	3
FGFR2	COSM29836	SNV	p.A648T	3
FGFR2	COSM36906	SNV	p.C383R	3
FGFR2	COSM1346276	SNV	p.G305R	3
FGFR2	COSM36909	SNV	p.K660E	3
FGFR2	COSM683054	SNV	p.K659N	3
FGFR2	COSM250083	SNV	p.N550H	3
FGFR2	COSM36902	SNV	p.N550K	3
FGFR2	COSM36912	SNV	p.N550K	3
FGFR2	COSM49170	SNV	p.P253R	2
FGFR2	COSM36903	SNV	p.S252W	3
FGFR2	COSM36904	SNV	p.Y376C	3
FGFR3	COSM721	SNV	p.A393E	3
FGFR3	COSM716	SNV	p.G372C	3
FGFR3	COSM24842	SNV	p.G382R	3
FGFR3	COSM24802	SNV	p.G699C	3
FGFR3	COSM719	SNV	p.K652E	3
FGFR3	COSM720	SNV	p.K652M	3
FGFR3	COSM726	SNV	p.K652Q	3
FGFR3	COSM731	SNV	p.K652T	3
FGFR3	COSM714	SNV	p.R248C	3
FGFR3	COSM715	SNV	p.S249C	2
FGFR3	COSM17461	SNV	p.S373C	3
FGFR3	COSM718	SNV	p.Y375C	3
FGFR1	COSM48380	SNV	p.T141R	2
FGFR2	COSM4994845	SNV	p.S252L	2
FGFR2	COSM250081	SNV	p.V395D	2

FGFR2	COSM36913	SNV	p.I547V	2
FGFR2	COSM4604460	SNV	p.N549D	2
FGFR2	COSM3665555	SNV	p.N549S	2
FGFR3	COSM296687	SNV	p.R399C	2
FGFR3	COSM29438	SNV	p.D641N	2
FGFR3	COSM732992	SNV	p.K715M	2
FGFR3	FGFR3-AES.F17A2	Fusion	FGFR3-AES.F17A2	3
FGFR3	FGFR3-BAIAP2L1.F17B2.COSF1347	Fusion	FGFR3-BAIAP2L1.F17B2.COSF1347	3
FGFR3	FGFR3-ELAVL3.F17E2	Fusion	FGFR3-ELAVL3.F17E2	3
FGFR3	FGFR3-TACC3.F14T11	Fusion	FGFR3-TACC3.F14T11	3
FGFR3	FGFR3-TACC3.F15T11	Fusion	FGFR3-TACC3.F15T11	3
FGFR3	FGFR3-TACC3.F16T10.COSF1359	Fusion	FGFR3-TACC3.F16T10.COSF1359	3
FGFR3	FGFR3-TACC3.F16T11.COSF1348	Fusion	FGFR3-TACC3.F16T11.COSF1348	3
FGFR3	FGFR3-TACC3.F17intron17T4	Fusion	FGFR3-TACC3.F17intron17T4	3
FGFR3	FGFR3-TACC3.F17Intron17T9	Fusion	FGFR3-TACC3.F17Intron17T9	3
FGFR3	FGFR3-TACC3.F17T10	Fusion	FGFR3-TACC3.F17T10	3
FGFR3	FGFR3-TACC3.F17T10.COSF1434	Fusion	FGFR3-TACC3.F17T10.COSF1434	3
FGFR3	FGFR3-TACC3.F17T11	Fusion	FGFR3-TACC3.F17T11	3
FGFR3	FGFR3-TACC3.F17T11.1	Fusion	FGFR3-TACC3.F17T11.1	3
FGFR3	FGFR3-TACC3.F17T11.2	Fusion	FGFR3-TACC3.F17T11.2	3
FGFR3	FGFR3-TACC3.F17T13.NGS	Fusion	FGFR3-TACC3.F17T13.NGS	3
FGFR3	FGFR3-TACC3.F17T5	Fusion	FGFR3-TACC3.F17T5	3
FGFR3	FGFR3-TACC3.F17T6	Fusion	FGFR3-TACC3.F17T6	3
FGFR3	FGFR3-TACC3.F17T7	Fusion	FGFR3-TACC3.F17T7	3
FGFR3	FGFR3-TACC3.F17T8	Fusion	FGFR3-TACC3.F17T8	3
FGFR3	FGFR3-TACC3.F17T9	Fusion	FGFR3-TACC3.F17T9	3
FGFR3	FGFR3-TACC3.F18T10	Fusion	FGFR3-TACC3.F18T10	3
FGFR3	FGFR3-TACC3.F18T10.1	Fusion	FGFR3-TACC3.F18T10.1	3
FGFR3	FGFR3-TACC3.F18T11	Fusion	FGFR3-TACC3.F18T11	3
FGFR3	FGFR3-TACC3.F18T4and5	Fusion	FGFR3-TACC3.F18T4and5	3
FGFR3	FGFR3-TACC3.F18T7.NGS	Fusion	FGFR3-TACC3.F18T7.NGS	3
FGFR3	FGFR3-TACC3.TruncatedF17T4	Fusion	FGFR3-TACC3.TruncatedF17T4	3
FGFR2	FGFR2-AFF3.F17A8	Fusion	FGFR2-AFF3.F17A8	3

FGFR2	FGFR2-BICC1.F17B2	Fusion	FGFR2-BICC1.F17B2	3
FGFR2	FGFR2-CASP7.F17C2	Fusion	FGFR2-CASP7.F17C2	3
FGFR2	FGFR2-CIT.F17C23	Fusion	FGFR2-CIT.F17C23	3
FGFR2	FGFR2-KIAA1967_CCAR2.F17C4	Fusion	FGFR2-KIAA1967_CCAR2.F17C4	3
FGFR2	FGFR2-MGEA5.F17M12	Fusion	FGFR2-MGEA5.F17M12	3
FGFR2	FGFR2-OFD1.F17O3	Fusion	FGFR2-OFD1.F17O3	3
FGFR2	FGFR2-TACC3.F17T11	Fusion	FGFR2-TACC3.F17T11	3
FGFR2	SLC45A3-FGFR2.S1F1	Fusion	SLC45A3-FGFR2.S1F1	3
FGFR2	SLC45A3-FGFR2.S1F2	Fusion	SLC45A3-FGFR2.S1F2	3
FGFR1	BAG4-FGFR1.B1F8	Fusion	BAG4-FGFR1.B1F8	3
FGFR1	BAG4-FGFR1.B2F6	Fusion	BAG4-FGFR1.B2F6	3
FGFR1	ERLIN2-FGFR1.E8F2	Fusion	ERLIN2-FGFR1.E8F2	3
FGFR1	FGFR1-TACC1.F17T7	Fusion	FGFR1-TACC1.F17T7	3

Molecular Analysis for Therapy Choice (MATCH)
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Appendix III

Patient Drug Information Handout and Wallet Card

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

The patient _____ is enrolled on a clinical trial using the experimental study drug, **AZD4547.** This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a healthcare provider need to know:

AZD4547 interacts with certain enzymes in the liver and certain transport proteins that help move drugs in and out of cells.

- The enzymes in question are CYP 3A4/5, 2D6, 1A1, and UGT1A8/9. AZD4547 is broken down by these enzymes and may be affected by other drugs that strongly inhibit or induce these enzymes. AZD4547 inhibits CYP 3A4/5 and may affect other drugs that are broken down by these enzymes.
- The transport proteins in question are OATP1B1 and OCT2. AZD4547 requires OATP1B1 to move and out of cells. AZD4547 is an inhibitor of OATP1B1 and OCT2 transport proteins and may affect transport of other drugs that require these proteins to move in and out of cells.

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

AZD4547 may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

AZD4547 must be used very carefully with other medicines that use certain liver enzymes and transport proteins to be effective or to be cleared from your system. Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered "strong inducers/inhibitors of CYP 3A4/5, 2D6, 1A1, UGT1A8/9 or OATP1B1 or substrates of CYP 3A4/5 and transport proteins OATP1B1 and OCT2." These characteristics may change how AZD4547 or other medicine works in your body.

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- Avoid ingesting grapefruit juice, grapefruit and Seville oranges while taking AZD4547.
- Avoid smoking or use of tobacco products as they may affect how AZD4547 works in your body.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine.

Your study doctor's name is

_____

and he or she can be contacted at:

_____.

STUDY DRUG INFORMATION WALLET CARD

You are enrolled on a clinical trial using the experimental study drug **AZD4547.** This clinical trial is sponsored by the NCI. AZD4547 may interact with drugs that are processed by your liver, or use certain transport proteins in your body. Because of this, it is very important to:

- Tell your doctors if you stop taking any medicines or if you start taking any new medicines.
- Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.
- Avoid ingesting grapefruit, grapefruit juice and Seville oranges and avoid smoking or use of tobacco products while on trial.
- AZD4547 interacts with CYP 3A4/5, 2D6, 1A1, UGT1A8/9 and transport proteins OATP1B1 and OCT2 and must be used very carefully with other medicines that interact with these enzymes and transport proteins.
- Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered "strong inducers/inhibitors of CYP 3A4/5, 2D6, 1A1, UGT1A8/9 or OATP1B1 or substrates of CYP3A4/5 and transport proteins OATP1B1 or OCT2."
- Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor.

Your study doctor's name is _____ and can be contacted at _____.